Peripheral Vascular Disease in Diabetes

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Abstract

Diabetes mellitus affects millions of Americans, incurs significant comorbidities, and costs billions annually in health-care dollars. Small and large vessel atherosclerotic changes contribute to coronary, cerebral, and peripheral vascular disease. Untreated macrovascular occlusion may result in loss of life or limb. However, multimodal management of this sequel may be achieved. The focus of this chapter's discussion will be on the lower extremity peripheral vascular complications of diabetes including diagnosis, treatment, and new advancements in care.

Keywords

Diabetes Mellitus • Microvascular • Macrovascular • Peripheral Vascular Disease • PVD • Vascular Surgery • Amputation • Atherosclerosis • Foot Ulcers • Ankle-brachial index • Angioplasty • Bypass

Contents

Introduction

Diabetes mellitus is a ubiquitous disease which affects millions of Americans (9% of the US population) [1], incurs significant comorbidities, and costs billions annually in health-care dollars. The morbidities associated with diabetes mellitus include a substantial increase in both small vessel (microvascular) and large vessel (macrovascular)

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diseases. The macrovascular effects of diabetes, causing serious morbidity and mortality, are found in the coronary, cerebral (extra-and intracranial), and peripheral vascular circulation. The focus of this chapter's discussion will be on the lower extremity peripheral vascular complications of diabetes.

The atherosclerotic nature of peripheral vascular disease (PVD) in patients with diabetes is histologically similar to that found in those without diabetes but tends to be more virulent and aggressive in its behavior and natural history. The early notion of "small vessel disease" unique to diabetes has been disproved. Initially proposed in 1959 [2], it led to the misguided conclusion that patients with diabetes have untreatable micro-occlusive arteriolar disease. This tenet, although subsequently disproved [3–5], is still espoused by many practitioners today. The very nature of modern vascular surgery and the concept of limb salvage that is so vital to the treatment of the diabetic patients are premised on the knowledge that these patients do not suffer from untreatable occlusive microvascular disease of the lower extremities. Their disease is almost always amenable to infrainguinal and tibial reconstruction for limb salvage, even in the most seemingly dismal circumstances.

There are approximately 21 million individuals with diabetes in the United States. As many as 25% will require medical attention, at some point in the course of their disease for diabetes-related foot problems. An astounding 60,000 major amputations are performed annually for these problems. Wound failure rates can be as high as 28%, with half of these patients eventually requiring partial amputations of the contralateral limb within 2–5 years [6]. Fortunately, improvements in screening and timely management of diabetes mellitus and its sequelae have reduced rates of major morbidities, with a decline in limb amputation by more than 50% over the last 20 years [7, 8].

Pathophysiology of Peripheral Vascular Disease in Diabetes

Exact factors responsible for the development of peripheral vascular disease in diabetes are poorly and incompletely understood (Table 1, Fig. 1).

Table 1 Factors predisposing patient with diabetes to PVD

Thickening of capillary basement membrane
Impaired white blood cell migration
Impaired vasodilatation response to injury
Maldistribution of dermal capillaries
Altered endothelium-derived nitric oxide release
Increased oxygen free radical production
Alteration in function of Na^+–K^+ ATPase

The recognition that the vascular endothelium plays a major role in impaired endothelial cell function and the development of diabetic vascular disease is pivotal [6]. The change that does characterize vascular disease in diabetes is most notably a thickening of the capillary basement membrane. This change, however, does not result in capillary narrowing or diminished arteriolar blood flow [9]. Nevertheless, white blood cell migration and response to injury of the diabetic foot may be impeded by thickening of the basement membrane and thus leave the diabetic foot more susceptible to severe infection [10, 11]. Patients with diabetes also suffer from an impaired ability to vasodilate in response to injury, with a misdistribution of skin capillaries which results in local skin ischemia, and impaired neurogenic vasodilatory response [10]. This microcirculatory dysfunction occurs in multiple tissue beds long before the onset of atherosclerotic symptoms [12]. All of these changes lead to an increased susceptibility to trauma and subsequently increased risk of infection.

Prolonged and persistent exposure to elevated glucose levels may alter the production, release, and action of endothelium-derived nitric oxide (EDNO) resulting in impaired vasodilation and abnormal relaxation of the vascular smooth muscle [13]. EDNO, previously known as endothelium-derived relaxing factor (EDRF), is a major mediator of endothelium-dependent vasodilation and arterial smooth muscle relaxation [14, 15], two critical protective mechanisms of healthy endothelium [16]. In people with diabetes, impaired synthesis, release, and response to EDNO play a significant role in diabetes-associated atherosclerotic disease [13]. Animal models have shown that eNOS deficiency

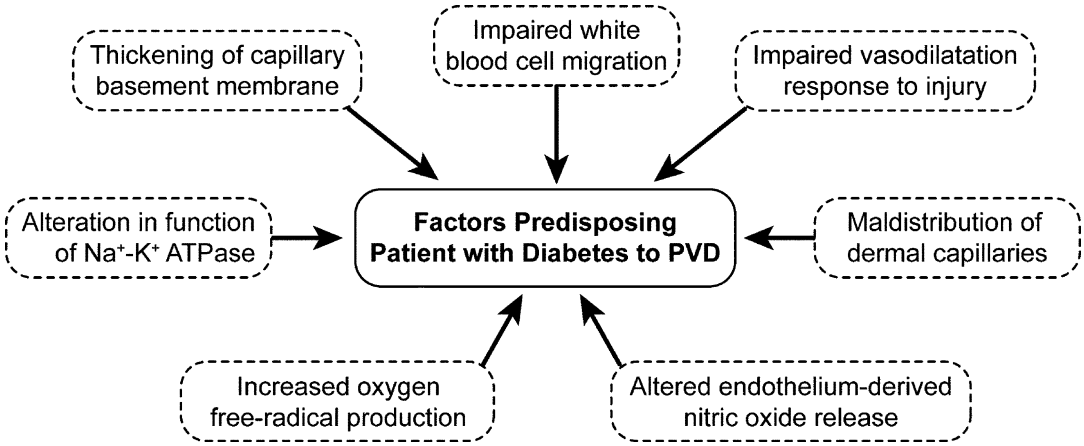

Fig. 1 Factors predisposing patient with diabetes to PVD

markedly increases endothelial leukocyte adhesion and accelerates atherosclerotic lesion development [17]. The generation of oxygen-derived free radicals may also be increased in diabetes with a concomitant decrease in free radical scavenger systems which may further impair the activity of EDNO [14]. In addition, it has been proposed that endothelium which is chronically exposed to elevated glucose levels produces elevated levels of vasoconstrictive prostanoids. Of note, PVD prevalence increases in individuals with impaired glucose tolerance, with the risk significantly increasing with higher hemoglobin A1c levels [18, 19]. For every percentage point above normal, there is a 28% increased risk of PVD, with the severity appearing to be related both to the duration of hyperglycemia and to the glycemic control [18, 20, 21]. Increase in deleterious free radicals may also exaggerate the effect of hyperglycemia on impaired endothelial relaxation as well as the vasoconstrictive properties of circulating prostanoids. Finally, reduction in the activity of Na^+, K^+ ATPase in the vascular smooth muscle may be yet another factor contributing to the impaired vessel response seen in the diabetic patient [6].

Additional mechanisms by which hyperglycemia may result in diabetic PVD include the following (Table 2): glycation of proteins which target receptors in serum and on endothelial and smooth muscle cells that stimulate proinflammatory activity [22–24]; interference with the fluid, vascular, and platelet phases of coagulation; hyperglycemia-induced oxidative stress resulting in enhanced peroxidation of arachidonic acid to form biologically active isoprostanes, an important biochemical link between impaired glycemic control and persistent platelet activation; abnormal lipid metabolism, i.e., increased low-density lipoprotein (LDL) cholesterol, elevated triglyceride levels, and decreased levels of high-density lipoprotein (HDL) cholesterol [25]; abnormal insulin/proinsulin levels; and an impairment in the immune system lymphokine production and polymorphonuclear leukocyte function [25]. Elevated plasma levels of advanced glycation end products, including S100A12 and carboxymethyl-lysine, were found to be associated with increased risk for mortality and limb loss [26]. Further study on the effects, application, and full implications of AGE and their receptors is ongoing.

Table 2 Mechanisms by which hyperglycemia increases the risk of PVD

Glycation of serum proteins – advanced glycation end-products (AGE)
Alteration in coagulation pathways
Hyperglycemia-induced oxidative stress
Abnormal lipid metabolism
Alteration in insulin/proinsulin levels
Impairment in polymorphonuclear leukocyte function/ cytokine production

A better understanding of the factors that contribute to "glucose toxicity" and ultimate vascular pathophysiology may allow for future targeted therapies. A recent concensus statement by the American Diabetes Association and American Heart Association support the administration of daily low-dose aspirin in diabetic individuals with increased cardiovascular risk factors who do not have increased bleeding risk [27]. Statins have been shown to improve both survival as well as long-term patency in infrainguinal bypass years after discontinuation [28, 29]. Further discussions of lifestyle modification and pharmacological therapies to target hyperglycemia and hyperlipidemia agents may be referenced in ▶ Chap. 47, "Treating Type 2 Diabetes Mellitus."

The Diabetic Foot

Nearly half of all patients with diabetes in the United States will develop some degree of PVD and significant lower extremity ischemia beginning approximately one decade after the onset of their disease. As previously noted, the atherosclerosis in patients with diabetes begins at an early age and is more severe than that in individuals without diabetes. Twenty-five percent of diabetic patients will seek medical attention for a foot lesion. In fact, foot lesions account for the majority of hospitalizations in this group. Patients with diabetes and foot lesions carry a 0.6% risk of major amputation per year, resulting in 60,000 major amputations annually in the country [30]. The likelihood of major amputation is 40 times greater in the diabetic than nondiabetic population and parallels the risk for vascular disease in general.

Diabetic foot ulcers are the result of a combination of peripheral neurotropic changes, chronic ischemic changes, rigid osseous deformities, infection, and recurring trauma of the lower extremity and foot. Peripheral neuropathy is a significant problem which contributes to and exacerbates the complications of PVD and is discussed in great detail in another chapter.

Careful attention to and fastidious care of the diabetic foot is of the utmost importance in an attempt to avoid ulceration, infection, gangrene, and limb loss. Ischemic ulcers are typically located on the digits or heel of the foot and are usually painful. Diabetic neuropathy, however, may dull the sensation of ischemic pain hence the absence of pain does not rule out ischemia. Furthermore, patients may not walk long-enough distances for claudication to develop. Neurotropic ulcers are typically found beneath the metatarsal heads on the plantar aspect of the foot and are present often in the setting of a well-perfused foot [6]. Table 3 represents a comparison between characteristics of neurophathic and ischemic ulcers.

Table 3 Comparison of neuropathic versus ischemic ulcers

Neuropathic	Ischemic
Metatarsal head	Tips of toes/heel
Painless	Painful
Pulses present (frequently)	Absent pulses

Even extensive infection in the diabetic foot often presents without the classic signs of fever and elevated white blood cell count. A thorough exam and a high degree of suspicion on the part of the physician evaluating the diabetic foot are mandatory to avoid underestimating the extent of infection and the grave consequences of delay in appropriate aggressive therapy [31]. When patients with diabetes mellitus present with foot lesions, early control of the spreading infection and surgical drainage of established infection remain the cornerstone of initial care [32]. Even a seemingly well-perfused diabetic foot with a normal pedal pulse exam may harbor a severe polymicrobial infection and abscess. The most common organisms involved in diabetic foot infections include *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus,* peptostreptococci, *Escherichia coli, Klebsiella, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa,* and *Bacteroides fragilis.* Pending results of cultures, empiric antibiotic coverage should include a cephalosporin or β-lactam antibiotic (activity against staphylococci and streptococci) and trimethoprim–sulfamethoxazole

(activity against MRSA). Alternatively a fluoroquinolone or linezolid is also acceptable. Early complete debridement of infected and devitalized tissue and drainage of abscess cavities in the operating room are required. Immobilization and non-weight-bearing on the affected extremity are also necessary. Wound and bone cultures and appropriate antimicrobial therapy in concert with frequent dressing changes, return trips to the operating room for further debridement, and wound care are required to treat the infection, promote tissue healing, and avoid major amputation and limb loss. When indicated, early revascularization should follow initial control of active infection.

Ischemia in the Diabetic Extremity: Assessment and Treatment

Assessment of the degree of peripheral vascular disease present in the diabetic patient is important (Table 4). It is not uncommon that the chronically ischemic diabetic foot will require revascularization in order to heal ulcers, control local sepsis, prevent progressive gangrene, and avoid digit, foot, or leg amputation. When physical exam and clinical judgment indicate that ischemia is present in the affected extremity and foot, complete evaluation of the arterial tree is required to plan appropriate intervention and revascularization.

A thorough history is required when assessing the diabetic patient for evidence of PVD. Patients may describe intermittent claudication as calf pain or heaviness, aching, or fatigue that is reproducible and consistent with ambulation and which is relieved with rest. This pattern of symptoms presents because the gastrocnemius muscle has the highest oxygen consumption of any leg muscle and develops ischemic pain earliest during exercise. More advanced ischemia may be manifested as rest pain when perfusion even in the non-exercising muscle is inadequate. Minimum nutritional requirements of resting skin, muscle, bone, and nerve are not met and lead to rest pain, ulceration, and eventual gangrene. Rest pain in the foot is worse at night with leg elevation in the recumbent position and improved with standing. Patients with severe rest pain often sleep with their leg and foot left dangling over the side of the bed. It is important to keep in mind that neuropathic foot pain may often be confused with ischemic rest pain. Moreover, the insensate diabetic foot may mask the rest pain that is the hallmark typical of severe atherosclerosis in individuals without diabetes.

Table 4 Assessment of ischemia

History
Physical exam
Noninvasive vascular studies (pulse/volume recordings; ankle-brachial index)
Magnetic resonance angiography
Angiography
Clinical judgment

Physical exam of the diabetic extremity must also be thorough. The examiner should look for signs of trophic changes that are consistent with chronic ischemia. These changes include thin, shiny skin, subcutaneous atrophy, brittle toenails, diminished muscle mass, and poor hair growth. The feet are often pale and cool with sluggish capillary refill, dependent rubor, and weak or absent pedal pulses. In severe ischemia, there is loss of sweating resulting from sympathetic denervation, signs of neuropathy, and signs of tissue loss with ulceration and gangrene. Ulcers are most often located on the tips of toes or on the heel of the foot, with irregular borders and a pale base [18]. Accuracy and success of different examiners in locating the site of arterial obstruction vary considerably with experience. In a study by Baker and String, medical students, resident physicians, and attending surgeons all determined the location of arterial disease based on physical examination. These assessments were then compared to vascular lab and arteriography findings. Residents and students were partially correct 35% of the time and totally correct only 65% of the time, while attending surgeons were accurate 98% of the time [21]. Thus, for most vascular specialists, physical exam is nearly as accurate as the vascular lab and angiography in identifying the level of occlusive disease.

When indicated, noninvasive vascular lab studies and angiography supplement the findings

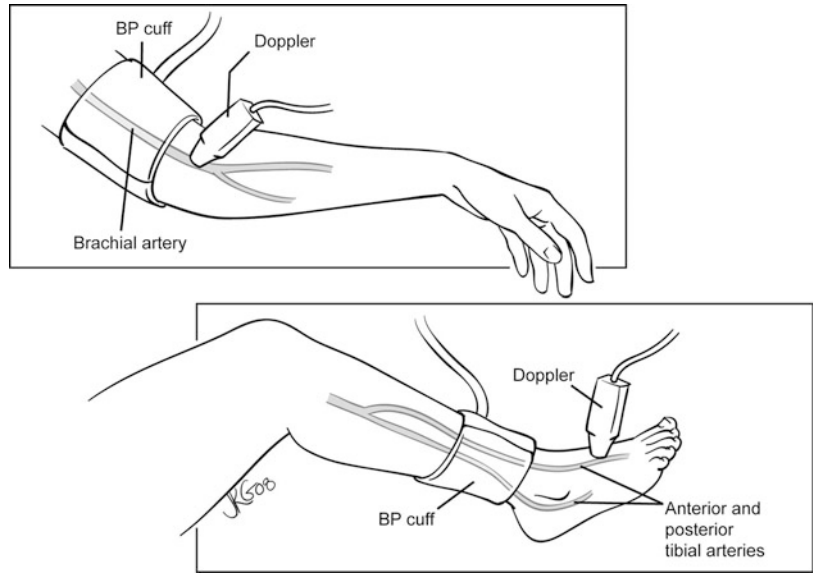

Fig. 2 Blood pressure measurements for ankle-brachial index

on the physical exam and are important tools in establishing whether or not PVD and ischemia are critical factors in the foot ulcer or infection. The ankle-brachial index (ABI) compares the systolic blood pressure at the ankle with that of the brachial artery (Fig. 2). A normal ABI is 1.0–1.1. Progressively diminishing ABIs are found in patients with worsening degrees of PVD – claudication is typically found with ABIs in the range of 0.5–0.9, rest pain is usually experienced with results less than 0.5, and tissue loss is common below 0.3. Pulse volume recordings (PVR) are wave tracings that reflect volume changes in the lower extremity with blood flow. Normally triphasic, the PVR tracing becomes biphasic, monophasic, and eventually flat with progressively more severe vascular disease. When interpreting the results of noninvasive studies in diabetic patients, it is important to keep in mind that medial calcification of tibial vessels may artificially elevate segmental limb pressures and ABI readings as a result of poorly compressible vessels. Absolute ankle pressures of less than 30–40 mmHg are reliable predictors of nonhealing in the diabetic patient. Because digital vessels, unlike tibial vessels, are rarely calcified even in diabetes patients, digital pressure readings may be even more accurate predictors of successful healing. Toe pressures less than 20 mmHg correlate consistently with no healing while toe pressures greater than 40 mmHg predict successful healing [16].

When the diabetic patient requires revascularization to treat rest pain and/or to heal tissue loss and infection, angiography is indicated. Additionally it is recognized that distal arterial reconstruction and the reversal of hypoxia halt the progression of diabetic nephropathy which is a significant factor in diabetic foot lesions and ulceration. This represents, therefore, another possible indication for angiography [18]. When performing lower extremity angiography, the use of selective digital subtraction angiography with attention to careful pre- and postangiography hydration to minimize the risk of renal toxicity has proven invaluable. The angiogram must not only demonstrate the more proximal extremity vessels but also define the tibial and pedal vessels to adequately assess the outflow. Only with this complete information can the appropriate intervention to revascularize the diabetic extremity be planned [32].

Revascularizing the Diabetic Extremity

As noted earlier, lower extremity peripheral vascular disease in the diabetic patient is a result of atherosclerosis which is grossly similar to the

atherosclerotic process seen in individuals without diabetes. However, the distribution of vessels involved and the virulence of the atherosclerotic process in diabetic patients are unique. Patients with diabetes classically have atherosclerosis involving the tibial and peroneal arteries with sparing of the relatively normal suprageniculate and foot vessels. Frequently though the diabetic patient also has other risk factors for atherosclerosis (most notably, tobacco smoking) and suffers from atherosclerosis of the more proximal arterial tree in addition to the classic vascular disease below the knee.

When physical exam and clinical judgment indicate that ischemia is present in the affected extremity and foot, complete evaluation of the arterial tree is required to plan appropriate intervention and revascularization (Table 5).

Table 5 Principles of lower extremity revascularization

Demonstrate necessity for improvement in blood supply
Define vascular anatomy (contrast or magnetic angiography)
Potential vascular anatomy (angioplasty ± stent) as adjunct to surgery
Appropriate choice of conduit (vein, PolyTetraFluoroEthylene)
Careful choice of surgical bypass

While occlusive disease of the proximal large arteries can often be successfully treated nonoperatively with a combination of percutaneous balloon angioplasty and stent placement, smaller vessel disease below the popliteal artery typically requires surgical bypass to patent distal tibial, peroneal, or foot vessels [33]. Often, a combined endovascular and open approach affords the patient the best result. Proximal stenosis should be treated to optimize inflow for a distal bypass and reduce failure rates.

Vital to planning a successful operation is the accurate and detailed assessment of the affected extremity's arterial tree. This typically requires contrast angiography or magnetic resonance angiography of the entire inflow and outflow tract, including foot vessels. To heal ischemic tissue in the lower extremity or foot, one must bring normal pulsatile arterial flow to the level of tissue loss. There are certainly cases where tissue healing is achieved without restoring pedal pulses, by improving the arterial inflow to the extremity at a more proximal point with or without bypass. These cases, however, are the exception and every attempt should be made to restore palpable distal flow when an acceptable patent outflow vessel exists in a medically suitable patient.

Autogenous greater saphenous vein (left in situ with valvulotomy or reversed ex situ and tunneled) is clearly the conduit of choice in below-the-knee distal bypasses with superior long-term patency and decreased risk of infection as compared to synthetic conduits (PolyTetraFluoroEthylene [PTFE] or Dacron). When the greater saphenous vein is not available for use, autogenous arm vein may also be used as the bypass conduit with good long-term results. However, many surgeons have achieved and described successful operations using a composite graft of autogenous vein and synthetic graft or PTFE alone [31].

LoGerfo et al. [34] described the reduction in major amputation rates with increased application of dorsalis pedis artery bypass. Bypass to patent dorsalis pedis vessels resulted in a 3-year patency rate of 87% and a limb salvage rate of 92%. Additionally, despite the increased rate of distal bypass surgery, the authors did not experience an increase in mortality in this patient population. Diabetic patients with reconstructable lesions demonstrated on angiography do just as well as nondiabetic individuals in terms of long-term graft patency and limb salvage. Pedal bypass is safe, effective, and durable and should be considered even in "high-risk" patients with critical ischemia before major amputation [35]. That noted, however, there can be a recurrence of diabetic foot ulcers despite patent distal bypasses.

Endovascular techniques were originally designed for diagnostic purposes. Today, vascular surgeons are trained to achieve full competence in the endovascular management (i.e., angiography, subintimal dissection, endoluminal stenting) of all vascular disease exclusive of coronary and intracranial pathology [36]. The revascularization paradigm for PVD has shifted strategies from traditional open surgical approaches toward percutaneous endovascular modalities While early studies showed mixed results in regard to

short- and long-term morbidity and mortality, current consensus supports reduced 30-day all-cause mortality and initial length-of-stay [37]. The limit of endovascular procedures for PVD is depicted in long-term outcomes. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial was a British multicenter randomized trial that compared an initial strategy of angioplasty versus open surgery in 452 patients with chronic limb ischemia. The primary outcome was time to amputation or death (amputation-free survival). While after 6 months, the two treatment strategies did not differ significantly in amputation-free survival, at 2 year follow-up there was evidence to suggest that those who had undergone bypass first fared better in overall survival and amputation-free survival [38]. New endovascular therapies, including the novel use of adjuvant brachytherapy, cryoplasty, drug-eluting balloon angiography, and drug-eluting stents, are being explored as means to reduce the rate of restenosis [39–42]. In multilevel vascular disease, a hybrid approach combining endovascular and more traditional open endarterectomy and grafting has shown great promise. As endovascular therapies show improvement in long-term durability and newer technologies are developed, minimally invasive procedures will increasingly limit the need for open surgery.

Summary

"Understanding the pattern of atherosclerotic occlusive disease in patients with diabetes mellitus is the foundation for a successful clinical management plan" [34]. Recognizing that the infrageniculate vessels are involved with atherosclerosis while the pedal vessels, particularly the dorsalis pedis artery, are often spared and are thus amenable to extreme distal revascularization is the cornerstone of successful management. Rejection of the concept of microvascular occlusive disease is stressed. There is no evidence to support the notion of diminished blood flow in the microcirculation as a result of basement membrane thickening – small vessel disease or microangiopathy.

General maintenance and preventive care of the diabetic patient with peripheral vascular disease are mandatory and include the following: control of hyperglycemia and hyperlipidemia and strict avoidance of smoking, a reasonable exercise regimen, close attention to and care of the feet, nails, and skin with avoidance of local trauma, antifungal care when indicated, control of hypertension, modification of lipid profile, and reduction of BMI. Additionally, various drugs that target coagulation may be useful adjunctive therapy: hemorrheologic agents (pentoxifylline), antithrombotic therapy, anticoagulants, platelet inhibitors, and thrombolytic agents.

Together, improved metabolic control, an appreciation of the nature of peripheral vascular disease typical of the diabetic patient, and the success of distal bypasses in this population will lead to decreases in lower extremity amputation and an increase in limb salvage in this patient population. Advances in endovascular techniques have prompted a paradigm shift in the management of PVD toward minimally invasive approaches which have the potential to lessen short- and long-term morbidity and mortality.

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Internet Resources

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46. http://www.fda.gov/diabetes
47. http://www.who.int/diabetes/en
48. http://www.americanheart.org
49. http://www.mayoclinic.org/peripheral-vascular-disease