Controversies Regarding Vascular Disease in the Patient with Diabetes: A Review of the Literature

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Vascular disease in the patient with diabetes represents a potentially devastating complication. Tri-neuropathy (sensory, motor, and autonomic) often predisposes patients to ulceration and vascular disease leads to delayed healing. Vascular pathology compromises blood flow and oxygen provision, affecting healing, infection, sepsis, amputation, and mortality. Recent research suggests that vascular reconstruction should not be withheld on the basis of arteriolar-capillary involvement and while oxygen levels may provide important prognostic and diagnostic information, no single noninvasive parameter or test can reliably predict healing of existing wounds. Hyperglycemia has been identified as a risk factor for macrovascular disease but evidence to substantiate that improved glucose control affects vascular pathology or wound healing is limited. Similarly, the exact role of vascular endothelial growth factor or nicotine on vascular pathology and healing remains unclear. Although the literature may be mired in discrepancies, vascular health is known to affect healing. Further research to resolve controversy and to better direct care is needed.

KEYWORDS: macrovascular, microvascular, peripheral vascular disease, diabetes, arteriosclerosis


Higher rates of lower extremity amputation, coupled with an increased incidence and severity of coronary artery disease and higher cardiovascular mortality rates, are well recognized in persons with diabetes. Foot and leg ulcer healing often is poor in patients with arterial insufficiency; in people with diabetes, compromised healing is substantially increased and the atherosclerotic process accelerated. Although both macro- and microvascular disease are implicated in complications in this patient group, diagnosis and treatment strategies remain controversial. For example, the concept diabetic small vessel disease has long been refuted yet still appears in the literature and often results in less aggressive treatments that inappropriately lead to amputation as a primary endpoint. The purpose of this paper is to provide an indepth examination of the mechanisms leading to peripheral vascular disease (PVD), as well as the role of hyperglycemia in persons with diabetes, to help elucidate potential diagnostic options, flaws in related research, and therapies that may prevent devastating sequella.

Anatomy and Physiology

The circulatory tree encompasses two distinct but connected vascular systems: macrovascular and...
microvascular. A reduction in macrovascular flow may predispose to flow reductions in the microvascular system. However, large and smaller vessel diseases in persons with diabetes do not progress at the same rate; small vessels in the toes may exhibit ischemia in the presence of palpable dorsalis pedis and posterior pulses. After reviewing the literature, Ennis and Meneses concluded that the importance of blood flow and oxygen delivery to a wound bed cannot be overstated. Despite heroic efforts by wound care specialists, ulcerations will not heal in the presence of pronounced PVD.

**Macrovascular disease.** Strandness demonstrated that the prevalence of arterial disease in the limbs of persons with diabetes was approximately 20 times higher than in comparable age- and sex-matched persons without diabetes. In a prospective study, Beach et al compared 252 volunteers between the ages of 50 and 70 years with type 2 (non-insulin-dependent) diabetes to 158 control subjects. The authors determined that in type 2 diabetes, new arterial disease developed in 14% of patients over a 2-year period with an 87% incidence of disease progression within the same time frame. More startling, the mortality rates for patients with occlusive disease reached 22% versus 4% in patients free of arterial disease.

A review of the literature confirms that although arteriosclerosis (ASO) in persons with type 2 diabetes is physiologically similar to ASO in persons who do not have diabetes, its distribution appears more diffuse with a predilection for arteries distal to the knee and femoropopliteal segments (distal arteries in the foot and ankle usually are spared) in persons with diabetes. However, in persons with diabetes, medial calcification (Monckeberg’s medial sclerosis) may develop in the tibial and peroneal arteries. This process, entirely confined to the media of the artery, remains distinct from ASO and therefore unrelated to occlusive disease.

A review of the literature confirms that risk factors for disease (macro- and microvascular) include cigarette smoking, duration of diabetes, levels of high density lipoprotein (HDL), total cholesterol, and blood pressure (systolic and diastolic). Additional risk factors include genetic predisposition, increasing age, hyperglycemia, truncal obesity, hyperinsulinemia, proteinuria, dialysis, and the use of some prescription drugs (eg, beta-blockers). The number of risk factors increases the prevalence of disease and the rate of progression.

**Microvascular disease.** Microcirculation refers to the web of tiny vessels located throughout the body that are responsible for transport of oxygen, nutrients, and metabolic waste. LoGerfo and Coffman conducted a review of research regarding vascular and microvascular disease in the diabetic foot, including evaluation of light microscopy, vascular casting, and physiologic studies. This investigation dispelled the myth perpetuated by Goldenberg et al that persons with diabetes suffered from arteriolar occlusive disease (rather than a functional and non-occlusive process) with subsequent ischemia, even in the presence of normal pedal pulses. Furthermore, no evidence was found to support the notion that persons with diabetes exhibited a propensity for intimal hyperplasia in the small arterial branches or capillaries. This paradigm shift regarding patients with diabetes prompted a study by Barner, who concluded that vascular reconstruction should not be withheld on the basis of arteriolar-capillary involvement. Distal bypass remains a durable procedure; limb salvage rates of >90% at 1 year are routinely reported. A literature review reveals that endovascular intervention represents a reasonable option; however, the outcomes of randomized, controlled trials with long-term follow-up are needed before confidently espousing its effectiveness.
However, LoGerfo and Coffman’s investigation confirmed that in patients with diabetes, capillary basement-membrane may thicken in muscle but not skin and exhibit no observable capillary narrowing or occlusion. In a review of the literature, Stonebridge clarified that these vessels possessed a reduced charge secondary to non-enzymatic glycosylation as well as diminished sulphonation of basement membrane components — hypothetically, this dynamic could account for the diffusion of highly charged molecules such as albumin across the capillary basement membrane that help alter cellular nutrition in the diabetic foot. Stonebridge’s laser Doppler ultrasound studies revealed that despite abnormally high capillary pressures, reduction of cutaneous microvascular blood flow, volume, and erythrocyte velocity prevalent in this patient population suggested skin blood flow impairment. A prospective study, conducted by Greenman et al involving 108 patients (21 control subjects without diabetes, 36 patients with diabetes who did not have neuropathy, and 51 patients with both diabetes and neuropathy), found similar results, especially in the presence of neuropathy in persons with diabetes. However, Vracko and Strandness reported that an increase in the basal lamina of the capillaries remained non-specific and should not impair oxygen transfer. Conrad and Marinelli et al’s prospective clinical studies involving 458 diabetic patients suggested that the small arteries of the foot functioned similarly in persons with and without diabetes except in patients requiring hemodialysis for chronic renal failure.

Investigators studying concordance rates for diabetic nephropathy in two sets of families in which both probands and siblings had diabetes mellitus concluded that genetic factors may predispose patients to developing diabetic microangiopathy. Jorneskog et al examined a cohort of 20 men — 10 with heredity for type 2 diabetes and 10 without hereditary predisposition — to substantiate the premise that healthy individuals at risk for the disease were likely to exhibit functional vascular disturbances. The studies of micro- and macrovascular function in normal-weight, middle-aged men showed that the subjects with diabetes heredity exhibited impaired microvascular responses to both endothelium and nonendothelium-dependent stimuli in non-nutritive skin microcirculation; similar disturbances were not observed in the macrocirculation (the small sample size may have precluded detection of these anomalies). The study confirmed that genetic factors could contribute to early functional microcirculatory abnormalities in the development of type 2 diabetes and/or cardiovascular disease. Although this study appeared well designed with appropriate statistical models, a larger sample size and consideration of factors such as exercise, smoking, and dietary habits of the participants, might have yielded more useful information.

In summary, ASO in persons with type 2 diabetes appears physiologically similar to ASO in individuals without this disease; however, its distribution has a predilection for arteries distal to the knee. Ironically, distal arteries in the foot and ankle often are spared. Additionally, obstructive microvascular disease represents a misnomer and patients with diabetes may benefit from vascular and endovascular intervention. Although controversial, genetic factors may contribute to early functional microcirculatory abnormalities.

**Evaluation of Vascular Disease**

As confirmed by an 8-month prospective study of 130 limbs in 68 individuals with no critical ischemia, detection of arterial compromise is vital to the prevention and treatment of foot disease. Palpating foot pulses and calculating ankle-brachial pressure index (ABPI) and/or the toe-brachial index (TBI) are commonly employed techniques; however, several research trials question the reliability of these tests. In a study of 24 patients with diabetes with either past or evolving gangrene due to arterial occlusive disease of the lower extremities, investigators found that persons with diabetes exhibited arterial “stiffness” (medial calcinosis); this rigidity, coupled with edema and tissue glycosylation, could alter the clinician’s ability to accurately palpate pedal pulses. Tanenbaum et al demonstrated that the average foot pressure in persons with diabetes measured 20 mm Hg higher than in persons without diabetes. Therefore, peripheral arteries in people with diabetes may be relatively incompressible, complicating the use of segmental pressures alone for assessing lower
extremity profusion. In extreme cases, occlusive compression has been shown to be impossible even at 300 mm Hg. The International Consensus on the Diabetic Foot (ICDF) guidelines suggest that an ABPI of 1.15 represents the upper limit, above which measurements are deemed unreliable.

When assessing distal macrovascular disease, an alternative technique — measuring the digital systolic pressures (TBI) — may provide more information. This approach permits evaluation of pressure proximal to the toes as well as changes distal to the ankle. Data and analysis of a prospective study of 30 limbs in 27 patients who underwent digit or trans-metatarsal amputation suggest that a range of 25 mm Hg to 45 mm Hg represents an appropriate indicator of ulcer healing potential and amputations in the diabetic foot. However, this wide variation may elicit inappropriate clinical opinions. A review of the literature substantiates the usefulness of arterial waveform analysis, especially 1) in the presence of noncompressable vessels in the population of persons with diabetes and 2) when evaluating femoral, popliteal, and tibial artery disease. Routine evaluation of waveforms in conjunction with segmental pressures and segmental indices has been shown to increase the accuracy of Doppler testing. An additional noninvasive technique includes transcutaneous oxygen profusion (TcPo2); results of a prospective study of 32 normal subjects and 100 patients with peripheral arterial occlusive disease (PAOD) indicate a predictive diagnostic accuracy of PAOD occurrence of >90%. However, the author and others have found this test to be technician-sensitive and may have wide variability; hence, a well-defined threshold remains vague. The literature review by Stonebridge confirms that measurement of transcutaneous partial oxygen pressure in the person with diabetes with ulceration remains unreliable. Such individuals often exhibit higher oxygen pressures than persons without diabetes and may fail to heal ulcerations at levels of oxygenation adequate in the person without diabetes. In summation, no single noninvasive parameter will reliably predict healing and a palpable pulse does not always indicate appropriate vascularity.

**Considerations regarding Reamputation**

A small and seemingly uncomplicated infection in the vascularly impaired person with diabetes may represent the harbinger of catastrophic events: gangrene and amputation. In a retrospective cohort study, Izumi et al examined the medical records of 277 patients with diabetes with a first lower extremity amputation performed at a major hospital facility between 1993 and 1997; reamputation rates were recorded through 2003. Investigators studied the risk of reamputation in persons with diabetes stratified by the original level of amputation. Reamputation rates of ipsilateral and contralateral limbs were presented as secondary endpoints. The problem was defined within a framework of existing knowledge and the literature search appeared adequate with inclusion of seminal references. The study determined that patients remained at greatest risk for further same-limb amputation during the first 6 months following the initial amputation and that although risk to the contralateral limb rose steadily, it never met the level of the ipsilateral limb.

This study has several potential limitations. Although the researchers acknowledged the importance of vascular (and neurological) status as “critical variables,” they offered no objective measurements to substantiate the extent of disease (ie, as noted by pedal pulses and ABPI, for example) so the influence of these factors on healing could not be ascertained. The demographics and characteristics of the study population (gender, ethnicity, peripheral arterial disease [PAD], end-stage renal disease, and history of smoking, among others) were presented but several of these variables (eg, kidney disease and tobacco use) did not factor into final discussions or conclusions, potentially skewing results. In a retrospective study that utilized a database from the Office of Statewide Planning and Development in California identifying all hospitalizations for lower-extremity amputations in the state in 1991, Lavery et al hypothesized that prognosis may be influenced by ethnicity. Although Lavery’s study may have been well designed, the study may have been limited by demographics. For example, in one center, 79.8% of patients were Hispanic. A heterogeneous cohort (ie, other ethnic groups) may have led to more meaningful insights.
In summation, existing research regarding risk for reamputation may be unreliable, calling its predictability into question.

**Hyperglycemia**

The results of a 12-year follow-up study by Nelson et al of 4,399 subjects showed a correlation between hyperglycemia and macrovascular disease. Most importantly, this was confirmed by the Diabetes Control and Complications Trial (DCCT), a landmark, multicenter trial designed to test the proposition that the complications of diabetes mellitus are related to the elevation of the plasma glucose concentration. This prospective, randomized controlled trial (n = 1,441 subjects with type 1 diabetes) provided evidence that intensive glycemic control with either insulin or oral therapy effectively slows the onset and progression of diabetic retinopathy, nephropathy, microvascular complications, and neuropathy. Although this study did not address lower extremity amputations (LEA), fewer PVD events occurred among members in the intensively treated group. Additionally, epidemiologic analysis of the United Kingdom Perspective Diabetes Study (UKPDS) showed correlations between glycemic control and microvascular/cardiovascular disease risk as well as mortality rates. Furthermore, in a study of 59 patients with insulin-dependent diabetes mellitus, Jensen-Urstad et al and Brownlee et al reported that improved glucose control appeared related to slower development of ASO and that intracellular hyperglycemia and the excessive nonenzymatic glycosylation of proteins led to irreversible tissue damage.

Strandness found no relationship between fasting levels and glycosylated hemoglobin and ASO. In an experimental study using a human wound-healing model, Black observed that glycemic control failed to influence collagen deposition in acute wound repair in type 1 or type 2 diabetes mellitus. Randomized controlled trials involving insulin-dependent patients with diabetes with background retinopathy conducted by Lauritzen et al and Viberti et al suggest that when complications in persons with diabetes already exist, improvement of glycemic control alone may not be sufficient to prevent continued progression of these maladies. Although debate continues regarding the role of blood sugar management and prevention of ASO, tighter control is intuitively advocated by most endocrinologists.

An additional dynamic relates to the ability of nonenzymatically glycosylated collagen to trap soluble proteins after being washed free of glucose, suggesting that glucose itself may not be required in protein crosslinking. If this process can progress in the absence of glucose, the perfect correction of hyperglycemia in persons with diabetes may not forestall the progression of complications. Conversely, Marston evaluated a secondary analysis of data from a prospective randomized study involving 245 patients treated with a bioengineered human dermal substitute (n = 130) or control treatment (n = 115). Analyzed variables included age, race, gender, ulcer duration, initial ulcer size, initial hemoglobin (HgbA1c), average HgbA1c, change in HgbA1c, diabetes type, average hours of weight-bearing, study ulcer infection, history of smoking or alcohol use, and laboratory values. In patients whose HgbA1C increased during the study (n = 101), 20.7% of all wounds and 21% of dermal substitute-managed wounds (n = 105) healed; whereas, in patients whose HgbA1C levels remained stable or decreased, 26.3% of all wounds, and 47% of dermal substitute-managed wounds healed (P <0.05). This was the first diabetic foot ulcer study to find a relationship between hyperglycemia, HgbA1C levels, and wound healing.

To summarize, evidence to support the intuitive belief that HgbA1C control is a factor in wound healing remains controversial.

**Additional Considerations**

There is a vast body of research regarding diabetes and the impact of vascular complications on healing but gaps exist in understanding the pathophysiology of vascular disease and potential therapeutic options remain, including the potential role of vascular endothelial growth factor (VEGF) and smoking in limb ischemia.

**Vascular endothelial growth factor in limb ischemia.** A potent mitogen for dermal microvascular endothelial cells expressed by keratinocytes as found in an *in vitro* trial in cultured human keratinocytes and in *in vivo* animal studies, VEGF plays a pivotal
role in the induction of angiogenesis during cutaneous wound healing. The lack of VEGF production in the distal tissues may represent a contributing factor for patients with limb ischemia; however, limited data support this hypothesis and all available studies involve gene therapy. Various routes of VEGF administration have been explored through research, including direct intramuscular injections of naked VEGF plasmids into the thigh muscle, noted in *in vivo* animal studies; a case report of a 71-year-old patient receiving VEGF intra-arterially using a coated hydrogel angioplasty balloon for adenoviral delivery; and the use of liposome carriers encapsulating VEGF plasmids as discovered in a randomized, placebo-controlled, double-blinded phase II study of patients with chronic lower-limb ischemia and atherosclerotic infrainguinal occlusion or stenosis. Although initial VEGF studies show evidence of biologic activity, many questions remain relating to optimal formulations, routes of administration, safety, dose, scheduling, and clinical benefits. As such, VEGF may be deemed an appropriate therapy only through the performance of large-scale clinical trials.

**Smoking.** The risks of smoking have been well documented. Beach and Strandness established a significant correlation between smoking and ASO in the patient with diabetes. Additionally, Kannel reported that cigarette smoking, impaired glucose tolerance, and hypertension are powerful predisposing factors for peripheral arterial disease. However, in a recent *in vivo* animal study, Jacob and colleagues discovered an endogenous cholinergic pathway for angiogenesis mediated by endothelial nicotinic acetylcholine receptors (nAChRs) that could serve as a potential target for therapeutic angiogenesis. This concept appears counterintuitive and additional research to examine the relationship between nicotine and wound healing rates is needed.

**Conclusion**

Vascular complications in persons with diabetes coupled with tri-neuropathy may lead to catastrophic results — common scenarios include slowly and non-healing wounds that often become infected, leading to sepsis, amputation, and death. However, the evidence base for some commonly accepted beliefs and practices is limited. Although ASO in individuals with type 2 diabetes is physiologically similar to persons without diabetes, its distribution appears more diffuse with a predilection for arteries distal to the knee as well as the femoropopliteal segments; distal arteries of the foot and ankle are usually spared, contradicting many ingrained beliefs related to diabetes and the feet. Research regarding vascular and microvascular disease dispelled the myth that persons with diabetes have arteriolar occlusive disease and confirmed the presence of capillary basement-membrane thickening in muscle but not skin with no observable capillary narrowing or occlusion. Hence, small arteries of the foot function similarly in subjects with or without diabetes except in patients requiring hemodialysis. This paradigm shift regarding patients with diabetes prompted articles concluding that vascular reconstruction should not be withheld on the basis of arteriolar-capillary involvement.

Measuring oxygen levels may provide important prognostic and diagnostic information. Due largely to arterial “stiffness” and neuropathy, no single noninvasive parameter or test can reliably predict healing and a palpable pulse does not always indicate adequate vascularity. Because a recent study concerning reamputation rates in persons with diabetes was flawed, the results are in question.

Hyperglycemia has been linked to macrovascular disease and, subsequently, delayed wound healing; therefore, improved glucose control may slow the development of ASO. However, several studies found no relationship between fasting blood sugars, glycosylated hemoglobin, and vascular pathology. It was shown that when complications relating to diabetes already existed, glycemic control alone did not prevent progression of disease. It was hypothesized that complications could progress in the absence of glucose, making tight glycemic control superfluous.

Noteworthy gaps in current knowledge exist relating to diabetes and vascular complications, including the use of VEGF and the potential roles of nicotine and angiogenesis. Despite the confusion surrounding this complex topic, one constant remains: blood flow and delivery of oxygen to a wound are mandatory for healing to occur. Ulcerations will not heal when patients present with severe peripheral vascular...
pathology. The details are fertile ground for debate and research. - OWM

Acknowledgment
This paper was written as part of the requirement for the PG diploma/MSc in Wound Healing and Tissue Repair, Cardiff University, University of Wales, UK.

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*November 2007 Vol. 53 Issue 11*


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