

## Chapter

# 34

## *Peripheral Vascular Disease in Diabetes: Special Considerations*

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### INTRODUCTION

Diabetes Mellitus (DM) is one unique disease, which increase morbidity and mortality by development of complications only. In diabetes, Peripheral Vascular Disease (PVD) is extremely prevalent and an indication of generalized atherosclerotic process. PVD is the third important manifestation of atherosclerosis after coronary artery disease and cerebrovascular disease but very often neglected by clinicians and the comorbidities are not properly focused.

### EPIDEMIOLOGY

Prevalence of PVD varies from 0 to 2% below 40 years, 0.5 to 2.5% at 50 years, 1 to 4.5% at age 60 years and 2 to 9% at age of 70 years as observed by Dormandy IA, et al<sup>1</sup>. Asymptomatic diseases were noted by Schroll M to be present in 0.9 to 22% cases of diabetes<sup>2</sup>.

But in India incidence is less (3.9%) as noted by V. Mohan et al, though prevalence increases with age<sup>3</sup>. In our country lower life span of diabetes, may be the explanation for lower incidence. In future, better diabetic control and increased longevity may lead to increased prevalence of PVD.

Significant independent risk factors for PVD are age, male gender, elevated systolic blood pressure, poor glycemic control, low HDL, smoking, co-existing cardiovascular or cerebrovascular disease. In terms of progression of PVD, the risk factors are, hyper homocystinemia, smoking, male sex, age and higher levels of fibrinogen. Hypertension and hypercholesterolemia are less important in diseases progression. Prevalence of claudication in DM is twice, if serum cholesterol is above 260 mg/dl. Prevalence of hyperlipidemia in PVD varies between 31 to 57%<sup>5</sup>.

Other risk factors are low RBC folate level, low serum Vit. B6, Chlamydia pneumonia infection and low birth weight (< 6.6 lb) explaining thrifty genotype. Compared to nondiabetics, diabetics have accelerated atherosclerosis, more claudication and poorer outcome. Peripheral neuropathy and susceptibility to infection aggravates PVD in diabetes. Diabetes is seen in 50% cases of non traumatic amputations. Major amputations are 11 times more in diabetes. Presence of PVD in DM establishes the atherosclerotic process and associated with higher risk of cardiovascular mortality and morbidity.

Diabetes patients show predilection for involvement of tibial and peroneal arteries often sparing posterior tibial and superficial femoral artery<sup>4</sup>.

### MACRO-VASCULAR AND MICRO-VASCULAR CONCEPT

Abnormalities of microcirculation involving arterioles and capillaries are one of the early changes in diabetes both in Type 1 DM and Type 2 DM. Like retinopathy, neuropathy and nephropathy small vessels of skin of the foot are also involved as a part of PVD in DM, when metabolic control is poor. There is no occlusion in the lumen of microcirculation, the baseline blood supply is restored but compromised during higher demands of infection or ischemia. Structural changes like thickening of basement membrane and reduction of capillary size are more marked in lower limbs, due to higher hydrostatic pressure especially in early DM with poor metabolic control. Increased hydrostatic pressure and resultant shearing force produces endothelial damage. This increases elaboration of extra vascular matrix proteins, leading to capillary basement membrane injury and auto regulatory capacity of capillaries to dilate<sup>6</sup>.

## PATHOPHYSIOLOGY OF DIABETIC VASCULAR DISEASE

Insulin resistance, hyperglycemia and dyslipidemia alters function of multiple cell types including endothelium, smooth muscles, platelets. DM impairs endothelium dependent (nitric oxide mediated) vasodilatation before the formation of atheroma. Hyperglycemia inhibits production of NO by blocking endothelial NO synthetase activation and increasing production of reactive oxygen, species specially superoxide anion  $O_2^-$  in endothelial and vascular smooth muscle cells<sup>7</sup>.

Insulin resistance leads to excess liberation of Free Fatty Acids (FFA) from adipocytes, which through protein kinase pathway increase reactive oxygen species impairing NO production. In addition to lowering of vasodilatory NO production, DM increases the production of vasoconstrictors like endothelin 1 which increases renal salt and water retention, stimulates renin angiotensin system and induces vascular smooth muscle hypertrophy. DM also increases endothelium derived vaso-active substances like vasoconstrictor prostanoids and Angiotensin II<sup>8</sup>.

Diabetes augments atherosclerosis by:

- i. Stimulation of monocytes in endothelial space to engulf oxidized LDL and become foam cells which leads to formation of fatty streaks, a hall mark for early atherosclerosis.
- ii. Activation of transcription factors like nuclear KB and activation protein 1 by decreased NO, increased oxidative stress and AGE activation which regulate the expression of the genes controlling atherogenesis.
- iii. Increase in VLDL and FFA increase endothelial nuclear factor KB, cell adhesion molecule and cytokine expression<sup>9</sup>. In addition to atherogenesis DM promotes plaque instability and triggers thrombosis by:
  - i. decreasing synthesis of collagen in vascular smooth muscle cells
  - ii. increasing matrix metalloprotein which causes breakdown of collagen.

In diabetic patients, elevated glucose level within platelets leads to activation of protein kinase C, decreased production of platelet derived NO and increased formation  $O_2^-$  — Other factors aggravating platelet adhesion are disordered calcium homeostasis, increased platelet surface expression of glycoproteins GpIb, IIb, IIIa<sup>10</sup>.

Diabetic process also augments blood coagulation by:

- i. Impaired fibrinolytic capacity due to elevated PAI 1
- ii. Increased tissue coagulation factors and plasma factor VII
- iii. Decreased antithrombin III and Protein C.

Thus vascular wall changes with platelet dysfunction leads to atherosclerotic thrombus and impaired fibrinolysis make them persistent.

## CLINICAL FEATURES OF PVD

Presenting symptoms of significant PVD are intermittent Claudication, a lower extremity pain, aggravated by walking and relieved with rest due to metabolic mismatch between demand and supply because of vascular compromise. Claudication can be aching, cramping, tightness, tiredness or pain occurring with walking. This symptom may be absent in presence of sensory neuropathy. Claudication typically occurs in muscles distal to occlusion, calf claudication indicates femoro popliteal, bilateral thigh and buttock claudication indicates aorto iliac disease.

Skin changes in terms of atrophy, hair loss, nail dystrophy and coldness of toes are the other features of PVD. With associated autonomic dysregulation, redness of foot in dependent position and paleness on elevation are also seen.

All the peripheral pulses should be palpated individually. In absence of posterior tibial artery pulsation, dorsalis pedis artery may be palpable if collaterals are good. Arterial bruits appears after 50% of narrowing.

Typically, the symptoms appear at predictable walking which diminishes with progression, ultimately complaining of rest pain even due to severe multilevel multivessel disease. Peripheral nerve ischemia is the cause of rest pain. Pain is worse at night, often precipitated by elevation of limb, exertion, emotion and relieved by dependent position up to 11% of patients of DM show claudication.

## DIFFERENTIAL DIAGNOSIS OF CLAUDICATION PAIN

- a. Neurogenic claudication or pseudoclaudication occurs due to lumbar stenosis or lumbar radiculopathy. Precipitation of level is variable, not relieved with cessation of walking but by sitting only, some times precipitated by standing only
- b. Painful diabetic neuropathy shows no relation to walking often aggravated with rest

- c. Reflex sympathetic dystrophy
- d. Arteritis
- e. Atheroembolism
- f. Popliteal nerve entrapment.

PVD may be classified into 4 stages according to Leriche and Fontaine classification.

- Stage I = Asymptomatic
- Stage IIa = Walking distance is more than 200 meters.
- IIb = Walking distance less than 200 meters.
- Stage III = Rest pain particularly at night.
- Stage IV = Ulcerations ranging from trophic lesions to gangrene.

Stage III and Stage IV are considered as Critical Leg Ischemia when ankle pressure is below 50–70 mmHg, toe pressure below 30-50 mmHg and transcutaneous partial pressure of oxygen (TcPO<sub>2</sub>) is diminished to 30-50 mmHg<sup>12</sup>.

The symptoms and signs of PVD are shown in Table 1 and investigations in Table 2.

Guidelines for assessing PVD are shown in Table 3<sup>3</sup>.

The comparison between diabetic and nondiabetic are shown in Table 4.

Ankle Brachial Pressure Index (ABPI) is a simple non-invasive method to assess lower extremity circulation. Using a blood pressure cuff and a Doppler ultrasound probe, we can measure systolic pressure in the brachial arteries of both arms; and in the dorsalis pedis and posterior tibial arteries of both lower extremities. The

**Table 1:** Showing symptoms and signs of PVDs stage wise

	Stage I	Stage II	Stage III	Stage IV
<b>Symptoms</b>				
Parasthesia	+ –	++	+++	++++
Cold Extremity	+ –	++	+++	++++
Pain	No	Intermittent claudication	Rest pain	Rest pain
<b>Signs</b>				
Pulselessness	+ –	++	+++	++++
Bruits	+	++	+++	++++
Hair loss	+ –	+	++	+++
Nail change	Absent	+ –	++	+++
Muscular hypotrophy	Absent	+	++	+++
Decreased tissue temperature	Absent	+ –	++	+++
Trophic lesions	Absent	Absent	Absent	Present

**Table 2:** Showing investigations of PVD (stage wise)

Examination	Stage I	Stage II	Stage III	Stage IV
Decreased ABPI (Doppler)	+	++	+++	++++
Decreased peak flow	+	++	+++	++++
Peak flow/rest flow	+	++	+++	++++
Doppler alterations	+	++	+++	++++
Echo Doppler alterations	+	++	+++	++++
Laser Doppler alteration	No	+ –	++	+++
Decreased TcPO <sub>2</sub>	No	No	++	+++
Whole blood viscosity	+ –	+	++	+++
RBC deformability	+ –	+	++	+++
Increased fibrinogen	+ –	+	++	+++
Increased platelet function	+ –	+	++	+++
Coagulation activation	+ –	+	++	+++
Fibrinolysis inhibition	+ –	+	++	+++

ankle pressure is determined by the higher of two readings between the dorsalis pedis and posterior tibial artery. ABPI is calculated by dividing the ankle pressure by higher of two brachial artery pressure.

**Correlation of PVD with ABPI**

ABPI	Severity
0.90 – 1.30	Normal
0.70 – 0.89	Mild
0.40 – 0.69	Moderate
≤ 0.40	Severe

In patients with isolated iliac artery stenosis, typical claudication feature is present with normal peripheral pulses and normal ABPI. In certain situation ABPI should be measured before and after exercise. If there is no deterioration following exercise then extravascular causes must be considered.

In diabetic patients, arteries are often calcified and non-compressible due to medial calcification of vessels. It leads to unpredictable ABPI. It should be suspected when ankle pressures are significantly higher than brachial artery pressure leading to ABPI of 1.3 or more.

**RADIOLOGICAL IMAGING IN DIABETIC VASCULAR DISEASE**

**Duplex Ultrasound**

It combines cross-sectional imaging of arteries and veins with simultaneous color flow and spectral Doppler

**Table 3:** Summary of recommendations for detection, management, and follow-up of lower extremity arterial disease in diabetic patients

Test	Diabetic patients	Frequency	Action
Claudication	All adults (>18 yr)	Annually	If present, do ABI annually, if ABI <0.90, start risk factor modification. If present and lifestyle-limiting, consider vascular invasive study, CTA, or angiography.
Signs of critical ischemia	All adults (>18 yr)	Annually	If present (i.e. gangrene, ulcer, skin changes, or ischemic rest pain), refer for SVA and start IRFM.
Peripheral pulse/femoral bruits	All adults (>18 yr)	Annually	If abnormal, do ABI annually, if ABI<0.90, start IRFM.
Ankle-brachial index (ABI)	T2DM adults (>35 yr or with>20 yr diabetes duration)	Depends on baseline result	If ABI<0.50, refer for SVA and start IRFM. If ABI 0.50-0.89, repeat within 3 mo. if confirmed to be >0.90, start IRFM and do ABI annually. If confirmed to be >0.90, repeat every 2-3 yr.
	T2DM adults (>40 yr)		If ABI > 0.90, repeat every 2-3 yr. If ankle BP $\geq$ 75 mmHg greater than arm BP, repeat within 3 mo. if confirmed, refer for risk factor modification and consider vascularization. If not confirmed, repeat every 2-3 yr. If ankle BP $\geq$ 300 mm Hg. Refer for SVA and start IRFM

CTA = Computed Tomography Angiography; IRFM = Intensive Risk Factor Modification; SVA = Specialist in Vascular assessment; T2DM = type 2 diabetes mellitus.

**Table 4:** Comparison of peripheral vascular disease

Factors	Non-diabetics	Diabetics
Age	Usually above 60 years	Younger age
Site	Proximal	Distal
Arteries involved	Single segment	Multiple segment
Collaterals	Non involved	Involved
Arteries	Large vessels	Medium and small
Risk factors	Smoking, hypertension, hyperlipidemia	Major risk factors smoking
Plain X-Ray	Calcification	More frequent
Lower limb involvement	May be unilateral	Usually bilateral

information. This allows accurate recording of velocity changes at specific sites within the vessels and detection of hemodynamically significant stenosis with high degree of sensitivity and specificity and in some cases may be superior to angiography<sup>14</sup>.

### Magnetic Resonance Imaging (MRI)

Two types of MRI may be used: 2 D time of flight sequences or gadolinium enhanced magnetic resonance angiography. MRI looks at the blood flowing in the vessels and not at the vessel itself. This means that a stenotic lesion may appear as a narrowed area, a very tight lesion or occlusion will be shown as a signal void. Because it is blood flow that is imaged, and MR is very sensitive for this, it is often possible to show distal

arteries with this technique that cannot be visualized otherwise.

In the future it is likely that MR proton spectroscopy will provide information about the microvasculature of the diabetic foot.

### Helical (spiral) Computerised Tomography (CT)

While CT angiography has been proved a useful tool in some situations, the presence of calcification in the arteries of diabetic patients means that resulting Artifacts render the technique of limited value.

### Angiography

This is usually performed by trans femoral retrograde approach. However, trans brachial route or intravenous digital subtraction angiography is also alternative approach. It involves intravascular injection of radio-opaque contrast media.

### Imaging Conclusions

Because of its ready availability and non-invasive nature, duplex ultrasound has become the first-line imaging modality of choice. In expert hands it is accurate and readily repeatable. At present the second-line investigation of choice is angiography (despite its invasive nature), perhaps leading on to endovascular treatment at the same session.

In the future, as MR scanning becomes faster, this will become the second-line imaging modality of choice.

At present, if expert duplex scanning is not available then angiography should be the choice for imaging.

## MANAGEMENT OF PERIPHERAL VASCULAR DISEASE IN DIABETES MELLITUS

Management protocol is based on control of precipitating factors and specific treatment for PVD.

### Control of Precipitating Factors

#### *Smoking Cessation*

It is the most common predisposing risk factor to PVD in the presence of DM, and has a two fold increase in their five year survival rate who stops smoking.

#### *Exercise Therapy*

Supervised walking exercise programme improves walking ability, quality of life as well as functional capacity and improves pain free walking time by 180% and maximal walking time by 120%<sup>15</sup>.

Walking on a treadmill or track is preferred. Initial advice is to exercise to a level that elicits claudication feature within 3-5 minutes. They should be encouraged to exercise to that level until moderate claudication appears followed by rest for a moment until symptoms subside. This is known as exercise-rest-exercise pattern. Initial duration of exercise should be of 35 minutes. Increment should be of 5 minutes per session. Aim is total of 50 minutes of intermittent walking. Patients should follow this advice at least three to five times a week.

#### *Hyperglycemia*

Epidemiological studies support that increasing levels of glycemia commensurately increase vascular events. In the UKPDS, this increase in risk began above a HbA<sub>1c</sub> level of 6.2%<sup>16</sup>. In the UKPDS, improvement of insulin resistance with metformin decreased macrovascular events. Thiazolidinediones improve glycemia by decreasing insulin resistance. It acts through peroxisome proliferators activated receptor  $\gamma$  (PPAR  $\gamma$ ), a nuclear receptor that participates in vascular cell and adipose tissue differentiation. Nowas because, PPAR  $\gamma$  activity may have anti-inflammatory activity, Rosiglitazone and Pioglitazone may directly benefit atherosclerotic lesions.

#### *Dyslipidemia*

Lipid lowering treatments have been shown to be of benefit in reducing cardiovascular outcomes in diabetic

patients and probably also improve outcomes in PVD and should be recommended.

Statins are the drug of choice. But niacin is a suitable alternative agent for patients who cannot tolerate statins or fibrates.

#### *Control of Fibrinogen*

There is a link between PVD and other factors associated with coagulation and/or fibrinolysis, such as plasminogen activator inhibitor 1 (PAI-1). No trials have been carried out to evaluate the effects of modifying fibrinogen levels on the underlying disease process drug. Iloprost (a prostacyclin analogue) is often used in patients with diabetes complicated by macro angiopathy. It is found to reduce levels of PAI-1. It also increases free walking capacity without affecting glycemic control or blood pressure<sup>17</sup>. Clearly, further research is needed in this area.

#### *Hypertension*

Hypertension is associated with the development of atherosclerosis, particularly in the coronary and cerebral circulations as well as with a two-to three fold increased risk of claudication and treatment of hypertension is necessary<sup>18</sup>. Hope trial has shown that ramipril is effective in lowering the risk of fatal and nonfatal ischemic events among patients with peripheral arterial disease.

#### *Homocysteine Levels*

It is a strong risk factor for PVD and the rate of progression of symptoms is also significantly associated with plasma homocysteine levels. However, there are currently no studies examining whether treating this problem reduces ischemic events.

## SPECIFIC THERAPY FOR PERIPHERAL VASCULAR DISEASE

### Medical Management

#### *Pentoxifylline*

Pentoxifylline increases maximal walking distance by 12 to 21% in different studies<sup>19</sup>. The effects of the drug on quality of life, however, were not evaluated.

#### *Aspirin*

The Anti platelet Trialist's collaboration evaluated the efficacy of prolonged (anti platelet therapy in preventing vascular events). The results from this study do not completely support the use of aspirin to prevent

cardiovascular events and death from stroke and myocardial infarction in patients with peripheral arterial disease, although the risk reduction is similar in peripheral arterial disease and cardiovascular disease.

FDA has not approved aspirin for treatment of patients with PVD, possibly because of the non-significant trend observed in the claudicating subpopulation<sup>20</sup>. However, it has been recommended by American college of chest physicians<sup>21</sup>. The Endothelial function improving property of Aspirin should be utilized to tackle PVD.

#### *Ticlopidine*

It has been reported to reduce cardiovascular and thrombotic events significantly in patients with intermittent claudication. Ticlopidine has been recommended in the dose of 250 mg twice daily.

#### *Clopidogrel*

**CAPRIE** study was the first to evaluate aspirin versus clopidogrel in patients with stable peripheral artery disease. The study has shown comparable efficacy and safety of clopidogrel and medium dose aspirin. Based on these data, clopidogrel has been approved by the FDA for the reduction of ischemic events in patients with peripheral arterial disease.

#### *Cilostazol*

It is a phosphodiesterase III inhibitor with significant antiplatelet and vasodilatory capacity as well as vascular antiproliferative properties. The drug has been shown to be effective in increasing maximal walking time. It also improves functional status and quality of life.

Cilostazol has also been shown to exert favorable effect on plasma lipids, promotes axonal regeneration may have renoprotective action by reducing urinary albumin excretion.

However, use of this drug is contraindicated if any degree of heart failure is present.

### **INTERVENTIONAL RADIOLOGICAL PROCEDURES**

Continued improvements in catheter and guide wire technology have contributed significantly to the reduction in morbidity and complication rates associated with radiological treatment of vascular disease. The principal indications for this in diabetic patients are severe claudications and critical limb ischemia. Treatment is most frequently by percutaneous

transluminal balloon angioplasty, but a variety of adjunctive procedures may also be employed.

#### **PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)**

The technique involves percutaneous entry of guide wire into the femoral artery at the groin under X-Ray control. PTA involves disruption of the atheromatous plaque, longitudinal splitting of the vessel lumen along with disruption of elastic media. Healing takes place at a cellular level with the growth of a new intima.

The best results are obtained in the iliac arteries with patency rates approaching 70% at 5 years. Within the past 5 years there has been an increase in the use of PTA for tibial vessels in diabetes.

#### **Subintimal Angioplasty**

In this variation of the technique used to treat occlusions, a deliberate attempt is made to cause a dissection in the arterial wall. This is commenced above the occlusion. Then the guidewire is passed in the subintimal layer beyond the occlusion where re-entry into the vessel lumen is achieved. The potential space in the subintimal layer is then dilated by balloon angioplasty to form a new lumen. It is claimed that because of relatively smoother new lumen, better results are obtainable. The technique certainly seems to be of benefit in diabetic patients with crural system occlusion. Conventional PTA is more difficult and less rewarding in crural artery involvement.

#### *Thrombolysis*

It has an important role in the management of critical limb ischaemia which occurs when a already stenosed lesion becomes occluded with thrombus's, both proximal and distal to the lesions. Before starting the process, limb viability should be ensured. Streptokinase or more costly recombinant tissue plasminogen activator (rt-PA) can be used.

#### *Endovascular Stenting*

The major limitation of balloon angioplasty is restenosis occurring most often within first year. Metallic stents has overcome this problem to a larger extent. Stents are generally used in the presence of suboptimal PTA result. The second indication is as a primary treatment as in the case of iliac artery occlusions. Stents should be used in these group of vessels only when angioplasty result is poor.

## CONCLUSIONS

Modern imaging technique plays a major part in the assessment of the diabetic patient with foot problems and interventional radiologist has a significant role in their management. Close co-operation between the diabetologist, vascular surgeon and interventional radiologist is essential to maximize the chances of a successful outcome for the patients.

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