Review Article

Peripheral Vascular Disease: A Contemporary Review

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Abstract:

Peripheral Vascular Disease (PVD) is an emerging public health problem in Bangladesh that has tremendous social and economic implications. Unfortunately, there is a general lack of adequate understanding about this disease among primary care physicians and common people. This is why patients present late to vascular care which poses significant difficulties in the treatment and increases cost burden. Late presentation also increases the rate of limb loss. Treatment of PVD is rapidly evolving with the advent of endovascular modalities. The article provides a review of the basic aspects of PVD as well as the present status of care.

Keywords: Peripheral vascular Disease; Vascular; Endovascular

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Background and Epidemiology:

Peripheral Vascular Disease (PVD) refers to narrowing (stenosis/occlusion) of peripheral arteries of the body. This includes arteries of essentially all areas of the body except those in the heart and brain. The terms Peripheral Arterial Occlusive Disease (PAOD) and Peripheral Arterial Disease (PAD) are used synonymously for the same disease condition. PAD is closely related to advancing age and there is a male preponderance which means it is more likely to affect elderly male. The prevalence of PAD- as defined by an ankle brachial index (ABI) of <0.90 ranges from 2.5% in the age group 50-59 years to 14.5% in subjects >70 years.[1-3] According to a recent study based on outpatient data, the prevalence of PAD in the US population more than 65 years of age is 11.8% and the incidence 22.4 per 1000 person-years.[4] A recent epidemiological study from Sri Lanka reported the incidence of PAD among general population aged between 40-74 years at 3.6% with no significant gender difference [5]. Worldwide, the disease affects nearly 2% of general population over the age of 40 years. No epidemiological data on PAD is available for Bangladeshi population. However, unpublished data from the National Institute of Cardiovascular Diseases (NICVD), Dhaka suggest that one in every 3 patients seen at the vascular outpatient department suffer from PAD. It is estimated that nearly 50% of the patients suffering from Coronary Artery Disease (CAD) also suffer from PAD and *vice versa*.

Clinical Features:

PAD may remain asymptomatic or may be associated with subtle, non-specific symptoms. Physical examination may reveal subclinical disease in these patients. Earliest manifestation of PAD is intermittent claudication that is patients experience pain in the leg on walking which is relieved by rest. Symptoms like rest pain and tissue loss such as non-healing ulcer ad gangrene are manifestations of more advanced disease. Severity of PAD has been described according to two well-known classifications. Rutherford classification divides the disease spectrum in to 6 stages while Fontaine classification describes the same in 4 categories[6,7,8].

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Fontaine and Rutherford stages of PAD:

	Fontaine	Rutherford		
Stage	Clinical	Grade	Category	Clinical
Stage I	Asymptomatic	0	0	Asymptomatic
Stage IIa	Mild claudication	I	1	Mild claudication
(Intermittent claudication after >200 meters of PFWD)		I	2	Moderate claudication
IIb	Moderate to severe claudication	I	3	Severe claudication
(Intermittent claudication after <200 meters of PFWD)		II	4	Ischemic rest Pain
Stage III	Ischemic rest pain	III	5	Minor tissue loss
Stage IV	Ulcers/gangrene	IV	6	Ulceration or gangrene

PFWD: Pain free walking distance

Critical Limb Ischemia (CLI):

Critical Limb Ischemia (CLI) also known as Chronic Limb Threatening Ischemia (CLTI) refers to severe ischemia of the limb manifested by rest pain and or tissue loss. Such cases belong to stages 4 through 6 of Rutherford classification and stages 3 and 4 of the Fontaine classification. Natural history of claudicants over 5 years includes worsening of claudication in 20% patients and development of critical limb ischemia in 5-10%; 5-10% of patients will die because of cardiovascular problems. In CLTI patients, however, 30% end up with amputation, 20% die and only 40% patients will be alive with both limbs intact at 1 year. [9,10]. Estimated annual incidence of CLTI is 220-3500 cases per 1 million persons with a prevalence of 1-2%. Among known PAD patients, prevalence of CLTI may be as high as 11%. In fact, 5-10% of asymptomatic PAD patients or those with claudication will progress to CLTI over a period of 5 years. Unless urgently intervened, the rate of limb loss is as high as 40% in this group of patients [8]. According to a German registry involving 40,000 PAD patients, two-thirds of those belonging to CLTI had their limb amputated within 4 years after diagnosis.[11,13]. In Bangladesh, most of the PAD patients present in advanced stages of CLTI with features of tissue loss (Figure 1).

Etiology and Risk Factors of PAD:

Major risk factors for PAD are the same as those for CAD. They are; Hypertension, Diabetes Mellitus, Dyslipidemia and Smoking. Additionally, factors like male sex, age, hypercoagulability, hyperhomocystinemia, chronic renal failure also play important role.

Hypertension is associated with a two to three-fold increased risk of PAD. Current recommendations of target BP is less than 140/90 mm Hg in high risk group. For those with diabetes and renal insufficiency, the target is even lower- less than 130/80[14].

The association between DM and PAD is well known. Study has shown that there is a 28% increase in the risk of atherosclerotic PAD for each incremental 1% increase in glycosylated hemoglobin. Current guidelines from American Diabetes Association recommend a hemoglobin A1C level less than 7% with a goal to maintain glucose level close to normal[14].

Serum total cholesterol level higher than 200 mg/dl especially in combination with a low high-density lipoprotein (HDL) fraction (<40 mg/dl in male and <50 mg/dl in female) has been shown to be associated with increased risk of cardiac-related events.

Smoking is arguably the most important risk factor for lower extremity ischemia. Progression of claudication to CLTI is delayed with cessation of smoking. Nicotine inhalation has been shown to reduce HDL cholesterol, promote platelet aggregation, decrease prostacyclin and promote vasoconstriction- thus contributing to progression of atherosclerotic disease. Studies on patients with peripheral arterial revascularization have shown that the incidence of graft failure is three-fold higher in those who failed to quit smoking.

Increased serum homocysteine level has been postulated as a risk factor for atherosclerotic cardiovascular diseases particularly those with early onset advanced atherosclerosis in the absence of conventional risk factors. Since homocysteine metabolism is partly regulated by vitamin B, a low level of vitamin B and folate is associated with an increased risk of PAD. Though recent studies failed to show the beneficial effect of vitamin B and folate supplements on cardiovascular end points reduction, serologic evaluation is still recommended in young patients with family history of thrombotic cardiovascular events.[14].

Diagnosis of Peripheral Arterial Disease:

History and Physical Examination:

A careful history to elicit the symptom of intermittent claudication is the key to early diagnosis of PAD. The patient will typically report leg pain on walking which is relieved by rest. Patients presenting with more advanced disease will have more obvious features like rest pain and tissue loss to speak for themselves. Pain may sometimes be absent or less in intensity in patients with long-standing diabetes mellitus because of neuropathy. When there is ulcer, differentiation from venous or neurotrophic ulcer may be possible on the basis of location of the ulcer and its characteristics.

In physical examination, careful inspection reveals characteristics features of ischemia. Shiny appearance of the limb with loss of hair and muscle bulk may provide early evidence of PAD even in the absence of tissue loss. An ischemic limb typically feels cold on palpation compared with the normal side (may sometimes remain warm in presence of infection). An increased capillary filling time is also an important physical finding. Absence of peripheral pulses constitutes the most important physical evidence of limb ischemia. The quality of the pulse should always be compared with the unaffected side. A lot of cases are missed only because of the fact that pulses are not carefully examined. Peripheral pulse is also the best way to differentiate PAD from other causes of limb pain such as musculoskeletal or neurological. A palpable distal pulse virtually excludes significant PAD.

Ankle-Brachial Pressure Index:

Measurement of Ankle Brachial Pressure Index (ABPI or ABI) is a very handy tool to assess disease severity. Values above 0.9 are normal and decreasing value indicates more severe disease. (Mild 0.8-0.89, Moderate 0.5-0.79, Severe <0.5). Nowadays, dedicated tools are available to measure ABI. Unfortunately, they are not universally available in Bangladesh. The problem, however, can be largely overcome by utilizing hand-held Doppler machine.

Thrombo-Angitis Obliterans (TAO):

Extremity ischemia in young patients with history of smoking should always give rise to the clinical suspicion of Thromboangiitis Obliterans (TAO). Also called Buerger's disease, TAO is a nonatherosclerotic, segmental, inflammatory disease that usually affects the small and medium-sized arteries and veins of the extremities[15-17]. TAO is histologically characterized by occlusive luminal thrombus that has high cellular and inflammatory contents with relative sparing of the blood vessel wall[18]. Patients are young smokers who present with distal extremity ischemia, ischemic digit ulcers, or gangrene[19].

Prevalence:

TAO is most prevalent in the Mediterranean, Middle East, and Asia [20,21], the reason being the high tobacco use in these areas. In North America, the prevalence of TAO has declined over the past 30 years due to a decline in smoking [21,22]. In other parts of the world, the prevalence of this disease among patients with arterial occlusive disease varies widely, ranging from 0.5 to 5.6 percent in Western Europe to as high as 45 to 63 percent in India [22].Men are more commonly affected than women, and the typical age of onset is 40 to 45 years. However, there are reports of increasing prevalence of

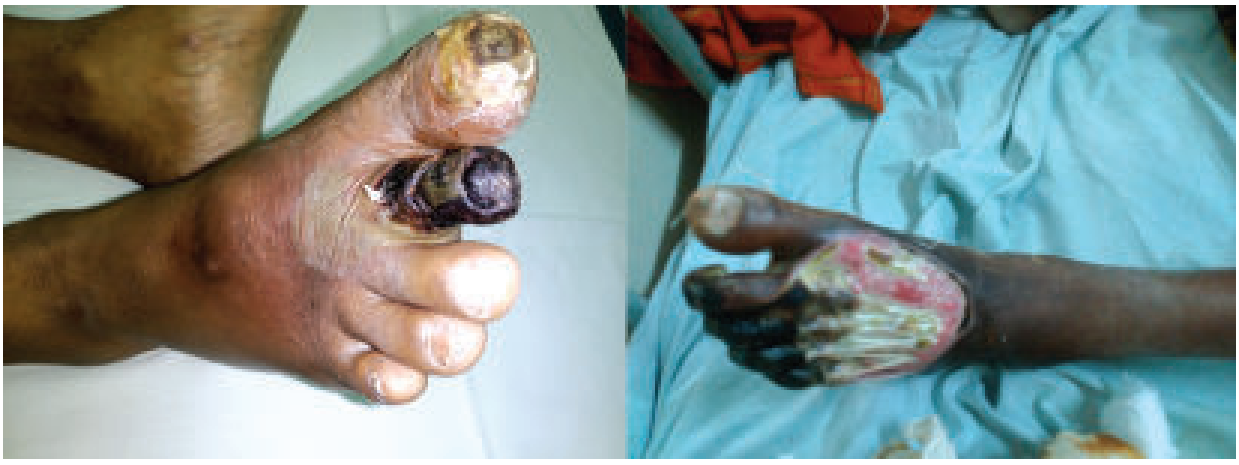

Fig.-1: *Manifestations of advanced Peripheral Arterial Occlusive Disease*

TAO in women, possibly due to the increasing tobacco consumption by women[23].

Risk Factors:

The use of tobacco is essential for the initiation and progression of TAO [21-23]. Most patients are heavy cigarette smokers. In one study, patients diagnosed with TAO smoked an average of 23 years [23]. TAO has also been reported in cigar smokers, marijuana users (cannabis arteritis), and those who use smokeless tobacco such as chewing tobacco and snuff [24, 25].Chronic anaerobic periodontal infection may also play a role in the development of TAO. Nearly two thirds of patients with TAO have severe periodontal disease. In one study, DNA fragments associated with anaerobic bacteria were found within both the arterial lesions and oral cavities of patients with TAO[26,27].

Diabetic Foot:

Diabetic foot represents a distinct subset of PAD patients who often present with advanced ischemia of the foot with varying degrees of tissue loss and deformity. Besides arterial insufficiency, factors like peripheral neuropathy, infection, osteoarthropathy and metabolic abnormality are implicated in the disease progression of diabetic foot. A careful history and meticulous physical examination can elicit vascular component of diabetic foot. Patients may give history of previous intermittent claudication or rest pain and pedal pulses may be absent or diminished in volume. Though a reduced ABI value is generally expected in diabetic foot patients having arterial insufficiency, it may sometimes be falsely high because of reduced vessel compressibility resulting from vessel wall calcification.

Work-up for PAD:

Vascular Duplex Study:

Vascular Duplex study done in expert hands can establish the diagnosis of PAD. Understanding of Doppler principles is key to vascular Duplex ultrasound examination. A triphasic spectral waveform on pulsed wave Doppler indicates normal flow while biphasic and monophasic patterns indicate varying severity of stenosis in the proximal arterial segment. Turbulence with velocity acceleration is a sensitive marker of hemodynamically significant localized stenotic disease while absence of Doppler signal indicates occlusion of that segment (Figure 2).

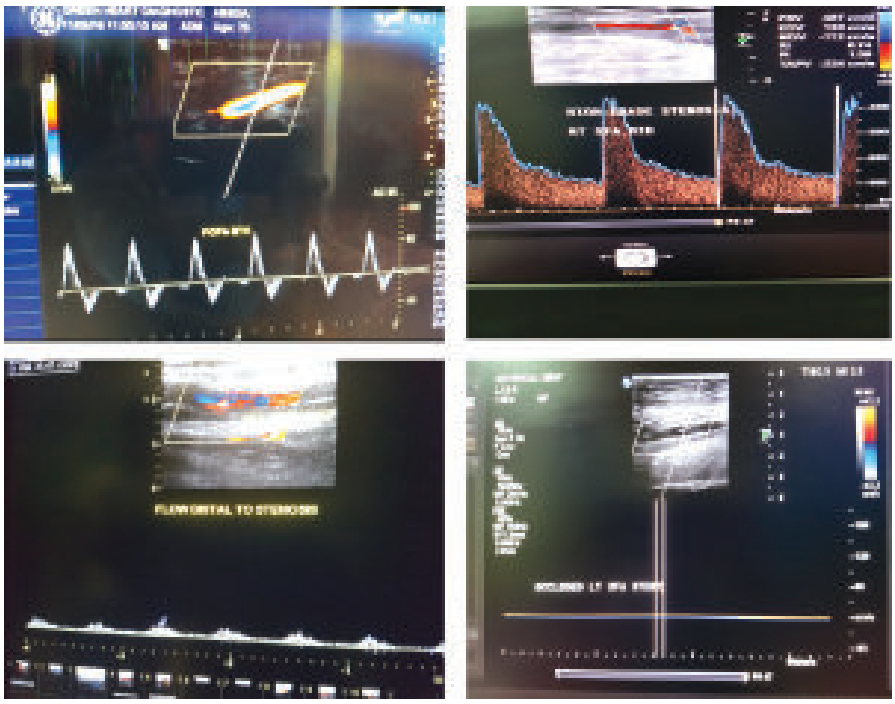

Figure 2: *A. Normal triphasic arterial flow. B. Turbulence with velocity acceleration at the point of arterial stenosis. C. Dampened low pulsatile monophasic flow distal to arterial stenosis. D. Totally occluded artery with absence of Doppler signal*

Angiography:

Angiography is rarely needed for diagnosis and is mainly reserved for planning revascularization strategy. There are 2 basic types of angiography; Computed Tomographic Angiography (CTA) and Catheter angiography (Figure 3). In both modalities, contrast agent is used to visualize the arterial tree. However, catheter angiography is a more invasive technique than CTA. The main advantage of catheter angiogram is that digital subtraction angiography (DSA) can be utilized which facilitates better visualization of the arteries. This is particularly useful for distal vessels. In catheter angiography, carbon di oxide is sometimes used instead of contrast agents for patients with renal insufficiency. Magnetic Resonance Angiography (MRA) without the use of contrast agent is also used at some centers.

Management of PAD

Lifestyle and Risk Factor Modification:

The goal in the treatment of PAD is reduction of pain (claudication or rest pain), improve quality of life and limb salvage. Treatment must begin with risk factor and lifestyle modification. This is applicable for patients of all categories of PAD. In early stages of PAD, aggressive risk factor and lifestyle modification not only helps in improving symptoms but also prevents progression of disease severity. The treatment goals for hypertension, DM and dyslipidemia has been discussed above. Cessation of smoking can be partly achieved by extensive counselling. Besides structured smoking cessation program, a number of pharmacologic agents such as Bupropion and more recently Varenicline are now available in the US and European markets to aid smoking cessation. Despite their encouraging early results, the fact remains that Nicotine addiction is a notoriously recurring behavioral problem which needs to be dealt with a combination of mental strength of the individual, knowledge and relentless social campaign.

Supervised Exercise Therapy:

The benefit of structured exercise protocol in improving pain-free walking distance has been documented in may studies. In fact, exercise therapy has been termed the best initial treatment for intermittent claudication. A recent Japanese study shows that supervised exercise therapy resulted in 5-year cardiovascular event-free survival of 80.5% in patients with PAD, compared with 56.7% in untreated matched controls [14]. The current ACC/AHA guidelines recommend supervised exercise therapy as a level IA recommendation for the treatment of intermittent claudication. The guideline recommends that exercise training in the form of walking- which may be treadmill walking or track walking should be performed for a

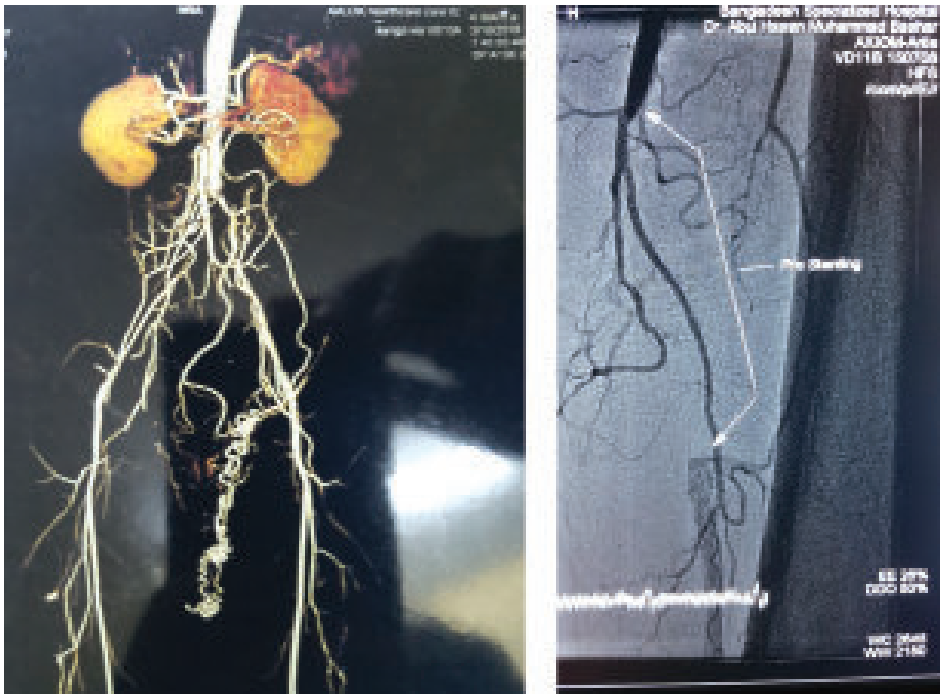

Fig.-3: *A. Computed Tomographic Angiogram (CTA) showing aorto-iliac occlusion. B. Catheter Angiogram showing occlusion of distal Superficial Femoral Artery.*

duration of 30-45 minutes three to four times a week for a period not less than 12 weeks. The walking should be intermittent in the form of walk-rest-walk. This means that the patient should walk until the lower extremity pain tolerance limit is reached. This should be followed by a brief period of rest until the pain relief is obtained, following which the patient should return to walk to repeat the cycle. Studies show that exercise protocol, though easy to follow, is not applicable in more than one third patient with claudication due to comorbid conditions. In another one third, there is considerable compliance issue.

Pharmacological Agents:

Despite extensive research over the last 30 years, progress in terms of pharmacologic treatment of intermittent claudication has been far from satisfactory. To date only two drugs have obtained approval from US FDA for symptomatic relief of lower extremity ischemia. They are Pentoxyphylline and Cilostazol.

Pentoxyphylline was the first drug to be FDA approved (1984) for use in claudicants. A methylxanthine derivative, it is thought to improve oxygen delivery to ischemic limb due to its effect on RBC wall flexibility and deformability. These effects result in reduced blood viscosity. Pentoxyphylline also decrease platelet aggregation and increase fibrinogen levels. Multiple well-designed clinical trials have documented increase in pain free walking distance with the use of Pentoxyphylline compared with placebo. The drug is available in Bangladesh market as 400 mg tablet to be taken three times daily.

Cilostazol gained FDA approval for the treatment of claudication in 1999. It's a phosphodiesterase III inhibitor which inhibits smooth muscle cell contraction and proliferation and platelet aggregation by increasing cyclic Adenosine Monophosphate. It also works on serum lipid metabolism to decrease triglyceride level and increase HDL level. Results of several clinical trials including a meta-analysis confirmed the efficacy of cilostazol. Increase of maximum PFWD by 50% along with significant improvement in the quality of life has been reported with use of cilostazol. Clinical trials have also documented superiority of cilostazol over pentoxyphylline in the treatment of claudication. Unfortunately, this drug has quite a few side effects that include headache, diarrhea and gastrointestinal discomfort. A progressively incremental dosing starting at low dose is an effective strategy to minimize side effects. Its use is contraindicated in advanced heart failure. Cilostazol is widely available in Bangladesh market being manufactured by a number of manufacturers.

Lipid lowering agents particularly statins decrease MI related death in high-risk patients. The beneficial effect of statin therapy on blood vessels is pleomorphic and not just reduction of serum cholesterol level. They stabilize atheromatous plaque, reduce vascular inflammation and oxidative stress. Though less well documented compared with CAD, aggressive statin therapy in PAD patients has been shown to improve survival over a mean follow-up period of 6 years. Modulation of HDL fraction has also been found beneficial in PAD patients. Studies have documented that addition of niacin to lower HDL resulted in atheromatous plaque regression in Femoral stenosis and carotid Intima-Media Thickness [14]. Statins have also been shown to increase pain free walking time in claudicants. Though the exact mechanism for this benefit is unclear, it is thought to be resulting from an increase in vasomotor blood flow and increased angiogenesis. Thus, drug treatment of patients with PAD should always include statins irrespective of their serum lipid levels. According to current ACC/AHA guidelines LDL cholesterol level should be less than 100 mg/dl in patients with PAD and less than 70 mg/dl in high risk patients.

Antiplatelet therapy is an important part of the drug treatment of PAD. Though it has no effect on claudication, there are compelling evidences that it reduces overall cardiovascular events. Antiplatelet therapy is also beneficial in maintaining graft patency after peripheral revascularization as evident from a significantly lower graft occlusion rate with its use compared with placebo. Therefore, antiplatelet therapy should be recommended for all patients with PAD[14].

Other pharmacologic agents used sparingly for PAD include levocarnitine, Naftodrofuryl, Ketansarin, calcium channel blockers etc. Vitamin B and Folates are used in young patients with hyperhomocystienemia. The use of prostaglandin analogues in the treatment of critical limb ischemia patients who are not candidates for revascularization is also increasing. Evidence suggest that they are effective in reducing ischemic rest pain and healing small ulcers. Therapeutic angiogenesis by gene therapy or bone marrow stem cell therapy is also an evolving strategy for this group of patients.

Role of Revascularization in the Treatment of PAD:

The decision of revascularization largely depends on the presentation of PAD. As long as PAD symptoms do not interfere with quality of life (QoL), patients can be managed conservatively with lifestyle modification and medical therapy. Even many of the patients having PAD symptoms

that affect QoL may benefit from conservative management including supervised exercise therapy and remain stable. Only those symptomatic PAD patients who do not improve with conservative management or those who deteriorate along with patients with CLTI will need angiographic evaluation and some form of revascularization- surgical or endovascular [9,10]. The Trans-Atlantic Intersociety Consensus (TASC) working group has published recommendations on the treatment strategy for APD in 2000 and 2007 based on which these decisions are generally made. About the type of revascularization to be employed, TASC II recommendations published in 2007 have categorized PAD according to severity of lesions for aorto-Iliac, Femoro-Popliteal segments. Lesion severity is described from category A through D with simpler lesions belonging to A and most complex ones to D. TASC II recommendations support revascularization of TASC A lesion by endovascular means while surgical intervention is reserved for TASC D lesions. There is insufficient data regarding TASC B and C lesions to support the superiority of one modality over the other. However, Type B lesions are probably better treated by endovascular means and Type C lesion by surgical means.[10,14].

Endovascular Intervention:

In the current era of rapid advances in technology, the scope and application of endovascular interventions are increasing. Though TASC recommendations are generally followed, sometimes, complex lesions are also treated defying TASC recommendations. This trend is particularly evident at high volume centers with adequate expertise, experience and logistic support. The commonest procedures employed to treat peripheral arterial stenotic/occlusive lesions are Plain Old Balloon Angioplasty (POBA) and stenting with bare metal stents (Figure 4). More recent procedures include the use of drug coated balloons, covered stent, debulking by atherectomy etc.

Surgical Intervention:

According to TASC II recommendations complex long segment occlusive lesions are better treated by surgical intervention. However, with growing expertise and experience, wire-based techniques have been successfully applied to many of the long lesions in the aorto-iliac and infra-inguinal segment thus changing the indications for surgery in this group of patients. According to a US in-patient data of 1996-2000, there was 850% increase in the use of percutaneous techniques to treat

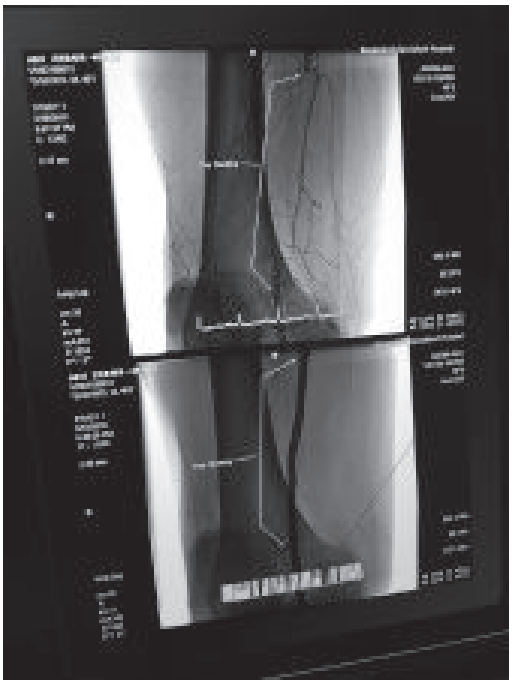

Fig.-4: *Catheter Angiogram showing occlusion of distal Superficial Femoral Artery and Popliteal at the top and its treatment by Percutaneous Transluminal Angioplasty (PTA)*

aorto-iliac disease and a 16% decrease in aorto-bi-femoral bypass procedure. Despite such paradigm shift in application, surgery still holds an important place in the treatment of PAD. Different types of surgical procedures are available. They are basically divided into two broad categories; anatomic and extra-anatomic. Aorto-femoral bypass, Femoro-Popliteal bypass, Femoro-distal bypass are examples of anatomic bypass (Figure 5) whereas Femoro-Femoral cross-over bypass, Axillo-Femoral bypass, obturator bypass are examples of extra-anatomic bypass. For aorto-iliac bypass procedures, a prosthetic graft is generally used as conduit whereas for infra-inguinal bypasses, the conduit of choice is autologous vein. In Bangladesh, surgical revascularization procedures for complex aorto-iliac, infraingunal and infrapopliteal diseases are now performed with results that are comparable to standard outcome for these procedures. In one study, Bashar et al. reported an 89% 2-year patency for aorto-bi-femoral bypass performed for complex aorto-iliac occlusive disease [28]. Besides bypass procedures, another mode of revascularization is endarterectomy which is reserved only for short segment lesions across joints or at the point of important bifurcations.

Fig.-5: *A. Prosthetic graft used in aorto-bi-femoral bypass for aorto-iliac occlusive disease. B. Prosthetic aorto-bi-femoral bypass graft anastomosed with abdominal aorta. C. Femoro-Popliteal bypass being fashioned using autologus long saphenous vein. D. Completed Femoro-Popliteal bypass.*

Conclusion:

In Bangladesh, presentation of patients with PAD to vascular surgeons is generally late. Most patients come in the stage of CLTI with some form of tissue loss. Though no published data exists, in-patient and out-patient experience at NICVD, Dhaka suggests that as high as 90% of patients of PAD present with CLTI. Systematic campaign to generate awareness among the common people as well as primary care physicians, neurologists, diabetologists, podiatrists and orthopedic surgeons can change this dismal scenario.

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