"A case control study of lipoprotein a levels in patients with atherosclerotic peripheral arterial occlusive disease"

A dissertation submitted to the Dr. M.G.R. Medical University, Tamil Nadu; in partial fulfillment of the requirement for the M.S. branch I (General Surgery) examination to be held in April 2013.

Certificate

This is to certify that the dissertation entitled *" **A case control study of Lipoprotein a levels in patients with atherosclerotic peripheral arterial occlusive disease"*** is a bonafide work done by Dr. Rajesh Joseph Selvakumar , post graduate resident in Masters of General Surgery 2010-2013 at the Christian Medical College, Vellore, towards partial fulfillment for the MS General Surgery-Branch 1 final examination to be held in April 2013.

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ABSTRACT

Title of the study-

" A case control study of Lipoprotein a levels in patients with atherosclerotic peripheral arterial occlusive disease"

DEPARTMENT	**Vascular Surgery, CMC- Vellore**
NAME OF THE CANDIDATE	**Rajesh Joseph Selvakumar**
DEGREE AND SUBJECT	**MS (General Surgery)**
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OBJECTIVE:

To determine the proportion of patients with atherosclerotic peripheral arterial occlusive disease (PAOD) who have elevated Lipoprotein (a) [Lp (a)] levels.

METHODS:

This was a prospective, non-randomized, case-control study conducted among patients who presented with symptomatic atherosclerotic peripheral arterial occlusive disease. Informed consent was taken for the cases and controls and the patients were subjected to a fasting blood sample of serum Lipoprotein a which was analysed in the Biochemistry laboratory.

RESULTS:

Elevated Lp (a) levels were found in 89.1% of the cases as opposed to 54.5% of the control population with an odds ratio of 6.8 with a p value of <0.001(95% CI 2.5-18.5). The type of presentation did not correlate with elevated Lp (a) levels. Other atherosclerotic risk factors did not have a statistically significant effect on Lp (a) levels suggesting that Lp (a) was an independent risk factor leading to the development of PAOD.

INTRODUCTION:

Peripheral arterial occlusive disease (PAOD) is a major contributor to hospitalisations to any Vascular Surgery Unit, worldwide. The prevalence of PAOD is on the rise around the world; more alarmingly among developing nations like ours. The majority of hospitalisations (both diagnostic and therapeutic) for lower limb arterial insufficiency worldwide are linked to PAOD. Since the current standard of care for atherosclerotic PAOD involves a multi-modality approach of risk factor reduction by life style modification, medications and interventions which include surgical and endovascular repairs, the financial burden of this disease is immense.

The risk factor profile for atherosclerotic PAOD encompasses the traditional risk factors associated with cardiac atherosclerotic vascular disease, which include age, smoking, dyslipidemia, diabetes mellitus and hypertension. Studies have demonstrated an association with elevated Lp (a) and cardiac atherosclerosis. Lp (a) accelerates atherosclerosis at various levels; starting from increased endocytosis of VLDL by macrophages in the arterial wall, to inhibiting clot lysis. Recent data from studies done in an Indian population corroborates the above; demonstrating a correlation between elevated Lp (a) levels and CAD.

Based on this information, therapeutic measures to lower Lp (a) levels have been demonstrated to improve outcomes in coronary artery disease. Since atherosclerotic PAOD shares the same risk factor profile as CAD, it is hypothesized that Lp(a) levels may be elevated in atherosclerotic PAOD patients.

Our study aims to determine whether there is a correlation between elevated Lp (a) levels and atherosclerotic PAOD. If so, further studies need to be undertaken to demonstrate whether lowering of Lp (a) in these patients contributes to improving patient outcomes.

Despite being included under the broad category of developing nations, the majority of India's population lives in rural and semi urban settings; where access to a tertiary care centre equipped to perform interventions, are limited. Thus, interventions to lower Lp(a) levels might have tremendous implications in the treatment of atherosclerotic PAOD in resource limited settings like ours.

RELEVANCE OF THE STUDY

The role of Lp(a) in coronary artery disease has been extensively studied and its role in atherosclerosis and thrombogenesis has been proved. The role of reducing Lp(a) levels in this subgroup of patients and the benefits achieved after lowering Lp(a) levels still remain controversial. The indications for lowering Lp(a) level also is still debated. However the role of Lp(a) in PAOD has not been studied in detail and there is still clear lack of evidence showing elevated levels of Lp(a) in patients with PAOD. No studies have been done to look at Lp(a) levels in an Indian population with atherosclerotic risk factors with PAOD.

AIMS AND OBJECTIVES

AIM:

To determine the proportion of patients with atherosclerotic peripheral arterial occlusive disease (PAOD) who have elevated Lp(a) levels.

OBJECTIVES:

1. To determine whether Lp(a) levels are elevated in patients with atherosclerotic PAOD.
2. To determine whether Lp(a) levels can be used as an independent predictor of atherosclerotic PAOD in symptomatic patients.

REVIEW OF LITERATURE:

EPIDEMIOLOGY OF PAOD:

Though classically described as a disease of developed nations, the prevalence of PAOD is on the rise worldwide. The prevalence of PAOD increases gradually with age, commencing after age 40(1-3). The 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) was then first to quantitatively describe the relationship between increasing age and the prevalence of PAOD(3). According to this survey, the prevalence of PAOD, which was described as an ankle-brachial index (ABI) <0.90 in either leg, was 0.9 percent in the age group between 40 and 49, 2.5 percent in the age group of 50 and 59, 4.7 percent in the age group between 60 and 69, and 14.5 percent age 70 and older(3). However, the PARTNERS program, a study conducted among primary care practices in the United States, showed an overall higher prevalence of PAOD(4). PAOD was present in 29 percent overall: 13 percent had PAD alone (55 percent newly diagnosed) and 16 percent had PAOD and cardiovascular disease (35 percent newly diagnosed) (4). Interestingly, only 11 percent of patients with PAOD presented with a classic history of claudication, as described below (4). Thus PAOD contributed greatly to the number of hospitalisations involving diagnostic and therapeutic measures for lower limb arterial insufficiency (5).

RISK FACTORS FOR PAOD:

The risk factor profile for patients with PAOD resembles that of patients with cardiac atherosclerotic disease. Based, in part, upon the observations of the Framingham Heart Study (6) the 2005 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on PAOD, which were produced in collaboration with major vascular medicine,

vascular surgery, and interventional radiology societies, identified the following groups at risk for lower extremity PAOD:

- Age ≥70 years.
- Age 50 to 69 years with a history of smoking or diabetes.
- Age 40 to 49 with diabetes and at least one other risk factor for atherosclerosis.
- Leg symptoms suggestive of claudication with exertion or ischemic pain at rest.
- Abnormal lower extremity pulse examination.
- Known atherosclerosis at other sites (eg, coronary, carotid, or renal artery disease).

The Framingham Heart study demonstrated the following results. There was an odds ratio of 1.2 for developing intermittent claudication with each 40 mg/dL (1 mmol/L) elevation in the serum cholesterol concentration, 1.4 for each 10 cigarettes smoked per day, 1.5 for mild and 2.2 for moderate hypertension, and 2.6 for diabetes mellitus [6]. Also, as per this study, diabetics have more advanced arterial disease and poorer outcomes than nondiabetic patients (6).

Further studies detailing the lipid profile and the lipid metabolism in patients with PAOD (7) demonstrated that patients with PAOD are more likely to have abnormalities in other aspects of the lipid profile such as triglycerides, cholesterol, apolipoprotein B, and very low density lipoprotein (7). Also, risk of intermittent claudication may also be increased in patients with elevated plasma Lp(a) and fibrinogen levels (7).

CLINICAL FEATURES:

A majority of patients with PAOD do not exhibit any symptoms and are incidentally detected while ABPI screening. Also, classical claudication is seen among 10 to 35% of symptomatic patients. As per the 2005 ACC/AHA guidelines on PAOD, the distribution of clinical presentation of PAOD in patients ≥50 years of age is as follows:

- No symptoms – 20 to 50%
- Atypical pain in the legs – 40 to 50%
- Claudication – 10 to 35%
- Critical limb ischemia – 1 to 2%

Classification —

The classification systems commonly used worldwide for chronic lower extremity PAOD are: the Fontaine system and the Rutherford system.

Both are based upon the symptomatology and the presence of clinical markers for severe chronic occlusive disease, such as ulceration and gangrene (5).

Fontaine staging of PAOD:

Stage	**Clinical**
I	Asymptomatic
IIa	Mild claudication
IIb	Moderate to severe claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

Rutherford categories of PAOD:

Grade	Category	Clinical
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss
III	6	Major tissue loss

Symptomatic disease:

Claudication pain might vary from mild with no effect on activities of daily living to severe and disabling rest pain. The severity of pain is determined by the degree of occlusion to the vessel, amount of collateral vessel formation, and the intensity of exercise. Based on the anatomic site of arterial occlusive disease, the location of the pain varies as follows:

- Buttock and hip – aorto-iliac disease
- Thigh – aorto-iliac or common femoral artery
- Upper two-thirds of the calf – superficial femoral artery
- Lower one-third of the calf – popliteal artery
- Foot claudication – tibial or peroneal artery

Physical examination in the patient with claudication may reveal no abnormality, but usually reveals decreased or absent pulses distal to the level of the stenotic lesion. Other signs such as bruits over stenotic lesions and delayed healing of wounds over the area of distribution of the vessel. The affected extremity may be cool and clammy, with prolongation of venous filling. Skin over the limb may be shiny and atrophied and there may be nail changes. The absence of hair is not a clinical predictor of the presence of PAOD.

Physical signs can also help determine the extent and distribution of vascular disease. These include an abnormal femoral pulse, lower extremity bruits, and the Buerger test (foot pallor with elevation of the leg and, in the dependent position, a dusky red flush spreading proximally from the toes).

Buttock and hip claudication: When the level of occlusion is at the aorto-iliac segment patients complain of pain at the buttock or the hip. In some instances claudication at the thigh may also be seen. Erectile dysfunction may be seen in patients with bilateral aorto- iliac disease. Leriche syndrome is the triad of claudication, absent or diminished femoral pulses and erectile dysfunction.

Thigh claudication: Pain in the thighs and calf is seen in patients with lesions at the level of the common femoral artery. When the lesion is at the level of the superficial femoral artery or distal to this segment patients may have normal groin pulses.

Calf claudication: Calf claudication is the commonest presenting symptom. It is defined as pain that increases in intensity as the patient continues to walk and subsides with discontinuation of the activity. Claudication pain involving the upper half indicates superficial femoral artery lesions and claudication pain involving the lower half indicates popliteal lesions.

Foot claudication — Atherosclerotic lesions of the tibial and peroneal vessels prsents as foot claudication. However, this symptom is more commonly associated with thromboangiitis-obliterans (TAO).

Ischemic rest pain — A severe lowering of the baseline limb perfusion produces ischemic rest pain. This is classically described as pain which is worse at night and is relieved by keeping the foot in a dependant position or by walking. This is due to increase on perfusion due to the effect of gravity.

DIAGNOSIS:

The diagnosis of PAOD is made based on a thorough history and detailed physical examination. The role of non-invasive vascular studies is only as an adjunct to confirm a clinical diagnosis. Non-invasive investigations used in the evaluation of the patient include: calculation of pressure index values (eg, ankle-brachial index, wrist-brachial index), exercise testing, segmental volume plethysmography, transcutaneous oxygen measurements and photo-plethysmography.

Ultrasound based imaging is the commonest method of vascular imaging. This provides various modes (eg, B-mode, duplex), which are crucial in acquiring specific information pertinent to the vascular disorder. With the arrival of more advanced technology, such as computed tomography (CT) and magnetic resonance (MR) imaging, more accurate and detailed evaluation of the vascular anatomy is possible. Thus, CT angiogram is the gold standard of evaluation; especially prior to any intervention; surgical or radiological.

Ankle-brachial index- This is the simplest and cheapest method of confirming arterial insufficiency (9). This involves comparison of the resting systolic blood pressure at the ankle with the systolic brachial pressure. The ratio of the two pressures is defined as the ankle-brachial index.

The patient rests for 15 to 30 minutes prior to measuring the ankle pressure. A blood pressure cuff is placed just above the ankle. While either the dorsalis pedis or posterior tibial artery signal is continuously monitored with a continuous wave Doppler, the cuff is insufflated to a pressure above which the audible Doppler signal disappears. The pressure is then slowly released until the pedal signal returns and this systolic pressure is recorded. The measurement is repeated in the same manner for the other pedal vessel in the ipsilateral

extremity and then repeated for the contralateral lower extremity. The systolic brachial artery pressure is measured bilaterally in a similar fashion with the blood pressure cuff placed around the upper arm and using the continuous wave Doppler. The ABI for each lower extremity is calculated by dividing the higher ankle pressure (dorsalis pedis or posterior tibial artery) in each lower extremity by the higher of the two brachial artery systolic pressures.

The disadvantage of using continuous wave Doppler is a lack of sensitivity at extremely low pressures where it may be difficult to distinguish arterial from venous flow (10).

The ABI roughly correlates with clinical indicators of lower extremity function such as walking distance, speed of walking, balance, and overall physical activity. Further evaluation is dependent upon the ABI value-

- ABI ≥0.9 to 1.3- normal. A Normal ABI generally excludes arterial disease, however mild disease and certain arterial entrapment syndromes produce false results and warrant exercise testing (11).
- ABI >1.3 suggests calcified vessels and suggests the need for other vascular studies, such as pulse volume recordings, measurement of the toe pressures and toe-brachial index, or arterial duplex studies.
- ABI ≤0.9 is diagnostic of arterial occlusive disease in patients with symptoms of claudication or other signs of ischemia. It has 95 percent sensitivity (and 100 percent specificity) for detecting occlusive lesions which are already established on an angiogram which demonstrate ≥50 percent stenosis in one or more major vessels (12).
- ABI of 0.4 to 0.9 suggests a degree of arterial obstruction often associated with claudication.

- An ABI below 0.4 represents multilevel disease (any combination of iliac, femoral or tibial vessel disease) and may be associated with non-healing ulcerations, ischemic rest pain or pedal gangrene.

A low ABI is an indicator of higher risk for more ominous comorbidities such as coronary heart disease, cerebrovascular accidents, progressive renal insufficiency, and is also associated with an increase in all-cause mortality (13).

In patient with advanced disease, high ABI values are associated with calcification of the vessels which may not compress normally. This results in falsely elevated pressure measurements. Therefore in the appropriate clinical setting, an ABI of more than 1.3 is suspicious for calcification of vessels (14).

Wrist-brachial index— The wrist-brachial index (WBI) is used to identify the level and extent of upper extremity arterial occlusive disease.

Toe-brachial index- Is more reliable in patients with diabetes since the small vessels of the toes are spared from calcification. The great toe is usually used but in case of amputation the second or other toes can be used to measure the TBI. A photo-electrode is placed on the end of the toe to obtain a photoplethysmographic (PPG) arterial waveform using infrared light.

Transcutaneous oxygen measurement- ($TcPO_2$) helps assimilate supplemental information with respect to local tissue perfusion. Also, this modality aids in assessment and monitoring of the healing potential of ischemic ulcers or amputation sites. Platinum oxygen electrodes are placed on the chest wall and lower limbs. Two values may be used: the absolute value of TcPO2 or the ratio between the chest and foot values. The normal TcPO2 level at the foot is 60 mmHg and the normal TcPO2 chest/foot ratio is 0.9(15).

However, local edema, variations in cutaneous temperature, highly emotional states (leading to peripheral sympathetic vasoconstriction), inflammation, and use of pharmacologic agents limit the precision of the test.

Imaging modalities

Ultrasound- Ultrasonography is used to evaluate the location and extent of vascular disease, arterial hemodynamics, and lesion morphology (16). The B-mode (brightness mode) and Doppler mode used together, each providing specific information has become a mainstay in vascular imaging.

B-mode provides a grey scale image useful for evaluating anatomic detail and the Doppler detects flow of blood across the vessels. Combining the two modes Duplex ultrasound has gained a prominent role in the noninvasive assessment of the peripheral vasculature. It overcomes the need for intra-arterial contrast and provides precise anatomic localization and accurate grading of lesion severity (17).

Depending on the site of the vessel to be studied probes with varying frequencies have been used. Assessment of the aorto-iliac segment and the renal vessels could be obscured due to gas in the bowel and due to the depth of these vessels and thus low frequency probes are used.

Contrast arteriography- Digital subtraction angiography remains the best modality for vascular imaging and can also be used in the setting of acute limb ischemia. Limitations include: radiation exposure and complications of arterial access. Owing to these limitations, other non-invasive methods like CT angiography and MR angiography are preferred.

The multi-detector computed tomography (MDCT) helps rapidly acquire high resolution, contrast-enhanced arterial images (18). The MDCT although inexpensive involves radiation exposure and injection of contrast material. The sensitivity and specificity for detecting a stenosis of ≥50 percent with MDCT and DSA were 95 and 96 percent, respectively.

Magnetic resonance angiography (MRA), using gadolinium contrast has shown to be a time-efficient and cost effective (cheaper than DSA) modality in the evaluation of PAOD. However, the tendency of gadolinium for inducing nephrogenic systemic fibrosis (NSF) in patients with renal insufficiency, limits its clinical use.

TREATMENT:

After confirming the diagnosis of PAOD, the management of PAOD involves a combined approach incorporating the following measures:

- Risk factor modification of hypertension, diabetes, obesity and hyperlipidemia
- Lifestyle modification including smoking cessation
- Pharmacotherapy
- Exercise to increase walking tolerance
- Interventional therapy (eg, balloon angioplasty, stenting, atherectomy, endarterectomy, and surgical bypass).
-

1. RISK FACTOR MODIFICATION:

PAOD shares common risk factors with atherosclerotic disease elsewhere in the body; including coronary and carotid atherosclerotic disease. In fact according to the third

report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel [ATP] III), PAOD is described as a coronary heart disease risk equivalent(19).

Diabetes Mellitus: Though aggressive control of blood sugar in both type 1 and type 2 diabetes reduces the risk of micro-vascular complications (eg, nephropathy, retinopathy, and neuropathy), there is no evidence to suggest that aggressive glycaemic control reducing the risk and progression of macro-vascular complications; including PAOD(20,21).

Hypertension: Currently there is no data evaluating whether antihypertensive therapy alters the progression of claudication. However, aggressive optimisation of blood pressure in these patients helps reduce morbidity from cardiovascular and cerebrovascular disease (5).

Hyperlipidemia: Studies performed even prior to the introduction of statin therapy for dyslipidemia, showed regression or less progression of femoral atherosclerosis with lipid-lowering therapy (22,23), and a decrease in the incidence of claudication pain and limb-threatening ischemia in patients with hyperlipidemia who were treated with surgery (24).

The following benefits have been noted with statin therapy for PAOD:

- Regression of femoral atherosclerosis (25),
- a lower rate of new or worsening claudication (26),

- improvements in walking distance and pain-free walking time (27,28)
- lowers the incidence of cardiovascular events in patients with PAOD (29)

Recommendations regarding lipid control made in the 2007 TASC II consensus document on the management of PAOD (5):

- Target LDL-cholesterol for patients with PAOD is <100 mg/dL (2.6 mmol/L).
- Target LDL-cholesterol to <70 mg/dL (1.8 mmol/L) is preferred in patients with PAOD and cerebrovascular or cardiac atherosclerosis.

2. LIFESTYLE MODIFICATION:

The progression of PAOD can be stopped with smoking cessation (30,31). There is no consensus whether cessation of tobacco use reduces the severity of claudication symptoms. In a meta-analysis (32) that looked at pain-free and total walking distance outcomes, smoking cessation was found useful, but only in nonrandomized trials.

The following recommendations regarding smoking cessation were made in the 2011 update to the ACC/AHA guidelines (33) for the management of patients with PAOD, and the 2007 TASC II consensus document(5) on the management of PAOD:

- All patients who have a history of smoking (i.e) are smokers or former smokers should be questioned about the status of tobacco use at every hospital visit
- All patients should be strongly counselled to stop smoking by their physicians
- All patients should be given pharmacotherapy, behavior modification, referral to a smoking cessation program, and counselling.

3. PHARMACOTHERAPY:

Pharmacological therapy is aimed at reduction of symptoms of claudication and slowing the course of natural disease. Many agents have been evaluated, however evidence for use has been convincing only for Cilostozol and antiplatelet agents (33,34).

1. **Cilostozol-** This drug is a phosphodiesterase inhibitor. Due to this action it acts directly on the arteries; leading to arterial vasodilation. It supresses platelet aggregation (35). Benefits of therapy are seen as early as within 4 weeks of initiation of treatment. Cilostazol is indicated for increasing walking distance among those patients with PAOD, in whom antiplatelet agents and exercise rehabilitation have failed and revascularisation is not possible (5,34). Cilostazol is well tolerated; even with antiplatelet medications like aspirin and/or Clopidogrel.
2. **Antiplatelet agents**- The currently available data suggests that there is no improvement or only a modest improvement of claudication with antiplatelet agents alone. Therefore, the indication for use is for secondary prevention of coronary disease and stroke.

   Of the available antiplatelet agents- Asprin, Ticlopidine, Dipyridamole and Clopdiogrel, Asprin remains the drug of choice as it is cost effective and reduces coronary disease and stroke.

   Ticlopidine was found to have best efficacy in terms of increase in walking distance (37) but side effects such as leukopenia and thrombocytopenia, requiring close hematologic monitoring for at least three months were seen.

Other unwanted effects include bleeding diathesis, dyspepsia, loose stools, nausea, anorexia, and giddiness.

Clopidogrel is similar to ticlopidine but considered a safer drug in terms of side effects. The CAPRIE trial demonstrated that clopidogrel (75 mg/day) had a minimal, although significant benefit over aspirin (325 mg/day) for the prevention of stroke, myocardial infarction (MI), and PAOD (38).

Antiplatelet summary (33,5)

The role of antiplatelet therapy is to reduce the risk of consequences of other atherosclerotic vascular disease like MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAOD, including those with claudication.

Aspirin is preferred and clopidogrel is indicated in settings which preclude the use of Aspirin.

3. **Pentoxifylline-** is a rheologic modifier which acts by increasing deformability of red cells and blood viscosity, decreases in fibrinogen concentration, and reduced platelet adhesiveness. Data suggests that Pentoxifylline is of questionable benefit and that its results can be matched with walking regimens alone (39).

   Other rheologic modifiers- Hydroxy-ethyl starch (HES) or a low-molecular-weight dextran (LMWD) one to two times weekly for several weeks have been used for decreasing the blood viscosity and hemodilution. There is very minimal benefit and thus this therapy is not recommended(40,41).

4. **Naftidrofuryl**- a 5-hydroxytryptamine-2-receptor antagonist whose mechanism of action of action is unclear but it is hypothezised to increase the

peripheral uptake of glucose; thereby leading to an increase in ATP levels (42).

5. **Ginkgo biloba-** Though this was presumed to have antioxidant effect, and antithrombotic effects, ACC/AHA guidelines concluded that there was no benefit from this therapy (8,33).

Investigational agents- The following agents have been proposed but these are not recommended yet-

- Angiotensin inhibition- Ramipril might provide symptomatic benefit in patients with claudication (43). Further studies are required before the use of ACE inhibitors for claudication can be recommended.
- Antichlamydophila therapy- It has been proposed that Chlamydophila (formerly Chlamydia) pneumoniae infection may promote the development of atherosclerosis and treatment with Roxithromycin prevents progression of disease (44). These observations need to be confirmed on a larger basis.
- Propionyl-L-carnitine- This is hypothezised to act by increasing energy metabolism in ischemic muscle (45,46). A double-blind placebo-controlled study reported improvement in quality of life, emotional status, and physical function among a subset of patient with more severe limitation of their walking capacity (<250 meters) at baseline (47). But, ACC/AHA guidelines concluded that benefit from this therapy is questionable (8,33).
- Defibrotide- is an agent that is hypothesised to stimulate fibrinolysis by increasing the release of tissue plasminogen activator and prostacyclin and reducing the release of plasminogen activator inhibitor from endothelial

cells. A placebo-controlled study evaluating its effects reported an increased maximal treadmill walking distance over a six-month period (48).

- Prostaglandins- PGE1 is a vasodilator and causes inhibition of aggregation of platelets. It is metabolised rapidly in the lungs and thus needs to be administered at high doses. Studies showed an increase in walking distance and improvement in quality of life when it was administered in its prodrug form (49). A Cochrane review of five studies comparing PGE1 (alprostadil) with placebo found that significant increases in walking distances were attained with PGE1, which persisted even after termination of treatment (50).

4. SUPERVISED EXERCISE THERAPY:

Both hospital and community based exercise programs have been useful in reducing the claudication pain in patients with PAOD (51-56). Although community based programs are associated with higher dropout rates, they still provide psychological support which is essential in any successful exercise program.

Mechanisms by which exercise training may improve claudication-

- Improved endothelial function increases endothelial-dependent dilation (57).
- Reduced local inflammation (induced by muscle ischemia) by decreasing free radicals (58).
- Increased exercise pain tolerance (59).
- Induction of vascular angiogenesis (60).
- Improved muscle metabolism by favourable effects on muscle carnitine metabolism and other pathways (61).

- Reduced red cell aggregation and in blood viscosity (62).

5. INTERVENTIONAL THERAPY:

TASC classification- Lesions have been classified as follows:

A) AORTO-ILIAC LESIONS

TASC classification of aorto-iliac lesions

Type A lesions	**Unilateral or bilateral stenoses of CIA** **Unilateral or bilateral single short (≤3 cm) stenosis of EIA**
Type B lesions	**Short (≤ 3cm) stenosis of infrarenal aorta** **Unilateral CIA occlusion** **Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA** **Unilateral EIA occlusion not involving the origins of internal iliac or CFA**
Type C lesions	**Bilateral CIA occlusions** **Bilateral EIA stenoses 3–10 cm long not extending into the CFA** **Unilateral EIA stenosis extending into the CFA** **Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA** **Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA**
Type D lesions	**Infra-renal aortoiliac occlusion** **Diffuse disease involving the aorta and both iliac arteries requiring treatment** **Diffuse multiple stenoses involving the unilateral CIA, EIA and CFA** **Unilateral occlusions of both CIA and EIA** **Bilateral occlusions of EIA** **Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery**

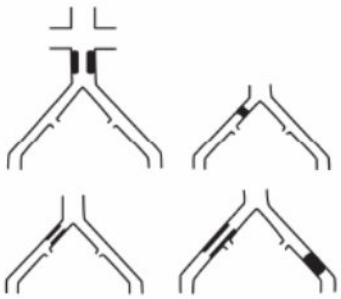
Figure F1 TASC classification of aorto-iliac lesions

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (≤3 cm) stenosis of EIA

Type B lesions:

- Short (≤3cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

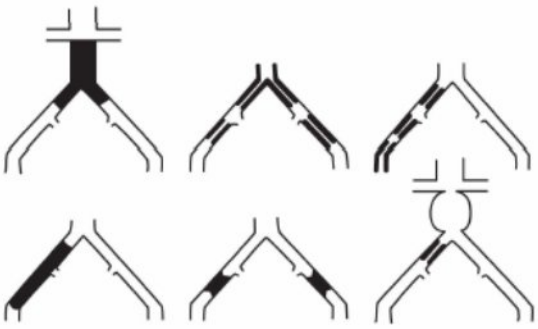


Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3–10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Infra-renal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusions of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery



Treatment of aortoiliac lesions:

• TASC A and D lesions: The treatment of choice for type A lesions is endovascular therapy and for type D lesions is surgery.

• TASC B and C lesions: The preferred treatment for type B lesions is endovascular therapy and for patients with type C lesions who do not have other co-morbid illnesses or those in whom the co-morbid illnesses are under control surgery is the preferred modality.

The patient is informed about the operators expertise and the risk factors associated with the various co-morbid illnesses before making treatment recommendations for both type B and C lesions.

B) FEMORAL POPLITEAL DISEASE

TASC classification of femoral popliteal lesions:

Type A lesions	Single stenosis ≤10 cm in length Single occlusion ≤5 cm in length
Type B lesions	Multiple lesions (stenoses or occlusions), each ≤5 cm Single stenosis or occlusion ≤15 cm not involving the infra geniculate popliteal artery Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass Heavily calcified occlusion ≤5 cm in length Single popliteal stenosis
Type C lesions	Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification Recurrent stenoses or occlusions that need treatment after two endovascular interventions
Type D lesions	Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery) Chronic total occlusion of popliteal artery and proximal trifurcation vessels

Treatment of femoral popliteal lesions:

As in aorto-iliac disease the treatment for type A lesions is endovascular repair and for type D lesions is surgery. Type B and C lesions can be treated either by endovascular repair or surgery depending on the comorbid illnesses of the patient and the expertise of the operator.

INDICATIONS FOR REVASCULARIZATION — The ACC/AHA and other guidelines suggest that the following issues need to be addressed when considering either percutaneous or surgical revascularization in patients with intermittent claudication (5,8):

- Lack of adequate response or failure of exercise rehabilitation and pharmacologic therapy.
- Significant disability due to claudication; as indicated by an inability to perform normal work or activities of daily living. This criterion indicates the symptom variability among patients with claudication and of the impact of these symptoms on the quality-of-life.
- The patient is able to benefit from an improvement in claudication (ie, exercise is not limited by another cause, such as angina, heart failure, chronic obstructive pulmonary disease, or orthopedic problems).
- Based on the evolution of the disease as seen in the natural history and prognosis of the patient.
- The characteristics of the disease permit appropriate intervention at low risk to the patient with a high chance of immediate and long-term success.

ROLE OF LIPOPROTEIN A :

Prior studies which evaluated the role of pharmacological management of dyslipidemia for the prevention of cardiovascular disease (CVD) focused on patients with elevated LDL-cholesterol levels. Despite evidence that other dyslipidaemias, like an elevated level of Lp (a), have also been shown to accelerate atherosclerosis, there is a dismal lack of clinical trial evaluating interventions directed toward lowering Lp (a) levels (63). Elevated serum Lp (a), is currently included as an independent risk factor for CVD. Also, there is direct correlation between high Lp (a) levels and patients presenting with an acute myocardial infarction.

STRUCTURE AND FUNCTION:

Lp (a) is a modified form of low density lipoprotein (LDL) in which a large glycoprotein, apolipoprotein (a) [apo(a)] is covalently bound to apolipoprotein B by a disulfide bridge (64). The apo (a) chain contains five cysteine rich domains known as "kringles"(65). The fourth kringle is similar in structure with the fibrin-binding domain of plasminogen, which is a plasma protein that dissolves blood clots when activated. Because of this structural similarity to plasminogen, Lp (a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells. This impairs plasminogen activation, plasmin generation, and fibrinolysis (66,67). Lp (a) also binds to macrophages via a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques.

GENETICS :

Lp(a) is an important molecule because its levels are mainly genetically determined and are not influenced by environmental factors , including the classical vascular risk factors. In families without familial hypercholesterolemia, greater than 90 percent of the variability in Lp(a) levels can be explained by polymorphisms at the apo(a) gene locus (isoforms), also referred to as the LPA gene (Online Mendelian Inheritance in Man [MIM] 152200) (68). One

important LPA polymorphism is the kringle IV type 2 size polymorphism, which results in a large number of differently sized isoforms of apolipoprotein (a) (70). There is a strong inverse relationship between the size of the apo (a) isoforms and the Lp (a) concentrations (68). A significant proportion (30 to 60 percent) of the population variation in Lp (a) levels is determined by this polymorphism (69).

EPIDEMIOLOGY:

The distribution of Lp (a) varies with race and ethnicity. Lp (a) levels are normally distributed in African-American populations. However, Caucasians, Eastern Asian, and Asian Indian populations have Lp(a) distributions where the baseline levels are lower than those of their African-American counterparts (70). According to the Framingham Heart Study, the 90th percentile of Lp (a) levels is 39 mg/dL (1.39 μmo/L) in men and 39.5 mg/dL (1.41 μmo/L) in women (units of mass) (71,72).

Among Indians, a study based among healthy Indians in Mumbai provided the reference intervals for all apolipoproteins, in both sexes from a general population (73). Also, among subjects of South Indian origin, Delhi and Chennai based case control studies of Lp (a) levels among diabetics with CAD, showed a correlation between elevated Lp (a) levels and CAD (74,75). However, conflicting evidence was published by a Bangalore based study; which stated that there was no correlation with elevated Lp (a) levels and coronary artery disease (76).

In PAOD, the role of Lp (a) in the pathogenesis of PAOD is unclear. Also there is limited evidence which supports the above hypothesis (77). There is thus a clear lack of adequate data to determine the role of Lp(a) in PAOD.

Measurement of serum Lp (a) concentration-

Lp (a) was previously analysed using gel electrophoresis method; where it was seen as a heavy band occurring prior to the beta globulin (78). Density gradient ultracentrifugation used to be the standard method by which Lp (a) was measured. ELISA tests were then made available for measurement. But these methods were flawed as they were unable to distinguish between apo(a) isoforms, and had cross-reactivity with plasminogen, which lead to erroneous estimation of Lp(a) levels (79,80).

Currently there is a commercially available assay which uses a latex-enhanced immunoturbidimetric method that measures Lp (a) independently of the apolipoprotein(a) size and number of kringle-IV repeats (81,82).

CARDIOVASCULAR DISEASE RISK:

Many small retrospective trials done in the early 1990s, demonstrated an association between elevated Lp (a) and cardiovascular disease (83-87).

Coronary artery disease- A meta-analysis of 24 cohort studies confirmed the continuous association between Lp (a) and coronary artery disease (88). Another study among patients who suffered an acute myocardial infarct, elevated Lp (a) levels (>30mg/dl) was associated with a 62 percent increase in cardiac death in a three year follow up (89).

Cerebrovascular disease- Elevated Lp (a) levels were found to be associated with an increased risk of cerebrovascular disease which was found to be stronger in men than in women (90, 91).

Patients with hypertension- Elevated Lp (a) levels accelerates target organ damage in hypertensive patients. Lp (a) levels were found to be the best predictor of target-organ damage involving the kidney, heart, and arterial wall (92).

MECHANISMS OF CVD RISK:

Atherothrombosis — A number of studies have been carried out to assess the role played by Lp (a) in atherothrombosis. Lp (a) excess is thought to promote atherosclerosis by the following mechanisms:

- The VLDL receptor found on the macrophages present in atherosclerotic lesions can bind to and mediate the catabolism of Lp (a) by endocytosis, leading to its degradation within lysosomes (93). This leads to accumulation of lipid within macrophages converting them into foam cells.
- Binding to the endothelium and components of the extracellular matrix (94) and also endothelial dysfunction due to selective impairment of vasodilator capacity of the blood vessels (95). The importance of the latter effect is uncertain since Lp (a) may not impair nitric oxide-mediated vasodilation, in contrast to the demonstrated adverse effect of oxidized LDL (96).
- Increased expression of intercellular adhesion molecule-1, which results in the recruitment of monocytes to the vessel wall and binding to macrophages (97). This promotes the formation of foam cells and the localization of Lp (a) in atherosclerotic plaques (98).
- Interaction with the fibrinolytic and coagulation systems causing increased tissue-factor mediated thrombosis and inhibition of clot lysis (99).

TREATMENT OF EXCESS LIPOPROTEIN A:

The indications for the treatment of Lp (a) have not been thoroughly investigated, although many clinicians are of the opinion that the primary goal of therapy is the reduce LDL cholesterol levels.

LDL-C reduction — There are many clinicians who are more aggressive in LDL-C reduction in the presence of elevated Lp (a) levels. This is based on data which showed that there was a progression in coronary atherosclerosis and CHD events in the presence of elevated Lp (a) if the LDL-cholesterol levels were not lowered by more than 10 percent (100).

Lp(a) reduction — When LDL-C levels cannot be optimally lowered, treatment for lowering Lp(a) is considered.

- Nicotinic acid(Niacin) at a dose of 2 to 4gm/day is initiated for reduction of Lp (a) (101). Niacin also reduces LDL-C and has beneficial effects on the lipid profile. Other salutary effects such as reduction of LDL-C, apo B-100, small LDL, and triglycerides and elevation of HDL-cholesterol levels have been shown. As much as 38 percent reduction of Lp (a) levels have been shown with treatment with Niacin (101).
- Neomycin at a dose of 2 to 3gm/day also reduces Lp (a), but is not used due to its numerous side effects (102). It has been shown to reduce Lp (a) levels by nearly 24 percent.

Lipid-lowering drugs — Other lipid lowering drugs have been shown to not have any effect on Lp (a). Statins and Fibrates used along with Niacin are beneficial in reducing the risk of coronary artery disease but do not have a direct effect on Lp (a) (103).

NORMAL VALUE OF LIPOPROTEIN A:

Studies regarding the normal value of Lp (a) have shown that there is variation between various ethnic groups. Lp (a) levels were shown to be as high as three times more in certain African populations. The atherosclerosis risk in communities (ARIC) study found that there was a significant risk in stroke and cardiovascular disease in patients with Lp (a) levels more than 30mg/dl (104).

Thus a Lp (a) level of below 30mg/dl was considered desirable to reduce the risk of stroke and cardiovascular disease (105).

The Lp(a) levels in the Indian population has not been studied in detail and there is a clear lack of knowledge if there is association with peripheral vascular disease.

MATERIALS AND METHODS

STUDY DESIGN

This is a case control study done among adult patients presenting with symptomatic atherosclerotic peripheral vascular disease, to the Department of Vascular surgery of Christian Medical College and Hospital, Vellore between August 2010 and December 2012.

Study setting:

Christian Medical College, Vellore is a 2200 bedded, tertiary care, multi-specialty teaching hospital in South India, which caters to the demands of patients not only from within Tamilnadu; but also to those from other states.

The Department of Vascular Surgery caters to patients with both arterial and venous diseases. The twice weekly Out Patient Clinic caters to approximately 120 patients with vascular disorders per day. Approximately one fourth of these patients, present with arterial disorders. A specialised Vascular Lab offers ABPI and Transcutaneous oxygen saturation (tcPO2) testing. About 12-15 operations are performed under the elective list and 2-5 emergency operations are performed on a weekly basis. Among these, 2-3 major arterial reconstructions are performed weekly.

APPROVAL:

This study was reviewed and cleared by the Institutional Review Board (IRB No: 7199) and the Ethics Committee of CMC Vellore.

Monetary funding of Rs.40,000 was provided by the Fluid Research Grant.

INCLUSION CRITERIA:

SELCTION OF CASES:

1. All adult patients (>18years of age) with atherosclerotic risk factors (i.e.) smoking, dyslipidemia, hypertension and diabetes mellitus.
2. Symptomatic patients with ABPI <0.90 or with radiological evidence of peripheral arterial occlusive disease

SELECTION OF CONTROLS:

1. No symptoms, signs or radiological evidence of peripheral arterial disease
2. Controls will be matched for age and sex.
3. Controls will be chosen from patients attending the Vascular Surgery outpatient clinic and also from inpatients of Vascular Surgery Unit.

EXCLUSION CRITERIA:

1. Patients with atherosclerotic PAOD on treatment with Niacin
2. Thromboangitis oblietrans (TAO)
3. Vasculitis
4. Other non-atherosclerotic causes of PAOD

STUDY DURATION:

1st August 2010 to 31st December 2012

DATA COLLECTION:

Basic demographic data pertaining to the patient and details of risk factors at presentation, with clinical findings, ABPI or imaging findings, were noted on the data information sheets. A fasting sample for serum Lp (a) level estimation was drawn after obtaining informed consent from the patient.

SAMPLE SIZE CALCULATION:

Sample size was calculated based on the data available from a previous study conducted in 2008 in Kuala Lumpur (77).

Sample size:

Probability of exposure given disease absent	0.5
Anticipated odds ratio	3
Power (1- beta) %	0.75
Alpha error (%)	80
Error (%)	5
1 or 2 sided	2
Required sample size in each of the case & control groups	58

STUDY METHODOLOGY:

All symptomatic adult patients presenting with clinical or radiological evidence of PAOD to the Vascular Surgery Unit of Christian Medical College were screened and recruited for the study. Patients who were diagnosed to have TAO, vasculitis, or non-atherosclerotic causes of

PAOD or those who were already on treatment with Niacin for atherosclerotic PAOD, were excluded from the study.

Criteria for diagnosis of atherosclerotic PAOD:

Based on clinical examination, ABI and findings on imaging, patients were diagnosed to have PAOD on the following basis:

- Leg symptoms suggestive of claudication with exertion or ischemic pain at rest.
- Abnormal lower extremity pulse examination.
- Abnormal ABPI
- Radiological evidence of PAOD

Among those patients included in the study, basic epidemiological data including age, sex, disease location and risk factors was collected.

Fasting serum samples were collected for estimation of lipoprotein (a) levels for all patients. All blood samples were collected in plain vacutainers, plasma separated and analysed by the Biochemistry laboratory. Lp (a) levels were analysed using immunoturbidometric assay . The assay was carried out in a Roche analyser, as per the manufacturer's protocol.

STATISTICAL ANALYSIS:

The statistical method used to test association between categorical variables was the Chi square test of significance. Association between continuous variables was done using Pearson correlation coefficient. Microsoft Excel was used for data entry and SPSS Version 18 was used for statistical analysis.

RESULTS

The various parameters that were analysed through the course of this study were :

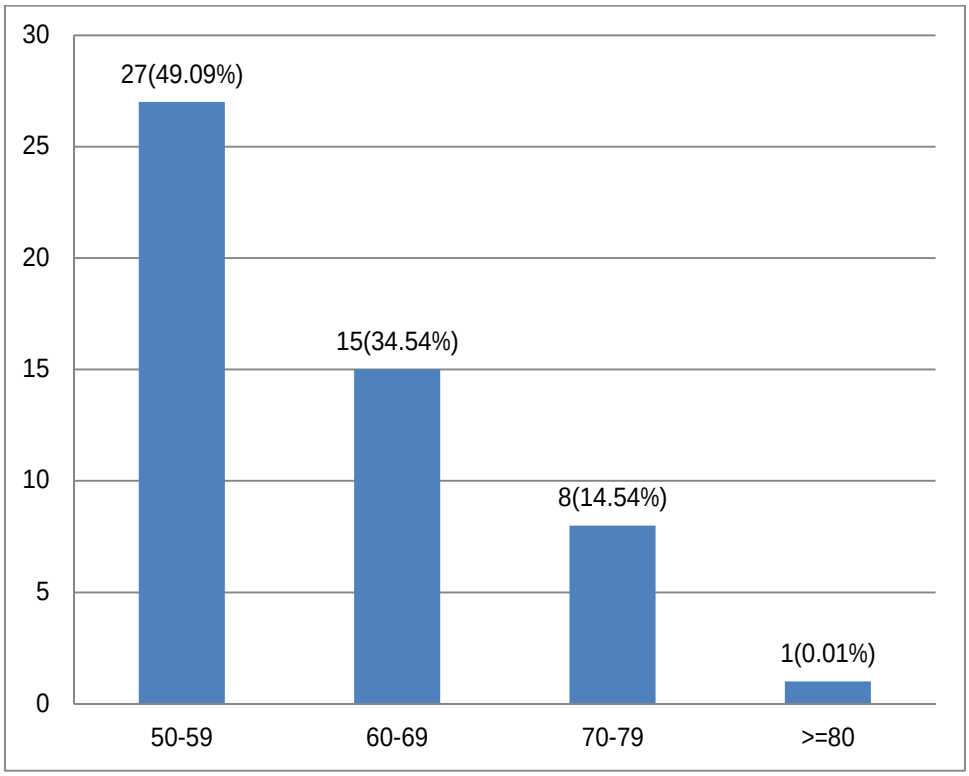
A. Baseline characteristics of the patients
    - Age distribution
    - Gender distribution
    - Risk factor profile- diabetes, hypertension, dyslipidemia and tobacco use.
B. Symptoms at presentation.
C. Lp (a) levels of cases and controls
D. Calculation of odds ratio
E. Logistic regression analysis

A. BASELINE CHARACTERISTICS:

A total of 55 cases were selected and an equal number of controls were matched for age and sex.

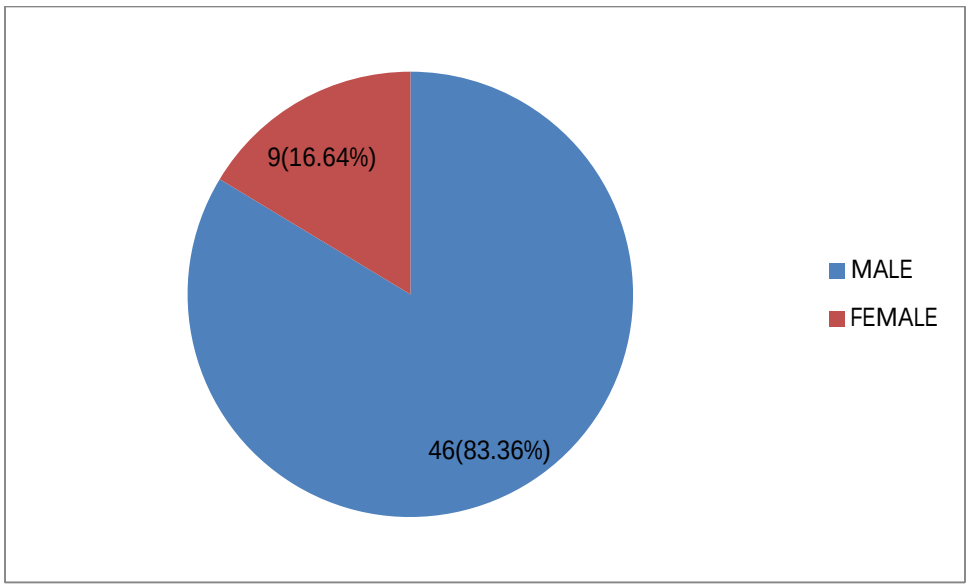
AGE: The age distribution of the patients was between 50 and 80 years. The mean age was 60.32 (SD=8.32) years.

Figure 1: Age distribution of patients with atherosclerotic PAOD N= 55:



GENDER: A total of 46 male patients and 9 female patients were identified and equal number of controls were matched.

Figure 2: Gender distribution of patients with atherosclerotic PAOD N= 55:

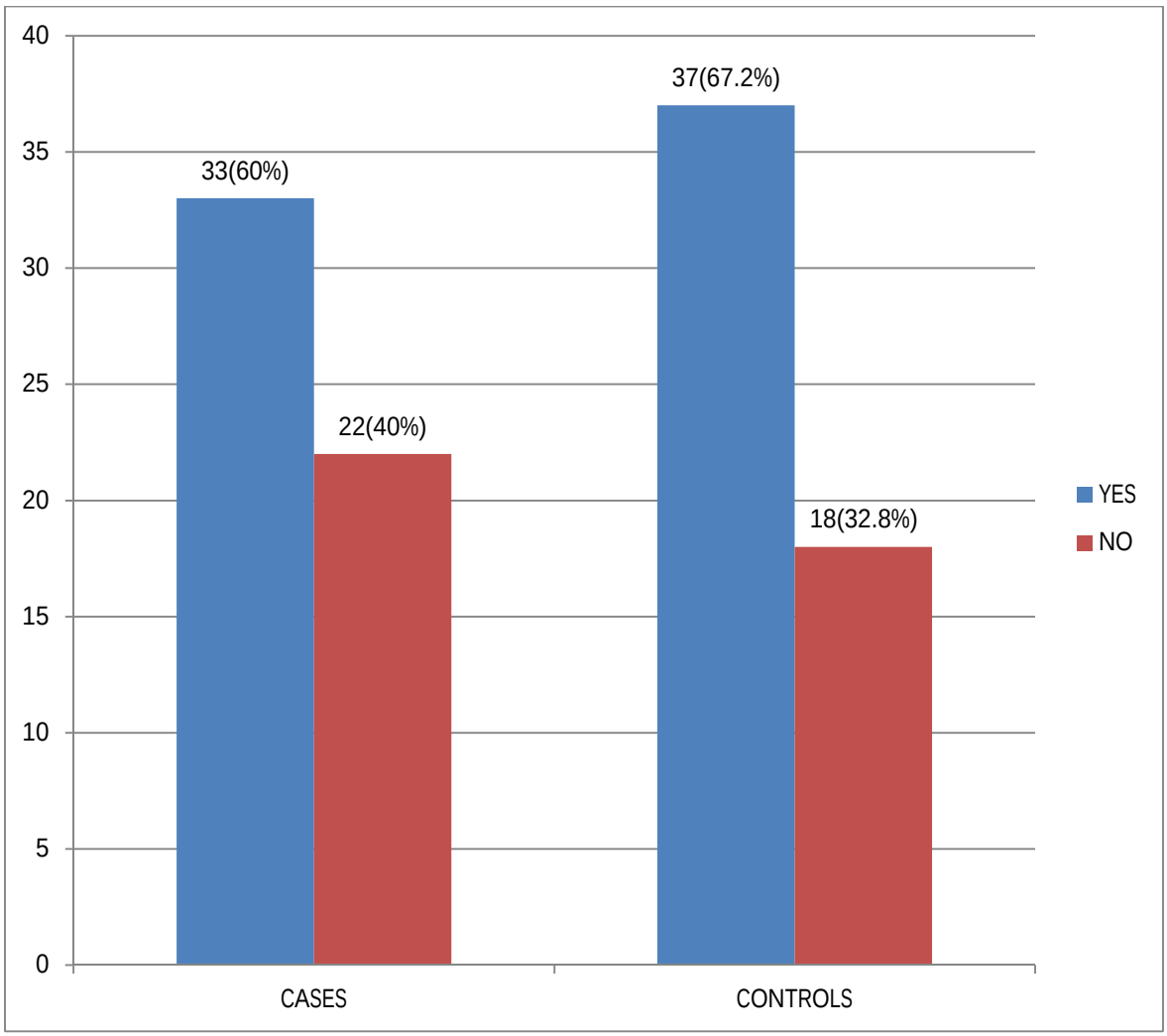


RISK FACTORS:

Of the identified patients 33(60%) cases and 37(67.37%) controls were diabetic, 26(47.27%) cases and 15(27.27%) controls were hypertensive, 16(29.09%) cases and 11(20%) controls were dyslipidemic and 45(81.81%) cases and 19(34.50%) controls used tobacco.

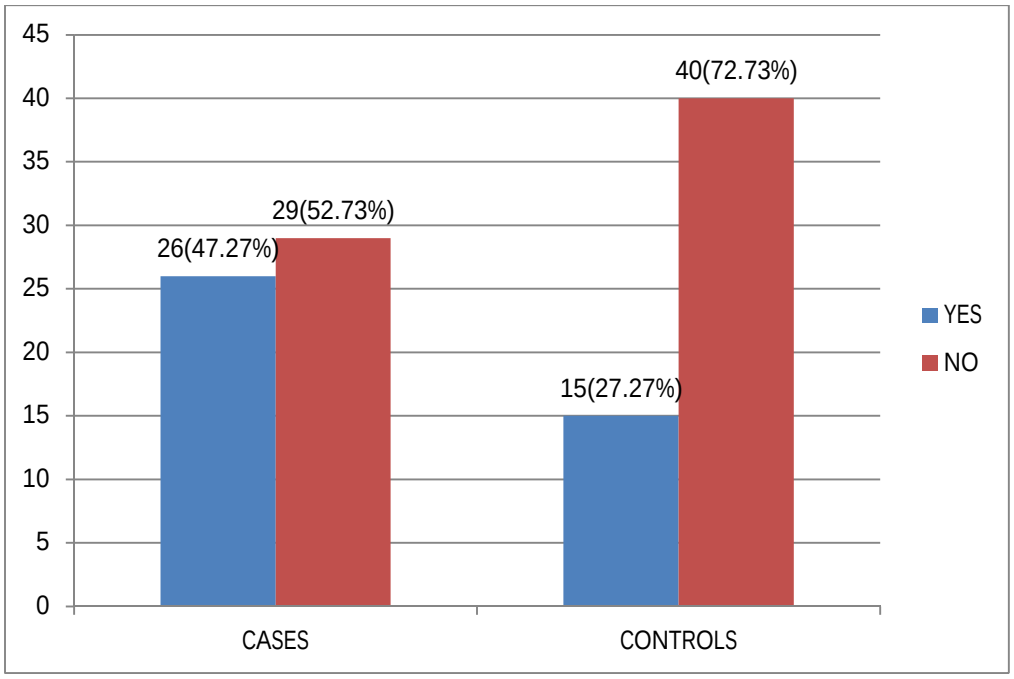
DIABETES MELLITUS:

Figure 3: Prevalence of diabetes mellitus among cases and controls N= 110:



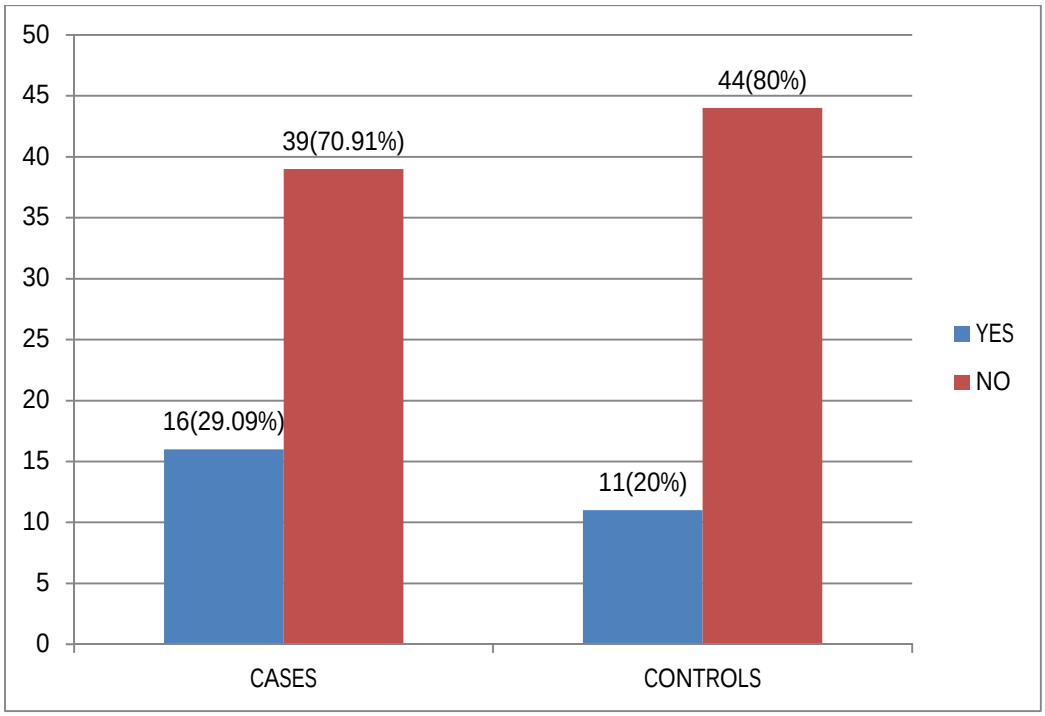
HYPERTENSION:

Figure 4: Prevalence of hypertension among cases and controls N= 110:



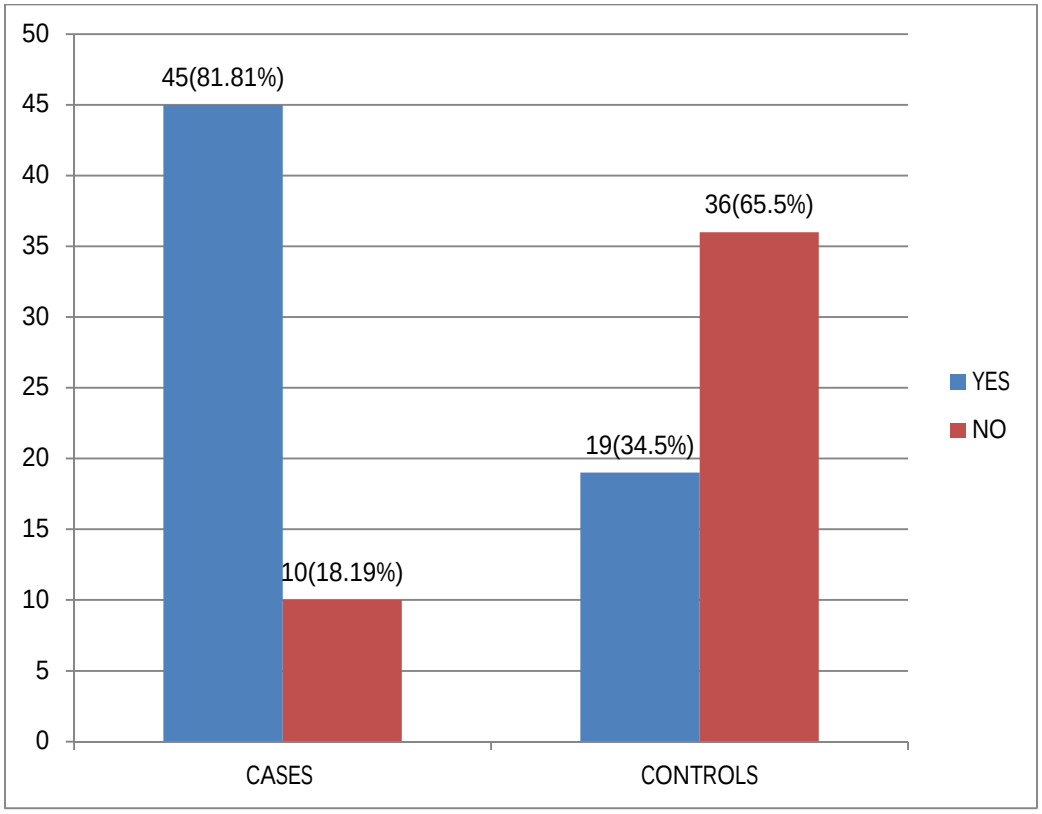
DYSLIPIDEMIA:

Figure 5: Prevalence of dyslipidemia among cases and controls N= 110:



TOBACCO USE:

Figure 6: Prevalence of tobacco use among cases and controls N= 110:



The table mentioned below summarises the baseline characteristics of both patient populations (i.e) cases and controls.

Table 1- Shows the baseline characteristics of the cases and controls used in the study.

Characteristic	**Cases %(n)**	**Controls %(n)**	**Total %(N)**
Gender			
Male	83.36(46)	83.36(46)	83.36(92)
Age(years)			
50-59	49.09(27)	49.09(27)	49.09(54)
60-69	34.54(15)	34.54(15)	34.54(30)
70-79	14.54(8)	14.54(8)	14.54(16)
>=80	0.01(1)	0.01(1)	0.01(2)
Diabetes	60.00(33)	67.20(37)	63.63(70)
Hypertension	47.27(26)	27.27(15)	37.27(41)
Dyslipidemia	29.09(16)	20.00(11)	24.54(27)
Tobacco use	81.81(45)	34.50(19)	58.18(64)

B. SYMPTOMS AT PRESENTATION:

Among cases, the commonest presenting symptom was gangrene (34.54%). However, claudication(29.09%) and rest pain(27.27%) were seen in almost similar numbers.

Figure 7- Presenting symptoms among cases N=55:

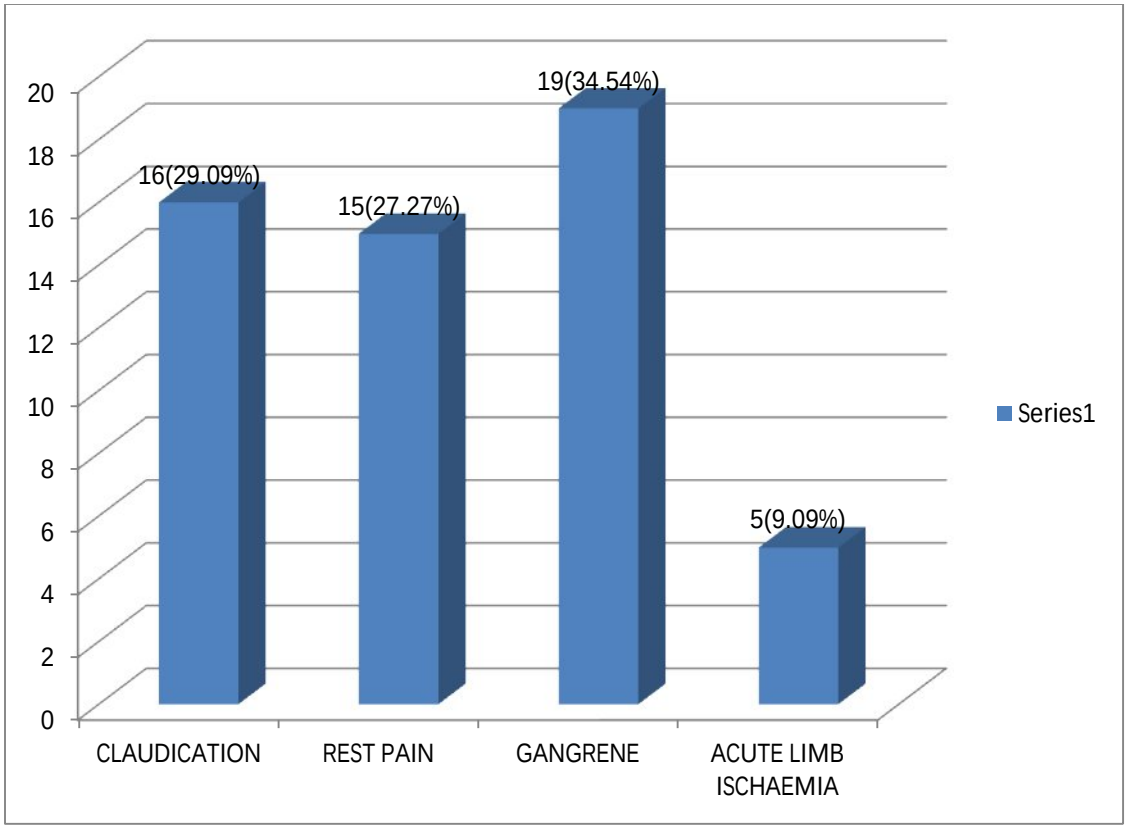


Table 2- Correlation between type of presentation and Lp(a) levels.

Presentation	Lp (a)< 30 %(n)	Lp (a) >= 30 %(n)
Acute limb ischemia	0%(0)	11%(5)
Gangrene	5.4%(3)	29.09%(16)
Rest pain	1.8%(1)	25.45%(14)
claudication	3.6%(2)	29.09%(14)
Total %(n)	10.9%(6)	89.09%(49)

Table 2 indicates that there was no association between the severity of presentation and elevated Lp(a) levels (p= 0.706)

C. Lp (a) LEVELS AMONG CASES AND CONTROLS:

Lp (a) levels were elevated in a greater proportion of cases (89.1%) (i.e) patients with documented PAOD. Among controls more than half (54.5%) of the patients also had elevated Lp (a).

Figure 8- Lipoprotein levels among cases and controls N=110:

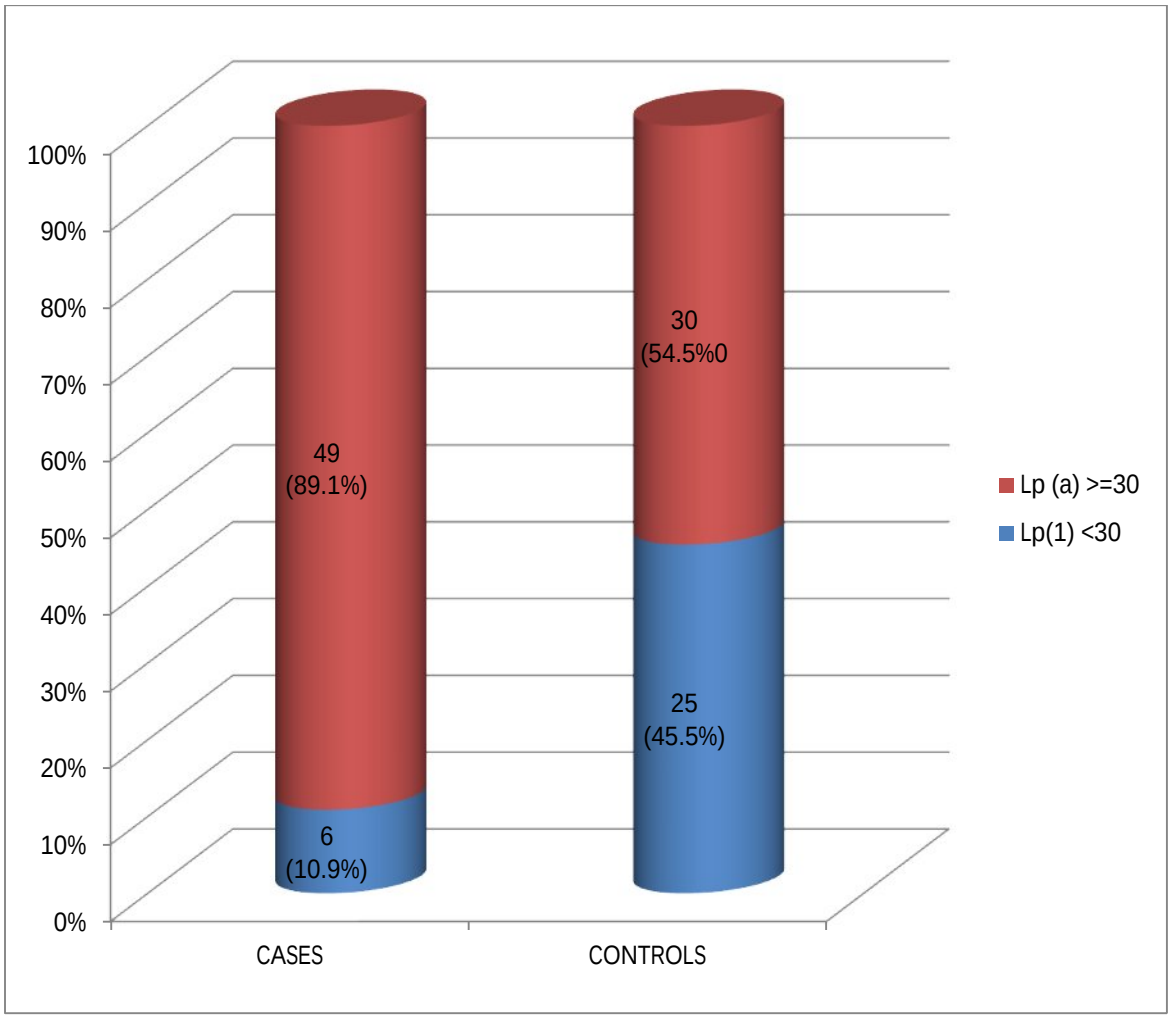
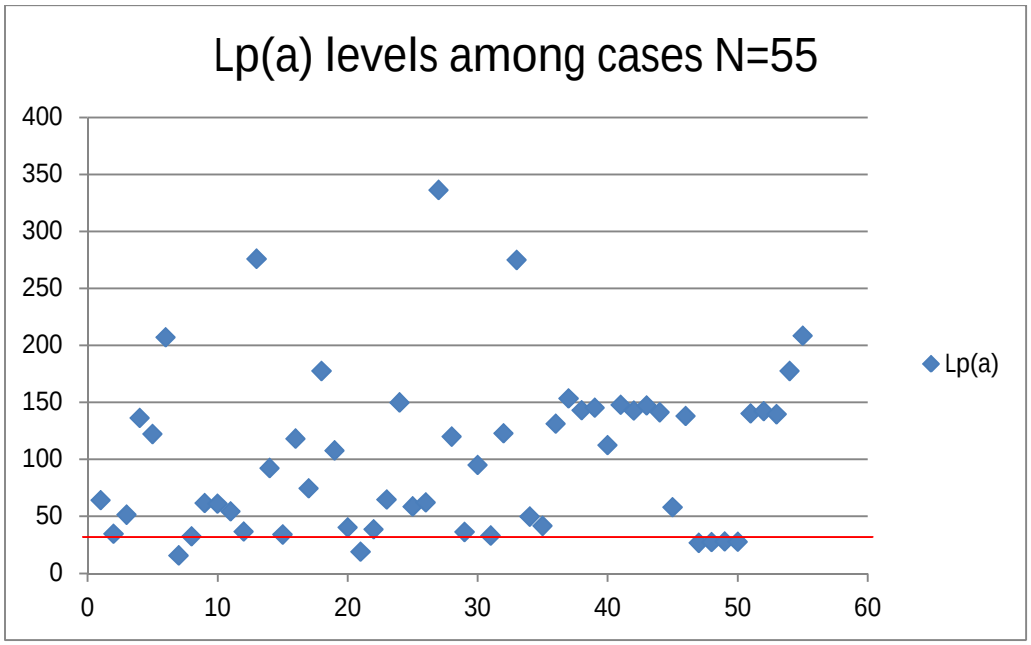
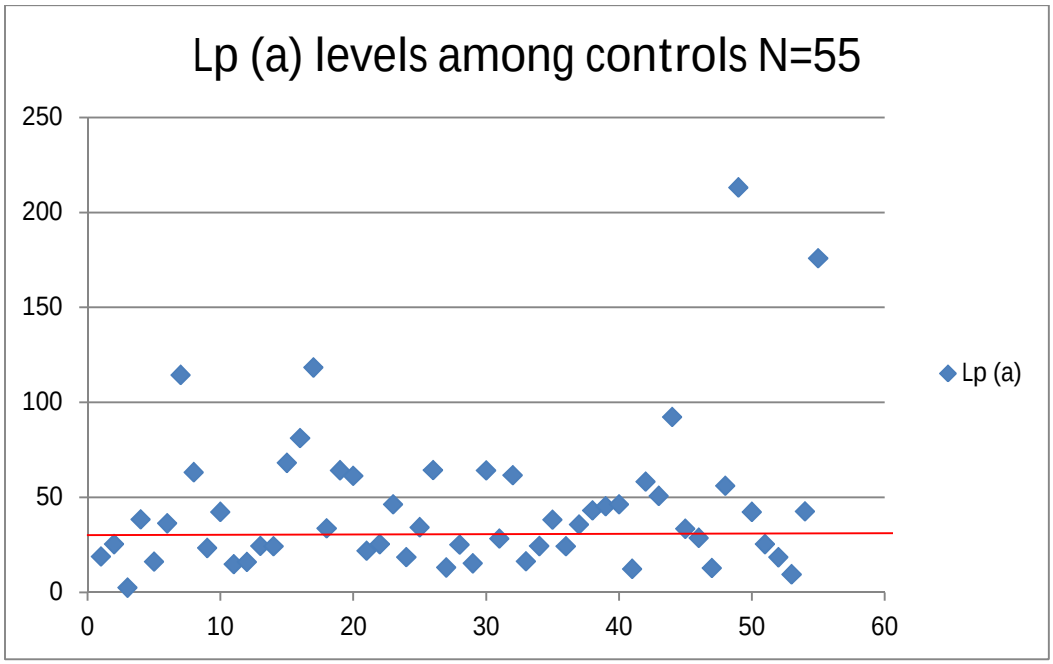


Figure 9- Scatter diagram showing the distribution of Lp (a) levels among cases



The mean Lp (a) level among the cases was 103.23mg/dl with a standard deviation of 69.97.

Figure 10- Scatter diagram showing the distribution of Lp (a) levels among controls



The mean Lp (a) level among the controls was 44.58mg/dl with a standard deviation of 38.14.

D. CALCULATION OF ODDS RATIO:

Odds ratio was calculated and a Chi-square test was performed to check the significance of elevated Lp (a) levels among the patient population.

Table 3- Lipoprotein levels among cases and controls

	Lp(a) < 30	Lp(a) >= 30	Total
Cases	6(10.9%)	49(89.1%)	55(100%)
Control	25(45.5%)	30(54.5%)	55(100%)

The odds ratio was found to be 6.8 with a p value of <0.001(95% CI 2.5-18.5).

E. LOGISTIC REGRESSION ANALYSIS:

Table 4- Logistic regression analysis to check correlation between other atherosclerotic risk factors and elevated Lp (a) levels.

Characteristic	Unadjusted			Adjusted		
	OR	95% CI	P value	OR	95% CI	P value
Group Case	6.8	2.5-18.5	<0.001	5.16	1.6-16.8	0.006
Tobacco use Yes	2.89	1.2-6.8	0.015	1.51	0.5-4.5	0.45
Diabetes Yes	0.95	0.4-8.3	0.90	0.89	0.3-2.5	0.82
Hypertension Yes	5.95	1.9-18.6	0.002	5.38	1.6-18.3	0.007
Dyslipidemia Yes	0.91	0.4-2.4	0.85	0.62	0.2-1.9	0.42

Table 4 indicates that there was a statistically significant association between patients with elevated Lp (a) levels and PAOD. However, there was no statistically significant association between other atherosclerotic risk factors such as tobacco use, diabetes mellitus, hypertension and dyslipidemia, with elevated Lp (a) levels.

DISCUSSION

Atherosclerotic peripheral artery occlusive disease shares the same classical risk factors as cardiovascular atherosclerotic disease. Elevated Lp (a) levels have been demonstrated in patients suffering from cardiovascular disease. We studied 55 patients who presented with atherosclerotic PAOD and an equal number of controls who were matched for age and gender to see if there is an association between elevated Lp (a) levels and atherosclerotic PAOD.

The most common presentation among the patients with PAOD was gangrene (either dry or wet) followed by claudication and rest pain. There were a few patients who presented with acute limb ischemia. Majority of the patients (i.e) 19 (34.54%) presented with gangrene, 16 (29.09%) with claudication, 15 (27.27%) with rest pain and 5 (9.09%) with acute limb ischemia. Analysis did not show any correlation between the type of presentation and elevated Lp (a) levels.

The risk factor profile was similar to patients with cardiovascular disease. The classical risk factors of smoking, diabetes mellitus, hypertension and dyslipidemia were analysed in the study. Among the patients with PAOD 33 (66%) were diabetic, 26(47.27%) were hypertensive, 16(29.09%) were dyslipidemic and 45(81.81%) used tobacco. Among the control population 37(67.2%) were diabetic, 15(27.27%) were hypertensive, 11(20%) were dyslipidemic and 19(34.5%) used tobacco. Thus both cases and controls were exposed to the risk factors of atherosclerosis; however the control population did not develop PAOD suggesting that there may be other factors which influence the development of PAOD.

Lp (a) levels have been shown to vary between various ethnic groups, however levels above 30mg/dl were shown to be associated with an increased risk of cardiovascular disease (104).

A cut off level of 30mg/dl was used in this study, and patients with values above this value were labelled as elevated Lp(a).

In this study 46 male patients and 9 female patients who presented with atherosclerotic PAOD were subjected to a fasting blood sample to analyse the level of Lp(a). An equal number of control patients were matched for age and gender and similar samples were collected.

Lp (a) levels more than or equal to 30mg/dl were seen in in 49(89.1%) of the cases. Interestingly elevated Lp(a) levels were seen in 30(54.5%) of the control group. The exact levels of Lp (a) were significantly higher in the patients with PAOD. The mean Lp (a) level among the cases was 103.23mg/dl with a standard deviation of 69.97 and the mean Lp (a) level among the controls was 44.58mg/dl with a standard deviation of 38.14.

The reason for this observation may be that the cut off level of 30mg/dl is based on western populations. More studies need to be conducted to ascertain the normal range among the Indian population.

CONCLUSIONS

- There was an elevated level of Lp (a) in both cases and controls.
- The elevated level was more significant in cases than in controls.
- Among the atherosclerotic risk factors only hypertension correlated with an increase in Lp (a) levels.
- More data needs to be collected to ascertain the normal level of Lp(a) in the Indian population.
- Randomised control trials need to be carried out to assess the effect on Lp (a) lowering therapy on patients with PAOD.

LIMITATIONS

- The sample size that was calculated initially was 58 cases and 58 controls, but only 55 patients could be enlisted into the study.
- The cut off value that was used for elevated Lp (a) levels is from western literature and that may not be an appropriate value among the Indian population.

BIBLIOGRAPHY:

1. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002;143(6):961.
2. Pasternak RC, Criqui MH, Benjamin EJ, Fowkes FG, Isselbacher EM, McCullough PA, Wolf PA, Zheng ZJ, American Heart Association. Atherosclerotic Vascular Disease Conference: Writing Group I: epidemiology. Circulation. 2004;109(21):2605.
3. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004;110(6):738.
4. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286(11):1317.
5. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5.
6. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation. 1997;96(1):44.
7. Vitale E, Zuliani G, Baroni L, Bicego L, Grego F, Valerio G, Fellin R. Lipoprotein abnormalities in patients with extra-coronary arteriosclerosis. Atherosclerosis. 1990;81(2):95.
8. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American

Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113:e463.

9. PASCARELLI EF, BERTRAND CA. COMPARISON OF BLOOD PRESSURES IN THE ARMS AND LEGS. N Engl J Med. 1964;270:693.
10. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton JD, Gavin JR 3rd, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA, Prevention of Atherothrombotic Disease Network. Critical issues in peripheral arterial disease detection and management: a call to action. Arch Intern Med. 2003;163(8):884.
11. McPhail IR, Spittell PC, Weston SA, Bailey KR. Intermittent claudication: an objective office-based assessment. J Am Coll Cardiol. 2001;37(5):1381.
12. Mohler ER 3rd. Peripheral arterial disease: identification and implications. Arch Intern Med. 2003;163(19):2306.
13. BundóM, Muñoz L, Pérez C, Montero JJ, MontellàN, Torán P, Pera G. Asymptomatic peripheral arterial disease in type 2 diabetes patients: a 10-year follow-up study of the utility of the ankle brachial index as a prognostic marker of cardiovascular disease. Ann Vasc Surg. 2010;24(8):985.

14. Wang JC, Criqui MH, Denenberg JO, McDermott MM, Golomb BA, Fronek A. Exertional leg pain in patients with and without peripheral arterial disease. Circulation. 2005;112(22):3501.
15. Bowers BL, Valentine RJ, Myers SI, Chervu A, Clagett GP. Bowers BL, Valentine RJ, Myers SI, Chervu A, Clagett GP. J Vasc Surg. 1993;18(3):506.
16. Olin JW, Kaufman JA, Bluemke DA, Bonow RO, Gerhard MD, Jaff MR, Rubin GD, Hall W, American Heart Association. Atherosclerotic Vascular Disease Conference: Writing Group IV: imaging. Circulation. 2004;109(21):2626.
17. AbuRahma AF, Khan S, Robinson PA. Selective use of segmental Doppler pressures and color duplex imaging in the localization of arterial occlusive disease of the lower extremity. Surgery. 1995;118(3):496.
18. Edwards AJ, Wells IP, Roobottom CA. Multidetector row CT angiography of the lower limb arteries: a prospective comparison of volume-rendered techniques and intra-arterial digital subtraction angiography. Clin Radiol 2005; 60:85.
19. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143.
20. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol. 1995;75(14):894.
21. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837.

22. Barndt R Jr, Blankenhorn DH, Crawford DW, Brooks SH. Regression and progression of early femoral atherosclerosis in treated hyperlipoproteinemic patients. Ann Intern Med. 1977;86(2):139.

23. Duffield RG, Lewis B, Miller NE, Jamieson CW, Brunt JN, Colchester AC. Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis. A randomised controlled trial. Lancet. 1983;2(8351):639.

24. Buchwald H, Bourdages HR, Campos CT, Nguyen P, Williams SE, Boen JR. Impact of cholesterol reduction on peripheral arterial disease in the Program on the Surgical Control of the Hyperlipidemias (POSCH). Surgery. 1996;120(4):672.

25. de Groot E, Jukema JW, Montauban van Swijndregt AD, Zwinderman AH, Ackerstaff RG, van der Steen AF, Bom N, Lie KI, Bruschke AV. B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). J Am Coll Cardiol. 1998;31(7):1561.

26. Pedersen TR, Kjekshus J, PyöräläK, Olsson AG, Cook TJ, Musliner TA, Tobert JA, Haghfelt T.
Effect of simvastatin on ischemic signs and symptoms in the Scandinavian simvastatin survival study (4S). Am J Cardiol. 1998;81(3):333.

27. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation. 2003;108(12):1481.

28. Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, Pastore M, Borrello F, Belcastro M, Picchi A, Nami R. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med. 2003;114(5):359.

29. Schillinger M, Exner M, Mlekusch W, Amighi J, Sabeti S, Muellner M, Rumpold H, Wagner O, Minar E. Statin therapy improves cardiovascular outcome of patients with peripheral artery disease. Eur Heart J. 2004;25(9):742
30. Quick CR, Cotton LT. The measured effect of stopping smoking on intermittent claudication. Br J Surg. 1982;69 Suppl:S24.
31. Ameli FM, Stein M, Provan JL, Prosser R. The effect of postoperative smoking on femoropopliteal bypass grafts. Ann Vasc Surg. 1989;3(1):20.
32. Girolami B, Bernardi E, Prins MH, Ten Cate JW, Hettiarachchi R, Prandoni P, Girolami A, Büller HR. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. Arch Intern Med. 1999;159(4):337.
33. 2011 WRITING GROUP MEMBERS, 2005 WRITING COMMITTEE MEMBERS, ACCF/AHA TASK FORCE MEMBERS. 2011 ACCF/AHA Focused Update of the Guideline for the Management of patients with peripheral artery disease (Updating the 2005 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;124(18):2020.
34. Sobel M, Verhaeghe R, American College of Chest Physicians, American College of Chest Physicians. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):815S.
35. Reilly MP, Mohler ER 3rd. Cilostazol: treatment of intermittent claudication. Ann Pharmacother. 2001;35(1):48.

36. Wilhite DB, Comerota AJ, Schmieder FA, Throm RC, Gaughan JP, Rao AK. Managing PAD with multiple platelet inhibitors: the effect of combination therapy on bleeding time. J Vasc Surg. 2003;38(4):710.

37. Libretti A, Catalano M. reatment of claudication with dipyridamole and aspirin. Int J Clin Pharmacol Res. 1986;6(1):59.

38. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348(9038):1329.

39. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113:e463.

40. Ernst E, Kollar L, Matrai A. [Hemodilution in peripheral arterial occlusive disease. Placebo controlled randomized double-blind study with hydroxyethyl starch or dextran]. Acta Med Austriaca 1991; 18 Suppl 1:27.

41. Kiesewetter H, Blume J, Jung F, et al. Haemodilution with medium molecular weight hydroxyethyl starch in patients with peripheral arterial occlusive disease stage IIb. J Intern Med 1990; 227:107.

42. De Backer TL, Vander Stichele R, Lehert P, Van Bortel L. Naftidrofuryl for intermittent claudication. Cochrane Database Syst Rev 2008; :CD001368.
43. Ahimastos AA, Lawler A, Reid CM, et al. Brief communication: ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. Ann Intern Med 2006; 144:660.
44. Wiesli P, Czerwenka W, Meniconi A, et al. Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in Chlamydia pneumoniae seropositive men: a randomized, double-blind, placebo-controlled trial. Circulation 2002; 105:2646.
45. Brevetti G, Perna S, Sabbá C, et al. Propionyl-L-carnitine in intermittent claudication: double-blind, placebo-controlled, dose titration, multicenter study. J Am Coll Cardiol 1995; 26:1411.
46. Corsi C, Pollastri M, Marrapodi E, et al. L-propionylcarnitine effect on postexercise and postischemic hyperemia in patients affected by peripheral vascular disease. Angiology 1995; 46:705.
47. Brevetti G, Perna S, Sabba C, et al. Effect of propionyl-L-carnitine on quality of life in intermittent claudication. Am J Cardiol 1997; 79:777.
48. Avellone G, Mandalà V, Pinto A, et al. Clinical evaluation of short-term defibrotide treatment of patients with atherosclerosis obliterans of the lower limbs. Haemostasis 1986; 16 Suppl 1:55.
49. Belch JJ, Bell PR, Creissen D, et al. Randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of AS-013, a prostaglandin E1 prodrug, in patients with intermittent claudication. Circulation 1997; 95:2298.
50. Reiter M, Bucek RA, Stümpflen A, Minar E. Prostanoids for intermittent claudication. Cochrane Database Syst Rev 2004; :CD000986.

51. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. Cochrane Database Syst Rev 2000; :CD000990.
52. Wolosker N, Nakano L, Rosoky RA, Puech-Leao P. Evaluation of walking capacity over time in 500 patients with intermittent claudication who underwent clinical treatment. Arch Intern Med 2003; 163:2296.
53. Hiatt WR, Regensteiner JG, Hargarten ME, et al. Benefit of exercise conditioning for patients with peripheral arterial disease. Circulation 1990; 81:602.
54. Gardner AW, Skinner JS, Bryant CX, Smith LK. Stair climbing elicits a lower cardiovascular demand than walking in claudication patients. J Cardiopulm Rehabil 1995; 15:134.
55. Frans FA, Bipat S, Reekers JA, et al. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. Br J Surg 2012; 99:16.
56. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation 2012; 125:130.
57. Brendle DC, Joseph LJ, Corretti MC, et al. Effects of exercise rehabilitation on endothelial reactivity in older patients with peripheral arterial disease. Am J Cardiol 2001; 87:324.
58. Tisi PV, Shearman CP. The evidence for exercise-induced inflammation in intermittent claudication: should we encourage patients to stop walking? Eur J Vasc Endovasc Surg 1998; 15:7.

59. Zwierska I, Walker RD, Choksy SA, et al. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. J Vasc Surg 2005; 42:1122.
60. Gustafsson T, Kraus WE. Exercise-induced angiogenesis-related growth and transcription factors in skeletal muscle, and their modification in muscle pathology. Front Biosci 2001; 6:D75.
61. Hiatt WR, Regensteiner JG, Wolfel EE, et al. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. J Appl Physiol 1996; 81:780.
62. Ernst EE, Matrai A. Intermittent claudication, exercise, and blood rheology. Circulation 1987; 76:1110.
63. Rosenson RS. Beyond low-density lipoprotein cholesterol. A perspective on low high-density lipoprotein disorders and Lp(a) lipoprotein excess. Arch Intern Med. 1996;156(12):1278.
64. Steyrer E, Durovic S, Frank S, et al. The role of lecithin: cholesterol acyltransferase for lipoprotein (a) assembly. Structural integrity of low density lipoproteins is a prerequisite for Lp(a) formation in human plasma. J Clin Invest 1994; 94:2330.
65. McLean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 1987; 330:132.
66. Loscalzo J, Weinfeld M, Fless GM, Scanu AM. Lipoprotein(a), fibrin binding, and plasminogen activation. Arteriosclerosis 1990; 10:240.
67. Palabrica TM, Liu AC, Aronovitz MJ, et al. Antifibrinolytic activity of apolipoprotein(a) in vivo: human apolipoprotein(a) transgenic mice are resistant to tissue plasminogen activator-mediated thrombolysis. Nat Med 1995; 1:256.

68. Boerwinkle E, Leffert CC, Lin J, et al. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 1992; 90:52.

69. 7.Thanassoulis G, O'Donnell CJ. Mendelian randomization: nature's randomized trial in the post-genome era. JAMA 2009; 301:2386.

70. Sandholzer C, Saha N, Kark JD, et al. Apo(a) isoforms predict risk for coronary heart disease. A study in six populations. Arterioscler Thromb 1992; 12:1214.

71. Bostom AG, Gagnon DR, Cupples LA, Wilson PW, Jenner JL, Ordovas JM, Schaefer EJ, Castelli WP. A prospective investigation of elevated lipoprotein (a) detected by electrophoresis and cardiovascular disease in women. The Framingham Heart Study.. Circulation. 1994;90(4):1688.

72. Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PW, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. JAMA. 1996;276(7):544.

73. Ashavaid TF, Kondkar AA, Todur SP, Dherai AJ, Morey J, Raghavan R. Lipid, lipoprotein, apolipoprotein and lipoprotein(a) levels: reference intervals in a healthy Indian population. J Atheroscler Thromb. 2005;12(5):251-9.

74. Mohan V, Deepa R, Haranath SP, Premalatha G, Rema M, Sastry NG, Enas EA. Lipoprotein(a) is an independent risk factor for coronary artery disease in NIDDM patients in South India. Diabetes Care. 1998 Nov;21(11):1819-23.

75. Clin Chim Acta. 2006 Oct;372(1-2):70-5. Epub 2006 May 15. Lipoprotein (a) and comprehensive lipid tetrad index as a marker for coronary artery disease in NIDDM patients in South India. Rajappa M, Sridhar MG, Balachander J, Sethuraman KR.

76. Govindaraju V, Neelam, Manjunath CN, Sundar KKJ Indian Med Assoc.Lipoprotein (a) in coronary artery disease in Indian population. J Indian Med Assoc. 2003 Aug;101(8):458-60, 4622.
77. Hakim NA, Hafizan MT, Baizurah MH, Zainal AA. Asian J Surg. 2008 Jan;31(1):11-5. Serum lipoprotein(a) levels in patients with atherosclerotic peripheral vascular disease in Hospital Kuala Lumpur.
78. Dahlen, GH, Ericson, C, Furberg, C, et al. Angina of effort and an extra pre-beta lipoprotein fraction. Acta Med Scand Suppl 1972; 53:11.
79. Marcovina SM, Albers JJ, Wijsman E, et al. Differences in Lp[a] concentrations and apo[a] polymorphs between black and white Americans. J Lipid Res 1996; 37:2569.
80. Superko HR. Beyond LDL cholesterol reduction. Circulation 1996; 94:2351.
81. Marcovina SM, Koschinsky ML, Albers JJ, Skarlatos S. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: recent advances and future directions. Clin Chem 2003; 49:1785.
82. Marcovina SM, Albers JJ, Scanu AM, et al. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem 2000; 46:1956.
83. Dangas G, Ambrose JA, D'Agate DJ, et al. Correlation of serum lipoprotein(a) with the angiographic and clinical presentation of coronary artery disease. Am J Cardiol 1999; 83:583.
84. Schaefer EJ, Lamon-Fava S, Jenner JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men. The lipid Research Clinics Coronary Primary Prevention Trial. JAMA 1994; 271:999.

85. Nguyen TT, Ellefson RD, Hodge DO, et al. Predictive value of electrophoretically detected lipoprotein(a) for coronary heart disease and cerebrovascular disease in a community-based cohort of 9936 men and women. Circulation 1997; 96:1390.
86. Wald NJ, Law M, Watt HC, et al. Apolipoproteins and ischaemic heart disease: implications for screening. Lancet 1994; 343:75.
87. Cremer P, Nagel D, Labrot B, et al. Lipoprotein Lp(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and other risk factors: results from the prospective Göttingen Risk Incidence and Prevalence Study (GRIPS). Eur J Clin Invest 1994; 24:444.
88. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009; 302:412.
89. Stubbs P, Seed M, Lane D, et al. Lipoprotein(a) as a risk predictor for cardiac mortality in patients with acute coronary syndromes. Eur Heart J 1998; 19:1355.
90. Ariyo AA, Thach C, Tracy R, Cardiovascular Health Study Investigators. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. N Engl J Med 2003; 349:2108.
91. Ohira T, Schreiner PJ, Morrisett JD, et al. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2006; 37:1407.
92. Sechi LA, Kronenberg F, De Carli S, et al. Association of serum lipoprotein(a) levels and apolipoprotein(a) size polymorphism with target-organ damage in arterial hypertension. JAMA 1997; 277:1689.
93. Argraves KM, Kozarsky KF, Fallon JT, Harpel PC, Strickland DK. The atherogenic lipoprotein Lp(a) is internalized and degraded in a process mediated by the VLDL receptor. J Clin Invest. 1997;100(9):2170.

94. Salonen EM, Jauhiainen M, Zardi L, Vaheri A, Ehnholm C. Lipoprotein(a) binds to fibronectin and has serine proteinase activity capable of cleaving it. EMBO J. 1989;8(13):4035.

95. Schachinger V, Halle M, Minners J, Berg A, Zeiher AM. Lipoprotein(a) selectively impairs receptor-mediated endothelial vasodilator function of the human coronary circulation. J Am Coll Cardiol. 1997;30(4):927.

96. Schlaich MP, John S, Langenfeld MR, Lackner KJ, Schmitz G, Schmieder RE. Does lipoprotein(a) impair endothelial function?. J Am Coll Cardiol. 1998;31(2):359.

97. Takami S, Yamashita S, Kihara S, Ishigami M, Takemura K, Kume N, Kita T, Matsuzawa Y. Lipoprotein(a) enhances the expression of intercellular adhesion molecule-1 in cultured human umbilical vein endothelial cells. Circulation. 1998;97(8):721.

98. Poon M, Zhang X, Dunsky KG, Taubman MB, Harpel PC. Apolipoprotein(a) induces monocyte chemotactic activity in human vascular endothelial cells. Circulation. 1997;96(8):2514

99. Deb A, Caplice NM. Lipoprotein(a): new insights into mechanisms of atherogenesis and thrombosis. Clin Cardiol. 2004;27(5):258.

100. Maher VM, Brown BG. Lipoprotein (a) and coronary heart disease. Curr Opin Lipidol 1995; 6:229.

101. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. J Intern Med 1989; 226:271.

102. Gurakar A, Hoeg JM, Kostner G, et al. Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. Atherosclerosis 1985; 57:293.

103. Stein JH, Rosenson RS. Lipoprotein Lp(a) excess and coronary heart disease. Arch Intern Med 1997; 157:1170.

104. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, Coresh J, Mosley TH, Morrisett JD, Catellier DJ, Folsom AR, Boerwinkle E, Ballantyne CM (January 2012). "Associations Between Lipoprotein(a) Levels and Cardiovascular Outcomes in Black and White Subjects: The Atherosclerosis Risk in Communities (ARIC) Study". Circulation 125 (2): 241–9. doi:10.1161/CIRCULATIONAHA.111.045120. PMID 22128224.

105. Genest J, Libby P. Lipoprotein disorders and cardiovascular disease. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia, PA:Saunders Elsevier; 2011:chap 47.

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ANNEXURE

VASCULAR SURGERY, CMC HOSPITAL, VELLORE
INPATIENT PROFORMA FOR VASCULAR DISEASE

NAME: **AGE:** SEX: M / F **HOSPITAL NO.:**

CONTACT NO.: MOB.: **HOME:**

Symptom: Claudication / Rest pain / Gangrene / Acute ischaemia

Duration: ---------- ---------- ---------- ----------

Ischemic symptoms in other systems: Cerebral / cardiac / GIT / impotence

Upper limb involvement: Yes / No

Contributory disease: Diabetes / Hypertension / Dyslipidemia / Vasculitis / Homocysteinemia /

Tobacco use: Cigarette / beedi / tobacco chewing / ------

Family history (vascular) ----------

Past treatment: Medical
Sympathectomy surgical / chemical
Bypass
Debridement
Amputation
Other

Nourishment: Under / Normal / Over

Blood pressure: Right arm Left arm

Pulses: (-/+ / ++)	Right	Left		Right	Left
Carotid			Femoral		
Brachial			Popliteal		
Radial			Post tibial		
Ulnar			Dors. Pedis		

Bruit: Yes / No **Site:**

Superficial thrombophlebitis: Yes / No
Temperature of affected part: Same / warm / cool / cold
Trophic change: Yes / No
Investigations

PCV

Vasculitic workup: ESR CRP PT (INR) APTT VDRL

cANCA pANCA Rh Factor ATIII

ANA dsDNA LEcells

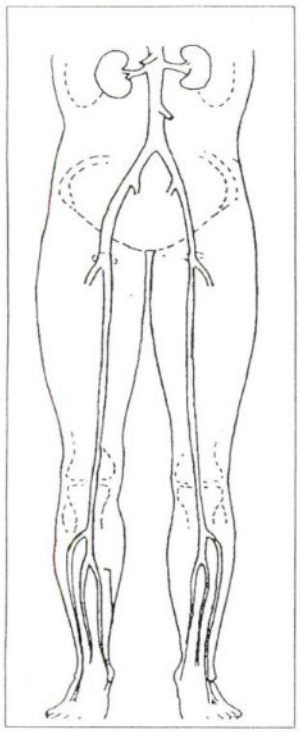
Lipid profile: Chol. ----- Trig. ------ HDL ---------- LDL ----------

Evidence of ischemic heart disease on ECG, Echo, TMT Yes / No

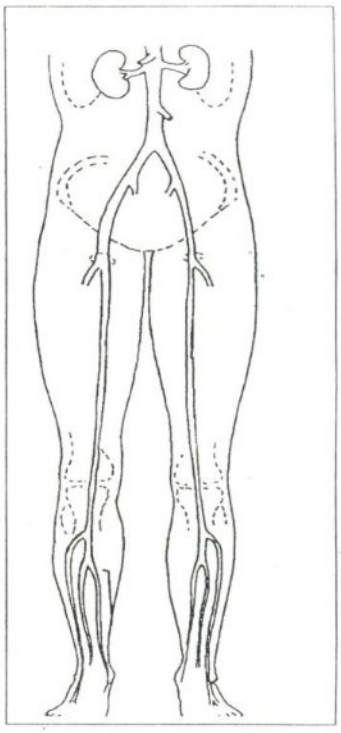
ABPI: RIGHT LEFT

Depiction of stenotic lesions N=0to49%, S=50to99%, o=100%

DUPLEX SCAN



ANGIOGRAM



PATIENT INFORMATION SHEET

1. Study title :-

   A case control study to assess the levels of serum lipoprotein A in patients with peripheral arterial disease.

2. Principal Investigator :- Dr. Rajesh Selvakumar

   Contact address: Department of Vascular Surgery, CMC,Vellore.

   Contact phone/email: 04162282085, drrajeshselvakumar@gmail.com

This study is a research project conducted in CMC Vellore, Department of General and Vascular surgery. We want to study the level of serum lipoprotein a in patients with peripheral arterial disease. If you decide to participate in the study, your blood sample will be collected for measuring serum lipoprotein a. This is the only invasive procedure that you will be subjected to. However this is not an extra procedure specific for the study. Even otherwise you will require a blood draw and lab tests as part of the standard OPD procedure for treatment purpose. So no extra risk is incurred to you due to participation in the study. However all precautions necessary will be taken to avoid any complications that may arise due to the venepuncture. Preferably a vein at the elbow will be the puncture site. The proposed area will be cleaned with spirit and left to dry for 1 min. Puncture will be made into the vein (all precautions will be taken to avoid any inadvertent arterial puncture) using a 24 G needle and a small amount of blood (10 – 15 cc) will be collected. After taking out the needle compression will be applied for 1-2 minutes to ensure haemostasis. This is all done as a one time process. By participating in the study you will not be made to incur any added expenses. Also there is no added risk of any kind for you by participating in this study. Any personal information about you that is collected as part of this study will be maintained strictly confidential.

INFORMED CONSENT FORM

I ……(Participant's name), Hosp no…… have fully read and understood the participant's information sheet for the study named "A case control study to assess the levels of serum lipoprotein a in patients with *peripheral arterial disease* "

By signing this form I agree that

(1) I understand that the purpose of this study is to improve the quality of medical care and that my involvement may not benefit me.
(2) I have been made aware of the procedures involved in the study and the expected inconvenience, risk, discomfort or potential side effects as far as they are currently known by the researcher.
(3) My participation in this study is fully voluntary

I do hereby agree to take part in this study.

Name Signature Date

Witness1. Name Signature Date

Witness2. Name Signature Date