A STUDY OF THE PREVALENCE OF PERIPHERAL VASCULAR DISEASE AND ITS ASSOCIATED RISK FACTORS AMONG ADULTS IN A RURAL COMMUNITY IN SOUTH INDIA

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI FOR THE DEGREE OF M.D. BRANCH-XV (COMMUNITY MEDICINE) EXAMINATION TO BE HELD IN MAY 2019

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CERTIFICATE

This is to certify that "A study of the prevalence of peripheral vascular disease and its associated risk factors among adults in a rural community in South India" is a bona fide work of Dr. Jackwin Sam Paul G in partial fulfilment of the requirements for the M.D. Community Medicine Examination (Branch-XV) of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in May 2019.

Dr. Vinod Joseph Abraham (MD, MPH)
Professor, Guide and Head
Department of Community Health
Christian Medical College, Vellore

Dr. Prabhu Premkumar (MS, MCh)
Associate Professor and Co-Guide
Department of Vascular Surgery
Christian Medical College, Vellore

Dr. Anna B Pulimood (MD, PhD)
Principal
Christian Medical College,
Vellore.

DECLARATION

This is to certify that this dissertation titled, "A STUDY OF THE PREVALENCE OF PERIPHERAL VASCULAR DISEASE AND ITS ASSOCIATED RISK FACTORS AMONG ADULTS IN A RURAL COMMUNITY IN SOUTH INDIA" is a bona fide work done by me, under the guidance of DR. VINOD JOSEPH ABRAHAM and DR. PRABHU PREMKUMAR, in partial fulfilment of the rules and regulations for the MD Branch XV (Community Medicine) Degree examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in May 2018.

I have independently reviewed the literature, collected the data and carried out the analysis and evaluation towards the completion of the thesis.

DR. JACKWIN SAM PAUL G.
POST GRADUATE STUDENT
DEPARTMENT OF COMMUNITY HEALTH
CHRISTIAN MEDICAL COLLEGE
VELLORE-632002

CERTIFICATE - II

This is to certify that this dissertation titled, “A study of the prevalence of peripheral vascular disease and its associated risk factors among adults in a rural community in South India” of the candidate Jackwin Sam Paul G. with registration number – 201625052 for the award of the degree of M.D. in the branch of Community Medicine (XV). I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains introduction to conclusion pages and the result shows 2 percentage of plagiarism in the dissertation.

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'Unless the Lord builds the house, the builders labour in vain.' Psalms 127:1

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LIST OF COMMON ABBREVIATIONS USED

PAD - **Peripheral Arterial Disease**

CVD - **Chronic Venous Disorders**

ABI - **Ankle Brachial Index**

TBI - **Toe Brachial Index**

BMI - **Body Mass Index**

LDL - **Low Density Lipoproteins**

HDL - **High Density Lipoproteins**

ACC/AHA - **American College of Cardiology / American Heart Association**

CEAP - **Clinical Etiologic Anatomic Pathophysiologic (Classification)**

1. INTRODUCTION AND JUSTIFICATION

Peripheral Vascular disease refers to the disorders affecting the vessels that are not directly in relation to the heart (1). The most commonly seen conditions are lower limb venous insufficiency and peripheral arterial disease. The prevalence and risk factors of these diseases have not been studied extensively at the community level in India.

Atherosclerosis is a systemic disease affecting the medium and large arteries. The pathophysiology of this disease involves the accumulation of fibrins and lipids between the tunica intima and media of the vessels leading to narrowing of the vessel lumen. This, in turn, causes decreased blood flow which may lead to ischaemia. If this occurs in a non-cardiac or cerebral vessel, it is called peripheral arterial disease. It is commonly diagnosed by measuring ankle brachial pressure index (ABI). An ABI of less than 0.90 is considered diagnostic of peripheral arterial disease (2). An ABI of more than 1.30 is suggestive of non-compressible vessels and is also indicative of arterial disease (3), especially of the systemic kind.

A U-shaped curve is seen while predicting all cause mortality and cardiovascular mortality as far as the ABI is concerned. Both low (adjusted OR 1.69, 95% CI 1.34-2.14) and high (adjusted OR 1.77, 95%CI 1.48-2.13) values predicted mortality (4).

There are various reasons for decreased peripheral blood flow, like inflammation, thrombosis and most commonly atherosclerosis. Most of the peripheral arterial disease patients are asymptomatic until the time they develop gangrene leading to loss

of limb. According to Sabiston's Textbook of Surgery, 20% - 50% Peripheral Arterial Disease (PAD) cases are asymptomatic. Only 10% – 35% present with claudication pain and another 20% present with nonspecific local symptoms. Diagnosis of PAD is critical because people with PAD have 4-5 times the risk of a heart attack or a stroke than the age-matched population (5). These asymptomatic patients realize their predicament too late, even for secondary prevention. They continue to smoke and are non-compliant with medications for diabetes mellitus as they are asymptomatic and lead a comfortable life, therefore not needing to change their current lifestyle. It is a known fact and proven by studies that prevalence of PAD is associated with diabetes (6), male gender, smoking, hypertension, dyslipidaemia, race, hyperhomocysteinemia and renal disease (5). According to a study done in urban Chennai, the prevalence of PAD in the general urban population was 3.2%. It found that age and hypertension were the major risk factors. The prevalence was 7.8% among those with known diabetes (6). In a cross-sectional study done in the United States of America over a period of five years between 2003 and 2008 among 3.6 million participants, the prevalence of PAD was 3.6% in the general population with an exponential increase in successive decades of life (7).

A study done in Japan comparing a cohort of 362 patients with PAD and a matched cohort without PAD revealed a higher risk of myocardial infarction (2.2% against 0.2%, p-value 0.019), ischaemic stroke (4.1% vs 0.5%, p-value 0.001) in the first year of the study. Total annual health costs were significantly higher in the PAD cohort (p-value <0.001)(8). In the United States, a total of $4.37 billion was spent by the national health insurance program (Medicare) on peripheral arterial disease-related

medical care in 2001, 88% of which was spent on inpatient care. The expenditure increased with age of the patient as they needed longer inpatient treatment (9). Over the past 17 years, the cost is bound to have dramatically risen. Early identification is a must in these circumstances.

In a study done in the US and five major European countries (France, Germany, Spain, Italy and the United Kingdom) increased absenteeism, overall work impairment and difficulty in activities of daily living were seen in people with PAD ($p<0.05$). Similarly, the number of outpatient visits, inpatient treatment and casualty visits were higher in the PAD group ($p<0.05$) (10). Another study estimated a cumulative cost of $7,445 for asymptomatic PAD patients, $7,000 for patients with claudication, $10,430 in patients with lower limb amputations secondary to PAD and $11,693 in patients who had revascularization over a period of two years (11). In France, a cohort study done from 2007-2011 evaluated that the total annual management cost in the PAD group was €14,949 as opposed to €3812 in the control group (12).

PAD can affect the mental well-being of those affected. A systematic review of 28 studies found the prevalence of depression among those with PAD to be as high as 36% to 48%. The study also found that women with PAD were more pre-disposed to have depression (13). Depressive symptoms among patients with PAD above the age of 65 was estimated to be 30% - 60% (14).

Low ABI can be used as a surrogate for predicting cognitive decline and may be used to identify people who could potentially end up with cognitive impairment (15). It has been said that 8% - 67% of patients with PAD perform poorly (<5% of controls) when

tested on non-verbal memory, concentration, executive function, perceptuo-motor speed and manual dexterity (16).

Peripheral venous insufficiency is a chronic condition, most commonly associated with incompetent valves. It encompasses a vast array of morphological and functional abnormalities over a prolonged period of time (17). In standing position, if the subcutaneous veins in the lower limbs are measured at more than 3 mm in diameter, then it is defined as a varicose vein (18). According to certain studies done in India and the United States (extrapolation), the prevalence of venous disease is 15-20% in India (17,18). Female gender, hereditary predisposition, trauma, occupation and pregnancy were found to be major risk factors (20). Congenital varicose veins are also seen in some individuals (17). Peripheral vascular disease, especially venous congestion, is a preventable cause of chronic ulcers/gangrene/ Deep Vein Thrombosis (DVT)/amputation if diagnosed at an early stage and treated appropriately. A spectrum of venous abnormalities including intradermal venous dilatation, 1-3 mm size venules as well as varicose veins falls under chronic venous disorder (17). Chronic venous disorders lead to chronic venous insufficiency which causes tissue damage due to perivascular inflammation. Due to various cytokine-mediated mechanisms, the dermal barrier is weakened and is easily infiltrated by pathogens and allergens (21).

The Bonn Vein Study done in Germany among 3072 patients showed that 49.1% of the men and 62.1% of the women between the ages of 18 and 79 had symptoms of chronic venous disease (22). The American Venous Forum conducted a National Venous Screening Program among 2234 individuals. The prevalence of venous

disease based on the CEAP classification from C0-C6 was 29%, 29%, 23%, 10%, 9%, 1.5% and 0.5% respectively (23). It is very common for less severe forms to progress to chronic venous congestion. 70% of people with advanced Chronic Venous Disease had had previous venous disorder as opposed to only 30% who had the disease after a thrombotic incident (24).

In the United States of America, it has been estimated that the annual expenditure (direct medical cost) on Chronic Venous Disease may be anywhere between 150 million and 1 billion US dollars (25). In the United Kingdom, 2% of the health care budget is spent on venous ulcers. GBP 5.7 billion is spent per year for managing all types of wounds.19% of these wounds were leg ulcers. According to this study, 1.5% of all adult population had an undifferentiated leg ulcer. There were 278,000 venous ulcers noted in that year which indicates that 1 in 170 adults had an ulcer in the study year (25).

It is commonplace to underdiagnose and subsequently not treat people with venous disease. This leads to the development of complications and the attending financial and social burden on the patient and the society. Chronic venous ulcers are recurring and it also is associated with discharge, foul smell, ghastly appearance and these have physical, psychological and emotional implications. A systemic review shows that chronic venous disease negatively affects the quality of life among individuals (27). Pain, fatigue and lack of mobility have been found to be some of the physical impacts. Lack of mobility in itself further leads to worsening of the venous congestion and ends up as a vicious cycle. Social isolation, altered body image, lack of sleep, frustration have all been associated with venous leg ulcers. Fear of isolation and dependence is

another key issue faced by patients with chronic venous congestion (28). Lower education and low income were further found to complicate quality of life among people with chronic venous disease. Younger people with the disease were found to have more psychosocial burden (29). A study done in Sao Paulo among 60 people, estimated prevalence of depression among patients with venous disease to be 91.66%. Sadness, negative body image, feeling of worthlessness, decreased libido and social withdrawal were the five main symptoms commonly associated with chronic venous disease. One person in the study even reported suicidal ideation (30).

As there is a paucity of information on peripheral arterial and venous disease particularly in the rural Indian community, this study was carried out to determine the prevalence and risk factors for peripheral vascular disease in such a population.

2. OBJECTIVES

- To estimate the prevalence of Peripheral Arterial Disease (PAD) among adults in a rural community in South India.

- To estimate the prevalence of Chronic Venous Disease (CVD) among adults in a rural community in South India.

- To assess the associated risk factors of Peripheral Arterial Disease among adults in this population

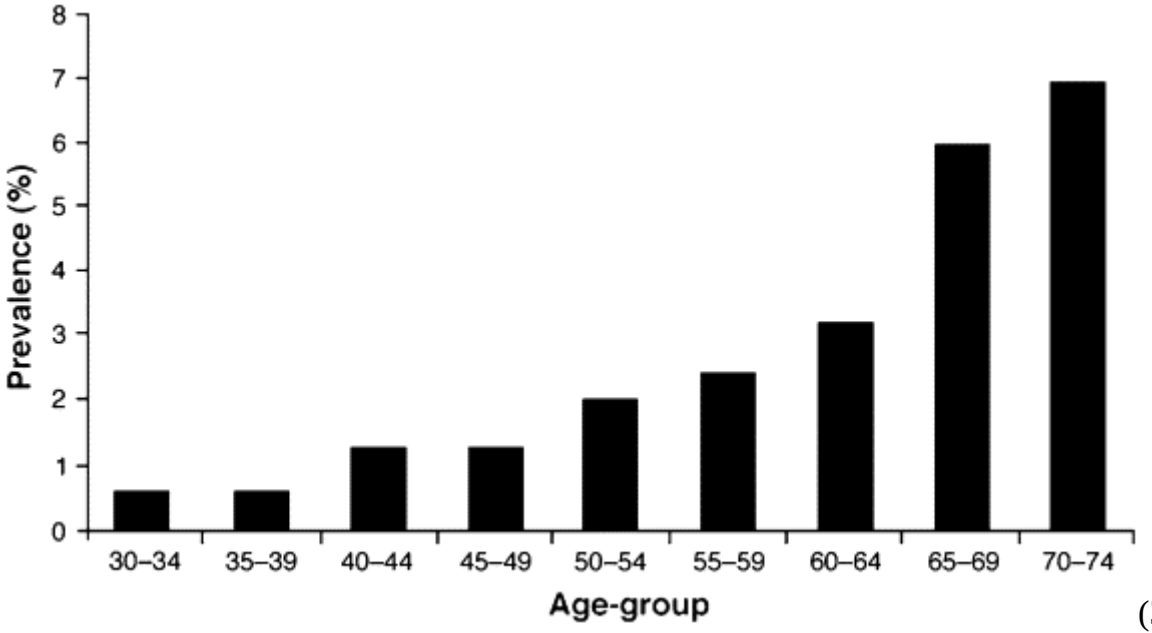
- To assess the associated risk factors of Chronic Venous Disease among adults in this population.

3. REVIEW OF LITERATURE

1. Peripheral Arterial Disease (PAD)

Peripheral arterial disease is the term used for partial or complete obstruction of one or more peripheral arteries (upper and lower limb extremities) (31). Globally 202 million individuals were living with peripheral arterial disease, out of whom 69.7% patients were from Low and Middle-income countries. 54.8 million individuals were from Southeast Asia alone (32). The prevalence of PAD by age as described by the Trans-Atlantic Inter-Society Consensus document is given below (33).

Fig 3.1 Prevalence of PAD by age group



(34)

Source: Journal of Vascular Surgery Volume 45, Issue 1, Supplement, January 2007, Pages S5-S67

1.1 Definitions and Nomenclature for vascular diseases as defined by the Atherosclerotic Peripheral Vascular Disease Symposium II published in 2008 (31) :

Asymptomatic PAD: Abnormal ABI at rest or after exercise, or other objective evidence of PAD but no limb symptoms. (31)

Claudication: Abnormal ABI at rest or after exercise with reproducible lower extremity muscle fatigue or discomfort on exertion, relieved by rest within 10 mins (31).

Atypical Claudication: Abnormal ABI at rest or after exercise with leg pain on exertion that is not consistent with classic claudication; may include calf, thigh, or buttock (31).

Critical Limb Ischaemia: Haemodynamic evidence of severe PAD with distal leg pain at rest, with or without ischaemic ulcers or gangrene (31).

Acute Limb Ischaemia: Haemodynamic evidence of severe PAD with acute limb pain and neurological dysfunction (31).

Abnormal ABI refers to an ABI <0.90 or >1.30 as both are associated with an increased prevalence of PAD both locally and systemically (35).

1.2 Anatomic localization of types of presentation

Asymptomatic: The Progression of Early Subclinical Atherosclerosis (PESA) study in 4184 asymptomatic participants between the ages of 40 and 54 showed subclinical atherosclerosis in 63% of the population (71% among men and 48% among women) (36). The obstructive plaques were most commonly seen in the iliofemoral region (44%), followed by the carotid arteries (31%) and the aorta (25%). The coronaries had plaques in only 18% of the people. In another study, 72% of men aged between 40 and

59 had asymptomatic atherosclerosis (37). Magnetic resonance angiography is however not necessary or indicated in asymptomatic patients.

Symptomatic: A series of 11.890 patients with atherosclerosis who were symptomatic were followed up for 25 years and were found to have the disease in four major arterial beds. These are, the coronary arterial bed, the major branches of the aortic arch, the visceral branches of the abdominal aorta and the terminal abdominal aorta and its major peripheral branches. In this study, it was found that prevalence was highest in the lower extremity arteries followed by the coronary arteries. It also showed that patients with coronary artery atherosclerosis and visceral artery disease presented much earlier and at a younger age group than patients with peripheral arterial disease. The rate of progression of the disease also differed substantially. It was fastest in the aortic arch and the visceral bed. Patients with concomitant risk factors like smoking and co-morbid illnesses like diabetes mellitus had the greatest risk for progression of the disease. Interestingly, a disease in the abdominal aorta and its terminal branches had the highest probability of developing the disease in a new arterial bed while the coronary disease patients rarely developed atherosclerosis in any further regions. Disease in the aortic branch was most likely to progress to disease in the abdominal aorta and its terminal branches and vice versa (38). It has been found that diabetes is more common among people with distal atherosclerosis ($p=0.004$) than in those with proximal arterial disease (39).

Risk Factors of PAD

44,985 men in the United States of America with no cardiovascular disease at baseline were part of the Health Professionals Follow-up Study and were followed up for a median of 24.2 years. There were 537 incident cases of PAD. After adjusting for each other factor, it was found that Type 2 Diabetes, smoking, hypercholesterolemia and hypertension were all significantly and independently associated with an increased risk of PAD. Men without any of the four risk factors were found to have a hazard ratio of 0.23 (95% CI 0.14-0.36) which signifies a 77% protection. Each additional risk factor had a multivariable-adjusted hazard ratio of 2.06 (95% CI 1.88-2.26) (40).

A systemic review of community-based studies showed that prevalence was less among men in Low or Middle-Income Countries (LMIC) as opposed to High-Income Countries (HIC), 2.89% vs 5.41% in the 45-49 year age group and 14.94% vs 18.83% in the 85-89 year age group. In LMIC, prevalence was higher among women than men especially in the lower age group (6.31% vs 2.89%). Smoking was found to be a major risk factor in both LMIC and HIC (OR 1.42, 95% CI 1.25-1.62 and OR 2.72, 95% CI 2.39-3.09 respectively). Other risk factors in LMIC and HIC respectively are, Type 2 Diabetes Mellitus (1.47[1.29-1.68] vs 1.88[1.66-2.14]), hypertension (1.36[1.24-1.50] vs 1.55[1.42-1.71]) and hypercholesterolemia (1.14[1.03-1.25] vs 1.19[1.07 vs 1.33]) (32).

The National Health and Nutrition Examination Survey (NHANES) done in the United States of America in 1999-2000 showed that Black Americans (OR 2.83), hypertensives (OR 1.75), diabetics (2.71), patients with dyslipidaemia (OR 1.68), people with poor renal function (OR 2.00) and above all, current smokers (OR 4.46)

were at a higher risk of developing Peripheral Arterial Disease. Elevated blood fibrinogen levels and C-reactive protein were also found to be associated with PAD (41).

Among a random sample of patients from the prospective cohort 'Men born in 1914'in Malmo, Sweden, it was found that the median plasma triglyceride levels and mean systolic blood pressure were higher in patients with ABI less than 0.90 (42). In the same cohort, the prevalence of PAD was found to be significantly higher among diabetics than non-diabetics (29% vs 12%, p=0.003) and also associated with increased cardiac events and a higher incidence of cardiac mortality among diabetics with PAD (43).

Data from the Atherosclerosis Risk in Community (ARIC) study showed that increased Low-Density Lipoproteins (LDL) and decreased High-Density Lipoproteins (HDL) were seen in people with lower ABI (<0.90). It was also found that ABI of <0.80 or >1.20 had a higher proportion of men and the mean height was significantly more ($p<0.001$) (44).

In a study done among 114 French Canadians who had had an angiography and been confirmed to have peripheral vascular atherosclerosis, it was found that high plasma triglyceride concentration was associated with increased severity of atherosclerosis, especially in the younger age group. On paper electrophoresis, 56.1% of patients with PAD had normal lipoprotein pattern (45). The original cohort of the Framingham heart study was followed up for 38 years and risk profile for intermittent claudication was identified. Cigarette smoking, coronary artery disease, diabetes, hypertension,

increased serum cholesterol, age and male sex were found to be associated with an increased risk of PAD (46). Relative risk was highest for cigarette smoking followed by diabetes, hyperhomocysteinaemia, hypertension and hypercholesterolemia (47).

A nested case-control study was done using blood samples which were collected initially from a concurrent cohort of 14,916 male physicians aged between 40 and 84 years in the United States, who were healthy at baseline. With a mean follow up of 9 years 140 men developed PAD. It was found that higher levels of CRP, fibrinogen, Apolipoprotein B-100, Total Cholesterol, Triglycerides, LDL and total cholesterol-HDL ratio and lower levels of HDL, Apolipoprotein A1at baseline were good predictors of developing PAD. High Total Cholesterol-HDL was found to be the strongest predictor (RR 3.9, CI 1.7-8.6) after multivariate analysis. CRP was also a strong predictor (RR 2.8, CI 1.3-5.9) according to the study (48). The extent of lower limb disease in young patients was found to be strongly associated with post-methionine plasma homocysteine level ($p=0.003$) (49). Another meta-analysis revealed a significant association between hyperhomocysteinemia and PAD (OR 6.8, CI 2.9-15.8) (50).

The Framingham cohort revealed that abdominal aortic calcification had a moderate positive linear relationship with hereditary factors ($R=0.49$, $p<0.001$) (51). Another study looked at the intimal-medial thickness of the common carotid artery and internal carotid artery and its heritability and found that the coefficient of correlation was high in both cases ($R= 0.92$ and 0.86 respectively) (52). A study done among Latin American families found that genetic factors were responsible for 50% of the variability of intima-media thickness of arteries (53).

Age: Increasing age has been found as an unequivocal risk factor for PAD. The NHANES study (41) has shown the following prevalence of PAD in each age group,

-above 80 years of age: 23.2%

-above 70 years of age: 14.5%

-from 60 to 69 years of age: 4.7%

-from 50 to 59 years of age: 2.5%

-from 40 to 49 years of age: 0.9%

Sex: Though literature is ambiguous about predominance in either sex, most of the available studies show a predilection in men. The comparison of global estimates of prevalence of peripheral artery disease shows no significant difference in prevalence between men and women (32).

The German Epidemiological Trial on Ankle Brachial Index (getABI) was done among 6880 consecutive primary care patients above the age of 65 years. It showed a prevalence of PAD as 19.8% among men as opposed to 16.8% among women (54).

Cigarette smoking: Cigarette smoking has also been shown as a significant risk factor for PAD. It is a predisposing factor of atherosclerosis by causing vascular endothelial damage, releasing free radicals and thrombosis (55). Nicotine and cotinine were found to cause smooth muscle cell proliferation resulting in intimal hyperplasia(56). It causes endothelial dysfunction, increases platelet adhesion and aggregation and also influences the formation of the fibrin framework thereby activating the coagulation cascade and promoting thrombus formation (57). This

process was found to be augmented in younger women who were on oral contraceptive pills. Cigarette smoking has also been found to increase total cholesterol, triglycerides and low-density lipoproteins and also decrease high-density lipoproteins which by themselves can increase the risk of atherosclerosis (58). Cigarette smoking was also found to influence the sympathetic outflow thereby causing increased blood pressure (59).

Diabetes Mellitus: Diabetes Mellitus is an established risk factor for atherosclerosis. A retrospective study of arteriograms revealed that diabetic patients had the more severe arterial disease in the lower limbs and also more likely to end up with an amputation (OR 5.4, $p<0.0001$) (60). A 10-year follow-up study showed that patients with type 2 diabetes who had an ABI < 0.90 were found to be at a higher risk of all-cause mortality ($p<0.05$) and also of cardiovascular disease (HR 2.32, 95% CI: 1.27-4.22) (61). A longitudinal cohort study done amongst residents in Minnesota aged 50-70 showed a higher risk of mortality (HR 2.9, 95% CI 1.3-4.0) among patients with both PAD and Diabetes (62).

A meta-analysis of 13 observational studies was done to find an association between HbA1C and cardiovascular disease. It revealed a 10% to 26% increased risk of cardiovascular disease for every 1% increase in glycosylated haemoglobin among Type 2 diabetics (63).

A retrospective study done amongst patients with atherosclerosis in the aorta and other peripheral arteries showed that diabetics had a 5 times higher risk of having an amputation and 10 times the risk of mortality in comparison to non-diabetics (64).

Chronic alcohol consumption (>20 years), though protective of atherosclerosis, was found to be a risk factor for PAD among patients with diabetes (OR 3.48, 95% CI 1.09-11.15) (65).

Hypertension: Hypertension is a very strong risk factor for PAD. Prevalence of hypertension in India was found to be 29.8% in a meta-analysis (66). This is in contrast to a prevalence of hypertension of 62.9% among patients with PAD in a study done in Kerala, India (67). The risk of developing intermittent claudication was found to be 2.5-4 times among hypertensives than non-hypertensive patients in the Framingham cohort (68). The NHANES study showed a higher prevalence of PAD among hypertensive patients (OR 1.75, 95% CI 0.97-3.13) (41). Prevalence of treatment for hypertension was also found to be lower among patients with PAD than in patients with Coronary Artery Disease (CAD) (69% vs 84%, $p<0.001$) (69).

In the United States of America, among people older than 60 years of age, PAD was found to be significantly associated with untreated hypertension (OR 1.68, 95%CI 1.13-2.50) as well as uncontrolled hypertension (OR 1.95, 95% CI 1.40-2.72) (70).

Health records of 1.25 million people above the age of 30 years were procured from the CALIBER (Cardiovascular research using Linked Bespoke studies and Electronic health Records) programme to analyse the effect of hypertension on 12 diverse presentations of cardiovascular disease including PAD.

This study found that PAD was associated more with raised systolic blood pressures than diastolic blood pressure readings. It also revealed an inverse relation with Mean

Arterial Pressure (MAP) (HR 0.90, 95% CI 0.86-0.94) and a strong association with pulse pressure (HR 1.23, 95% CI 1.20-1.27) (71).

A non-concurrent cohort study which reviewed a database of over 4.2 million people between 30 and 90 years of age from 1990-2013 in the United Kingdom revealed a 63% increase in the risk of PAD for a 20mmHg increase in systolic blood pressure (HR 1.63, 95% CI 1.59-1.66) (72).

Dyslipidaemia: Lipids and lipoprotein abnormalities are an established cause of cardiovascular disease and are known to be associated with long-term adverse events. A case-control study showed that the prevalence of hyper-triglyceridaemia among men with PAD was higher by 42% compared to age and sex-matched controls (p-value <0.05). In the same study, it was found that prevalence of hypercholesterolemia and hyper-triglyceridaemia was higher among women with PAD as opposed to age and sex-matched controls (19% more, p value<0.01 and 82% more, p value<0.05 respectively) (73). On the other hand, High-Density Lipoproteins (HDL) and apolipoproteins A-I and A-II were found to be lower in patients with PAD (74).

A cohort of men aged between 35 and 64 years was followed up from 1974 to 1990 and the study revealed that lipoprotein-a levels were higher in men who developed intermittent claudication than others (46+/- 45 vs 33+/-35 mg/dL, p<0.05) (75).

A study done on 55 Caucasian men with premature PAD (onset of disease before 45 years of age) showed that increased lipoprotein a levels (>30 mg/dL) was a significant risk factor (OR 3.9, 95% CI 1.1-13.7). Raised apolipoprotein-B levels (>95 mg/dL)

was also found to be an independent risk factor for premature PAD among Caucasian men (OR 3.2, 95% CI 1.0-10.0) (76).

In the Framingham study, it was found that the odds of developing symptomatic PAD went up by 1.2 for every 40 mg/dL increase in total cholesterol (46). As discussed earlier total cholesterol by HDL ratio was found to be a strong predictor of risk of PAD (48).

Groups at risk for disease:

The ACC/AHA (American College of Cardiology/American Heart Association) guidelines have listed out specific population groups at risk for Peripheral Arterial Disease in the lower extremities (77). These groups are:

*People <50 years of age with diabetes and one other risk factor for atherosclerosis (hypertension, dyslipidaemia, current smoking etc.).

*People aged 50-69 years with a history of smoking OR diabetes.

*Any person who is 70 years old or above.

*Anyone with a history of symptoms suggestive of intermittent claudication or ischaemic rest pain.

*People with abnormal lower limb pulse examination.

*Patients with coronary artery disease or known atherosclerosis in any other vascular site (carotid artery, renal artery).

Clinical Presentation of PAD

The distribution of symptomatology among patients with PAD above 50 years of age is as follows (78),

- Threatened limb/Critical Limb Ischaemia (1%-2%)
- Classic Claudication (10%-35%)
- Atypical leg pain (40%-50%)
- Asymptomatic (20%-50%)

Fontaine classified PAD based on the clinical presentation of the patients. The following table is the Fontaine's classification of peripheral arterial disease (79).

Table 3.1 Fontaine's Classification of PAD

Stage	Symptoms
I	Asymptomatic
II	Intermittent Claudication
II a	Classic claudication on walking>200 m
II b	Classic claudication on walking<200 m
III	Ischaemic Rest pain
IV	Necrosis or Gangrene

Asymptomatic PAD: A vast majority of patients with PAD are asymptomatic. They may be picked up while screening, by ABI or Toe Pressure Index. Identifying asymptomatic PAD patients is essential as it is a vital indicator of systemic vascular atherosclerosis. Therefore, these people are at an increased risk of cardiovascular or cerebrovascular events. Asymptomatic patients can be started on conservative and

even medical management to prevent and control risk factors. Diet, exercise, smoking cessation, drugs like aspirin may all be started to reduce the risk of a major vascular event (78).

Atypical leg pain and Intermittent Claudication: As previously defined, claudication is a reproducible discomfort or pain in a particular group of muscle which is induced by exercise and relieved on resting. This is because of the insufficiency of blood supply to the concerned muscle during contraction. The blood supply may be adequate while the muscle group is at rest. Claudication and atypical lower limb pain are the most common symptoms associated with peripheral arterial diseases.

Patients with PAD who had intermittent claudication were found to have a higher prevalence of neuropathy, diabetes and spinal stenosis than controls. Similarly, people with atypical leg pain had fewer symptoms and their activities of daily living were lesser affected than patients with intermittent claudication (80).

In the PARTNERS program, 6417 people who were 'at risk' of PAD were studied. It was found that among people who already knew that they had PAD, 25% had no history of leg symptoms, 61% had atypical leg pain and 14% had intermittent claudication. Among those who were newly diagnosed to have PAD, 47% were asymptomatic, 47% had atypical leg symptoms and 6% had claudication (81).

Critical Limb Ischaemia: 1%-2% of patients with PAD above the age of 50 years present with threatened limb (82). Decreased perfusion, severe or extensive ulcers, presence and seriousness of infection can all be reasons for the threat to limb. Patients who present within 2 weeks of decreased limb perfusion are said to suffer from acute

limb ischaemia. If they present more than 2 weeks later then it becomes chronic ischaemia (33).

Acute limb ischaemia is most commonly due to thromboembolism secondary to atrial fibrillation or similar illnesses. It can also be due to a sudden occlusion of a chronically narrowed arterial lumen or due to dissection of the artery. By-pass or stent thrombosis may also be a common cause of acute limb ischaemia in people who have previously undergone intervention for PAD (78).

Chronic limb ischaemia is usually due to multiple occlusions in various segments of the arterial tree. However, isolated tibial artery disease has been known to cause chronic ischaemia in patients with diabetes mellitus especially among the elderly. Aortoiliac, femoropopliteal, and tibial segments are most frequently affected by atherosclerosis (83). Atherosclerotic plaques at various levels affect collateral circulation as well as decreasing the distal systolic blood pressure thereby affecting distal tissue perfusion. Chronic ischaemia may present with rest pain, gangrene or ulceration.

Symptomatology

Lower Limb Pain – This is the most common presentation of PAD. Patients may have different types and severity of pain depending on the extent of ischaemia. Most commonly, patients present with complaints of pain during activity which is relieved on rest especially over the buttocks, thigh and calf. This is repeatable and is called intermittent claudication. Patients may also present with rest pain, wherein they have a constant foot pain which increases on elevating the foot and is relieved by

dependency. Atypical lower limb pain is also a common but non-specific symptom of PAD (78).

Claudication - Claudication is a term derived from the Latin word for limp. Classically Claudication presents as pain in the lower limbs after walking for a certain period of time and is relieved in less than 10 minutes of rest (31).

Isolated claudication of the foot is an uncommon presentation in PAD. It occurs in tibial or peroneal vessel occlusive disease. Calf pain, on the other hand, is the most common presenting complaint in PAD. It is usually due to femoropopliteal occlusive disease. Aortoiliac disease and common femoral artery atherosclerosis may cause buttock/hip or thigh claudication and also impotence in men (84).

Atypical limb discomfort - Atypical leg symptoms may be more common than claudication among patients with PAD as the perception of pain may vary due to co-morbid illnesses and physical inactivity. Atypical limb complaints may be due to various other causes like neuralgia, myalgia, arthritis etc. All other causes must be considered before attributing the cause of this symptom to PAD (80).

Rest pain- According to John Cranley ischaemic rest pain is the pain that occurs over the toes and metatarsal heads at rest. Occasionally, the pain occurs proximally. The pain is usually aggravated on elevation or at horizontal position and is relieved in a dependent position(85). As opposed to claudication, pain may be relieved on walking as it increases local perfusion due to gravity. Chronic ischaemia can lead to ischaemic neuropathic pain which may present as burning, throbbing or shooting pain of the lower limbs.

Ischaemic Ulcers - Minor trauma can lead to small ulcers which worsen due to poor blood supply that does not meet the requisite demands of the healing tissue. These ulcers may also start out as pressure sores. The ulcers may themselves get infected and may also end up causing osteomyelitis in the underlying bone. Prompt recognition and treatment of an ischaemic ulcer are essential in saving the tissue. 84% of limb amputations were as a result of ulceration (86).

Gangrene - Ischaemia tends to alter skin colour. Pallor or blackening of the skin can both occur. This will lead to necrosis and may spread to the deeper tissues also. 55% of all limb amputations in diabetics could be attributed to gangrene (86).

Diagnosis of PAD

In 1962, the WHO/Rose questionnaire was developed as a screening tool for PAD. It was noticed to have a high specificity (90%-100%) but low sensitivity (60%-68%) (87).

The Edinburgh Claudication questionnaire was found to be more sensitive (91.3% [95% CI 88.1-94.5%]) and equally, if not more, specific (99.3% [95% CI 98.9-100%]). It also had good repeatability ($\kappa = 0.76$, $p<0.001$) after 6 months (87). However, the sensitivity and specificity are based on the physician's diagnosis and not necessarily using a gold standard method such as an angiogram. The Edinburgh Claudication questionnaire has been used in this study to diagnose symptomatic PAD.

Physical examination

*Appearance of the peripheries- Prolonged inadequate blood flow to the extremities may cause thinning of the skin which becomes dry, shiny and devoid of hair (79). The nails may be brittle and disfigured.

*Skin Temperature is a good indicator of decreased perfusion. The affected limb will be cool and demarcation of the warmth can help in assessing the extent and location of the occlusion. However, it may be confounded if both limbs are affected

*Skin Colour- Buerger's test is a serviceable adjunct to routine assessment of PAD (88). In this test, the lower limb is elevated above the level of the central venous pressure usually around 25 cm. This drains the deoxygenated blood from the peripheries and provides a valid assessment of the arterial blood flow. A normal limb will remain pink. However, an affected limb may become pale or dusky and a return to normal colour may take more than 20 s.

*Ulcers- Ischaemic ulcers are most frequently seen on the tips of the toes and the intertriginous areas between the toes. It may also be seen in focussed areas where there is increased pressure like the head of the metatarsals and the lateral malleoli.

*Gangrene- Both dry and wet gangrene may be seen in PAD. Dry gangrene is more common in PAD and there is a clear demarcation between the necrotic tissue and the viable tissue. Wet gangrene is a surgical emergency and should be dealt with appropriately at the earliest.

*Pulse- Palpation of the peripheral pulses is absolutely essential in any patient suspected to have PAD. At the very least the brachial pulse, radial pulse, posterior tibial artery pulse and dorsalis pedis pulse should be assessed (78).

Non-invasive diagnostic tests for PAD

History and examination of suspected PAD patients have to be corroborated with further investigations as independently clinical examination may not be sufficient proof to rule in, or rule out PAD (89).

Ankle-Brachial Index (ABI) is a simple, relatively inexpensive and accurate method of diagnosing PAD by assessing the ratio of systolic blood pressures in the upper and lower limbs using a Doppler ultrasonography apparatus (90). ABI predicts sites of occlusion found in angiography more accurately than just history and examination (83).

Using an ABI evaluation was found to be justified (ROC area 0.95+/-0.02) for detecting significant PAD (>50% occlusion)(91). This translated to a sensitivity of 79% and a specificity of 96% with an ABI cut off of 0.90.

The ACC/AHA guideline for the management of peripheral arterial disease patients (2005) prescribes computing ABI by dividing the higher of the two ankle systolic pressures to the higher of the two brachial systolic pressures (83).

$$\text{Ankle Brachial Index (ABI)} = \frac{\text{Higher Ankle Systolic Pressure}}{\text{Higher Brachial Systolic Pressure}}$$

The interpretation of ABI according to the ACC/AHA guidelines are as follows (83),

Table 3.2 ACC/AHA (2011) interpretation of ABI

ABI	Interpretation
>1.30	Non-compressible
1.00-1.29	Normal
0.91-0.99	Borderline
0.41-0.90	Mild to Moderate PAD
0.00-0.40	Severe PAD

An ABI cut-off of <0.90 has been found to be 95% sensitive and 99% specific in identifying angiogram positive cases of PAD (92).

An ABI measurement of more than 1.30 is also strongly indicative of PAD. It has to be corroborated with a Toe-Brachial index. A higher ABI (>1.30) is considered predictive of systemic atherosclerosis and may indicate a higher risk of a cardiovascular event (35).

Higher ABI was found to increase risk of foot ulcers and neuropathy as well has having a poorer Quality of Life as against people with normal ABI (93).

Advantages of ABI:

- High Specificity
- Easy to perform
- Relatively inexpensive
- Can be done in a community set-up without many hassles
- Not time consuming

Disadvantages of ABI:

- Accurate values may not be arrived at in patients with non-compressible arteries
- A few studies have shown low sensitivity resulting in higher false negative rates (94).

Toe-Brachial Indices: Toe pressure index is arrived at by measuring the systolic pressure at the toes. It is an extremely useful method as it can be used in patients with non-compressive arteries. Non-compressive arteries are very common among diabetics and the elderly who also form the majority of the population at risk for PAD. A toe brachial index of <0.7 is diagnostic of lower limb PAD (83).

Digital perfusion can be measured and hence even small artery disease maybe picked up by TBI. The equipment may be difficult to handle and the personnel should be appropriately trained. It may not be feasible to carry out a community based screening using TBI as the reading requires expert technique and careful handling to preserve accuracy.

Angiography: Contrast angiography (Digital Subtraction Arteriography) is the definitive method for evaluation of peripheral vessels. CT angiogram and MR angiogram are also useful tools in diagnosis of PAD (95).

Other Methods of Diagnosis (96)

- Segmental pressure examination
- Pulse Volume recording
- Doppler Ultrasound

Natural history of the disease

Peripheral Arterial Disease presents with a wide array of symptoms which depends on the location and extent of atherosclerosis in the peripheral arteries and can range from mild calf pain on walking, to limb-threatening ischaemia.

A longitudinal study done on 403 patients to identify risk factors for progression of the disease, showed current smoking was a major risk factor. Elevated CRP, lipoprotein (a) and total cholesterol by HDL levels were also found to be associated with progression of disease in large vessels. In small vessel PAD, diabetes was found to be the prime risk factor(97). In a multi-ethnic study on atherosclerosis, ABI was measured 3 years apart on subjects from a varied ethnicity. In the study men and people with higher BMI were found to have a higher risk of having a high ABI (>=1.4) which is suggestive of intravascular calcification and atherosclerosis. African-Americans were found to be at a higher risk of having low ABI(<0.9) which indicates limb ischaemia (98). Thus, ethnicity, gender and BMI were found to be factors in the progression of the disease.

A systematic review of 35 studies with follow up periods ranging from 1 to 13 years was done and it found similar predictors of disease progression as mentioned above. In the follow-up period, it was found that 7% of asymptomatic patients developed Intermittent Claudication. Also, 21% of patients who had previously had intermittent claudication had developed critical limb ischaemia with 4%-27% of the patients ending up with an amputation (99). A population-based cohort study on 6915 PAD patients found that there was no significant difference between the two sexes as far as

the progression of peripheral arterial disease was concerned. However, men with PAD were found to be at a higher risk of having a myocardial infarction (adjusted HR=1.15) (100). In a study done on 59 ex-servicemen who were diagnosed to have PAD before the age of 45, it was found that 71% of them had significant (more than 50%) coronary artery disease. During the time of the study, five of the participants died. Four of them died due to acute coronary syndrome and one of them had a stroke (101).

A cross-sectional study was done among 416 patients with PAD. They were screened for internal Carotid artery disease. Major Internal Carotid Artery Disease (MICAD) (>75% obstruction) was seen in 14.9% of patients with PAD (102). This proportion of carotid artery disease was significantly higher than the proportion of patients with an aneurysm who have carotid artery disease ($p<0.05$) (102).

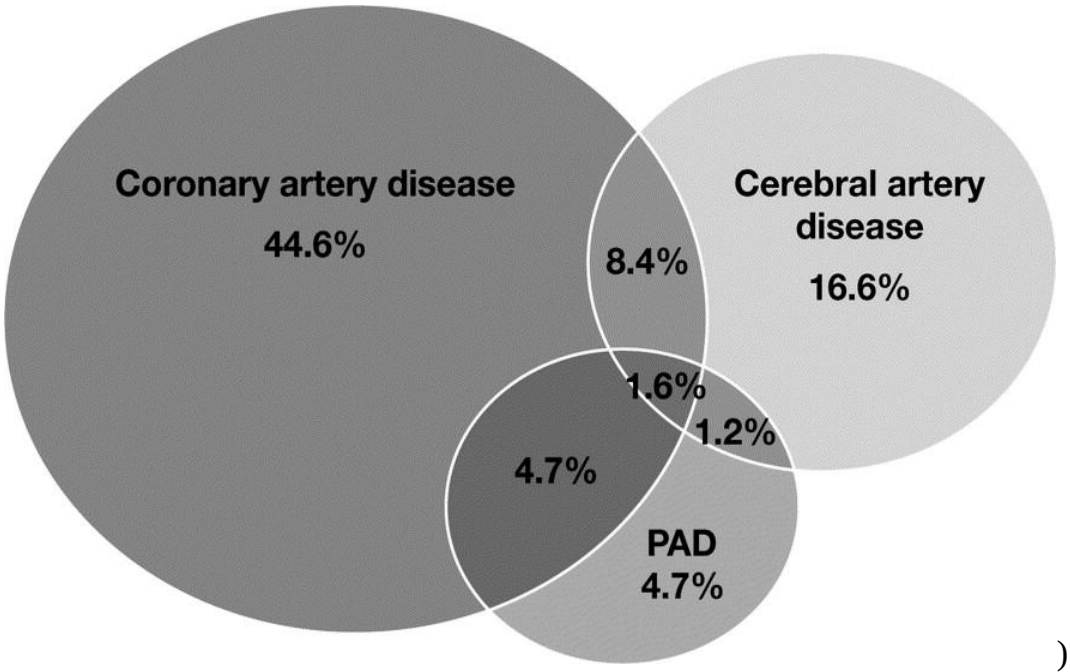
A majority of patients with PAD are unaware of their disease. More than half the patients with the condition are aware that they have the disease. Physicians pick up only 30% of the patients with PAD that they see (103).

In a prospective cohort study done among 6880 people above the age of 65 12.1% were found to have asymptomatic PAD. A further 8.6% had symptomatic PAD. PAD was found to be a strong predictor of all-cause mortality as well as severe vascular events (104). The PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study was a multi-centre cross-sectional study done among 6979 patients who were either over 70 years of age or high-risk population (diabetics, smokers) between the ages of 50 and 69. 29% of these people had PAD. 13% had

PAD only while 16% had PAD and coronary artery disease. 47% had neither PAD nor CAD. Among patients with PAD, classic claudication was rare and seen only in 11% of the subjects. Interestingly 83% of patients with PAD at the time of recruitment knew that they had the disease but less than half (49%) their physicians knew about the diagnosis (81).

The Reduction of Athero-thrombosis for Continued Health (REACH) registry is an international, prospective, cohort study. Its database includes 68,000 patients who have been confirmed to have vascular disease(105). The following figure is based on the REACH data.

Fig 3.2 Overlap of atherosclerostic vascular diseases (106)

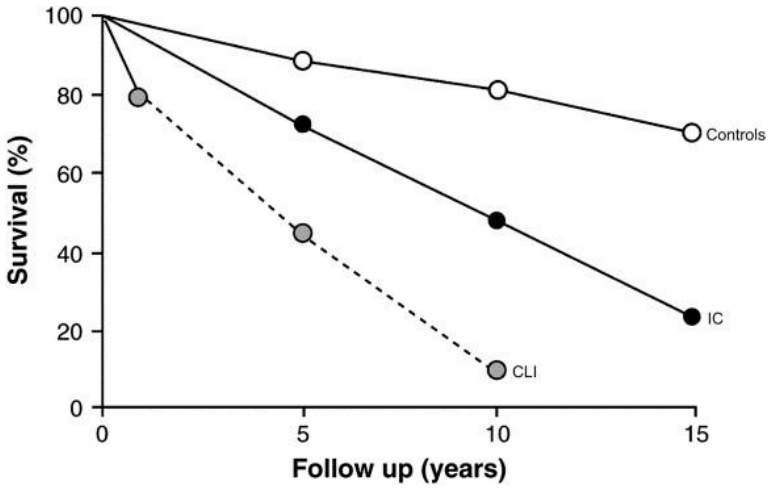


)

Source: Journal of Vascular Surgery Volume 45, Issue 1, Supplement, January 2007, Pages S5-S67 (106).

A longitudinal cohort study done in Minnesota among 50-70-year-old people with PAD, Diabetes or both showed that a decrease of 0.1 ABI had a 13% increase in the risk of death(62). A systemic review showed that PAD is an indicator of extensive atherosclerotic disease. It showed a 150% increase in the risk of mortality among patients with claudication (33). A graph showing the survival rate is shown below.

Fig 3.3 Survival rate in patients with Claudication (107)



Source: Journal of Vascular Surgery Volume 45, Issue 1, Supplement, January 2007, Pages S5-S67 (107)

In the above graph, IC stands for Intermittent Claudication, CLI stands for Critical Limb Ischaemia.

The Minnesota study also showed that the relative hazard of mortality in patients with Diabetes and progressive PAD was 2.29 times as that of diabetics without PAD (62). The original cohort of the Framingham Heart Study was followed up for 38 years and 381 people who previously had asymptomatic PAD developed intermittent claudication. Cigarette smoking, diabetes, hypertension, age and dyslipidaemia were found to be associated with the progression of the disease (46).

In a concurrent cohort study done among 1244 men with claudication, over a period of 15 years with a mean follow-up of 45 months, the cumulative risk of a person with claudication developing rest pain and ulceration over a 10 year period was 30% and 23% respectively. The study also inferred that diabetes mellitus and ABI were the only significant predictors for both ischaemic rest pain and ulcers (108).

A study done in Australia among 456 patients with intermittent claudication estimated a 5-year risk of amputation as 6.2% among patients who underwent early revascularization and 0.7% among patients who were managed conservatively initially (p=0.003) (109). A critical review of PAD among people over 50 years of age showed that 70%-80% of patients with intermittent claudication developed stable claudication within 5 years. A further 20% had a non-fatal cardiovascular event, including acute coronary syndrome and cerebrovascular accidents. The claudication worsened in 10%-20% of the patients and 1%-2% even developed critical limb ischaemia. 15%-30% of the people died within 5 years and three-fourth of the mortality was because of cardiovascular events (77,110). Another study showed that patients who had severe impairment due to pain while climbing stairs had a higher risk of all-cause mortality(Hazard ratio: 1.70; CI: 1.08-2.66) and cardiovascular system related deaths(Hazard ratio: 3.11; CI:1.30-7.47) than those with lesser impairment (111).

A study done among 109 symptomatic patients in Germany followed them for an average period of 104 months. 28 (25.7%) of the participants passed away and 10 (9.2%) of them died due to cancer. This amounts to 36% of the total all-cause mortality among symptomatic PAD patients. This can be explained by the high

prevalence of smokers among patients with PAD which may be the actual cause of the malignancy (112).

A cross-sectional study done among 423 people with PAD in Chicago estimated a prevalence of depression among PAD patients as 21.7% and was associated with increased impairment(113). Symptoms and subsequent impairment were also associated with poorer quality of life among older individuals in a cross-sectional study done among eighty symptomatic patients (114).

Critical limb ischaemia is manifested as ulcers or resting pain in the peripheries. Of all patients with symptomatic PAD 1%-2% patients have critical limb ischaemia. According to a systematic review, 21% of patients with intermittent claudication progressed to critical limb ischaemia(99). Smoking, dyslipidaemia and diabetes were found to be the major risk factors associated with critical limb ischaemia. Diabetes and ABI were found to be good predictors of the disease (97,108). In a review of 20 publications of 6118 patients with critical limb ischaemia, the cumulative mortality rate was 26%, 44% and 56% at 1 year, 3 years and 5 years respectively. Patients were classified as critical and sub-critical based on symptoms and ankle pressure in this study. 27% of patients in the low-risk group (only rest pain and ankle pressure > 40 mmHg) did not have an amputation after being managed conservatively. However, in the high-risk group (peripheral ulcers or ankle pressure < 40 mmHg) 95% of patients managed conservatively ended up with an amputation as opposed to only 25% who underwent arterial reconstruction (115). According to a non-concurrent cohort study, the amputation rates were higher (17% v 3.9%, p value= 0.02) among people who had

early onset of atherosclerosis in their peripheral arteries than the cohort with older people. The overall outcome was also found to be poorer (116).

Insulin resistance was also found to be associated with PAD and the progression of disease in older adults (117). The POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial was a multi-centre randomised control trial and it showed that 16% of 1276 asymptomatic patients with either Type 1 or Type 2 diabetes developed intermittent claudication at six years. Critical limb ischaemia was seen in 3% of the patients and 1.6% ended up with a major limb amputation. The study primarily found that aspirin and anti-oxidants have no role in influencing the progression of the disease (118).

2. Chronic Venous Disease (CVD)

Chronic Venous Disease/Disorders refer to the entire spectrum of functional or morphological abnormalities of the venous system (119). These disorders have been associated with significant morbidity and mortality.

Varicose veins are the most common and recognisable form of venous disease. Varicose veins are subcutaneous veins that are dilated ≥3 mm in diameter while the person is in an upright position (17). The Great Saphenous Vein (GSV) and the Small Saphenous Vein (SSV) are the most frequently affected veins. Lesser recognized forms of venous disease are telangiectasia, ankle oedema secondary to poor venous drainage, eczema, lipodermatosclerosis and healing or non-healing ulcers.

Chronic Venous Insufficiency is a term used to describe the severe forms of venous disease. Ankle oedema, skin changes and ulcers due to venous disease are all classified as chronic venous insufficiency (119).

Pathophysiology of the disease

Retrograde venous blood flow for an abnormal period of time is called Venous Reflux. It can be due to idiopathic or congenital dysfunction/absence of valves. Trauma and thrombosis are two other major factors resulting in venous reflux. Pregnancy is another reason for venous reflux which may ultimately lead to varicosities.

Labropoulos et al. have concluded that the development of venous reflux is mostly due to a local process. This is most likely due to a weakness in the vessel wall. This issue can be multifocal, thereby resulting in venous disease in more than one place (120).

Bicuspid venous valves are present throughout the peripheral venous system directing the blood flow from distal to proximal and superficial to deep, except in the foot (121). Any pathology in these valves, either congenitally or due to trauma, thrombosis et cetera will cause backflow resulting in either venous congestion or deep venous thrombosis.

Lower muscle strength is also very important for the normal functioning of the venous system. People with chronic venous disease were found to have impaired lower limb muscle strength (122). The muscles, mainly the calf and the thigh muscles play an

important role in the circulation of venous blood as they serve as a pump that pushes the blood against gravity.

Various studies have shown that varicose veins are not because of thin walls but because of wall thickening in response to venous hypertension. This causes an increased production of collagen, proliferation of smooth muscle cells and elastin. It was also found that there is an abnormal accumulation of extracellular matrix in venous disease (123–125). The breakdown of the vascular extracellular matrix leads to increased vascular permeability leading to oedema.

The RBCs migrate from the vascular space into the tissues and subsequently degrades in the tissue leading to extravasation of iron and ferritin. This results in the characteristic discolouration of the skin specifically in the gaiter area of the leg (126).

Studies have shown that there is an increased accumulation of mast cells around the vessels in chronic venous disease leading to increased collagen accumulation and fibrosis (127). There is also increased permeability of the vessels leading to surrounding oedema (128). Together they cause severe fibrosing inflammation of the subcutaneous fat (Panniculitis) which binds the skin to the subcutaneous tissue. This condition is called Lipodermatosclerosis.

The accumulation of matrix metalloproteinases (MMP) leads to ulcer formation which is non-healing in nature. These end up as chronic ulcers (129).

Epidemiology

A cross-sectional survey done in Edinburgh among 1566 subjects between the ages of 18 and 64 found a prevalence of Chronic Venous Insufficiency of 9% among men and 7% among women (p value<0.05) (130).

A cross-sectional study done in Italy among adult men (mean age 59.1) and women (mean age 50.4) showed a prevalence of telangiectasia among 14.7% asymptomatic women and 8.9% asymptomatic men (131). The same study estimated a prevalence of varicose veins at 15.1% among asymptomatic women and 8.0% among asymptomatic men.

A study done in the USA showed that the prevalence of varicose veins among Asians in the US was 18.4% above the age of 40 (132).

A study done in Perth, Western Australia, showed a prevalence of chronic venous ulcers as 0.62 per 1000 population (133). 90% of people with ulcers were found to be above the age of 60, who comprised 16.7% of the general population.

Risk Factors

Male gender, increasing age, obesity and a history of leg trauma were all found to be significant risk factors for CVD (134).

Obesity: Overweight and obesity has been found to be a major risk factor for venous disease (135–137). The Edinburgh Vein study showed 2.1 times (95% CI 1.0-4.4) higher risk of developing reflux in overweight patients (138). The Mean BMI was found to be higher in the group with superficial reflux (26.2kg/m², 95% CI 25.5-27.0) than in normal subjects (25.2 kg/m², 95% CI 24.8-25.6) (139).

A group of 104 healthy post-menopausal women between the ages 48-64 were chosen from the DIANA (DIet and ANdrogens) project and assessed for venous disease. It was found that a BMI of more than 30 in these women was significantly associated with venous disease (OR 5.8, 95% CI 1.2-28.2) (140).

Trauma: A case-control study done in the USA showed that a previous history of trauma or inflammation of the vessels (phlebitis) was found to be significantly associated with the development of chronic venous disorders (OR 2.4 and 25.7 respectively) (134).

Pregnancy: Previous pregnancy has been an established risk factor for venous reflux (139). Both hormonal and hydrostatic reasons are attributed to this. It is reckoned that new varicose veins develop in 28% of all pregnancies. This increases with each subsequent birth (141). Increased number of childbirths were associated with a higher risk of CVD(136). The San Diego Population study estimated a risk of chronic venous disease at 1.14 (95%CI 1.05-1.23) per birth (142).

Gender: A cross-sectional study done in Serbia showed a higher prevalence of venous disease among women than in men. However, the proportion of more severe form of the disease was significantly higher among the men (136). This was corroborated by the San Diego Population study where venous disease was more prevalent among women though the men had more frequent advanced disease (142). Another study showed that visible venous disease may be seen in 20%-25% of women but only in 10%-15% men (143).

Height: The Edinburgh Vein study revealed that increased height proved a significant risk factor for Venous Disease (OR 1.13, 95% CI 1.02-1.26) (139). A cross-sectional study done in rural Maharashtra showed by linear regression analysis that increased height contributed to a 12.9% increase in the saphenous vein diameter in the supine position. Height was also found to cause an 11.9% increase in diameter during Valsalva manoeuvre in people with chronic venous insufficiency (144).

Genetic predisposition: Hereditary factors have been known to predispose venous disease (135). A study done in France has shown a prevalence of venous disorders in 90% of people for whom both the parents have venous disease. The proportion becomes 25% in men and 62% in women for whom only one parent had venous disease and 20% of people whose parents did not have the disease (145).

A genetic study of chronic venous congestion was conducted in Italy. This study identified a marker on chromosome 16q24 which may be related to the development of varicose veins (146).

Varicose veins have been associated with Klippel-Trenaunay Syndrome (congenital defective/absence of venous valves), Lymphedema-distichiasis syndrome (associated with FOXC2 gene mutation), Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (associated with Notch3 gene mutation), Chuvash Polycythaemia (an autosomal recessive disease caused due to a mutation in the von Hippel-Lindau gene in chromosome 3p25) and various other genetic disorders (147).

Clinical Presentation

History

An entire spectrum of symptoms can be seen in chronic venous disease. The most common ones are:

- Lower limb pain/discomfort
- Muscle cramps
- Pruritus
- Skin changes (hyperpigmentation, dryness)
- A Feeling of heaviness in the lower limbs
- Swelling of the lower limbs
- Non-healing ulcers

Physical Examination:

Telangiectasia/reticular veins- Telangiectasia is a confluence of intradermal venules <1 mm in diameter. They are the most commonly seen manifestation of venous disease. Reticular veins are dilated subdermal veins 1 mm-3 mm in size (131).

Varicose Veins- These are serpentine, dilated subcutaneous veins >3 mm in diameter. They are the most recognisable form of venous disease.

Oedema- Unilateral oedema in association with venous malformations should lead to a high suspicion of venous insufficiency. It is limited to the extremities and decreases on lying down. Diuretics may not be helpful in this setting and may even lead to hypo-perfusion.

Skin changes- As discussed previously, the breakdown of the extravasated RBCs lead to deposition of hemosiderin in the subcutaneous tissue leading to pigmentation. This pigmentation is usually seen around the medial malleolus.

Avascular fibrosis leads to Atrophie Blanche, which are hypo-pigmented spots which are prone for ulceration in the future. Atrophie Blanche is again commonly seen around the medial aspect of the ankle.

Lipodermatosclerosis- As mentioned earlier, chronic venous congestion causes fibrosing panniculitis of the subcutaneous tissue leading to induration causing lipodermatosclerosis. This starts off locally but progresses and involves the entire lower limb circumferentially.

Chronic Venous Ulcers: Venous ulcers are the common ending point of severe chronic venous congestion. A study done in Brazil showed that age above 60 years was found to have 4 times the risk of developing a non-healing venous ulcer. Extensive lipodermatosclerosis was found to have an 8.7 times higher risk while previous ulcers were attributed a whopping 19.9 times risk of developing a recurrence (148).

They are usually seen in the Gaiter area. They can occur elsewhere in the leg if there is preceding trauma. But chances of ulceration above the knee and in the forefoot are extremely rare. There may be more than one ulcer. Venous ulcers exhibit exquisite tenderness, are shallow, have a granulation base and are exudative. The ulcer borders are irregular but well demarcated.

The CEAP classification is used for diagnosing and classifying chronic venous disorders. Physical examination is hence an important part in the diagnosis of the disease.

The revised CEAP (Clinical, Etiologic, Anatomic and Pathophysiologic) classification of venous disease is described below (149).

Clinical Classification

C0- No physical signs of venous disease

C1- Reticular veins or telangiectasia

C2- Varicose veins

C3- Ankle Oedema

C4a- Eczema or hyperpigmentation

C4b- Atrophie Blanche or Lipodermatosclerosis

C5- Healed Ulcer (Venous)

C6- Active Ulcer (Venous)

S- Symptomatic (as listed above)

A- Asymptomatic

Etiologic Classification:

Ec- Congenital

Ep- Primary

Es- Secondary (post trauma/thrombosis)

En- No identifiable venous cause

Anatomic Classification:

As- Superficial veins

Ap- Perforators

Ad- Deep veins

An- No identifiable venous locations

Pathophysiologic Classification:

Pr- Venous Reflux

Po- Venous Obstruction

Pr, o- Venous reflux and obstruction

Pn- No identifiable venous pathophysiology

Diagnosis

The diagnosis of venous disorders is mainly clinical. The CEAP classification is used for diagnosis as well as classification.

Venous reflux is diagnosed by duplex ultrasound by measuring the duration of retrograde flow. Labropoulos et al. defined the cut off for venous reflux as a reversed flow of more than 500 ms in the calf veins (both superficial and deep) and more than 1000 ms in the more proximal femoropopliteal veins(150).

Duplex ultrasound helps in identifying the nature of reflux and also the geography (superficial, perforator or deep vein). This helps in planning management.

Definition of complications:

Complications are classified as major and minor based on the following factors(152).

Minor Complications-

- No treatment, no long-lasting consequences
- Nominal treatment, overnight hospital stay

Major Complications-

- Requires treatment, short-term hospital stay (<48 hours)
- Requires major intervention, long-term hospital stay (>48 hours)
- Adverse sequelae with permanent effect
- Death

Assessment of Severity: The severity of venous disease can be ascertained by the scores described in the following table (151).

Table 3.3 Revised Venous Clinical Severity Score

	None- 0	Mild- 1	Moderate- 2	Severe- 3
Pain/Discomfort		Occasional (not restricting daily activities)	Daily pain (restricting but not preventing daily activities)	Daily pain (limits regular daily activities)
Varicose veins (≥3mm in standing position)		Few, scattered	Affects calf OR thigh	Affects calf AND thigh
Venous Oedema		Restricted below the ankle	Above the ankle but below the knee	Extends above the knee
Skin pigmentation (presuming venous origin)	None or focal	Limited to the peri-malleolar region	Diffuse, but below the lower third of the calf region	Widely distributed, involving the upper third of the calf region
Inflammation		Limited to the peri-malleolar region	Diffuse, but below the lower third of the calf region	Widely distributed, involving the upper third of the calf region
Induration		Limited to the peri-malleolar region	Diffuse, but below the lower third of the calf region	Widely distributed, involving the upper third of the calf region
Active Ulcer number	0	1	2	≥3
Active Ulcer duration		<3 months	3 months-1 year	>1 year
Active Ulcer size		Diameter <2 cm	Diameter 2cm-6 cm	Diameter >6 cm
Compression therapy	Not used	Intermittent use	Used on most days	Full compliance

4. MATERIALS AND METHODS

Study Setting

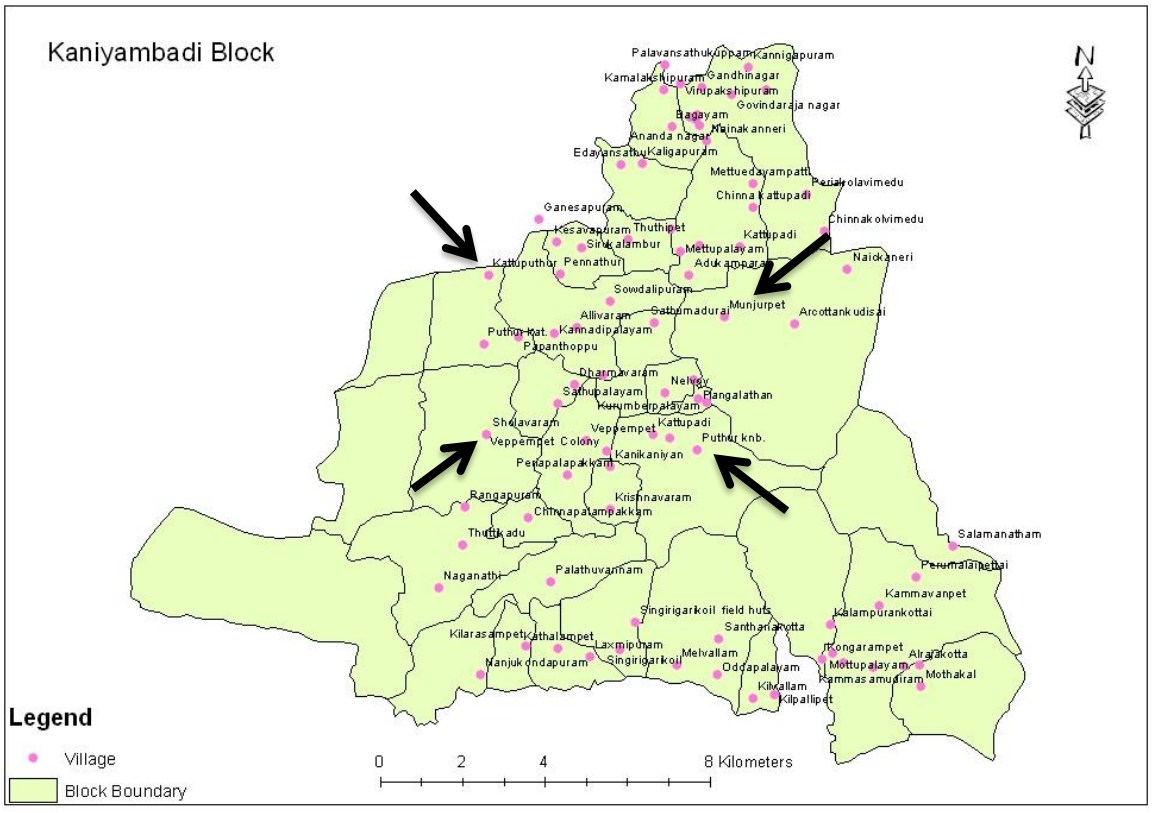
The study was conducted in the **Kaniyambadi block**, Vellore District, Tamil Nadu, India. There are 82 villages in Kaniyambadi block and it and has a population of over one lakh twenty thousand people. The Community Health and Development (CHAD) program run by the department of Community Health, Christian Medical College (CMC),Vellore is located in Bagayam. The Government Vellore Medical College (GVMC) is in the Adukkamparai village of Kaniyambadi. There are also four peripheral health centres (PHCs) located within the block in Kammavanpet, Kathalampet, Kaniyambadi and Sholavaram villages. Apart from these there are many private clinics and hospitals providing health care to the people of Kaniyambadi block.

The study was done in 4 villages, namely Munjurpet, Kattuputhur, Veppempet, and Kaniyambadi Puthur. These villages were chosen as they had the largest population among all the villages in each PHC area.

The CHAD programme has been functioning in Kaniyambadi block for over 40 years. It provides primary and secondary care and is at close proximity to two tertiary/quaternary care centres (CMC and GVMC). CHAD operates based on a pyramid system. At the base of the pyramid are the Part Time Community Health Workers (PTCHWS) who are local villagers who provide a vital liaison between the community and the health system. Each village has a PTCHW and they report to a Health Aide. The Health Aide is a qualified Auxiliary Nurse and Midwife (ANM)

who cover 3-5 villages, which accounts to a population of 5000-7000. All vital events births to deaths, marriages to pregnancies are documented and reported by the Health Aides to the Public Health Nurses (PHNs). The PHNs visit the villages weekly and have a record of all pregnancies and an immunization register. A list of patients with Non-communicable disease is also maintained and updated regularly by the Health Aides in conjunction with the PHNs. Each village is visited once in 4 weeks by the area doctor (usually a PG registrar) and health care is provided in the village. This ensures an efficient system of record maintenance and enables proper follow-up of patients. It is in this resource rich setting that this study was embarked upon as there was a veritable void in knowledge of peripheral arterial disease in the community. The following is a map of Kaniyambadi.

Fig 4.1 Map of Kaniyambadi



Study Design

This study was a community based cross sectional study.

Study Population

Inclusion Criteria: Adults above the age of 18 years who were permanent residents of Kaniyambadi Block, Vellore and were willing to participate in the study.

Exclusion criteria: Bilateral upper/lower limb amputees/absence of limbs

Study Variables

Peripheral arterial disease was diagnosed by measuring the Ankle-Brachial Index (ABI). ABI was measured using a handheld Doppler apparatus and an aneroid sphygmomanometer.

Steps of measuring ABI

- The participant was made to lie supine on a flat surface (floor/cot).
- Systolic BP reading was measured in all 4 limbs using the aneroid sphygmomanometer and a Doppler apparatus.
- The highest recorded reading in the lower limb was divided by the higher reading between the upper limbs to arrive at the ABI.

The diagnostic criteria are as below:

Table 4.1 ACC/AHA ABI Interpretation guidelines

ABI	Interpretation
>1.30	Non-compressible
1.00-1.29	Normal
0.91-0.99	Borderline
0.41-0.90	Mild to Moderate PAD
0.00-0.40	Severe PAD

<0.90 and >1.30 were considered abnormal ABI and probable PAD.

Chronic Venous Disorders were diagnosed and classified based on the CEAP (Clinical, Etiology, Anatomy, and Pathophysiology) classification. The Clinical Classification is as follows (149),

- Class 0 – No visible or palpable signs of venous disease
- Class 1 – Telangiectasia, reticular veins, malleolar flare
- Class 2 – varicose veins
- Class 3 – Oedema without skin changes
- Class 4 – 4a) hyperpigmentation, venous eczema, 4 b) lipodermatosclerosis
- Class 5 – Skin changes with healed ulceration
- Class 6 - Skin changes with active ulceration

Exposure variables

- Smoking
- Alcohol
- Gender
- Diabetes Mellitus
- Systemic Hypertension
- Education
- Occupation
- Socio-economic Status
- Race
- HbA1C, Creatinine, Lipid profile

The data was collected using the following sources.

Table 4.2 Sources of data

Data	**Sources**
Smoking Alcohol Gender Age Diabetes Mellitus Systemic Hypertension Education Socio-economic Status Obesity	Semi-structured, pilot tested questionnaire to collect data on socio demography and risk factors of the disease Chart Review was done to confirm medical history.
Ankle Brachial Index	Handheld Doppler ultrasound probe, Aneroid Sphygmomanometer
Chronic Venous Disorder	Clinical examination
Haemoglobin, serum creatinine, Lipids, HbA1C	Blood investigations

Socio Economic Status was calculated using the BG Prasad scale January 2018. The BG Prasad scale uses per capita family income per month to classify SES as follows:

- Upper class : ≥ ₹ 6528
- Upper Middle class: ₹ 3264 - ₹ 6527
- Middle class: ₹ 1959 - ₹ 3263
- Lower middle class: ₹ 979 - ₹ 1958
- Lower class: ≤₹ 978

The cumulative dose of cigarette smoking was expressed as pack-years. One pack-year was regarded as the equivalent of 20 cigarettes smoked per day for one year (153).

The definition of a standard drink varies from nation to nation. In India, 10 mL of absolute alcohol is considered a standard drink. The classification based on the strength of alcohol is given below (154),

Table 4.3 Standard drink in India

Type	Percentage of Alcohol	Quantity (mL)
Champagne	13	100
Wine	13	100
Fortified Wine	20	60
Light Beer	2.7	425
Regular Beer	4.9	285
Spirit	40	30

Body Mass Index was calculated and classified according to the WHO Asia-Pacific classification,

Table 4.4 WHO Asia/Pacific Classification of BMI

BMI	Classification
<18.5	Underweight
18.5-22.9	Normal
23.0-24.9	Overweight
≥25	Obese

Study Tools

- An Aneroid Sphygmomanometer is a device used to measure blood pressure, composed of an inflatable cuff to collapse and then release the artery under the cuff in a controlled manner and a mechanical manometer to measure the pressure.
- A weighing scale was used for measuring weight that uses gravity as the primary source of resistance and a combination of simple machines to convey that resistance to the person using the machine
- A height rod is a standardized instrument used for measuring the height of subjects
- A Semi-structured, pilot tested questionnaire was used to collect data on socio demography and risk factors of the disease. It has been attached in the Annexure.

Sample Size Calculation

The prevalence of PAD has been estimated to be anywhere between 3% and 7% in the general population (155). The sample size was therefore calculated using prevalence as 3%.

p = 3; q= 97

Absolute precision, d = 1.5

$n=4pq/d^2 =517$

Design effect = 2 x n

Therefore, n= 1034 participants

Sampling Technique

A 2 stage cluster random sampling technique was used.

- Four villages with the largest population in their respective PHC areas were chosen purposively.
- Starting with the centre of the village, consecutive streets were selected.
- All eligible members of the households in each street were taken until a sample of 300 people was attained in each village except one (Munjurpet) where 251 participants were recruited.
- If there was a member temporarily absent in a household the particular household was visited thrice before not including that person in the study.

Training in measurement of ABI

The investigator was trained in the vascular lab of the department of Vascular Surgery for 10 days in the technique of measuring ABI.

Data entry and analysis

Data was entered in Epidata v3.1.

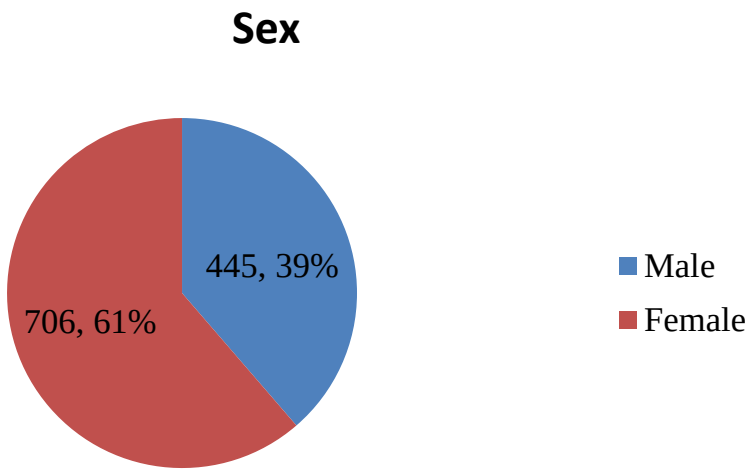
Analysis was carried out in SPSS v23.0.

5. RESULTS

Sociodemographic profile:

A total of 1151 individuals were included in the study. The distribution of the study population by age is described below.

Fig 5.1 Sex distribution in the study population



The majority of the study population (61%) were women.

Table 5.1 Age distribution of the study population

Age Group	Frequency	Percent
<30	218	18.9
30-39	220	19.1
40-49	226	19.6
50-59	207	18
60-69	175	15.2
70-79	80	7
≥80	25	2.2
Total	**1151**	**100**

Most of the study population are between the age group 30-49 (38.7%)

Fig 5.2 Age Distribution of the study population

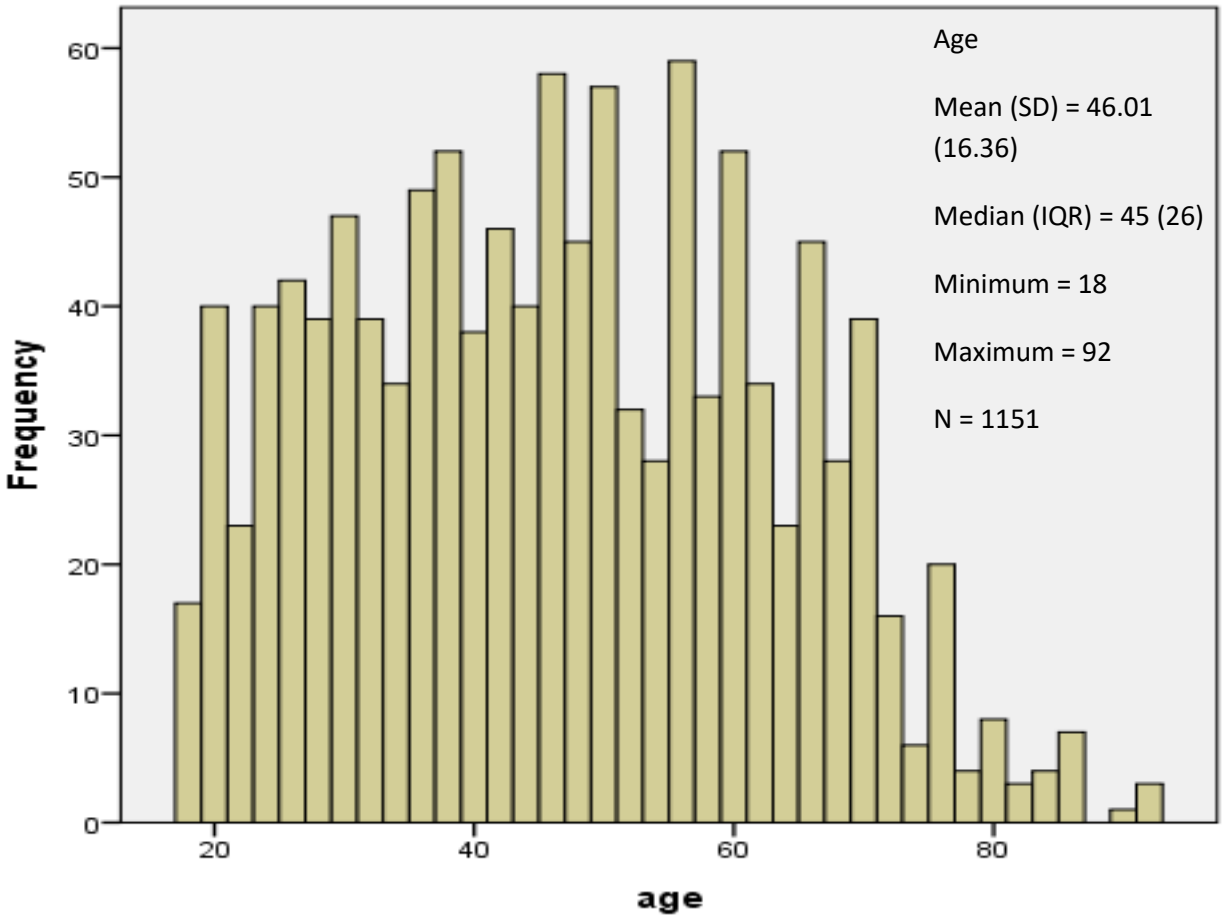


Table 5.2 Description of study population by Religion

Religion	Frequency	Percent
Hindus	1098	95.4
Muslims	33	2.9
Christians	20	1.7
Total	1151	100

The majority of the study population was Hindu. All the 33 Muslims were from one village (Veppempet).

Table 5.3 Description of the study population by Education

Education	Frequency	Percent
Nil	249	21.6
Primary	176	15.3
Middle	240	20.9
High	247	21.5
Higher Secondary	144	12.5
Graduate / Post Graduate	84	7.3
Professional / Honours	11	1.0
Total	1151	100

42.3% of the study population have completed high school education. 21.6% have never had formal education.

Table 5.4 Description of the study population by Literacy

Literacy	Frequency	Percent
Illiterate	313	27.2
Read Only	70	6.1
Read And Write	768	66.7
Total	1151	100

From the above tables, the literacy rate corroborates with the level of education.

27.2% of the study population were illiterate. 66.7% knew how to read and write.

Table 5.5 Description of the study population by Occupation

Occupation	Frequency	Percent
Unemployed	504	43.8
Unskilled	330	28.7
Semi Skilled	144	12.5
Skilled	49	4.3
Clerical/Shop Owner	86	7.5
Semi-Professional	27	2.3
Professional	11	1.0
Total	1151	100

Most of the study population were unemployed, possibly due to the high unemployment rates among women who constituted the majority of the subjects. Occupation was classified based on the Modified Kuppuswamy Scale January 2017(156).

Table 5.6 Description of study population by Family Type

Family	Frequency	Percent
Joint/Extended	463	40.2
Nuclear	688	59.8
Total	1151	100

Almost 60% of the participants were part of a nuclear family.

Table 5.7 Description of Study Population by SES

SES (BG Prasad Jan '18)	Frequency	Percent
Lower	224	19.5
Lower Middle	398	34.6
Middle	295	25.6
Upper Middle	157	13.6
Upper	77	6.7
Total	1151	100

The bulk of the study subjects were from the lower middle class (34.6%). There was a sizeable chunk of participants from the Middle class (25.6%) also.

Table 5.8 Description of Study Population by Smoking Habits

Smoking	Frequency	Percent
Current	94	8.2
Past	56	4.9
Never	1001	87.0
Total	1151	100

All the 150 people with a history of smoking were men (33.7%).

Table 5.9 Description of Study Population by Alcohol Consumption

Alcohol	Frequency	Percent
Current	199	17.3
Past	46	4.0
Never	906	78.7
Total	1150	100

All 245 people who had or have been consuming alcohol were men (55.1%). None of the women smoked tobacco or consumed alcohol in their life.

Table 5.10 Frequency of Oral Contraceptive Pills (OCP) use among women

OCP Use Among Women	Frequency	Percent
Yes	19	2.7
No	687	97.3
Total	706	100

Table 5.11 Description of study population by the frequency of vegetable consumption

Vegetable Consumption	Frequency	Percent
Daily	1085	94.3
Six times a week	0	0
Five times a week	6	0.5
Four times a week	0	0
Thrice a week	3	0.3
Twice a week	9	0.8
Once a week	44	3.8
Thrice a month	0	0
Twice a month	0	0
Once a month	3	0.3
Less than monthly	1	0.1
Total	1151	100

Most of the study subjects consumed vegetables on a daily basis.

Table 5.12 Description of study population by the frequency of fruit consumption

Fruits	Frequency	Percent
Daily	261	22.7
Six times a week	1	0.1
Five times a week	5	0.4
Four times a week	15	1.3
Thrice a week	119	10.3
Twice a week	301	26.2
Once a week	252	21.9
Thrice a month	15	1.3
Twice a month	81	7.0
Once a month	77	6.7
Less than monthly	24	2.1
Total	1151	100

Fewer people consumed fruits daily (22.7%) than vegetables and 2.1% consumed fruits less than once a month

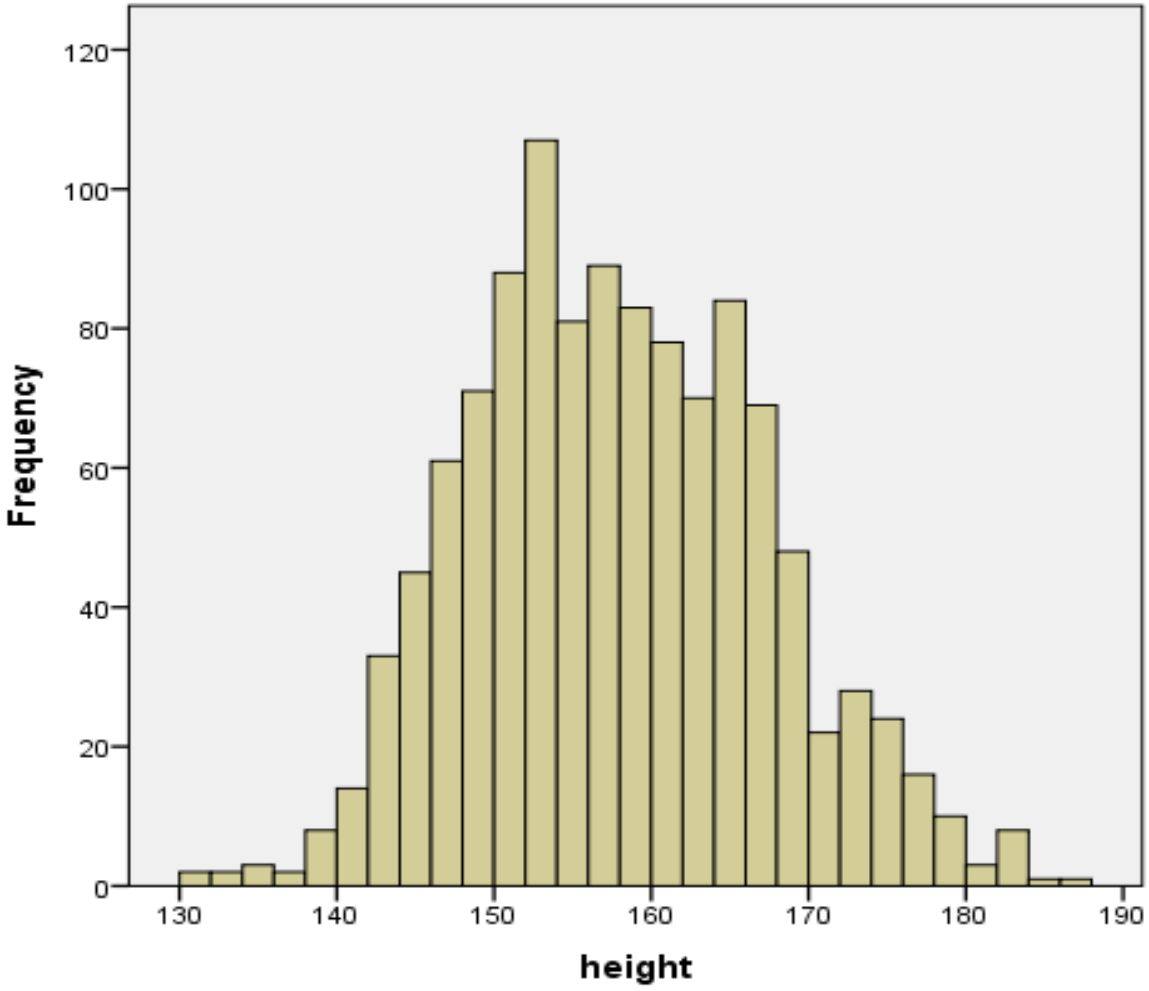
Table 5.13 Median Intake of Fruits and Vegetables.

Intake per Month	Median (IQR) in Days
Vegetable	30 (0)
Fruits	8 (8)

More than 50% of the people consumed fruits at least twice a week.

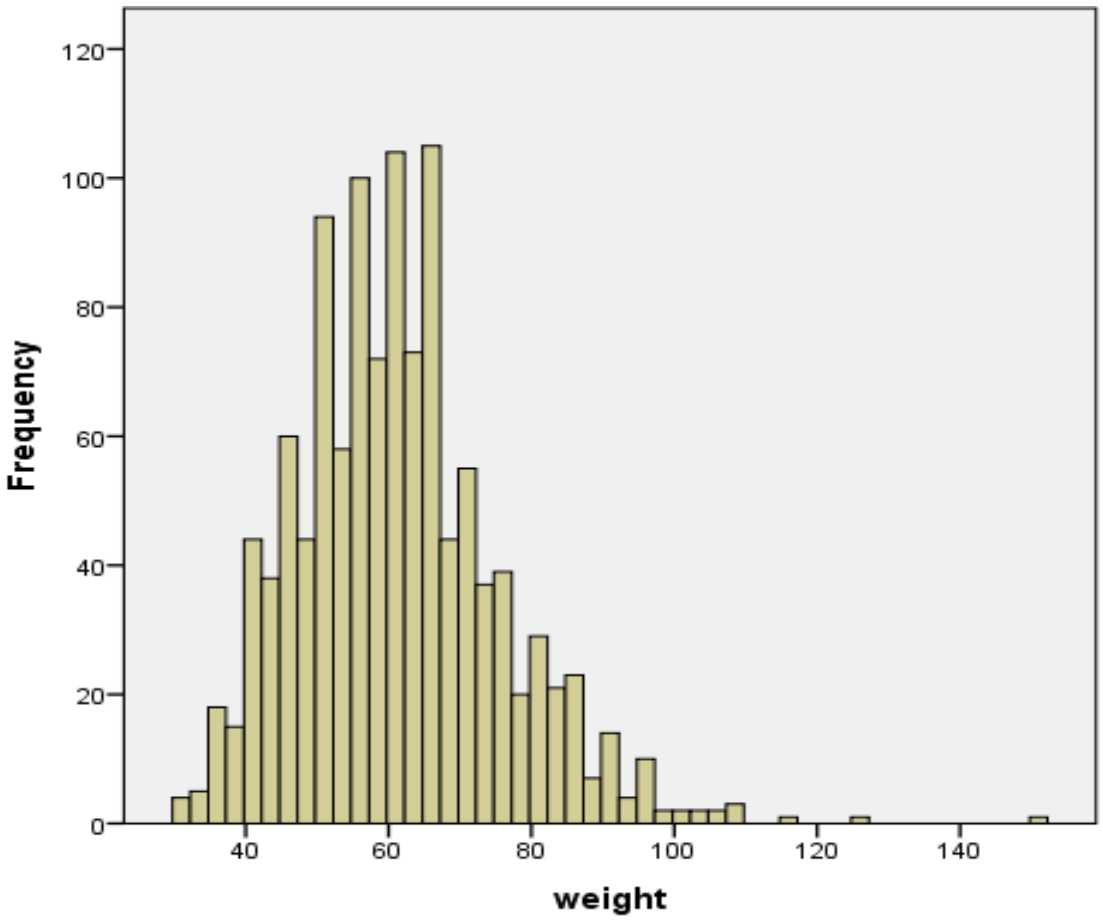
Description of Study Population based on Physical Characteristics such as Height, Weight and BMI

Fig 5.3 Height distribution among the study population



N =1151

Fig 5.4 Weight distribution among the study population



N=1151

Table 5.14 Physical Characteristics of the study population

Characteristics	Height	Weight	BMI
Mean (STD DEV)	157.38 (0.276)	61.18 (14.11)	24.72 (5.20)
Median (IQR)	157 (13)	60 (17)	24.39 (6.79)
Minimum	131	31	12.98
Maximum	186	151	56.14

Table 5.15 Description of the Study Population based on the Body Mass Index

BMI (WHO Asia-Pacific)	Frequency	Percent
Underweight (<18.5)	119	10.3
Normal (18.50-22.99)	328	28.5
Overweight (23.00-24.99)	193	16.8
Obese (>25.00)	511	44.4
Total	**1151**	**100**

A large proportion - 44.4% of the study population fall under the obesity range. A further 16.8% were overweight. 10.3% were underweight leaving behind a measly 28.5% of the population in the normal BMI group.

Description of Study Population based on comorbid illnesses:

Table 5.16 Prevalence of hypertension in the study population

History of Hypertension	Frequency	Percent
Yes	168	14.6
No	983	85.4
Total	1151	100

14.6% of our study population were known cases of hypertension.

Table 5.17 Prevalence of diabetes mellitus in the study population

History of Diabetes Mellitus	Frequency	Percent
Yes	141	12.3
No	1010	87.7
Total	1151	100

The proportion of people with a history of Diabetes in our study population is 12.3%.

Table 5.18 Duration of comorbid illnesses

Duration of illness in months among those previously diagnosed (by history)	Median (IQR)
Hypertension	36 (66)
Diabetes	48 (83)

The median history of the duration of hypertension was 36 months (3 years) and diabetes mellitus was 48 months (4 years).

Table 5.19 History of Ischaemic Heart Disease in the study population

Ischaemic Heart Disease	Frequency	Percent
Yes	15	1.3
No	1136	98.7
Total	**1151**	**100**

1.3% of the population have given a history of Coronary Artery Disease (CAD

Table 5.20 History of Stroke in the Study Population

Cerebrovascular Accident	Frequency	Percent
Yes	11	1
No	1140	99
Total	1151	100

11 people (1%) of the study population have had a documented history of stroke in the past.

Table 5.21 Prevalence of Intermittent Claudication

Claudication Pain	Frequency	Percent
Yes	44	3.8
No	1107	96.2
Total	1151	100

Prevalence of intermittent claudication in the study population was 3.8%.

Table 5.22 Prevalence of Chronic Venous Disorders (CVD)

Venous Disease	Frequency	Percent
Telangiectasia	24	2.1
Varicose veins	52	4.5
Ankle oedema	4	0.3
Lipodermatosclerosis	3	0.3
Healed ulcer	0	0
Active ulcer	0	0
No disease	1068	92.8
Total	**1151**	**100**

Chronic Venous Disease (CVD) was seen in 7.2% (95% CI 5.7%-8.8%) of the study population

Prevalence of Abnormal ABI in the Study Population

Table 5.23 Prevalence of Peripheral Arterial Disease (PAD)

ABI	Frequency	Percent
<0.9	3	0.3
0.9-1.3	1128	98.0
>1.3	20	1.7
Total	1151	100

The Prevalence of Abnormal ABI in the study population has been estimated at 2% (95% CI 1.3%-3%). In a much smaller study done elsewhere, the prevalence of Abnormal ABI in normal individuals was 4%(157).

ABI was also analysed as a continuous variable. It was a skewed distribution.

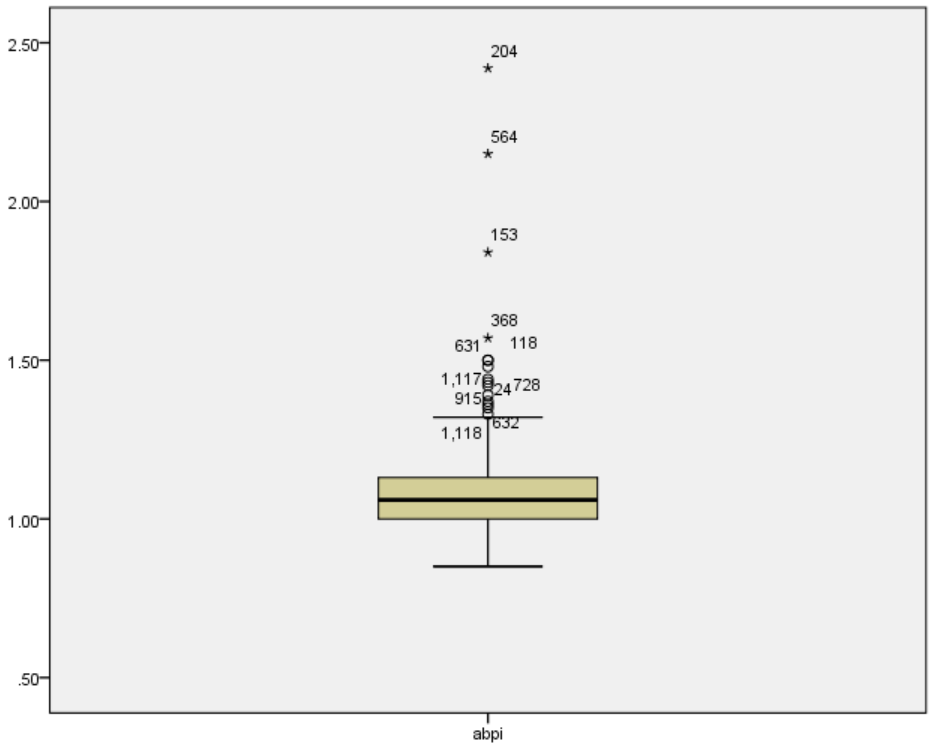
Mean (Std. dev) = 1.07 (0.12)

Median (IQR) = 1.06 (0.13)

Minimum = 0.85

Maximum = 2.42

Fig 5.5 Distribution of ABI among the study population.



Percentiles	5	10	25	50	75	90	95
ABI	0.92	0.95	1.0	1.06	1.13	1.20	1.25

Table 5.24 ABI by Age Groups

Age Distribution (Years)		ABI		Total
		Abnormal	Normal	
<30	Frequency	3	215	218
	%	**1.4 %**	98.6 %	100.0 %
30-39	Frequency	2	218	220
	%	**0.9 %**	99.1 %	100.0 %
40-49	Frequency	1	225	226
	%	**0.4 %**	99.6 %	100.0 %
50-59	Frequency	4	203	207
	%	**1.9 %**	98.1 %	100.0 %
60-69	Frequency	7	168	175
	%	**4.0 %**	96.0 %	100.0 %
70-79	Frequency	5	75	80
	%	**6.3 %**	93.8 %	100.0 %
≥80	Frequency	1	24	25
	%	**4.0 %**	96.0 %	100.0 %
Total	Frequency	23	1128	1151
	%	**2.0 %**	98.0 %	100.0 %

There was a gradual increase in the number of cases in the older population groups.

Age group 70-79 contained the maximum proportion of people with probable PAD.

Socio-economic status V PAD:

Middle SES was taken as the reference and each class of SES was cross-tabulated along with the Middle SES against PAD to look for any association. None of the groups had a significant association. There was no consistent pattern of increase or decrease in effect between the groups either.

Table 5.25 ABI by Socio Economic Status

SES (BG PRASAD JAN '18)		ABI		OR (95% CI)	P value
		Abnormal	Normal		
Lower	Frequency	4	220	0.65 (0.19-2.19)	0.487
	%	1.8%	98.2%		
Lower Middle	Frequency	6	392	0.55 (0.19-1.60)	0.265
	%	1.5%	98.5%		
Middle	Frequency	8	287	1.00	1.000
	%	2.7%	97.3%		
Upper Middle	Frequency	3	154	0.70 (0.18-2.67)	0.601
	%	1.9%	98.1%		
Upper	Frequency	2	75	0.96 (0.20-4.60)	0.956
	%	2.6%	97.4%		
Total	Frequency	23	1128		
	%	2.0%	98.0%		

Nutritional Status, as understood by calculating the Body Mass Index (BMI), was cross-tabulated against PAD using Normal BMI as the reference. As has been already discussed, the WHO Asia-Pacific classification of BMI has been used to classify the study population. No significant association has been found. However, both undernutrition and overweight/obesity are identified as risk factors.

Table 5.26 ABI by Nutritional Status

Nutritional Status		ABI		OR (95% CI)	P value
		Abnormal	Normal		
Underweight	Frequency	3	116	2.10 (0.46 – 9.50)	0.327
	%	2.5%	97.5%		
Normal	Frequency	4	324	1.00	1.000
	%	1.2%	98.8%		
Overweight	Frequency	6	187	2.60 (0.72-9.33)	0.143
	%	3.1%	96.9%		
Obese	Frequency	10	501	1.62 (0.50-5.20)	0.420
	%	2.0%	98.0%		
Total	Frequency	23	1128		
	%	2.0%	98.0%		

Consumption of Alcohol in the past has been found to be significantly associated with an abnormal ABI. People who have consumed alcohol in the past were found to have 5.66 times the risk of having an Abnormal ABI than someone who has never consumed alcohol.

Table 5.27 ABI by Alcohol Intake

Alcohol Intake		ABI		OR (95% CI)	P value
		Abnormal	Normal		
Current	Frequency	4	195	1.22 (0.40-3.71)	0.728
	%	2.0%	98.0%		
Past	Frequency	4	42	**5.66 (1.80 – 17.79)**	**0.001**
	%	8.7%	91.3%		
Never	Frequency	15	891	1.00	1.000
	%	1.7%	98.3%		
Total	Frequency	23	1128		
	%	2.0%	98.0%		

Similarly, a past history of smoking tobacco confers a risk of 4.74 times than that of a non-smoker.

Table 5.28 ABI by Smoking

Smoking		ABI		OR (95% CI)	P value
		Abnormal	Normal		
Current	Frequency	3	91	2.03 (0.58-7.10)	0.258
	%	3.2%	96.8%		
Past	Frequency	4	52	**4.74 (1.53-14.67)**	**0.003**
	%	7.1%	92.9%		
Never	Frequency	16	985	1.00	1.000
	%	1.6%	98.4%		
Total	Frequency	23	1128		
	%	2.0%	98.0%		

Table 5.29 BIVARIATE ANALYSIS FOR PAD

Factors	Abnormal ABI	Normal ABI	Odds Ratio (95% CI)	P Value
Sex				
Male	16 (3.7%)	429 (96.3%)	**3.72 (1.52-9.13)**	**0.002**
Female	7 (1.0%)	699 (99%)		
Age				
≥60	13 (4.6%)	267 (95.4%)	**4.19 (1.82-9.67)**	**<0.001**
<60	10 (1.1%)	861 (98.9%)		
Smoking				
Ever	7 (4.9%)	143 (95.1%)	**3.01 (1.219-7.45)**	**0.012**
Never	16 (1.6%)	985 (98.4%)		
Diabetes				
Yes	7 (5.2%)	134 (94.8%)	**3.25 (1.31-8.03)**	**0.007**
No	16 (1.6%)	994 (98.4%)		
Hypertension				
Yes	7 (4.3%)	161 (95.7%)	**2.63 (1.06-6.49)**	**0.03**
No	16 (1.7%)	967 (98.3%)		
Fruit Intake				
Less Than Daily	18 (2.0%)	872 (98.0%)	1.06 (0.39-2.88)	0.914
Daily	5 (1.9%)	688 (98.1%)		
Vegetable Intake				
Less Than Daily	2 (3.0%)	64 (97.0%)	1.58 (0.36-6.90)	0.537
Daily	21 (1.9%)	1064 (98.1%)		
Alcohol				
Ever	8 (3.4%)	237 (96.6%)	2.01 (0.84-4.77)	0.110
Never	15 (1.7%)	891 (98.3%)		

Sex, Age, history of Diabetes, Hypertension and ever smoking were found to be significant risk factors for peripheral arterial disease in bivariate analysis.

Table 5. 30 ABI by Alcohol consumption among men

Alcohol among men		**ABI**		**Total**	Odds Ratio (95% CI)	P value
		Abnormal	Normal			
Ever	Frequency	8	237	245	0.81 (0.30-2.20)	0.68
	%	3.3%	96.7%	100.0%		
Never	Frequency	8	192	200		
	%	4.0%	96.0%	100.0%		
Total	Frequency	16	429	445		
		3.6%	96.4%	100.0%		

Table 5.31 COMPARISON OF MEANS WITH PAD PATIENTS (Part I)

Exposure	ABI	N	Mean	Std. Deviation	Mean Difference (95%CI)	P value
Age	Abnormal	23	56.3	16.7	**10.5 (3.8-17.2)**	**0.002**
	Normal	1128	45.8	16.3		
Pack years	Abnormal	7	8.4	8.6	-1.2 (-11.8-9.5)	0.831
	Normal	143	9.6	14.1		
Height	Abnormal	23	156.1	8.9	-1.3 (-5.1-2.6)	0.518
	Normal	1128	157.4	9.4		
Weight	Abnormal	23	60.1	13.6	-1.2 (-7.0-4.7)	0.693
	Normal	1128	61.30	14.1		
DM duration	Abnormal	7	99.7	97.9	35.7 (-54.8-126.3)	0.375
	Normal	134	64.0	61.4		
HTN duration	Abnormal	7	71.3	76.4	12.2 (-33.3-57.6)	0.598
	Normal	161	59.1	58.9		

People with an abnormal ABI were found to have a significantly higher mean age than people with normal ABI.

Table 5.32 COMPARISON OF MEANS WITH PAD PATIENTS (Part II)

Exposure	ABI	N	Mean	SD	Mean Difference (95% CI)	P Value
Creatinine	Abnormal	23	1.0	0.2	0.0 (-0.1-0.1)	0.916
	Normal	23	1.0	0.2		
HbA1c	Abnormal	23	6.5	1.4	-0.2 (-1.0-0.7)	0.661
	Normal	23	6.7	1.5		
Total Cholesterol	Abnormal	23	159.0	22.9	-23.2 (-46.9-0.4)	0.054
	Normal	23	182.2	50.6		
Triglycerides	Abnormal	23	149.9	80.4	-51.0 (-111.1-9.2)	0.095
	Normal	23	200.9	118.4		
HDL	Abnormal	23	49.7	9.5	0.4 (-5.2-6.2)	0.866
	Normal	23	49.3	9.6		
LDL	Abnormal	23	97.5	29.5	**-19.9 (-39.0- -0.7)**	**0.043**
	Normal	23	117.4	34.8		
Haemoglobin	Abnormal	23	12.7	2.8	0.0 (-1.5-1.5)	0.958
	Normal	23	12.7	2.2		

LDL has been found to be significantly lesser in patients with abnormal ABI. Similar findings have not been seen in any previous study.

Table 5.33 LOGISTIC REGRESSION ANALYSIS FOR PAD

Variable	Abnormal ABI	Normal ABI	Unadjusted OR (95%CI)	P value	Adjusted OR (95% CI)	P value
Sex						
Male	16 (3.7%)	429 (96.3%)	3.72 (1.52-9.13)	0.002	**3.28 (1.20-8.97)**	**0.021**
Female	7 (1.0%)	699 (99.0%)				
Diabetes						
Yes	7 (5.2%)	134 (94.8%)	3.25 (1.31-8.03)	0.007	2.23 (0.77-6.42)	0.138
No	16 (1.6%)	994 (98.4%)				
Hypertension						
Yes	7 (4.3%)	161 (95.7%)	2.63 (1.06-6.49)	0.03	1.14 (0.38-3.37)	0.818
No	16 (1.7%)	967 (98.3%)				
Smoking						
Yes	7 (4.9%)	143 (95.1%)	3.01 (1.22-7.45)	0.012	1.27 (0.45-3.54)	0.651
No	16 (1.6%)	985 (98.4%)				
Age						
≥60	13 (4.6%)	267 (95.4%)	4.19 (1.82-9.67)	<0.001	**3.11 (1.25-7.72)**	**0.015**
<60	10 (1.1%)	861 (98.9%)				

Multiple logistic regression analysis was carried out for all variables which were significant in the bivariate analysis. Age and Sex continued to be strongly associated with abnormal ABI, however Diabetes, Smoking and Hypertension were no longer found to be significantly associated with abnormal ABI values.

Table 5.34 Chronic Venous Disorder (CVD) by Age group

Age		Chronic Venous Disorder		Total
		Yes	No	
<30	Frequency	11	207	218
	%	**5.0%**	95.0%	100.0%
30-39	Frequency	11	209	220
	%	**5.0%**	95.0%	100.0%
40-49	Frequency	14	212	226
	%	**6.2%**	93.8%	100.0%
50-59	Frequency	22	185	207
	%	**10.6%**	89.4%	100.0%
60-69	Frequency	19	156	175
	%	**10.9%**	89.1%	100.0%
70-79	Frequency	5	75	80
	%	**6.3%**	93.8%	100.0%
≥80	Frequency	1	24	25
	%	**4.0%**	96.0%	100.0%
Total	Frequency	83	1068	1151
	%	**7.2%**	92.8%	100.0%

There is an equal distribution of people with Venous Disorders in each group.

SES analysis:

Association between CVD and SES was assessed. The Middle SES group was used as the reference and odds ratio was calculated.

Table 5.35 Chronic Venous Disorder by SES

SES		CVD		OR (95% CI)	P Value
		Yes	No		
Lower	Frequency	15	209	0.89 (0.45-1.76)	0.739
	%	6.7%	93.3%		
Lower Middle	Frequency	27	371	0.90 (0.50-1.62)	0.732
	%	6.8%	93.2%		
Middle	Frequency	22	273	1.00	1.000
	%	7.5%	92.5%		
Upper Middle	Frequency	11	146	0.93 (0.44-1.98)	0.861
	%	7.0%	93.0%		
Upper	Frequency	8	69	1.44 (0.61-3.37)	0.402
	%	10.4%	89.6%		
Total	Frequency	83	1068		
	%	7.2%	92.8%		

The middle SES group was taken as the reference point and the association was analysed. There was no association found between the different SES groups.

Table 5.36 Chronic Venous Disorder by Nutritional Status

Nutritional Status		ABI		OR (95% CI)	P value
		Abnormal	Normal		
Underweight	Frequency	3	116	0.40 (0.12-1.37)	0.130
	%	2.5%	97.5%		
Normal	Frequency	20	308	1.00	1.000
	%	6.1%	93.9%		
Overweight	Frequency	11	182	0.93 (0.44-1.99)	0.853
	%	5.7%	94.3%		
Obese	Frequency	49	462	1.63 (0.95-2.80)	0.075
	%	9.6%	90.4%		
Total	Frequency	83	1068		
	%	7.2%	92.8%		

Obese individuals were found to be at a higher risk of developing chronic venous disease. However, the association was not statistically significant.

Table 5.37 BIVARIATE ANALYSIS FOR CHRONIC VENOUS DISORDER

Factors	CVD	No CVD	Odds Ratio (95% CI)	P Value
Sex				
Male	40 (9.0%)	405 (91.0%)	1.52 (0.97-2.38)	0.064
Female	43 (6.1%)	663 (93.9%)		
Age				
≥60	25 (8.9%)	255 (91.1%)	1.37 (0.84-2.24)	0.202
<60	58 (6.7%)	813 (93.3%)		
Parity				
0 And 1	1 (0.7%)	150 (99.3%)	**0.08 (0.01-0.60)**	**0.002**
>1	42 (7.6%)	513 (92.4%)		
Smoking				
Ever	14 (9.3%)	136 (90.7%)	1.39 (0.76-2.54)	0.281
Never	69 (6.9%)	932 (93.1%)		
Diabetes				
Yes	13 (9.2%)	128 (90.8%)	1.36 (0.73-2.54)	0.325
No	70 (6.9%)	940 (93.1%)		
Hypertension				
Yes	16 (9.5%)	152 (90.5%)	1.44 (0.81-2.55)	0.210
No	6.8 (67%)	916 (93.2%)		
Frequency of Fruit Intake				
Less Than Daily	53 (6.0%)	837 (94.0%)	**0.49 (0.30-0.78)**	**0.002**
Daily	30 (11.5%)	231 (88.5%)		
CAD				
Yes	1 (6.7%)	14 (93.3%)	0.92 (0.12 – 7.07)	0.935
No	82 (7.2%)	1054 (92.8%)		
Frequency of Vegetable Intake				
Less Than Daily	6 (9.1%)	60 (90.9%)	1.31 (0.55-3.13)	0.543
Daily	77 (7.1%)	1008 (92.9%)		
Alcohol				
Ever	23 (9.4%)	222 (90.6%)	1.46 (0.88-2.42)	0.138
Never	60 (6.6%)	846 (93.4%)		

Table 5.38 COMPARISON OF MEANS WITH CVD PATIENTS

	CVD	N	Mean (Std. dev)	MEAN DIFFERENCE (95% CI)	P VALUE
ABI	Yes	83	1.09 (0.10)	**0.03 (0.00-0.05)**	**0.036**
	No	1068	1.07 (0.12)		
Height	Yes	83	159.8 (9.3)	**2.6 (0.5-4.7)**	**0.016**
	No	1068	157.2 (9.3)		
Weight	Yes	83	66.9 (14.3)	**6.0 (2.9-9.2)**	**<0.001**
	No	1068	60.9 (14.0)		
BMI	Yes	83	26.20 (5.13)	**1.60 (0.44-2.76)**	**0.007**
	No	1068	24.60 (5.19)		
Pack Years	Yes	14	8.6 (8.7)	-1.0 (-8.8-6.6)	0.788
	No	136	9.6 (14.3)		
Smoking Duration	Yes	14	13.4 (10.8)	-3.1 (-10.8-4.7)	0.438
	No	136	16.5 (14.1)		
Diabetes Duration	Yes	13	71.5 (57.4)	6.3 (-30.4-43.1)	0.733
	No	128	65.2 (64.5)		
Hypertension Duration	Yes	16	46.7 (46.2)	-14.3 (-45.2-16.6)	0.362
	No	152	61.0 (60.7)		
Age	Yes	83	49.4 (15.0)	3.6 (-0.002-7.303)	0.050
	No	1068	45.8 (16.4)		

Comparison of means revealed that the mean ABI was significantly higher among patients with CVD. Patients with CVD were also found to be 2 cm taller on an average. However, the strongest association was found between weight and CVD. A patient with CVD averaged 6 kg more than a normal person**.**

Table 5.39 LOGISTIC REGRESSION ANALYSIS FOR CVD

Factors	**CVD**	**No CVD**	**Unadjusted OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Parity						
0 and 1	1 (0.7%)	150 (99.3%)	0.08 (0.01-0.60)	0.002	**0.07 (0.01-0.53)**	**0.010**
>1	42 (7.6%)	513 (92.4%)				
Frequency of Fruit Intake						
Less Than Daily	53 (6.0%)	837 (94.0%)	0.49 (0.30-0.78)	0.002	**0.26 (0.14-0.49)**	**<0.001**
Daily	30 (11.5%)	231 (88.5%)				

Multiple Logistic Regression analysis was done which reiterated earlier findings.

Increased frequency of fruit intake and multiparity were found to be significant risk factors.

6. DISCUSSION

The majority of the study population were women, followed Hinduism and literate. We can decipher that 36.9% have studied till primary school and unsurprisingly 27.2% are illiterate with 6.1% people knowing how to read alone. This amounts to only two-thirds of the study participants knowing how to read and write which is consistent with the rural literacy rate in Tamil Nadu of 73.54% (158).

33.7% of the men had ever smoked and 55.1% of the men had ever consumed alcohol. This was a less than the prevalence of current smoking (37.6%) and alcohol consumption (62.4%) estimated among men in a study done in a rural area in Kanchipuram district of Tamil Nadu (159).

The mean height of the study population was approximately 157 cm and the mean weight was 61 kg. The Mean BMI of the participants was 24.72 kg/m². This is very similar to findings in another study done in another rural area in Villupuram, Tamil Nadu which showed a mean BMI of 24.5 kg/m² (160).

The prevalence of overweight individuals in this study is similar to study findings done in Tamil Nadu in 2015 (161) which showed a prevalence of 15.2% of people with a BMI between 23.00-24.99 kg/m². Another study estimated a prevalence of 39.64% people with a BMI above 25 in rural Tamil Nadu (162) which is similar to our study numbers (44.4%).

14.6% of our study population were on medications for hypertension. A study done in rural Tamil Nadu showed a prevalence of 21.4% (163).

The proportion of people on medications for diabetes mellitus in our study population was 12.3%. This is similar to the estimated prevalence of 10.4% in another large-scale cross-sectional study (164)

15 people (1.3%) have had pre-existing Coronary Artery Disease (CAD). A study on the prevalence of CHD among a similar population showed the prevalence of pre-existing CAD as 0.6% (165).

1% of the total study population had suffered a stroke in their lifetime. In another study done in a rural area of Tamil Nadu, the prevalence of CVA confirmed by CT/MRI findings was 1.3 per 1000 population (166).

Prevalence of intermittent claudication in the study population was 3.8%. A previous study was done in rural Vellore using the Rose questionnaire which estimated a prevalence of classical claudication at 3.8% (167).

Chronic Venous Disorder (CVD) was seen in 7.2% (95%CI 5.7%-8.8%) of the study population. As has already been mentioned, it has been extrapolated that 15%-20% of our population have Chronic Venous Disorders (19).

The Prevalence of Abnormal ABI in the study population has been estimated at 2% (95% CI 1.3%-3%). Other studies have shown the prevalence of PAD to be between 3 % to 7%. (155, 157).

Arterial Disease:

As previously discussed, the NHANES study(41) has shown the following prevalence of PAD in each age group,

Table 6.1 NHANES study vs Present Study with regards to age distribution

Age Group	NHANES study(41)	Present Study
> 80 years	23.2%	4.0%
> 70 years	14.5%	6.1%
60 - 69 years	4.7%	4.0%
50 - 59 years	2.5%	1.9%
40 - 49 years	0.9%	0.4%
30-39 years	N/A	0.9%
<30 years	N/A	1.4%

Increasing age has thus been found to be a significant risk factor for peripheral arterial disease in this study with an adjusted Odds Ratio of 3.11 (1.25-7.72).

In this study, the prevalence of PAD in men above 18 years of age was 3.7% and among women in the same age group was 1.0%. Though in dissimilar populations (age >65) it is similar to findings in others studies that have been mentioned above(54).

In bivariate analysis, a history of Diabetes Mellitus was found to be significantly associated with PAD (OR 3.25, 95%CI 1.31-8.03). However, while accounting for

age, sex, smoking and hypertension in logistic regression, the association was found to be not significant (adj OR 2.23, 95% CI 0.77-6.42).

Similarly, hypertension was found to be significantly associated with PAD (OR2.63, 95%CI 1.06-6.49) in bivariate analysis but was not significant in logistic regression (adj OR 1.14, 95% CI 0.38-3.37).

Another variable which was a significant risk factor in bivariate analysis but not significant after regression analysis was smoking (OR 3.01[1.22-7.45] vs adj OR 1.27[0.45-3.54]).

This shows that age and sex were the predominant risk factors and acted as confounders during bivariate analysis.

The mean age in the abnormal ABI group was significantly higher (10.5, 95% CI 3.8-17.2) than in the normal ABI group.

LDL has been found to be significantly lesser in patients with abnormal ABI (-19.9, 95% CI -39.0 to -0.7). Similar findings have not been reported in any previous study.

There were no significant differences in any of the other blood investigations.

Venous Disease:

Multigravida women were found to be at a higher risk of developing chronic venous disorders than nulliparous women and women who have had only one delivery in the

past. Women with lesser parity were 92% (OR 0.08, 95%CI 0.01-0.60) less likely to develop venous disease as opposed to women with parity >1.

Though the association between obesity and chronic venous disease was not significant, the mean BMI was significantly higher in the CVD group (Mean Difference 1.60 kg/m², 95% CI 0.44-2.76).

The CVD group were also significantly taller (Mean Difference 2.6 cm, 95%CI 0.5-4.7) and remarkably heavier (Mean Difference 6.0kg, 95% CI 2.9-9.2) than their counterparts.

The Ankle Brachial Index (ABI) was also found to be minimally but significantly higher (0.03, 95%CI 0.00-0.05) in the CVD group.

7. LIMITATIONS

Toe-Brachial Index (TBI) would have been the ideal tool to diagnose PAD. This is because ABI values >1.30 must be confirmed by TBI for diagnosis of PAD. However, due to practical constraints it could not be done.

8. CONCLUSIONS

- The prevalence of Peripheral Arterial Disease in Kaniyambadi block was 2% (95% CI: 1.3%-3%).

- The prevalence of Chronic Venous disorders in Kaniyambadi block was found to be 7.2% (95% CI: 5.7%-8.8%).

- Peripheral Arterial disease was significantly associated with increased age (>60 years) and male gender.

- Chronic Venous Disorders were significantly associated with increased parity.

- The mean height, weight and BMI were all significantly higher among people with Chronic Venous Disorders.

9. RECOMMENDATIONS

- Routine Ankle Brachial Index should be done in men above the age of 60 years to screen for Peripheral Arterial Disease.

- Ankle Brachial Index may also be useful to screen for Peripheral Arterial Disease among diabetics and hypertensives.

- Lifestyle modification in the community may be essential to bring down the high proportion of obese people.

- A dwindle in number of people with overweight and obesity may decrease the prevalence of chronic venous disorders.

- Early screening and intervention at the community level may help in avoiding the natural progress of both PAD and CVD thereby improving quality of life and reducing morbidity and mortality.

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Annexure 1 - Questionnaire

Date

1. S.No:
2. Household No:
3. Subject Id:
4. Name :
5. Village : Street: Door No:
6. Age:
7. Sex: Male Female Transgender
8. Religion: Hindu Muslim Christian Others
9. Caste (specify):
10. Education: Nil Primary school Middle school
    High school
    Higher Secondary/Diploma Graduate/Post Graduate Professional/Honours
11. Literacy: Illiterate Read Read & write
12. Occupation:_____
    Unemployed / Unskilled / Semi-skilled / Skilled / Clerical, shop owner, farmer / Semi-professional / Professional
13. How often do you eat fruits: daily/..... a week/.....a month/less than monthly

14. How often do you eat vegetables: daily / ..... a week / ..... a month / less than monthly
15. Type of family: Nuclear / Extended or Joint
16. Number of members in the family: _____
17. Family income /month (total) _____
18. BG Prasad scale-social class _____
19. CHAD/CMC Hospital number:
20. Are you a diabetic? Yes / No
21. If yes, how long have you had diabetes? _____ Yrs _____Mths
22. What type of Medications are you on for Diabetes?
23. Is there documented evidence of Diabetic Retinopathy: Yes / No

24. Are you a hypertensive? Yes / No
25. If yes, how long have you had hypertension? _____ Yrs _____Mths
26. What medications are you on for Hypertension?

27. Have you ever smoked? Yes-Current / Yes-Past / Never (If Never, go to Q.33)
28. *(If 'Yes to 27)* – Do/Did you smoke Daily? Yes/No (if No, go to Q.33)
29. How many **cigarettes** do/did you smoke per day?_____
30. How many **beedis** do/did you smoke per day?_____
31. How long have you been smoking?_ _ _ _ _ _ _ _ (yrs)

32. Pack Years of smoking _ _ _ _ _ _ _ _

33. In the last 7 days, on how many days were you exposed to a person who was smoking in your home/workplace_____(range 0-7)?

34. Have you ever consumed alcohol? Yes-Current / Yes-Past / Never (If Never, go to Q.37 or 40)

35. If yes, how often do/did you consume alcohol?

daily / ..... a week / ..... a month / less than monthly

36. On an average (usually) how much alcohol (hard liquor/beer/wine/local drinks) do you consume on the days that you drink?_ _ _ _ __ _ml of _ _ _ _ _ _ _ _ _ _ _

_ _ _ _ __ _ml of _ _ _ _ _ _ _ _ _ _ _ _

_ _ _ _ __ _ml of _ _ _ _ _ _ _ _ _ _ _ _

_ _ _ _ __ _ml of _ _ _ _ _ _ _ _ _ _ _ _

37. *(For females only)*Parity:

38. *(For females only)*Have you taken OCPs? Yes / No

39. *(If yes to Q38)*Total duration: _ _ _ _ _ _ _Yrs _ _ _ _ _ _ _ _Months

40. Past history of Stroke/TIA: Yes / No

41. Past history of coronary artery disease: Yes / No

The Edinburgh Claudication questionnaire:

42. Do you get pain or discomfort in your leg(s) when you walk? Yes / No / Unable to walk (if no, proceed to Q. No 48)

43. If yes, does this pain ever begin when you are standing still or sitting?

Yes / No

44. Do you get pain if you walk uphill or hurry? Yes / No
45. Do you get it when you walk at an ordinary pace on level ground? Yes / No
46. What happens to it when you stand still? Continues > 10 mins / Disappears in <10 mins
47. How long do you walk before you get the pain/discomfort in your legs? _____ m
48. Height (cm)_ _ _ _ _ _ _ _ _
49. Weight (kg) _ _ _ _ _ _
50. Left upper limb peripheral pulse: Present / Absent
51. Right lower limb peripheral pulse: Present / Absent
52. Left lower limb peripheral pulse: Present / Absent
53. *(Local exam)* : Gangrene Yes / No
54. *(Local exam)* CEAP classification: Telangiectasia / Varicose veins / Ankle Oedema / Lipodermatosclerosis / Healed Ulcer / Active Ulcer
55. Left Upper limb Systolic Blood pressure:_____
56. Right Lower Systolic limb Blood Pressure: _____
57. Left lower limb Systolic blood pressure:_____
58. ABPI :
59. Peripheral Vascular Disease: Yes / No

For Selected Cases and Controls

60. Category: Case / Control

61. Value of Creatinine: (Date of last creatinine:)

62. HbA1C value: (Date of last HbA1C :)

63. Lipid Profile Value: (Date of last Lipid profile :)

64. Haemoglobin:

Annexure 2 – Information Sheet and Consent Form – English

Information sheet

Name of the principle investigator: [redacted]., CHAD, Bagayam, Vellore – 632002. Phone no : [redacted]. E-mail id : [redacted]

Name of the organization: Department of community health, Christian Medical College, Vellore

Title: Prevalence of Peripheral Vascular Disease in the Community and associated risk factors: a cross sectional study

We are doing a study to find out the prevalence of peripheral vascular disease among the general population and its causes in kaniyambadi block. We are inviting you to participate in the study. Please review this form carefully and ask any questions about the study before you agree to join. You may also ask questions at any time after joining the study

Purpose:

Diabetics are at an increased risk for peripheral occlusive arterial disease. Peripheral arterial disease has a huge economic burden on the family and the community there are no existing data regarding prevalence of peripheral vascular disease in a rural community. This study aims to fill the knowledge gap and find out the prevalence of peripheral vascular disease among diabetics in Kaniyambadi block.

.

Procedure: You are invited to participate in the study. A questionnaire will be administered to you. Your blood pressure will be measured, both upper and lower limbs, using a Doppler machine and a ratio is taken to determine disease (Ankle Brachial Ppressure Index).A blood test will be taken from you. Not more than 6 mL will be drawn from you.

Side effects: There may be bleeding or infection at the site of drawing blood.

Risks and discomfort: There will not be any or discomfortto you as the procedure is non-invasive. Blood sample will be taken in CMC to check for your haemoglobin, white blood cell counts, platelet counts, fasting and post prandial blood glucose levels, serum creatinine values as well as lipid (cholesterol) levels.

Benefits: Your participation is likely to help us find answers about peripheral vascular disease among diabetics in Kaniyambadi block.

Expenses: All investigations will be done free of cost for the patient. No cash incentives will be given for taking part in the study.

Confidentiality: The information that we collect from this research project will be kept confidential. Information about you that will be collected from the study will be stored in a file and will be kept locked with access only to the primary investigator.

Right to refuse or withdraw: You do not have to join in this research if you do not wish to do so. You may stop participation in the research at any time without losing any of your rights as a patient here. Your treatment at this center will not be affected in any way.
If new information becomes available: Sometimes, after a research study has started, the researchers learn new things about peripheral vascular disease or ankle brachial pressure index. If this happens, we will tell you about the new information. Then you can decide whether you will continue participating.
Whom to contact: If you have any questions you may ask them now or later. If you wish to ask questions later, you may contact the principal investigator in CHAD, Bagayam, Vellore.

Informed Consent form to participate in a research study

Study Title: Incidence of Diabetic Neuropathy among diabetics and associated risk factors: a concurrent cohort study

Study Number: _____Subject's Initials:_____

Subject'sName: _____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signat.ure of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____Name & Address of the Witness: _____

Annexure 3 – Information Sheet and Consent Form – Tamil

முதன்மை ஆய்வரின் பெயர் மற்றும் முகவரி	:	[redacted] சமுதாய சுகாதாரம் மற்றும் வளர்ச்சி மையம் கிறிஸ்தவ மருத்துவக் கல்லூரி மருத்துவமனை, பாகாயம், வேலூர் - 632 002 தொ. [redacted] மின்னஞ்[redacted]
நிறுவனத்தின் பெயர்	:	சமுதாயச் சுகாதாரத் துறை கிறிஸ்தவ மருத்துவக் கல்லூரி வேலூர் - 632 002
ஆய்வுக் கட்டுரையின் தலைப்பு	:	**தென்னிந்தியாவில் உள்ள ஒரு ஊரக பகுதியில் 18 வயதுக்கு மேற்பட்டோரின் புற அமைவு இரத்த ஓட்ட மண்டல பாதிப்பின் பரவலையும் அதன் மூல காரணங்களையும் கணிக்கும் ஓர் ஆய்வு**

புற அமைவு இரத்த ஓட்ட மண்டலத்தில் ஏற்படும் நோய்களும், அதினால் ஏற்படும் பாதிப்பும் குறித்து கண்ணியம்பாடி ஒன்றியத்தில் வாழும் சமுதாயத்தினரினிடையே மேற்கொள்ளப்படும் ஓர் மருத்துவ ஆய்வு இது. நீங்கள் உங்கள் ஒத்துழைப்பை கொடுத்து, பங்கேற்க வேண்டுகிறோம். இந்தப் படிவத்தை நன்கு வாசித்து, ஏதாவது சந்தேகத்திற்குரிய கேள்விகள் இருக்குமென்றால் அதை தெளிவுபடுத்தி அதற்கு பின் இந்த ஆய்விற்கு உங்கள் சம்மதத்தை தெரிவியுங்கள். ஆராய்ச்சி மேற்கொள்ளும் போதும் நீங்கள் தயங்காமல் கேள்விகளை கேட்கலாம்.

ஆய்வின் நோக்கம்

சாதாரணமாக புற அமைவு இரத்த ஓட்ட மண்டலத்தில் (தமனி) இடையூறை ஏற்படுத்த காரணமாய் உள்ளது. இரத்த தமனிக் குழாய் நோய் வந்தால் அது குடும்பத்தின் பொருளாதாரத்தை மட்டுமல்ல, சமுதாயத்தையுமே தளர வைக்கும். ஊரக மற்றும் கிராம சமுதாயங்களில் இந்த தமனி நோய் பிரச்சனையைக் குறித்து சரியான புள்ளியியல் விவரங்கள் கிடைக்கப் பெறவில்லை. இந்த அறிவியல் பூர்வமான அறிவு இடைவெளியை நிரப்பவும், புற அமைவு இரத்த ஓட்ட மண்டலத்தில்

ஏற்படும் நோய்களும் அதினால் நோயாளியை பாதிக்கும் காரணங்களையும் கண்டறிவதே இந்த ஆய்வின் முக்கிய நோக்கமாகும். இந்த ஆய்விற்கு கண்ணியம்பாடி ஒன்றியம், வேலூர் மாவட்டம் தெரிந்து கொள்ளப்பட்டது.

ஆய்வின் வழிமுறைகள்

நீங்கள் இந்த ஆய்வில் பங்கேற்க அழைக்கின்றோம். 'கேள்விகள் பட்டியல்' ஒன்று உங்களிடம் தரப்படும். உங்கள் கை மற்றும் கால் இரத்த அழுத்த அளவீடுகள் – டாப்ளர் என்னும் கருவியோடு விகிதாச்சாரங்கள் கணக்கிடப்பட்டு, நோயின் கணுக்கால் மற்றும் தோள்பட்டை அழுத்தக் குறியீடு கண்டறியப்படும். ஒரு இரத்த பரிசோதனை செய்யப்படும். உங்கள் உடம்பிலிருந்து 6 மி.லி. இரத்தம் எடுக்கப்படும்.

பக்க விளைவுகள்

ஒரு வேளை இரத்தம் எடுத்த இடத்தில் சிறு கசிவு வரலாம் அல்லது அழற்சி அந்த இடத்தில் ஏற்படலாம்.

அசௌகரியங்கள் மற்றும் விளைவுகள்

உடலில் இதினால் எந்த அசௌகரியமும் ஏற்பட வாய்ப்பில்லை. ஏனெனில் துளையிட்ட வழிமுறைகள் ஒன்றும் செய்யப்படவில்லை. இரத்த பரிசோதனை ஒன்று கிறிஸ்தவ மருத்துவமனையிலிருந்து எடுக்கப்படும். இதன் மூலம் உடலில் எத்தனை சிவப்பணுக்கள், வெள்ளையணுக்கள், இரத்த தட்டுகள், உணவிற்கு முன்பு / பின்பு இரத்தத்தில் காணப்படும் குளுக்கோஸ் அளவு, நிண சீரம், கிரியாட்டினின் அளவீடுகள் மற்றும் கொழுப்பு சார்ந்த பொருட்களின் அளவும் கணக்கிடப்படும்.

ஆய்வின் பயன்கள்

இந்த ஆய்வில் நீங்கள் பங்கேற்பதினால் சரியான அறிவியல் ரீதியான கண்டுபிடிப்புகளுக்கு உதவுகின்றீர்கள், மற்றும் நோயாளிகளில் புற அமைவு இரத்த மண்டல தமனி நோய் எவ்வித தாக்கத்தை ஏற்படுத்துகிறது என்று கண்ணியம்பாடி ஒன்றியத்தை ஓர் ஆய்வுக்களமாக வைத்து பல கண்டுபிடிப்புகள் செய்ய உதவியாய் உள்ளது.

செலவினங்கள்

எல்லா பரிசோதனைகளும் பணமின்றி இலவசமாக செய்து தரப்படும். இந்த ஆய்வில் பங்கு பெற்றதற்கு எந்தவித ஊக்கத் தொகையும் தரப்பட மாட்டாது.

ரகசியம் பாதுகாக்கப்படும்

இந்த ஆய்வில் தெரியவரும் எல்லா புள்ளி விவரங்களும் மிகவும் ரகசியமாக, பாதுகாப்பாக வைக்கப்படும். நீங்கள் பகிர்ந்து கொள்ளும் செய்திகள் அனைத்தும் ஒரு கோப்பு இணைப்புதொகுப்பில் போடப்பட்டு, பூட்டப்படும். முதன்மை ஆய்வாளர் மட்டுமே இந்த விவரங்களை பயன்படுத்துவர்.

மறுப்பதோ, பின் வாங்குவதோ - உங்கள் உரிமை

உங்களுக்கு விருப்பம் இல்லை என்றால் தைரியமாக நீங்கள் இந்த ஆய்வில் பங்கேற்க முடியாது என்று சொல்லலாம் அல்லது ஆய்வுக்கு இடையே ஏதாவது காரணத்தால் பங்கேற்க முடியாது என்ற சூழலில் நீங்கள் பின்வாங்கி ஆய்வை விட்டு வெளியேறலாம். இது உங்கள் அடிப்படை உரிமை. இதன் காரணமாக சமுதாய சுகாதார மற்றும் வளர்ச்சி மையத்தில் உங்களுக்கு அளிக்கப்படும் சிகிச்சையின் தரமோ, அளவோ குறைந்து விடும் என்ற அச்சம் யாருக்கும் வேண்டாம்.

ஆய்வில் புதிய தகவல், விவரங்கள் கிடைத்தால்.. .. ..!

சில வேளைகளில், ஆய்வு முடிந்த பின், முதன்மை ஆய்வாளர் புற அமைவு இரத்த தமனி நோயைப் பற்றியோ, கணுக்கால் மற்றும் தோள்பட்டை அழுத்த குறியீடு பற்றியோ ஒரு புது செய்தி, விபரம் அறிந்தால் அது உங்களுக்கு சொல்லப்படும். அப்போது நீங்கள் இந்த ஆய்வில் தொடரலாமா ? இல்லையா? என்று நீங்கள் தீர்மானம் செய்து கொள்ளலாம்.

யாரை அணுகுவது ?

இந்த ஆய்வைக் குறித்து ஏதாவது சந்தேகங்கள், கேள்விகள் இருப்பின் இப்போதோ, அல்லது ஆய்வுக்கு பின்போ கேட்கலாம். ஆய்வுக்குப் பின் கேட்க வேண்டும் என்றால் சமுதாய சுகாதார மற்றும் வளர்ச்சி மையத்தில் (பாகாயம்), வேலூரில் பணிபுரியும் முதன்மை ஆய்வாளரிடம் நீங்கள் தெரிவிக்கலாம்.

விபரமறிந்து தெரிவிக்கும் இசைவுப் படிவம் –
மருத்துவ கல்வி ஆய்வில் பங்கேற்பு படிவம்

ஆய்வுத் தலைப்பு : தென்னிந்தியாவில் உள்ள ஒரு ஊரக பகுதியில் 18 வயதுக்கு மேற்பட்டோரின் புற அமைவு இரத்த ஒட்ட மண்டல பாதிப்பின் பரவலையும் அதன் மூல காரணங்களையும் கணிக்கும் ஓர் ஆய்வு

ஆய்வு எண் : _____

பங்கேற்பவரின் கையொப்பம் : _____

பங்கேற்பவரின் பெயர் : _____

பிறந்த தேதி / வயது : _____

(1) இந்த ஆய்வுக் கருத்தை நான் படித்து நன்றாகப் புரிந்து கொண்டேன் என உறுதியளிக்கிறேன். விபரப்படிவம் / தேதி _____ மற்றும் இதனைக் குறித்த கேள்விகளையும் கேட்க எனக்கு வாய்ப்புகள் அளிக்கப்பட்டது. [ ]

(2) இந்த ஆய்வில் நான் பங்கேற்க தன்னார்வத்தோடு சம்மதம் தெரிவிப்பதோடு, ஆய்வின் இடையே எந்த காரணமும் சொல்லாமல் இடைநிற்பதற்கு எந்த தடையும் இல்லை என்பதனையும் அதனால் என்னுடைய சட்ட ரீதியான உரிமை மற்றும் மருத்துவ பராமரிப்பு எவ்விதத்திலும் பாதிக்கப்படாது என்பதையும் புரிந்து கொண்டேன் [ ]

(3) எனது உடல்நலம் பற்றி விபர கோப்புகள் மற்றும் ஆய்வு மூலம் பெறப்பட்ட செய்திகள் மற்றும் எதிர்காலத்தில் நடத்தப்படும் ஆய்வு குறிப்புகளை ஆதரவாளர் அல்லது அவருக்கு பதிலீடு செய்பவர் அல்லது நன்னெறிக் கோட்பாட்டு குழு அல்லது ஒழுங்கு நெறி மேலாளர்கள் பார்ப்பதற்கோ, கேட்டு அறிவதற்கோ எந்தத் தடையும் இல்லை என்று நான் புரிந்து கொண்டேன். (இடைநின்றல் ஏற்பட்டாலும்) அப்படியிருந்தும் என்னுடைய அடையாளத்தை எந்த ஒரு மூன்றாம் நபரிடமோ, குழுவினரிடமோ தெரிவிக்கப்பட மாட்டாது என்றும் அறிக்கை வெளியிடப்படமாட்டாது என்றும் நான் புரிந்துள்ளேன். [ ]

(4) இந்த ஆய்வுத் தரவுகள், முடிவுகள், புள்ளியியல் செய்திகள் அறிவியல் ரீதியான பகுப்பாய்வுக்கு எந்தவித தடையுமின்றி பயன்படுத்தலாம் என்று சம்மதம் தெரிவிக்கிறேன். [ ]

(5) நான் இந்த ஆய்வில் பங்கேற்க சம்மதம் தெரிவிக்கின்றேன். [ ]

கையொப்பம் (அல்லது பெருவிரல் பதிவு)
(சட்ட விதிமுறைகளுக்கு உட்பட்டது)

தேதி _____

_____ _____
கையொப்பமிடும் நபரின் பெயர் கையொப்பம்

அல்லது

அவரின் பிரதிநிதி :

தேதி _____

பிரதிநிதியின் பெயர் : _____

முதன்மை ஆய்வாளரின் கையொப்பம் : _____

தேதி _____

முதன்மை ஆய்வாளரின் பெயர் : _____

தேதி _____

சாட்சியின் கையொப்பம் / : _____
பெருவிரல் பதிவு

தேதி _____

சாட்சியின் பெயர் : _____

முகவரி _____

_____

Annexure 4 – Institutional Review Board Approval letter

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

June 24, 2017

[redacted]
PG Student,
Department of Community Medicine,
Christian Medical College,
Vellore - 632 004.

Sub: **Fluid Research Grant: New Proposal:**
Prevalence of Peripheral Vascular Disease among Diabetics in a rural community in South India and its associated risk factors.
[redacted], Post graduate student, Dr. Vinod Joseph Abraham, Employment Number: 28095, Dr. Anu Mary Oommen, Employment number – 28649, Associate Professor, Community Health, Dr. Prabhu Premkumar, Surgeon, Department of Vascular surgery

Ref: IRB Min No: 10426 [OBSERVE] dated 05.12.2016

Dear [redacted]

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Vinod Joseph Abraham, Dept. of Community Medicine, CMC, Vellore

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

June 24, 2017

[redacted]
PG Student,
Department of Community Medicine,
Christian Medical College,
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Ref: IRB Min No: 10426 [OBSERVE] dated 05.12.2016

Dear [redacted]

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Prevalence of Peripheral Vascular Disease among Diabetics in a rural community in South India and its associated risk factors" on December 05th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Questionnaire
3. Patient Information Sheet
4. Informed Consent Form
5. Cvs of Drs. Prabhu, [redacted]braham and Anu
6. No. of documents 1 - 5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 05th 2016 in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Rekha Pai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal,Basic Medical Scientist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Simon Pavamani	MBBS, MD	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Prevalence of Peripheral Vascular Disease among Diabetics in a rural community in South India and its associated risk factors" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:
A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty Thousand only) each will be released at the end of the first year as 2 nd Installment..

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 10426 [OBSERVE] dated 05.12.2016