"STUDY OF LIPOPROTEIN(a) LEVELS IN PATIENTS WITH ISCHEMIC HEART DISEASE"

By

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Under the guidance of

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Signature

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ABBREVATIONS

Lp (a) – Lipoprotein (a)

IHD –Ischemic heart disease

CVD –Cardiovascular diseases

AUC –Area under curve

CHD-Coronary heart disease

LDL-Low density lipoprotein

HDL –High density lipoprotein

M.I.-Myocardial infarction

Apo A1-Apolipoprotein A1

Apo AII-Apolipoprotein AII

DM-Diabetes mallitus

IDDM-Insulin dependent diabetes mellitus

NIDDM-Non insulin dependent diabetes mellitus

LVH –Left ventricular hypertrophy

TGL-Triglycerides

CAMP-Cyclic adenosine mono phosphate

FFA-Free fatty acids

VSMC –Vascular smooth muscles

CRP –C-Reactive protein

CMV-Cytomegalovirus

LCAT – Lecithin cholesterol acyl transferase

apo B – Apolipoprotein B

apo C – Apolipoprotein C

apo D – Apolipoprotein D

apo E – Apolipoprotein E

apo A – Apolipoprotein A

Ca^{2+} – Calcium

ABSTRACT

BACKGROUND: Lipoprotein(a) is an LDL like molecule consisting of an apoprotein (apo) B-100 particle attached by a disulphide bridge to apo(a). Lipoprotein(a)) is a predictor of many forms of vascular disease, including premature coronary artery disease. Lipoprotein[a] has been recognized as an independent risk factor for ischemic heart disease. Elevated lipoprotein(a) levels are associated with myocardial infarction (MI) in some but not all studies.

OBJECTIVES : To study the levels of Lipoprotein (a) and as an risk factor for Ischemic heart disease**.**

MATERIALS AND METHODS:50 age and sex matched cases and controls were taken and estimation of Lipoprotein (a)were done Study was conducted from December 2011- November 2011.Cases were observed with reference to presentation, confirmed by ECG changes,cardiac biomarker CK MB/Trop T ,2D –ECHO.Data was analysed with descriptive statistical tools .

RESULTS AND CONCLUSIONS :50 patients of Ischemic heart disease were taken up for study .The male to female ratio were approximately.The maximum number of patients were in the age group of 51-60 years.Majority of the patients presented with chest pain (80%),breathlessness(40%).Major risk factors being smoking(88%) and hypertension (88%),diabetes mellitus (80%).Cardiac biomarker CK MB /Trop T were estimated and found to be significantly elevated in ischemic heart disease patients .Lipoprotein (a) levels were estimated in 50 cases and 50 controls .Lp(a) levels were significantly more in cases compared to controls.

KEY WORDS

Lipoprotein(a) ,Ischemic heart disease ,Risk factors.

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INTRODUCTION

Ischemic heart disease (IHD) is emerging as a major public health problem in the Indian subcontinent especially in the younger patients. Ischemic heart disease is the dominating cause of morbidity and mortality in all industrialized nations and accounts for twice as many deaths as cancer, which is the second major cause of human death. It is responsible for 30% of all cardiac disease, and 90% of all cardiac deaths. Hence the extreme urgency for its therapy and even more for its prevention.[1]

Lipoprotein (a) [Lp (a)], first described by Berg in 1963, is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B-100 and a molecule of apolipoprotein A.[1]

Human coronary atherosclerosis is a chronic inflammatory disease that is superimposed on a background of lipid abnormalities. Proinflammatory oxidized low-density lipoprotein (LDL) may be a unifying link between lipid accumulation and inflammation in the vessel wall. In humans, oxidized LDL in plasma and within atherosclerotic lesions is strongly associated with coronary artery disease, acute coronary syndromes, and vulnerable plaques.[2-7]

Lipoprotein(a) is composed of a low-density lipoprotein (LDL) particle bound to a plasminogen-like glycoprotein named apolipoprotein(a).[8] Previous in vitro, animal, and epidemiological studies suggest that lipoprotein(a) could contribute to the development of atherosclerosis or thrombosis and thus myocardial infarction (MI) and ischemic heart disease (IHD).[8-23] However, the use of lipoprotein(a) as a risk factor for MI and IHD has not been implemented in clinical practice. In addition, only very

few studies have provided information on the association between extreme lipoprotein(a) levels and risk of MI and IHD.[15, 16, 17] Finally, we lack absolute risk estimates in the general population to help clinicians use extreme lipoprotein(a) levels in risk assessment of individual patients.

Lipoprotein(a) may contribute to the development of M.I. and IHD by 2 different mechanisms: lipoprotein(a) consists of an LDL particle that may promote atherosclerosis and a plasminogen-like apolipoprotein (a) particle that may interfere with fibrinolysis and increase the risk of thrombosis.

Lipoprotein(a) can enter into human atherosclerotic Plaques[6] and results from in vitro and animal studies implicate lipoprotein(a) in foam cell formation, smooth muscle cell proliferation, and plaque inflammation and instability.[2, 7, 8] Lipoprotein(a) has also been shown to bind Proinflammatory oxidized phospholipids recently associated with coronary artery disease.[24] Lipoprotein(a) enters into and leaves the arterial wall by mechanisms similar to LDL[3,4] and appears to accumulate more at sites of arterial injury than LDL.[5] Mechanisms by which lipoprotein(a) may contribute to thrombus formation include inactivation of tissue factor pathway inhibitor, thus promoting coagulation, and attenuation of fibrinolysis through inhibition of plasminogen activation. [2, 8]

Lipoprotein(a) Lp(a) is an established risk marker of cardiovascular diseases (CVD) which is independent from other risk markers[25.] Elevated Lp(a) levels may promote atherosclerosis via Lp(a)-derived cholesterol entrapment in the intima, via inflammatory cell recruitment, and/or via the binding of pro-inflammatory-oxidized phospholipids.[26] Lp(a) is the marker with the best clinical accuracy, being the marker

with the largest area under the curve (AUC) and the best sensitivity and specificity among other lipid markers, as well as atherogenic indexes in all patient groups.[27] Asian Indians with high Lp(a) levels may represent a group with particularly high risk for CVD and should receive aggressive risk factor reduction.[28] Clinical evidence suggests that Lp(a) has a potential for the atherogenic and pro-thrombotic episodes as well as for its causative role in coronary heart disease[29] (CHD).

Promising results are emerging with therapeutic interventions targeting the 'inflammatory pathways' by inhibition of Interleukin-6 (IL-6) signalling with natural compounds (e.g., Ginko biloba) or the IL-6 receptor antibody Tocilizumab. These may both lower Lp(a) and cardiovascular risk of the patients. Besides inhibiting platelet function, antiplatelet therapy with aspirin may also decrease the plasma concentration of Lp(a) and modulate its influence on platelets.[30] High-risk levels of Lp(a) are associated with female gender, African-American race and CHD.[31] Increasing Lp(a) levels tend to correlate positively with low-density lipoprotein cholesterol (LDL) and negatively with triglycerides.[32]

Lipoprotein(a) may have effects on atherothrombotic vascular disease that are only relevant at specific sites. There is comparable strength of associations of the LPA score with coronary disease and peripheral vascular disease but not with stroke[33]. Clinical evidence suggests that Lp(a) has a potential for the atherogenic and pro-thrombotic episodes as well as for its causative role in coronary heart disease.[34]
Screening for elevated Lp(a) in those at intermediate or high CVD/CHD risk, is recommended as a function of global cardiovascular risk, and also use of

niacin for Lp(a) and CVD/CHD risk reduction.[35] Lipoprotein(a) 14–15 pentanucleotide repeats predict elevated levels of lipoprotein(a) and a 2-3 fold increased risk of MI and IHD in the general population.[31]

Apart from the traditional risk factors like Diabetes, Hypertension (HTN), Obesity, Smoking, hypercholestermia, recently more studies are done to know the pathogenicity of IHD. Dyslipidemia is considered as an important risk factor and has gained momentum and better insight in the role of lipoprotein factors in CAD. Earlier, low density lipoproprotein(LDL) was thought to be a marker for risk of the disease and later was replaced by high density lipoprotein cholesterol (HDL). Now the focus of study is on various sub fractions of atherogenic LDL and protective HDL as a better discriminator of IHD.[36]

AIMS AND OBJECTIVES

To study the levels of LIPOPROTEIN(a) in 50 patients of Ischemic Heart Disease and 50 age and sex matched healthy controls attending R. L. JALAPPA HOSPITAL, affiliated to SRI DEVRAJ URS MEDICAL COLLEGE, KOLAR.

REVIEW OF LITERATURE

Ischemic Heart Disease (IHD):

Ischemia refers to a lack of oxygen due to inadequate perfusion which results from an imbalance between oxygen Supply and demand.

Coronary Atherosclerosis:

Atherosclerosis is derived from the Greek word "Athero″ meaning gruel or porridge and "Sclerosis" meaning hardening.

Risk Factors:

It is defined broadly as "any habit or trait that can be used to predict on individuals probability of developing the disease. A risk factor may be a causative agent or may not be one necessarily.

I. Traditional Risk Factors:

A. Positive risk factors:

1. Cigarette smoking
2. HTN
3. DM/Insulin resistance
4. Hyperlipidemia / dyslipidemia

   Increased TGL>200 mg/dl

   Increased LDL >100mg/dl

   Decreased HDL < 35 mg/dl

   High apo B > 100 mg/dl

   High ratio TC/HDL > 4.5 mg/dl

   LDL *I* HDL > 3.5 mg/dl

   Low ratio LDL/ Apo B < 1.2

Apo A_1/Apo B < 1. 2

5. Family history of IHD

B. Negative risk factor:

Increased HDL

II. Other traditional risk factors:

1. Sedentary life style
2. Obesity (Central obesity)
3. Post-menopausal female /premature menopause /polycystic ovarian disease.
4. Age
5. Type A personality and stress.

1. CIGARETTE SMOKING

Smoking is a leading preventable cause of premature death in Myocardial infarction (M.I.).In the Framingham heart study cardiovascular mortality increased 18% in men and 31% in women for each 10 cigarettes smoked per day. [37]

The use of tobacco products decreases HDL cholesterol in an observational epidemiological study. HDL cholesterol was 12% lower in male smokers and 7% lower in female smokers than in non-smokers. Tobacco smoke may adversely affect HDL mechanism and structure by modifying the activity of Lecithin cholesterol acyl transferase (LCAT). Additionally plasma exposure to cigarette smoke resulted in cross linking between Apo A-I and Apo A-II, which may alter the function of HDL. Because of the cardio-protective effect of HDL, these alterations may provide a mechanism which cigarette smoke increases risk for CAD.

2. HYTERTENSION (HTN):

Numerous observational epidemiological studies in geographically and ethnically diverse population have established a direct relation between blood pressure elevation and incidence of CAD and stroke. In a meta-analysis of nine prospective studies that together included almost 42,000 individuals without prior M.I. or stroke who were followed up for an average of 10 years, baseline blood pressure level correlated with subsequent incidence rates or CAD death and non-fatal M.I.[38]

Elevated blood pressure frequently correlates with other risk factors. Evaluation of other risk factors that occur with HTN is of special clinical importance because controlling blood pressure with certain antihypertensive medications may adversely affect other risk factors.

3. DIABETES MELLITUS (DM) / INSULIN RESISTANCE:

CAD is a major complication of both Insulin dependent diabetes mellitus (IDDM) and Non-insulin dependent diabetes mellitus (NIDDM). In a 14 year follow up of the Rancho Bernardo study, in which 334 men and women with NIDDM were compared with 2137 men and women without diabetes, the relative risk for CAD death was 1.9 in diabetic men and 3.3 in diabetic women compared with non-diabetic men and women after adjustment for other CAD risk factors. [39]

Diabetes results in increased TGL and decreased HDL concentration in conjunction with small dense LDL particles. Resistance of to the action of circulating insulin may play role in the dyslipidemia of diabetes.

According to various studies the relationship between the risk or atherosclerotic coronary heart disease and lipoprotein levels is well established.

4. FAMILY HISTORY OF IHD:

Coronary atherosclerosis tends to aggregate in families. In studies that controlled by other risk factors, a family H/O CAD has been shown to be a strong independent risk factor for CAD. For example a study in relatives of 223 patients with angiographically demonstrated CAD and 57 control subjects found that, after stratification by age, gender, blood pressure, total cholesterol, smoking, diabetics, Left ventricular hypertrophy (LVH), relatives and patients had a significantly greater risk for CAD than relatives of controls as reflected in odd's ratios of 2.0 to 3.9 for various CAD end points. [40]

The increased CAD risk associated with a positive family history may be mediated by genetic effects on other risk factors such as obesity, hypertension, dyslipidemia and diabetes. Apart from these risk factors other traditional risk factors like, sedentary lifestyle. Obesity, age and type 'A' personality and stress, all play an important role in the pathogenesis of CAD. Regular physical activity has been shown to reduce risk for CAD events in number of observational epidemiological studies.

Approximately four fifth of fatal M.I. are in patients aged 65 years and older. Excess CAD mortality attributable to hypercholesterolemia, increased more than five times with age in the observational Kaiser Permanent coronary heart disease in the elderly study, conducted in 2746 men without CAD aged 60 to 79 years.

The role of personality type and emotional stress in risk stratification for CAD remains controversial. Type 'A' personalities are highly competitive, ambitious and in constant struggle with their environment, whereas type 'B' personalities are passive

and less disturbed by environmental stress. Type 'A' personality was reported to be an independent risk factor for CAD in 8.5 year follow up of 3154 men aged 39 to 59 years and without CAD at baseline, in the western collaborative group study. Type 'A' is twice as likely to have angina or M.I. as compared to type 'B' subjects.[41]

5. OBESITY *(*CENTRAL OBESITY):

In the Framingham Heart study, obesity was found to be an independent risk factor for cardiovascular disease in both men and women. Among subjects aged less than 50 years, incidence of cardiovascular disease was two times higher in men and almost 2.5 times higher in women in the most obese tertile compared with the leanest tertile.

NORMAL LIPID METABOLISM:

Triglycerides (TGL) and Cholesterol are transported through Lipoproteins. The two major lipids are triglycerides, a major storage form of energy in the body and cholesterol an essential component of cell membranes and a precursor in the synthesis of bile salts, steroid hormones and vitamin D. Both are obtained from dietary fat (especially meat, eggs and dairy products) and are also synthesized by liver.[42]

TGL are formed by the esterification of glycerol with fatty acids, which have a hydrocarbon group attached to a carboxyl group. Naturally occurring fatty acids usually have even number of carbon atoms most of them linked by single bonds, but some contain double bonds. Those with double bonds are termed unsaturated while those with single bonds are saturated fatty acids. Fatty acids with one double band are termed monosaturated and those with more are referred to as polyunsaturated. Triglycerides are stored in the adipose tissue and provide principal energy source.[42]

For other organs to utilize energy in adipose tissue the stored triglycerides should first be hydrolysed to give its constituent glycerol and non-esterified fatty acids, process known as lipolysis. This is accomplished by tissue lipase an intracellular enzyme, which is inhibited by insulin.[43]

Triglycerides the major storage forms of energy in the body. In the mammals the adipose tissue plays all important roles in metabolism. It serves as a storage sites for excess calories ingested as well as a reserve store of energy which can be mobilized when there is need. The trigylycerides synthesis in adipose tissue is for storage of energy whereas in the liver it is mainly secreted as VLDL and it is transported under well fed conditions active lipogenesis occurs in the adipose tissue. The dietary fats transported by chylomicrons and the endogenously synthesised triglycerides brought by VLDL from liver are both taken up by adipose tissue and esterified and stored as TGL.[43]

The Metabolic pattern totally changes under conditions of fasting TGL in the adipose tissues is mobilised under the effect of hormones, glucogan and epinephrine that are lipolytic. The intracellular hormone sensitive lipase of the adipose tissue is activated by the c-AMP mediated activation cascade. Insulin has an antilipolytic effect and inhibits lipid mobilization.[43]

Total plasma lipid is 750-1000 mg/dl roughly 1/3rd is phospholipids TGL and cholesterol are insoluble and have to be complexed with proteins to allow the transport from the gut and liver to tissue. The complexes of proteins with lipid are called Lipoproteins.[43]

PLASMA LIPOPROTEINS

Blood contains triglycerides, cholesterol and cholesterol esters at concentrations that far exceed their solubilities in water. Blood lipids are kept in solution or at least thoroughly dispersed in the circulation by virtue of being incorporated into macromolecular structures called lipoproteins.[44]

Structure of lipoproteins:

The lipoproteins are spherical particles in which the most hydrophobic lipids such as cholesterol esters and triacylglycerols are located in the core of the structure, sequestered away from water, whereas free (non-esterified) cholesterol, phospholipids and proteins are arrayed on the surface. All plasma lipoproteins contain one or more of surface proteins called apoproteins. It is mainly the amphipathic phospholipids and proteins that keep highly insoluble lipids like cholesterol and triacylglycerols in solution.

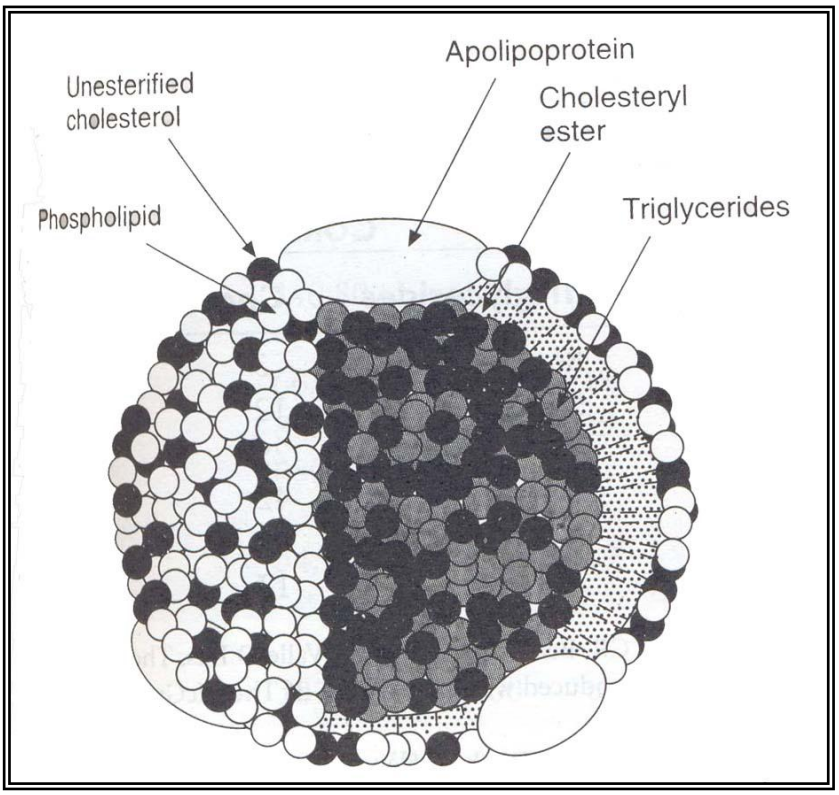


Fig 1 : Structure of lipoprotein particle[45]

Functions of lipoproteins: The plasma lipoproteins are the vehicles by which cholesterol, cholesterol esters and triacylglycerols are transported from one tissue to another in the body.

1) The plasma lipoproteins facilitate lipid metabolism by acting as substrate for lipid metabolising enzymes in blood.

The apolipoproteins on the surface of the particles also serve as structural components, ligands for cell receptors and cofactors for enzymes involved in lipoprotein metabolism.[44]

Classification of lipoproteins:

Lipoproteins are mainly classified into five groups according to their density on ultracentrifugation and their mobility on agarose gel electrophoresis.[45]

- Chylomicrons
- Very Low Density Lipoproteins (VLDL)
- Low Density Lipoproteins (LDL)
- Intermediate Density Lipoproteins (IDL)
- High Density Lipoproteins (HDL)

Characteristics of Human plasma lipoproteins:

Variable	Chylomicron	VLDL	IDL	LDL	HDL	Lp (a)
Density (g/ml)	< 0.95	0.95-1.006	1.006-1.019	1.019-1.063	1.063-1.210	1.040-1.130
Electrophoretic mobility	Origin	Prebeta	Between prebeta and beta	Beta	Alpha	Prebeta
Molecular weight (Da)	$0.4\text{-}30x10^9$	$5\text{-}10x10^6$	$3.9\text{-}4.8x10^6$	$2.75x10^6$	$1.8\text{-}3.6x10^5$	$2.9\text{-}3.7x10^6$
Diameter (nm)	> 70	26-70	22-24	19-23	4-10	26-30
Lipid-lipo protein ratio	99:1	90:10	85:15	80:20	50:50	75:26 -64:36
Major lipids	Exogenous triglycerides	Endogenous TG	Endogenous TG and Cholesteryl esters (CE)	CE	Phospholipids (PL)	CE PL
Major proteins	A-I B-48 C-I C-II C-III	B-100 C-I C-II C-III E	B-100 E	B-100	A-I A-II	(a) B-100

Phospholipid, specific proteins termed as Apoproteins, and a little free cholesterol. The protein component of lipoprotein is termed Apoprotein, a group of proteins of immense structural diversity some of which have a structural role and others of which are major metabolic regulators. In addition enzymes are found as components of lipoprotein. The leading example is located is lecithin cholesterolacyl transferase (LCAT) which is located on HDL which are also its site of action.

Lipoprotein metabolism [43]:-

The lipoproteins are metabolized by 2 different ways:

a) Exogenous pathway

b) Endogenous pathway

Exogenous pathway begins with dietary fat in the gut and employs TGL rich chylomicrons to deliver free fatty acids to the tissue and cholesterol to the liver. Endogenous pathway uses VLDL, containing TGL synthesized in the liver to supply FFA and cholesterol to the peripheral tissues.

a) EXOGENOUS PATHWAY:

The products of fat digestion (fatty acids, monoglyceride, lysolecithin and free cholesterol) enter the enterocytes from mixed micelles. They are re-esterified the smooth endoplasmic reticulum of these cells long chain fatty acids(14C) are esterified with monoglyceride to form triglycerides and Lysolecithin to lecithin. Free cholesterol is esterified by the enzyme acyl COA, cholesterol O-acyl transferase.

The triglycerides, phospholipids and cholestryl esters are then combined with an apolipoprotein known as APO-B48 .The lipoprotein thus formed are secreted from lymph(chyle) called chylomicrons. They are large in size (diameter 75nm density 950 gm/l) and are rich in triglycerides, but contain only relatively small amount of protein. In addition to cholesterol absorbed from the diet, the chylomicrons may also receive cholesterol that has been newly synthesized in the gut and transferred from other lipoprotein present in the lymph and plasma. The newly secreted or nascent, chylomicrons, receive apolipoprotein C from HDL, which later in the course of metabolism of the chylomicron, the apolipoprotein C are transferred back to the HDL pool.

Once the chylomicron has acquired the apolipoprotein apo c II, it is capable of activating the enzyme, lipoprotein lipase. This enzyme is located on the vascular endothelium of tissues which need a great amount of triglycerides such as skeletal muscle and cardiac muscle (for energy), adipose tissue (for storage) and lactating mammary gland (for milk). Lipoprotein lipase releases triglycerides from the core of the chylomicron by hydrolysing them to fatty acids and glycerol which are taken up by the tissues locally. In this way the circulating chylomicron becomes progressively smaller, its triglyecrides content decreases and it becomes relatively richer in cholesterol and protein. As the core shrinks, its surface materials (phospholipids free cholesterol) apolipoproteins becomes too crowded and they are transferred to HDL, the cholesterol-ester enriched, triglycerides depleted product of chylomicron metabolism is known as the chylomicron remnant. These remnants are largely removed from the circulation by the liver.

b) ENDOGENOUS PATHWAY:

The liver itself secrets triglycerides rich lipoprotein known as VLDL this allows the supply of TGL to tissues in the fasting state as well as post prandial. VLDL particles are somewhat smaller than the chylomicrons (diameter 30-45 nm density < l006g/l). Once secreted they undergo exactly the same sequence of changes as chylomicrons, that by the acquisition of apolipoprotein and the progressive removal of TGL from their core by the enzyme, lipoprotein lipase in man, the liver, unlike gut does not esterify cholesterol before its secretion in the human most of the cholesterol released from the liver each day into the circulation is secreted in the VLDL as free cholesterol and it undergoes esterification in the circulation. Free cholesterol is transferred to HDL along a concentration gradient. There it is esterified by the action

of the enzyme lecithin. Cholesterol acyl transferase, which esterifies the hydroxyl group in the 3- position of cholesterol to a fatty acyl group.

Esterified cholesterol on HDL is transferred back to VLDL. This cannot take place by simple diffusion because cholesterol ester is intensely hydrophobic and because the concentration gradient is unfavourable a special protein called cholesterol ester transfer protein, or lipid transfer protein, is present in the plasma, which transports cholesterol ester from HDL to VLDL. It does this in exchange for triglyecrides in VLDL and thus also contributes to the removal of core triglyecrides from VLDL. The major mechanism for the removal of triglycerides from VLDL is however lipolysis catalysed by lipoprotein lipase.

The apolipoprotein produced by the liver in man is not B-48 but is almost entirely Apo B-100. It is probable that each molecule of' VLDL contain one molecule of Apo B-100. The circulating VLDL particles become progressively smaller as their core is removed by lipolysis and surface materials are transferred to HDL. In normal man most of the VLDL is converted to smaller LDL particles through the intermediary of a lipoprotein known as the IDL.

In man LDL particles which are relatively enriched in cholesterol but are small enough to cross the vascular endothelium and enter the tissue fluid, serve to deliver cholesterol to the tissue. This concentration in the ECF is probably about 10% of that in the plasma cells required cholesterol for membrane repairs and growth and in the case of specialized tissues such as adrenal gland, gonads and skin as a precursor for steroid hormone and vitamin B synthesis. LDL is able to enter cells by two routes making a major contribution to its catabolism, one which is regulated according to its

cholesterol requirement of each individual cell and one which appears to depend almost entirely on the extracellular concentration of LDL.

APOLIPOPROTEINS:-

The surface proteins of the lipoproteins are called apoproteins or apolipoproteins. In addition to providing a structural stability to the lipoproteins, they play a critical role in determining the metabolic fate of the particles on which they reside. They are named in an arbitrary alphabetical order such as A, B, C and E they are associated with a particular major lipoprotein class. The apoprotein that is essential for the assembly and secretion of chylomicrons is ApoB-48. Apo B 100 is the major apoprotein of VLDL, IDL and LDL comprising approximately 30% x 60% and 95% of the protein in this respective life of proteins. It is the largest of apoproteins.[46]

There are three C apolipoproteins CI, CII and CIII and liver is the site of synthesis of all the three types of the C apoproteins. Apo CI is the minor component of VLDL, IDL and HDL whose exact function is unknown. Apo CII is a constituent of VLDL and is also present on IDL, HDL and chylomicrons. Apo CII is an essential activation of the enzyme lipoprotein lipase, which hydrolyses triglycerides in chylomicrons and VLDL. Subjects lacking Apo CII have severe hyper triglycerides. Apo CII is a major component of VLDL in which it accounts for about 40% of the protein.[46]

Apo E is synthesized in liver and is found in all the lipoproteins. It appears to regulate the removal of remnant lipoproproteins from the plasma by the liver although the exact mechanism of the activity is not known .[46]

Apo AI is the major protein present in HDL, constituting about 70-80% of the protein mass Apo AI is synthesized in both the liver and small intestine. Apo AI is the activator of the enzyme LCAT (Lecithin cholesterol acyl transferase) which esterifies free cholesterol in plasma. It may also play a critical role in maintaining the integrity of HDL particles in the plasma and therefore prolonging their life time in the circulation. Subjects without Apo AI have been described and have been shown to lack HDL. Some of these patients develop severe, early atherosclerosis, xanthomatosis and corneal opacities.

Apo AI is the second most abundant, apoprotein in HDL similar to Apo AI. AII is synthesized both in the liver and small intestine in humans. The function of ApoAII has not been determined. Apo AIV is a minor component of HDL and chylomicrons. It is synthesized only in the small intestine in humans. Apo AIV plays a role in the activation of LCAT. Recently a new apolipoprotein F has been reported within HDL of molecular weight 26000-30,000. APO F is reported to carry its own complement of lipid and to form a distinct lipoprotein species within HDL. Further work, however is required in order to define the composition and metabolism of this apoprotein.[47]

Apo AI^{milano} results from a mutation in the gene for APO AI. Individuals having APO AI have low HDL, cholesterol and hyper APO AI may be more easily dissociated from HDL thus potentially increasing the role of free APO AI in cholesterol efflux despite low HDLC lands in these patients; coronary artery disease risk doesn't appear to be increased .[48]

CHARACTERISTICS OF MAJOR APOLIPOPROTEINS

Apolipoprotein	Molecular Weight	Lipoprotein	Metabolic Functions
Apo AI	28,016	HDL, Chylomicrons	Structural component of HDL, LACT activator.
Apo AII	17,414	HDL, Chylomicrons	Unknown
Apo AIV	46,465	HDL, Chylomicrons	Unknown, possibly facilitates transfer of other apolipoproteins between HDL and Chylomicrons.
Apo B-48	264,000	Chylomicrons	Necessary for assembly and secretion of chlylomicrons from small intestine.
Apo B-100	514,000	VLDL, IDL, LDL	Necessary for assembly and secretion of VLDL from liver, structural protein of VLDL, IDL and LDL, ligand for LDL receptor.
Apo CI Apo CII Apo CIII	6630 8900 8900	All major lipoproteins All major lipoproteins All major lipoproteins	Activator of lipoprotein lipase, inhibitor of lipoprotein lipase, may inhibit hepatic uptake of chylomicron and VLDL remnants.
Apo E	34,145	All major lipoproteins	Ligand for binding of several lipoproteins to the LDL receptor and possibly to a separate hepatic apo E receptor.

HDL=High density lipoprotein; LCAT= Lecithin cholesterol acyl transferase; VLDL=Very low density lipoprotein: IDL=Intermediate density lipoprotein; LDL=Low density lipoprotein.

APO-A CONTAINING LIPOPROTEINS:

HDL mediates the transport and metabolism of plasma cholesterol through interaction with the enzyme lecithin cholesterol acyl transferase. It does this through several of its apoplipoproteins, the major ones being Apolipoprotein AI and AII further more HDL regulates tissue cholesterol pools and clearance cholesterol from actual arterial wall. Infact HDL cholesterol levels are as strong an indicator of protection from CAD as LDL is an indicator of risk. It is embracing therefore that, although a great deal about HDL transport system is known, it is yet undecided as to the way this lipoprotein protect against coronary heart disease. [46] This uncertainty is because of complexity and of the HDL, lipid and lipoprotein transport system. It is possible to isolate and characterise a variety of HDL subclasses which vary in size, density, lipid composition and lipoprotein components.

Apo A is the major protein component of HDL. The two major components of Apo A are AI and Apo AII. They are both synthesized by liver and catabolised by the liver and kidney.[48] Apo AI constitutes about 75% of the Apo A in HDL it consists of 243 to 285 Amino acids with a molecular weight of 28KD.[48] Apo AII constitutes about 25% of Apo A in HDL. It consists of 154 amino acids and has a molecular weight 17,000. The physiological role of Apo AII is not known.[48] Apolipoprotein AI has been shown to remove cholesterol from aortic smooth muscles. Apolipoprotein AI has also been shown to activate LCAT enzyme.

Alber et al. (1976) showed that Apo AI showed a slight increase with age in men and women. Apo AI levels correlated closely with HDL cholesterol. It was weakly related to total triglyceride in women but was inversely related in men. Women on estrogens have the highest AI levels (149 mg/dl ± 26 mg/dl) followed by

women on combination oral contraceptives (141 mg/dl ± 26 mg/dl) whereas women on non-medication had lower levels of (129 mg/dl ± 25mg/dl). But men had lowest levels (120 mg/dl ± 20mg/dl) in a separate group of 14 women given estrogen for 2 weeks (1mg/kg/day) Apo AI increased by 24%. Thus AI is increased by exogenous and most likely endogenous estrogen. Among hypertriglyceridemia men both AI and HDL cholesterol values were decreased (115mg/dl ± 20 and 37mg/dl ± 3 respectively). But were significantly lower among group of M.I survivors (107 mg/dl ± 16 and 27 mg/dl) HDL levels and the content of cholesterol in HDL associated with AI appear to be decreased in CAD.[49]

Apo AI and Apo AII constitute about 90% of total HDL protein with an Apo AI to Apo AII ratio about 3:1 by weight. Apo AI and Apo II plasma levels are less than 30% of normal in patients with LCAT deficiency and less than 5% of normal in untreated hyperglycaemic patients. Patients with familial HDL deficiency (Tangier's disease) have Apo AI plasma levels that are 1% less of normal where in APO AII levels are around 7% of normal.[50]

RELATIONSHIP OF METABOLISM OF APOLIPOPROTEIN AI TO ATHEROGENESIS:-

It is clear that the number of cholesterol molecules (particularly the esterified cholesterol) in each HDL particle and to number of HDL particles determine the plasma concentration of HDL cholesterol we cannot state with similar certainty why HDL cholesterol (which is considered a measure of cholesterol ester enrichment of HDL particles) and Apo AI (which is considered as an indicator, of the number or HDL particles) concentration in plasma are such strong predictors of risk for development of atherosclerosis.

Several studies have shown that humans deficient in Apo AI (caused by mutations in the gene) appear to be predisposed to atherogenesis. Several studies have shown that mice expressing human AI gene to understand the role of this gene in atherogenesis C57BL 16, a strain of mice when fed on high fat diet, showed reduced levels of HDL as compared to normal mice. They subsequently developed atheromatous plaque.[51]

Reubin et al. showed that transgenic (57BLl6) mice over expressing human Apo AI were significantly protected from the development of fatty streak lesions. These studies suggest that high plasma levels of Apo AI have a direct inhibiting effect on the early stages of atherogenesis. The genes of apoproteins, especially Apo AI, are located on long arm of chromosome number 11.[52]

The genes of apoproteins have been cloned, and their structure, properties and chromosomal locations have been determined. One approach to determine the cause of lipoprotein diseases is to look for polymorphism of the apoprotein genes. A restriction fragment length polymorphism (RELP) refers to altered pattern of gene fragments resulting from some abnormality in the structure of genomic DNA. The most widely studied RELP involving the apolipoportein gene involves the genes for Apo AI and Apo CII. These polyrnorphisms in Apo AI genes is usually associated with hypertriglyceridemia low HDL coronary heart disease and familial combined hyperlipidemia.[53]

It appears that only in cases does a local HDL level simply mean that an individual makes less of the structural components of HDL (particularly Apo AI) or that there is a defect in the initial step in reverse cholesterol transport (that is efflux of

free cholesterol from cells to HDL 3) Low HDL cholesterol levels are commonly associated with other lipid and lipoprotein abnormalities.

In particular increased plasma levels or VLDL and LDL (or chylomicrons and their remnants) might not only serve to stimulate HDL cholesterol ester transferase but also to deliver of cholesterol esters into the vessel wall. The latter could be mediated directly by these lipoproteins or via their conversion to LDL. Thus, when the number of Apo B lipoproteins in plasma is increased, the later steps of reverse cholesterol transport may be altered and HDL derived cholesterol esters may be transported back to peripheral tissues including the vessel wall[46].

This scheme would explain the commonly observed clinical relationship between hypertriglyceridemia, HDL cholesterol levels (with cholesterol ester depleted particles) and atherosclerosis. Increased exchange of HDL cholesterol esters for triglycerides could also lead to accelerated removal of Apo AI from plasma by the kidney. Increased Apo AI removal from plasma would lead to reduced number of HDL particles with circulation further compromising reverse cholesterol transport. Apart from serving as a vehicle for reverse cholesterol transport, HDL also has other potential mechanisms for the antiatherogenic nature including its ability to remove cholesterol directly from foam cells in atherosclerotic lesions, its ability to protect LDL from oxidative modification and its role in the metabolism of eicosanoids. These additional mechanism when added to the likely role in HDL increase cholesterol transport, may explain the powerful antiatherogenic potential of HDL.

APO B CONTAINING LIPOPROTEINS

The two isoforms of apolipoprotein (Apo B), Apo B-48 and Apo B -100 are important proteins in human lipoprotein metabolism. Apo B - 48, so named because it

appears to be about 48% of the size of Apo B-100 on sodium dodecylsulphate (SDS) - polyacrylamide gels, is synthesized by the intestine in humans. Apo B-100 which is produced in liver in humans is required for the synthesis and secretion of VLDL. LDL which contains about 2/3rd of Cholesterol in human plasma is metabolic products of VLDL. Apo B-100 is virtually the only protein component of LDL.[54]

Elevated concentration of Apo B-100 and LDL cholesterol in plasma are recognised risk factors for developing atherosclerotic CAD. Because of the Central roles of the two isoforms of Apo-B in lipoprotein metabolism and the atherogenic potential of Apo-B containing lipoproteins Apo-B has been a prime target for study by investigators in the lipoprotein and arteriosclerosis field.[54]

ROLE OF APO B IN LIPOPROTEIN METABOLISM:

Apo B-100 containing lipoproteins are assembled within hepatocytes secreted into the space of disease, and ultimately enter the circulation through the hepatic vein. Most of the Apo B-100 is secreted from the liver on triglyceride rich VLDL particles, which also contain Apo E and various Apo C's after release of nascent VLDL particles into the blood stream, the initial phase of their metabolism resemble that of chylomicron. The triglyceride rich core of VLDL particles is hydrolysed by lipoprotein lipase along the capillary endothelium.[55]

As the particles core reduced in volume, the Apo B-100 and Apo E on the Surface of VLDL particle probably change their configuration is such a way that they can serve as ligands for uptake of the particle by hepatic receptors. Probably one half of all VLDL particles are removed from the circulation into liver through in interaction with the LDL receptor (also known APO - B, receptor). The other half remains in the circulation and is further metabolised to denser particles of the LDL

fraction. The half-life of VLDL particles in the plasma is heterogeneity ranging from minutes to hours.[55]

Existing evidence suggests that large VLDL particles which may contain a substantial number of Apo E molecules are quickly removed from the circulation whereas smaller VLDL particles stand to be metabolised more slowly. With a greater likelihood of being metabolised to the smaller, denser particles of the IDL and LDL fractions. By the line to particles are metabolised to the size and density of LDL large, they have become enriched in cholesterol esters, and virtually the only remaining protein component is Apo B-100. The average evidence time of LDL is 2-3 days, about 80 % of LDL receptor and the remainder by non-receptors pathways. Approximately one half of the LDL is removed from human plasma by the liver, once LDL is bound and internalised by cells, it is directed to the lysosomes where both its protein and lipid components are digested.[55]

APO B-100 concentration can be re-measured by a variety or immunoassays and normal levels ranges from 60 to 120 mg/lit. More than 90% of the APO B-100 within the plasma of normal lipid mimics and individuals is contained within the LDL fraction; hence there is normally very little difference between the total plasma Apo B and LDL Apo B levels. The LDL size and chemical composition are known to be heterogeneous in the population, and more of the heterogeneity is probably due to genetic factors. A variety of data indicates that plasma of patients with CAD tends to contain an increased number of small, dense LDL levels to contain as increased number of small, dense LDL particles that have a decreased cholesterol ester to Apo B-100 ratio. The metabolic basic for tissues finding is incompletely understood but is under active investigation to recommend measuring Apo B levels in addition to LDL

cholesterol levels in patients at risk for CAD, Apo B-100 can become associated with Apo (a) a large glycoprotein structurally related to plasminogen to a unique lipoprotein Lp (a).[5]

STRUCTURE OF APO-B 100:

Apo B is known to be a glycoprotein, with about 4-9% of its mass as carbohydrate linked to asparagine. There are 19 potential linked glycosylation sites on apo B by direct sequence. Apo B-100 is reportedly post transnationally modified by conveniently bound fatty acids. There are seven different regions of Apo B-100 molecule that strongly bind to heparin. Heparin binding sites on Apo B may serve to promote the binding of triglyceride rich lipoproteins to the capillary endothelium where their lipid cores are digested by lipoprotein lipase.[56]

Apo B contains 25 cysteine residues and these are distributed in asymmetric fashion within the molecule 12 occur within the first 500 residues. Sixteen of the 25 cysteines are known to exist in disulfide form including all 12 in the first 500 amino acids. Recently colomental reported that there are two free cysteine in LDL - Apo B 100 located at positions 3,734 and 4,390. Either of these carboxy terminal cysteines (or both) could potentially form a disulphide bond with Apo (a) to form lp(a). Apo B 100 contains numerous hydrophobic remains throughout its length that are believed to be important in lipid binding. In addition, there are nine amphipathic helices found in the putative lipid binding domains of other apoplipoproteins. Nearly all of the Apo B 100 sequences are located in the carboxy terminal half of Apo B 100 molecule sequences predicted to form amphipathic B sheets and B turns, these are located throughout the Apo B source except for the amino-terminal 1,000 amino acids.

All though amphipathic these structure are thought to have high lipid binding potential. Thus Apo B has many potential lipid binding regions throughout its length. As a result thought to be adequate for explanation of the fact that Apo B never exchanges between lipoprotein particles. In contrast to other apoplipoproteins, which have one of two putative lipid binding domains and radially exchange between lipoproteins.

Young and co-workers found that a truncated Apo B of 2046 amino acid (Apo-B 46) was found primarily in the 1.006 G/ml fraction of both fasting and post prandial plasma, but a large portion of the Apo B 37was contained in the HDL fraction a sub fractions of HDL and in the 1.21G/ml fraction. So the shorter the Apo B protein, the denser and more lipid poor the particles. There are regions of the Apo B molecule on LDL particles that were accessible to trypsin and therefore readily releasable from LDL, particles (The Trypsin releasable (TR) peptides) and the portion that were accessible only after the LDL particles and been decapitated and retrypsinized) (the trypsin non releasable (TN) peptides) some peptides were contained in both the TR and TN fraction they were designated mixed (MX) peptides. All together they sequenced more than 88% of the Apo B-100 proteins with many peptides being repeatedly sequenced.[56]

On the basis of trypsin releasability of various regions of the molecule, they identified five broad domains of Apo B on LDL particles : domain I amino acid 1-1000 predominately TR, domain II amino acids 1001 to1,700 alternating regions of TR and TN peptides with an significant proportion of MX peptides , domain III amino acids 1,701 to 3070 occasional TR peptides but primarily TR regions, domain IV amino acids 3,071-4, 100 mainly TR and mix peptides and domain V amino acids

4101-4536 almost excluding TN peptides in general the more hydrophobic the region, the less likely it was to accessible to trypsin.

For several years, it has been observed that the LDL receptor binding regions of Apo B 100 is in the carboxy terminal portion of the molecule. The receptor studied by Miline and co-workers, may determine the location of the epitopes of more than 30 Apo B- 100 specific monoclonal antibodies and which of the antibodies were capable of inhibiting the binding of LDL particles to the LDL receptor. The antibodies with epitopes located between amino acids, 2,980 and 3,780 completely block the surface binding of LDL to the LDL receptor when bound to LDL antibodies that bind to epitopes immediately flanking this region partially block binding of LDL to its receptor, whereas non clonal antibodies binding of LDL antibodies binding elsewhere in the molecule had for the most part little or receptor blocking activity.[57]

Apo B-100 is virtually the only protein of LDL a cholesterol-ester enriched class of lipoproteins that are metabolic products of VLDL. The Apo B-100 of LDL serves as a ligand for the LDL receptor mediated uptake of LDL particles by the liver and extra hepatic tissues. The LDL receptor binding regions Apo B-100 is located in carboxy-terminal portion of the molecule, whereas the lipid binding regions appear to be broadly dispersed throughout its length. Apo B-48 contains the amino-terminal 2,152 amino acids of Apo B-100 and is produced by the intestine as a fault of editing of a single nucleotide of the Apo B RNA, which changes the codon specifying Apo B 100 amino acids 2,153 to a premature stop codon.[57]

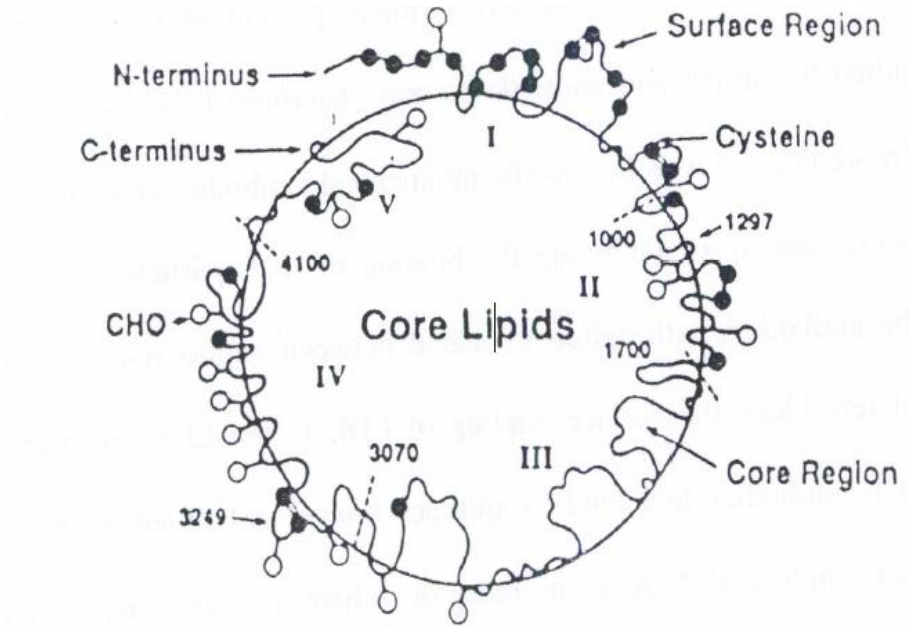


FIGURE 2. Schematic diagram of apolipoprotein (Apo) B 100 structure on low density lipoprotein particle. Tile location of 01'0series where thrombi" cleaves Apo B on low density lipoprotein particles (residues 1,297 and 3, 2-19) are indicated. Indicated are the locations of 16 N-linked carbohydrates (CHO; c), cysteineresidues (.) and disulfide bridges (=). Additional data on disulfide bridges are given in subsequent abstract.[5] Trypsin releasable regions of Apo B are shown on outside of particle; trypsin non-releasable regions are inside core of particle. Young and co-workers[58] emphasized the surface SILS core location of apo l peptides shown in this illustration is hypothetical. [59]

Apo B 48 and Apo B 100 are included on chromosome 2 by a single gene that contains 29 exons and 28 introns. A missense mutation in the codon for Apo B 100 amino acid 3,500 is associated with hypercholesterolemia. This mutation results in the poor binding of Apo B to the LDL receptor, thereby causing the cholesterol ester enriched LDL particles to accumulate in the plasma. This disorder is called familial defective Apo B 100; and is probably a cause of premature atherosclerotic disease. Familial hypo betalipoproteinemia is a condition associated with abnormally low

levels of Apo B and cholesterol affected individuals may actually evidence suggests that neither familial defective Apo B 100 nor familial hypobetealipoproteinemia is particularly rare, thus Apo B mutations may help explain a small portion of the variation in serum cholesterol levels in the general population. Future research will undoubtedly uncover many more Apo B gene mutations affecting cholesterol levels.

NEW RISK FACTORS OF IHD:

Above discussed conventional risk factors are commonly observed risk factors for IHD. However many patients have precautious atherosclerosis without having any of these standard risk factors. Identification of other markers that increased the risk of CAD may improve our understanding of pathophysiological mechanisms of this disorder and allow the development of new preventive and therapeutic measures. As high as 100 risk factors are identified as putative new risk factors in the causation of' CAD.[60] Important amongst them are, proposed newer cardiovascular disease risk factors.

1) Pro-atherogenic (increased levels):-

1. Homocysteine.
2. Lipoprotein particle oxidation
3. Hyperinsulinemia
4. Cholesterol ester transfer protein.

2) Prothrombogenic (increased levels):-

1. Plasminogen
2. Fibrinogen
3. Factor VII
4. Plasminogen activator inhibitor I
5. Lipoprotein (a)

3) Antiatherogenic (decreased levels):-

1. ApolipoproteinA1
2. Lecithin - cholesterol acyl transferase
3. Hepatic lipase
4. Low density lipoprotein receptor
5. Apolipoprotein E

4) Other new risk factors:-

1. Micro albuminuria
2. Infections (chlamydiapneumoniae, helicobacter pylori, viruses-cytomegalo virus, herpes -simplex,Epsteinbar virus)
3. Endothelial dysfunction
4. Decreased thrombomodulin
5. Intrauterine growth retardation / weight and height at one year of life (Barker hypothesis)
6. Coronary artery calcification in young adults
7. Increased C reactive protein.

1. LIPOPROTEIN(a) :-

Although Lp (a) is similar to LDL in core lipid composition and having B-100 as a surface apolipoprotein (Apo), it is recognised as a distinct lipoprotein class that also contains the unique glycoprotein Apo(a) which is disulphide bound to Apo-B 100. It has a striking homology to human plasminogen.[61]

The Apo (a) gene is expressed in first 2-5 days of postnatal life. Full expression of Apo (a) gene by 8-24 months of age has been documented, with infants having Lp(a) levels identical to that of their affected parents. Early expression of this

gene results in virtually a lifelong exposure to this powerful risk factor and in various studies it was found that Lp (a) causes premature atherosclerosis and M.I. even in the absence of conventional risk factors.[61]

Its levels are genetically determined with environmental factors having only negligible impact LP(a) levels>30mg/dl are generally considered the threshold at which high risk at premature CAD increases rapidly.

Serum levels of LP(a) vary 10 - fold among populations and 1000 fold among individuals. Its levels vary from 0 to more than 200 mg/dl, but remain remarkably constant in a given person from infancy to death. LP(a) levels are governed almost exclusively by race, ethnicity and genetics, unlike other blood fats, the levels of which are influenced by age, gender, diet and other environmental factors.[61]

By virtue of its structural homology to plasminogen it prevents conversion of plasminogen to plasmin and hence acts as antifibrinolytic. This genetically determined lipoprotein also promotes early atherosclerosis, its atherogenicity is 10 times higher than LDL and 15 times higher than total cholesterol.

Lp(a) assumes its maximum levels in infancy; hence it begins to block the arteries 10-20 years earlier than other risk factors. This explains why people with high levels of Lp(a) develop CAD at a very early age in the twenties and thirties. A high level of Lp(a) is now considered a stronger risk factor than diabetes in premenopausal women. A family history of early M.I. in combination with high Lp(a) levels is now considered a strong indicator of MI or death at an early age, unless aggressive corrective measures are taken.

Enas et al. were the first to report high level of Lp (a) in Asia. Elevated Lp (a) was the most common risk factor in CADI study. Although levels >30 mg/dl were found in 25% of Asia and other studies in north America shows an even higher prevalence of elevated Lp(a) as high as 50 %. A genetic predisposition to CAD in also is strongly supported by several reports of high levels of Lp(a) in Asia, Canada, Singapore, UK and India.[61]

2. Hyperproinsulinemia.

It is defined as a situation in which the plasma insulin is higher than the expected for a given plasma glucose concentration. Hyperinsulinemia may occur in the presence of normoglycemia or hyperglycaemia but raised plasma insulin with normal plasma glucose is diagnostic of hyperinsulinemia.[62]

Proinsulin is the precursor of insulin proinsulin contains insulin A and B chain and the connecting peptide. The conversion of proinsulin takes place within secretory granules of the pancreatic beta cells.

Recent data suggest that proinsulin is strongly associated with cardiovascular risk factors in diabetic subjects. Haffnner et a1.[63] studied the relation of proinsulin to lipids obesity (body mass index) and waist to hip ratio. Fasting insulin was significantly associated with body mass index, waist to hip ratio, triglycerides and systolic blood pressure, but not to diastolic blood pressure .Fasting proinsulin was significantly associated with body mass index, waist to hip ratio, triglyceride, systolic blood pressure and diastolic blood pressure proinsulin was more strongly related to elevated triglycerides level.

Further studies are needed to establish whether proinsulin and insulin like molecules are casually related to the pathogenesis of NIDDM and IHD. In the present state of knowledge it appears unlikely that either Hyperinsulinemia or hyperproinsulinemia are the main etiological factors in pathogenesis of either NIDDM or IHD. It is more likely that the etiology of these conditions is due to a complex interplay of genetic and environmental factors both known and unknown.

Insulin has both atherogenic and antiatherogenic properties. In the presence of normal amount of insulin without insulin resistance antiatherogenic properties supervene which causes vasodilatation, nitric oxide formation and prevention of vascular smooth muscle cell (VSMC) proliferation and migration.[63]

In presence of insulin resistance excess amount of proinsulin is secreted which causes atherogenesis by immigration of VSMC and formation of foam cells. Hence it is a new risk factor of CAD.

3. Microalbuminuria:-

From various studies (Ex..Haffnner et al.,) it was found that Microalbuminuria (i.e. C.A 20 to 200) acts as a risk factor for CAD both in diabetic and non-diabetic patients.

4. Plasminogen activator inhibitor (PAI):-

Decreased fibrinolytic activity may result from elevated levels of PAl-I. In any case control and cross sectional studies Plasma PAI-l has been reported to be increased in patients with CAD. For example in a study of and woman who had a M.I. before age 45, PAI-I level was higher than in healthy subjects. This study also found PAI-l level was found to be directly related to insulin level, confirming the role of

PAI-l in the insulin resistance syndrome. Increased PAI-l has also been shown to be a risk factor re-infarction in a prospective study of men whose first MI occurred before age 45. In addition to systemic increases in PAl-I, atherosclerotic lesions have been found to contain higher levels of PAl-I than the normal arterial wall.[64]

5. Homocysteine:-

Plasma homocysteine is elevated in patients with homozygous homocystinuria, a rare autosomal recessive disorder, but levels are also increased in patients with CAD who do not have homocystinuria. Homocysteinemia has been established as an independent risk factor for coronary vascular disease,cerebrovascular disease and peripheral vascular disease.[65]

In 271 men in the physicians health study who had a MI during the 5 years study plasma homocysteine level was significantly higher (mean l1.1 nmol/ml) than in controls matched for age and smoking habits (mean 10.5 nmol/ml/dl).Compared with subjects with plasma homocysteine, no higher than the 90th percentile, relative risk for subjects with plasma homocysteine above the 95th percentile was 3.4 after adjustment for other cardiovascular risk factors.[65]

Although the precise mechanism by which elevated plasma homocysteine increases risk for CAD has not been determined, possibilities include endothelial damage and altered anticoagulant activity. Deficiency of vitamin B6 and B12 and folic acid can cause elevated plasma homocysteine, and supplementation with these vitamins can decrease plasma homocysteine.[65]

6. Fibrinogen:

Thrombogenic factors have been demonstrated to predict CAD events.Although elevated fibrinogen levels occur in conjunction with other CAD risk factors such as age, cigarette smoking, hypertension and obesity, fibrinogen has been demonstrated to be an independent risk factor of CAD. In the 6 year follow up of 2116 men in the PROCAM study, mean plasma fibrinogen level was significantly higher in men who had coronary events (2.88 gm/litre) than in men who did not have events (2.63gm/litre) and the incidence of coronary events was 2.4 times higher in subjects the highest tertile of plasma fibrinogen distributor (72.77 gm/litre) than in subjects in the lowest tertile (<2.36 gm/litre). In combined analysis of the Caerphilly and speed well prospective studies which together evaluated almost 5000 men, age adjusted relative risk for IHD events was 4.1 for men in the highest quintile of fibrinogen distribution compared with men in the lowest quintile.[66]

7. Coagulation factors:

Increased levels of coagulation factor VII and VIII have been shown to increase risk of CAD. These factors lead to hypercoagulant state. [67]

8. Increased oxidative stress / low levels of circulating antioxidants:

Blood concentration of antioxidants may affect the susceptibility of LDL and Lp(a) to oxidation. Because lipoprotein oxidation is thought to be prerequisite to the recognition of these particles by the scavenger receptor on macrophages, decreased levels of substances that protect against oxidation may increase atherosclerotic risk.

9. Infections:

The potential role of common infectious agents in the pathogenesis and progression of atherosclerosis has been increasingly studied over the last decade.

Clinical data and clinical models suggest that common chronic infections may also contribute to the pathogenesis of atherosclerosis. [68] Some of the common are.

1. **Chlamydia Pneumoniae:**

Many studies implicate C. pneumoniae as the pathogen most likely to have an aetiological role in CHD.

Possible mechanisms: How Chlamydia pneumoniae enters atheromatous plaques and whether its presence reflects pathogenic involvement in the atherogenesis are not known.

Chlamydia pneumoniae is a plausible candidate for triggering and perpetuating inflammatory changes that contribute to the development of atherosclerosis. Infection with chlamydia pneumoniae might induce a chronic immune activation mediated by cytokines that contributes to direct, chronic endothelial cell damage or stimulates the synthesis of acute phase reactants such as Fibrinogen and CRP. Chronic infection might also increase expression of monocyte derived procoagulants such as tissue factor and thereby increases the risk of local or distant thrombosis.[68]

2. Herpes Virus:

Cytomegalo virus (CMV) is ubiquitous and like other herpes viruses is retained in a latent state for life. Most interestingly, CMV infection that is newly acquired or due to reactivation of latent virus has been associated with one of the most common complications of cardiac transplantation, accelerated atherosclerosis in the coronary arteries of the transplanted heart.[69]

Possible Mechanism: Infection with CMV leads to the expression of growth factors in the smooth muscle cells. It also activates a transcription factor in to

stimulating a broad range of genes including those that have roles in inflammatory and immune responses. The virus also increases the adhesion of leukocytes and platelets to endothelial cells by inducing cellular expression of adhesion molecules and causes changes that are procoagulant. [38]

3. Helicobacter pylori and atherosclerosis:

Epidemiological and clinical reports have suggested seropositivity for H-pylori may be a risk factor for CHD. However a recent prospective study investigating this association showed that H pylori seropositivity was not necessarily associated with atherosclerosis. More studies are needed to study this association.[38]

10. Endothelial Dysfunction:

The present concept of pathogenecity of atherosclerosis is based on response to injury hypothesis initially proposed by Russell Ross. The initiating event in atherosclerosis is an injury to endothelium leading to atherogenic cascade.[70]

FACTORS CAUSING DIRECT DAMAGE TO VASCULAR ENDOTHELIUM

A number of factors are involved in causing this injury and is shown in the following**.**

1. Sheer stress and mechanical factors
2. Cigarette smoke
3. Oxidised LDL cholesterol
4. Homocysteine
5. Environmental toxins
6. Free radicals
7. Virus and bacteria
8. Immunological injury.

This injury may alter the functional characteristics of the endothelium leaving the endothelial morphology intact. This endothelial injury could alter the permeability of the endothelium. It is non thrombogenic character, its ability to form vasoactive substances and growth factors and its ability to regenerate. Endothelial injury can also lead to endothelial cell to cell non disjunction and endothelial retraction, exposing the underlying connective tissue and accumulation of foam cells, such as macrophages that form the first and ubiquitous lesion of atherosclerosis the fatty streak.

On the basis of available data it appears that at least two processes are pivotal.

1. An enhanced focal endothelial transcytosis of plasma proteins including LDL which accumulates in the widened edematous proteoglycan rich subendothelial space.
2. The preferential recruitment of blood monocytes to the intima, a process that is markedly augmented by even short periods of hyperlipidemia. The cause of initial endothelial damage and subsequent triggering and perpetuation of inflammatory changes is not well known in patients who do not have hyperlipidemia.

11. Coronary Artery Calcification:

The relationship between coronary artery calcification and atherosclerotic plaque has been established in post-mortem heart specimens. Calcified deposits detected radio graphically correlate with an identifiable atherosclerotic plaque on histological examination and these deposits occur almost exclusively with CAD is present, especially in younger populations. Coronary artery calcification has been shown to be associated with coronary risk factors.[71]

12. Intra Uterine growth retardation (IUGR) (Barrker hypothesis):

According to this hypothesis if antenatal nutrition is poor it causes IUGR. The developing islet cells of pancreas are adjusted to such microenvironment and subsequently after birth if nutrition is poor it causes low weight and height at one year, and islet cells are programmed to such low levels of nutrition. If subsequently in the later life is followed by abundant food supply, westernised life style that impairs burden on the pancreas causes secretion of proinsulin causes insulin resistance .This ultimately results in diabetes mellitus, dyslipidemia and ultimately CAD .This is confirmed in a cohort study in Hertford Shire in England.[72]

13. Decreased Thrombomodulin.

Thrombomodulin is an integral membrane glycoprotein secreted by endothelium, which has a major role in the regulation of intravascular coagulation and acts as a marker of endothelial damage.[73]

Functions:

Increased expression of thrombomodulin (e.g. endothelial damage, activates C reactive proteins and increases its production the activated protein C breaks down factor Va and VIII and hence prevents thrombus propagation and tilts its balance towards fibrinolysis. Hence patients with abnormalities in structure or concentration of thrombin have an increased risk of thromboembolic disease.[73]

14. Increased CRP:

It is one of the acute phase reactant and is elevated where there is endothelial injury. Various studies indicated that during acute phase of M.I. if CRP is raised, it is a poor prognostic indicator.[74]

HISTORICAL REVIEW

The earliest isolation of the protein lipid complex dates back to 1949, when Macheboef in an experiment successfully isolated it from horse plasma. Geomanetal in early 1950's brought out the role if lipoprotein in atherogenesis.[75] Alaupovic et al. in 1964**,** provided the basis of new system in which lipoproteins are classified into families, each of which contain a distinct apolipoprotein, they classified and recognised apolipoprotein, as A, B, and C.[76]

Riesan et al[77], has indicated that apolipoprotein A and B levels, total cholesterol and LDL- C are good discriminators of the severity of coronary heart diseases, while HDL-C is more suitable practice for epidemiological studies of 63 patients who underwent coronary angiography 30 patients had 50% or more stenosis, among these patients 71% had hyperlipoproteinemias. Maciejko et al., who assayed apolipoprotein AI in 83 angiographically assessed patients of coronary artery diseases stoned a significant disease in its level when compared with subject coronary artery disease, thus they concluded that apolipoprotein AII has itself is more useful than HDL - with for identifying patients with coronary artery disease.[78]

Sainani et al., in case control study of 225, angiographically assessed coronary artery disease patients, showed that the level of apolipoprotein AI and Apo B/A inversely proportional to coronary artery disease.[12]

In a study of serum lipids apoplipoproteins among students whose parents suffered prematurely from a myocardial infarction, Se Backer et al**.,** have observed highly significant differences between cases and control subject appropriate in A1 levels. This goes to show that positive family history has consequence on coronary heart disease.[79]

In a series of 304 patients undergoing coronary angiography and identifying significant coronary artery disease. Kottke et al., have shown that apolipoprotein followed by Apolipoprotein AII B, were better discriminators than plasma coronary artery disease. It did not however predict the severity of the disease.[80]

Onitri and Jover, in their study, reported significantly low levels of apolipoprotein A I in survivors of myocardial infarction. They also found that the ratio of Apo AI to Apo B significantly low in patients of Myocardial infarction.[81]

Darne, Tasker et al., who studied 60 Myocardial Infarction survivors, showed that these patients showed a decrease in apolipoprotein AI levels and the ratio of apolipoprotein AI Apo 8 was significantly low in these subjects.[82]

Cho JY et al[83] (2010) conducted a study on high Lipoprotein (a) levels are associated with long-term adverse outcomes in acute myocardial infarction patients in high Killip classes. They measured serum Lp(a) levels in 832 consecutive AMI patients on admission. It was concluded that, in patients in high Killip classes, high serum levels of Lp(a) were significantly associated with long-term adverse outcomes after AMI.

MATERIALS AND METHODS

50 patients of Ischemic Heart Disease and 50 age and sex matched healthy controls will be included in the study who are attending R.L.JALAPPA HOSPITAL, affiliated to SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

STUDY PERIOD- DECEMBER 2010- NOVEMBER 2011.

Inclusion Criteria

1. Patients with clinically and electrocardiographically proven ischemic heart disease.

Exclusion Criteria

1. Patients aged less than 18 years.

METHODOLOGY

Subjects will be selected according to the above mentioned criteria and detailed history and physical examination will be done. The levels of Lipoprotein(a) were measured in Ischemic heart disease patients and 50 age and sex matched controls. Lipoprotein(a) levels were measured by Immuno-turbidometry method. Detailed history taking, physical examination and following investigations were assessed.

INVESTIGATIONS

1. Complete haemogram
2. Urine Routine
3. ECG
4. 2D Echo
5. Serum Lipoprotein(a)
6. CK-MB or Cardiac troponin

7. Lipid profile.

8. Random blood sugar /blood urea/serum creatinine

Study Design: A case-control study with 50 patients with Ischemic heart disease and 50 controls is undertaken to study the levels of LIPOPROTEIN(a)

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the *present* study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data are made, **Assumptions: 1.**Dependent variables should be normally distributed. 2. Samples drawn from the population should be random; Cases of the samples should be independent.

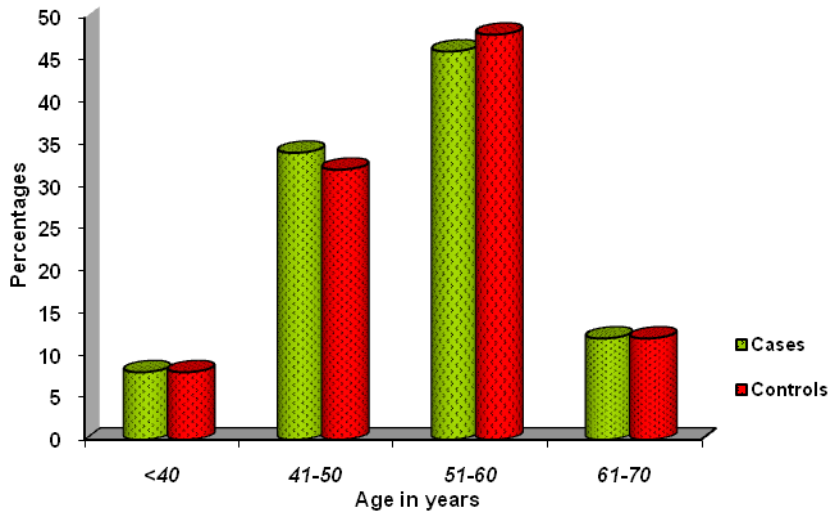
Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

Table 1: Age distribution of patients between 2 groups

Age in years	Cases		Controls	
	No	%	No	%
<40	4	8.0	4	8.0
41-50	17	34.0	16	32.0
51-60	23	46.0	24	48.0
61-70	6	12.0	6	12.0
Total	50	100.0	50	100.0
Mean ± SD	50.44±11.18		50.64±11.23	

Samples are age matched with P = 0.929

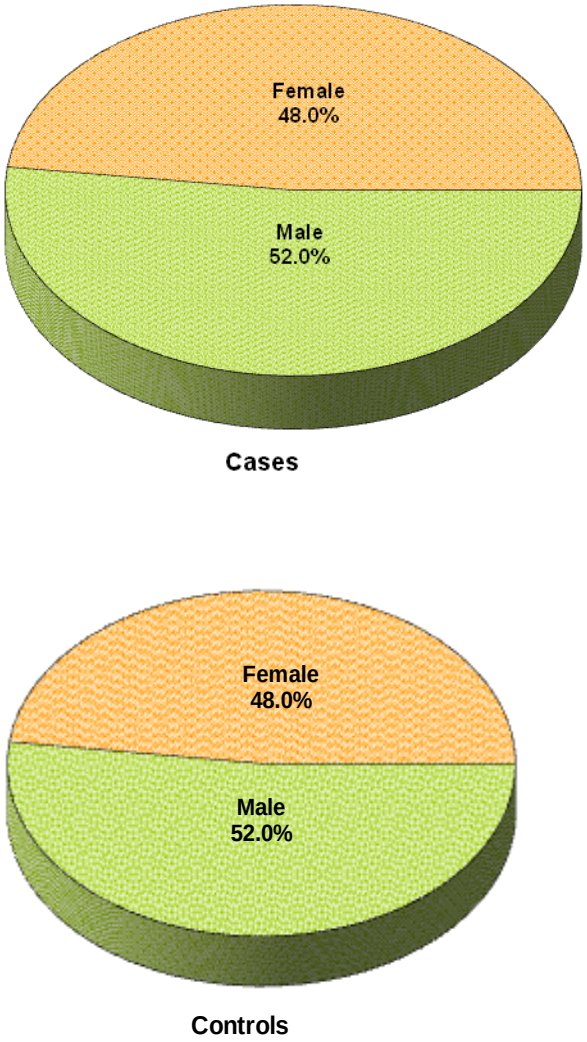


Graph1: Depicting age between cases and controls

Table 2: Gender distribution between 2 groups

Gender	Cases		Controls	
	No	%	No	%
Male	26	52.0	26	52.0
Female	24	48.0	24	48.0
Total	50	100.0	50	100.0

Samples are gender matched with P =1.000

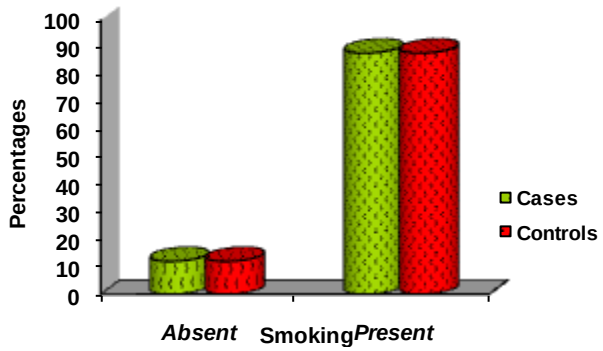


Graph 2: Depicting gender distribution between 2 groups

Table 3: Distribution of co morbid conditions between 2 groups.

Co morbid conditions	Cases (n=50)		Controls (n=50)		P value
	No	%	No	%	
Smoking					
• Absent	6	12.0	6	12.0	1.000
• Present	44	88.0	44	88.0	
Hypertension					
• Absent	6	12.0	6	12.0	1.000
• Present	44	88.0	44	88.0	

Graph 3: Depicting co-morbid conditions between 2 groups



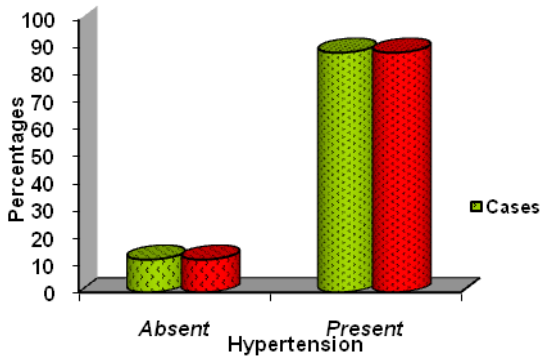
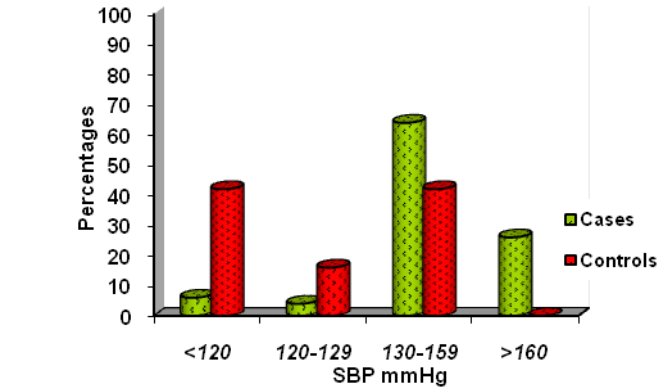


Table 4: Distribution of blood pressure of two groups of patients studied

Blood pressure	Cases (n=50)		Controls (n=50)		P value
	No	%	No	%	
SBP mmHg					
• <120	3	6.0	21	42.0	<0.001**
• 120-129	2	4.0	8	16.0	
• 130-159	32	64.0	21	42.0	
• >160	13	26.0	0	0.0	
DBP mmHg					
• <80	1	2.0	2	4.0	<0.001**
• 80-89	5	10.0	14	28.0	
• 90-99	27	54.0	34	68.0	
• >100	17	34.0	0	0.0	

Graph 4: Depicting the blood pressure between 2 groups



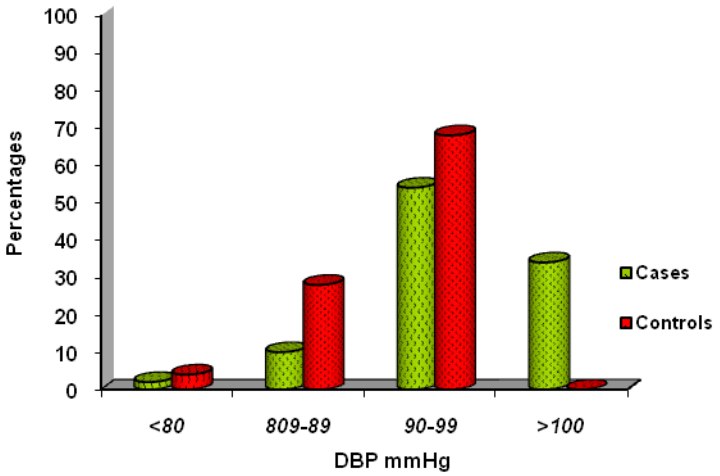
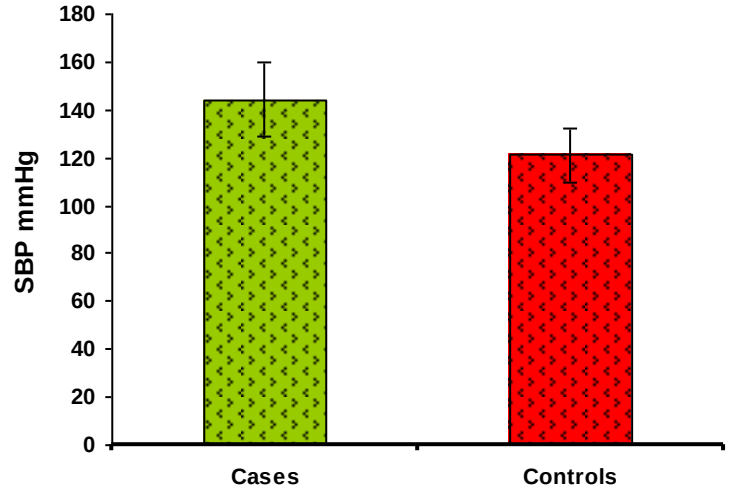


Table 5: Comparison of BP parameters between 2 groups.

Blood pressure	Cases	Controls	P value
SBP mmHg	144.20±15.46	121.16±11.53	<0.001**
DBP mmHg	94.96±8.07	88.24±6.07	<0.001**

Graph 5: Comparison of blood pressure between 2 groups



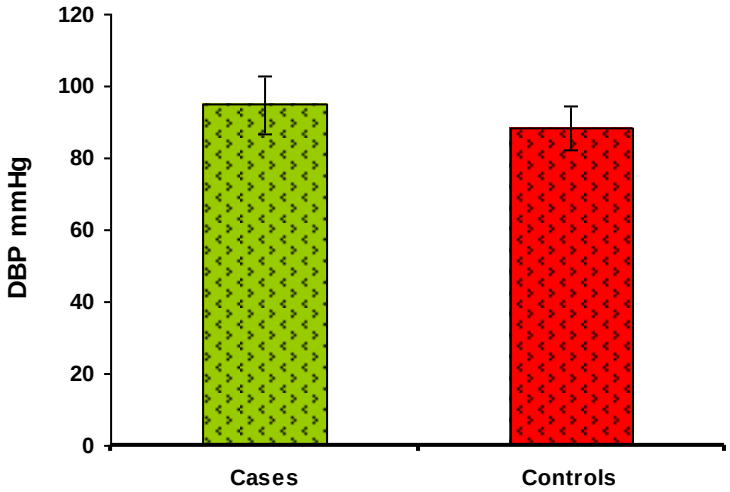


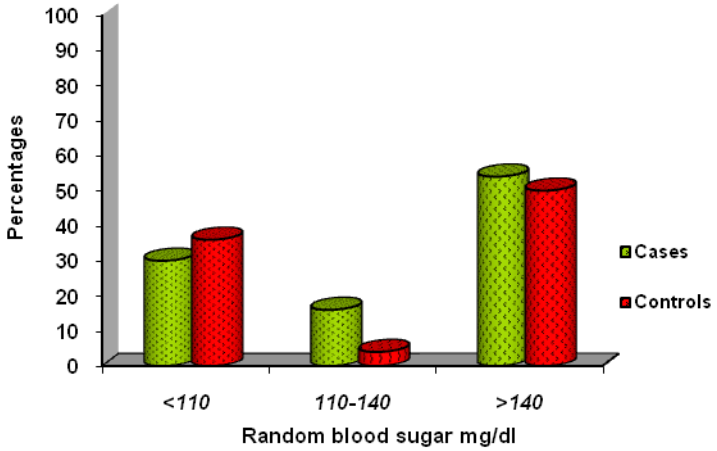
Table 6: Comparison of hematological parameters in two groups of patients studied

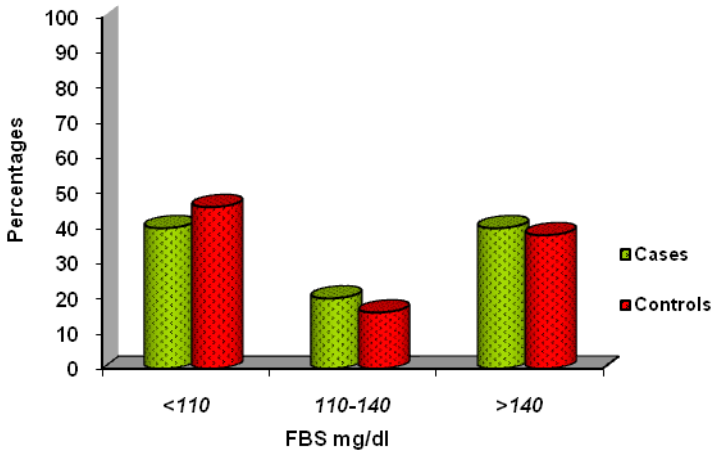
Hematological parameters	Cases	Controls	P value
Hemoglobin mg/dl	11.33±1.45	14.60±1.01	<0.001**
Total count	9467.50±2402.52	12392.98±1910.21	<0.001**
ESR	20.00±5.29	17.34±2.93	0.002**
Platelet count	2.39±0.76	3.08±0.86	<0.001**

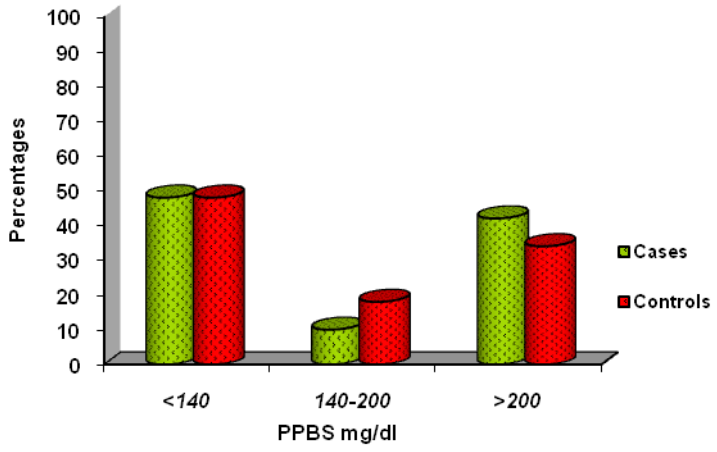
** Statistically highly significant

Table 7: Distribution of sugar parameters between two groups

Sugar parameters	Cases (n=50)		Controls (n=50)		P value
	No	%	No	%	
Random blood sugar mg/dl					
• <110	15	30.0	23	36.0	0.068+
• 110-140	8	16.0	2	4.0	
• >140	27	54.0	25	50.0	
FBS mg/dl					
• <110	20	40.0	23	46.0	0.809
• 110-140	10	20.0	8	16.0	
• >140	20	40.0	19	38.0	
PPBS mg/dl					
• <140	24	48.0	24	48.0	0.482
• 140-200	5	10.0	9	18.0	
• >200	21	42.0	17	34.0	



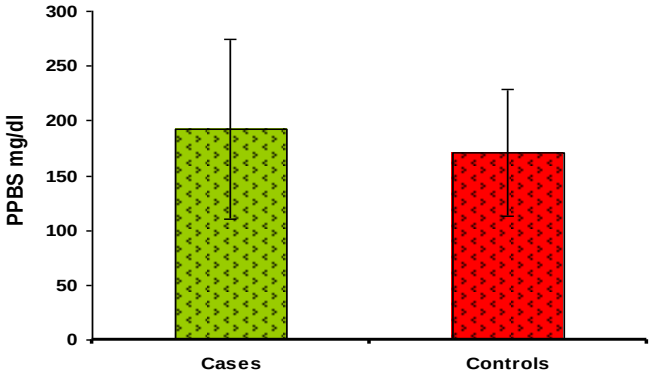


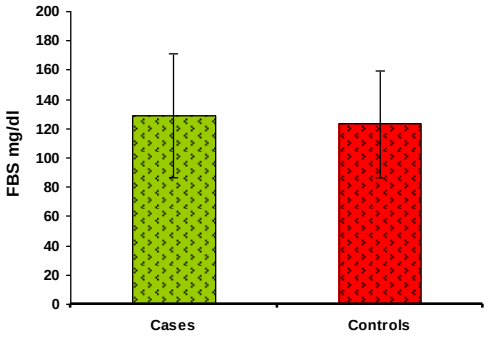


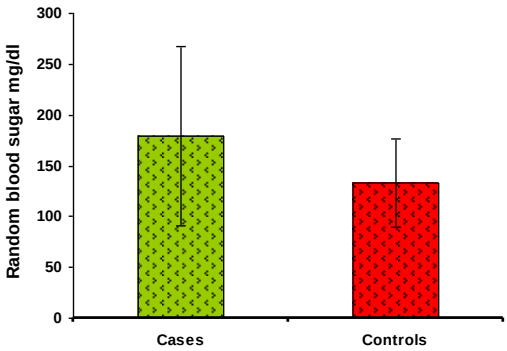
Graph 6: Depicting blood sugar parameters between 2 groups.

Table 8: Comparison of sugar parameters between 2 groups

Sugar parameters	Cases	Controls	P value
Random blood sugar mg/dl	179.02±88.71	133.56±43.43	0.002**
FBS mg/dl	129.16±42.43	123.08±36.39	0.444
PPBS mg/dl	192.50±81.83	170.94±57.53	0.131



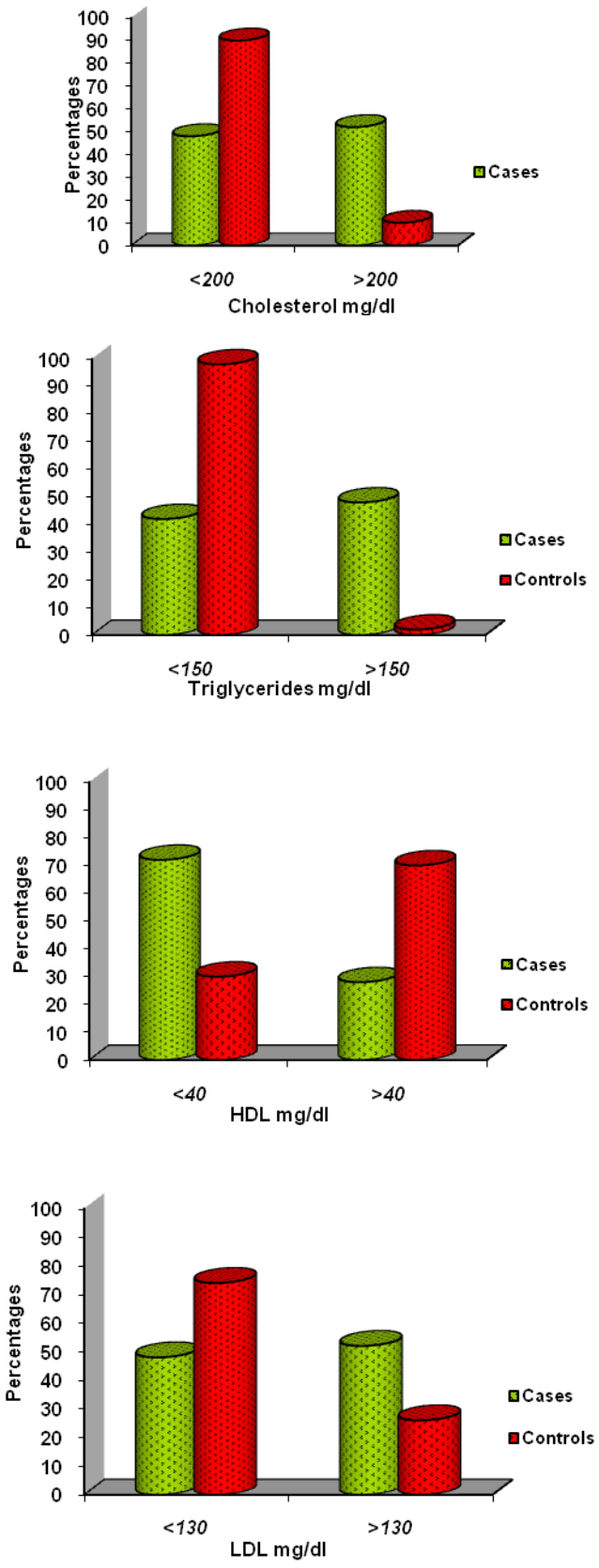




Graph 7: Comparison of sugar parameters between 2 groups.

Table 9: Distribution of lipid parameters between 2 groups

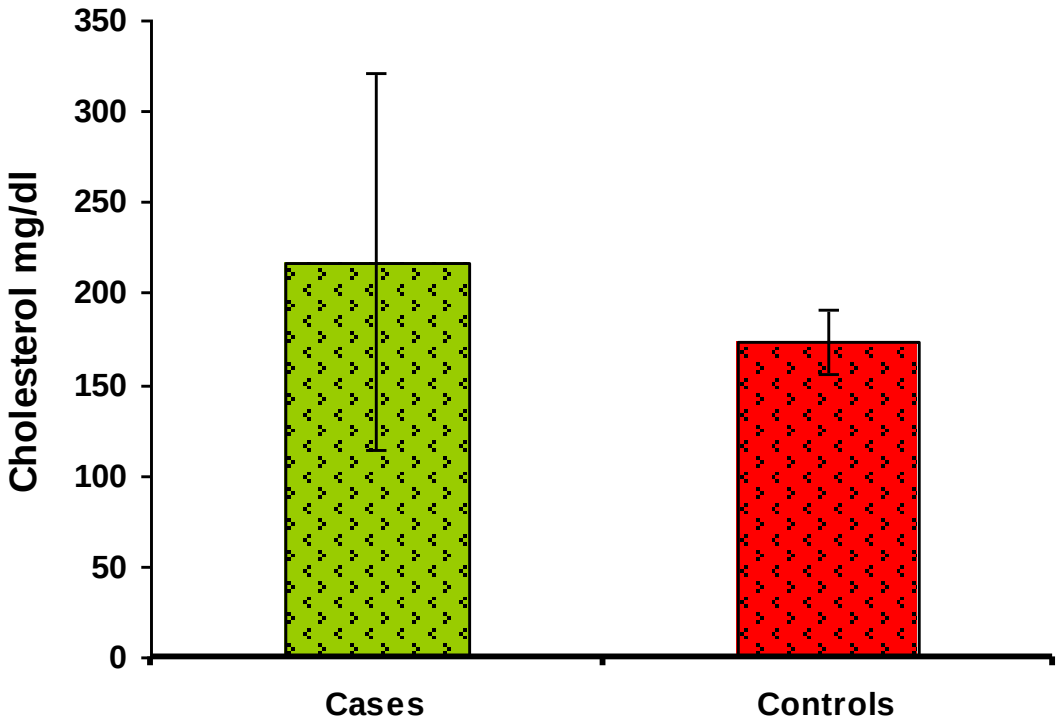
Lipid parameters	Cases (n=50)		Controls (n=50)		P value
	No	%	No	%	
Cholesterol mg/dl					
• <200	24	48.0	45	90.0	<0.001**
• >200	26	52.0	5	10.0	
Triglycerides mg/dl					
• <150	21	42.0	49	98.0	<0.001**
• >150	29	48.0	1	2.0	
HDL mg/dl					
• <40	36	72.0	15	30.0	<0.001**
• >40	14	28.0	35	70.0	
LDL mg/dl					
• <130	24	48.0	37	74.0	0.008**
• >130	26	52.0	13	26.0	

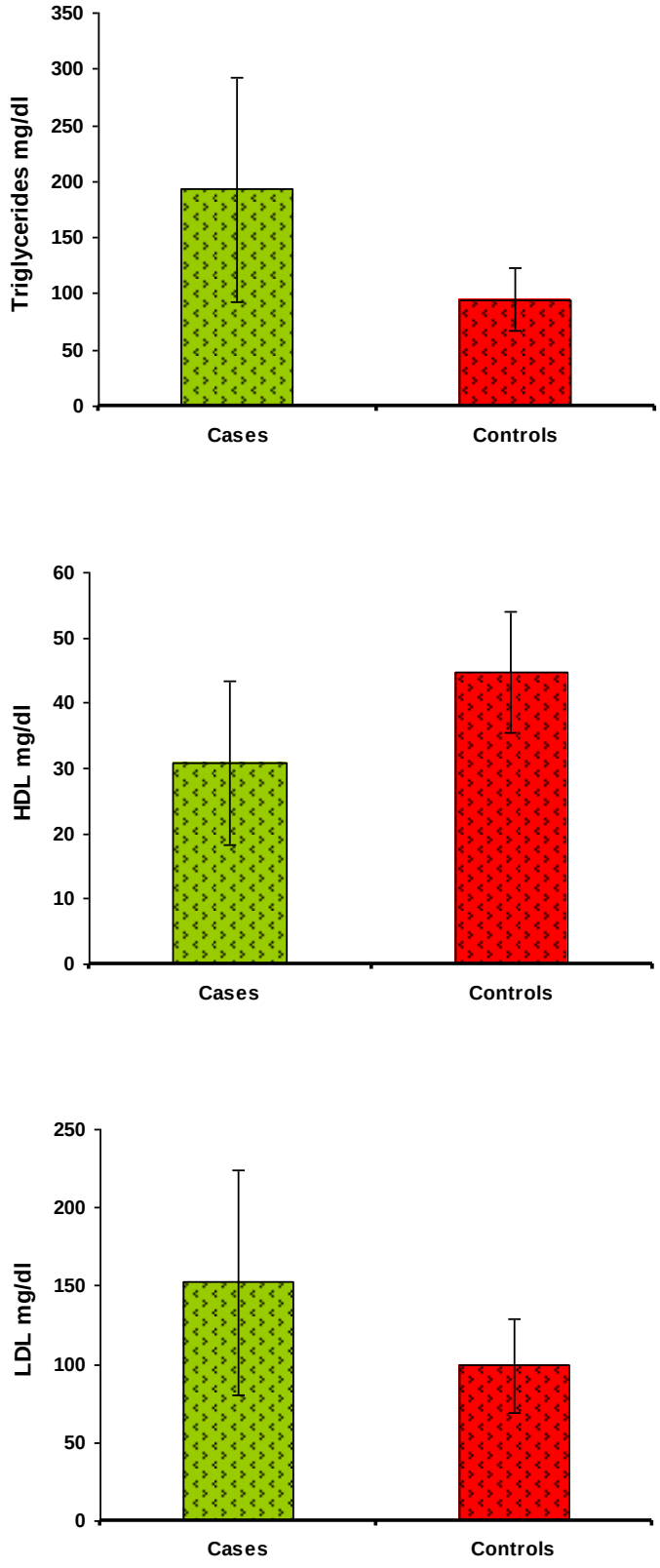


Graph 8: Depicting lipid parameters between 2 groups

Table 10: Comparison of lipid parameters between 2 groups

Lipid parameters	Cases	Controls	P value
Cholesterol mg/dl	217.14±103.73	173.38±17.12	0.004**
Triglycerides mg/dl	192.58±99.10	94.60±27.72	<0.001**
HDL mg/dl	30.82±12.60	44.70±9.20	<0.001**
LDL mg/dl	152.20±71.32	99.16±30.01	<0.001**



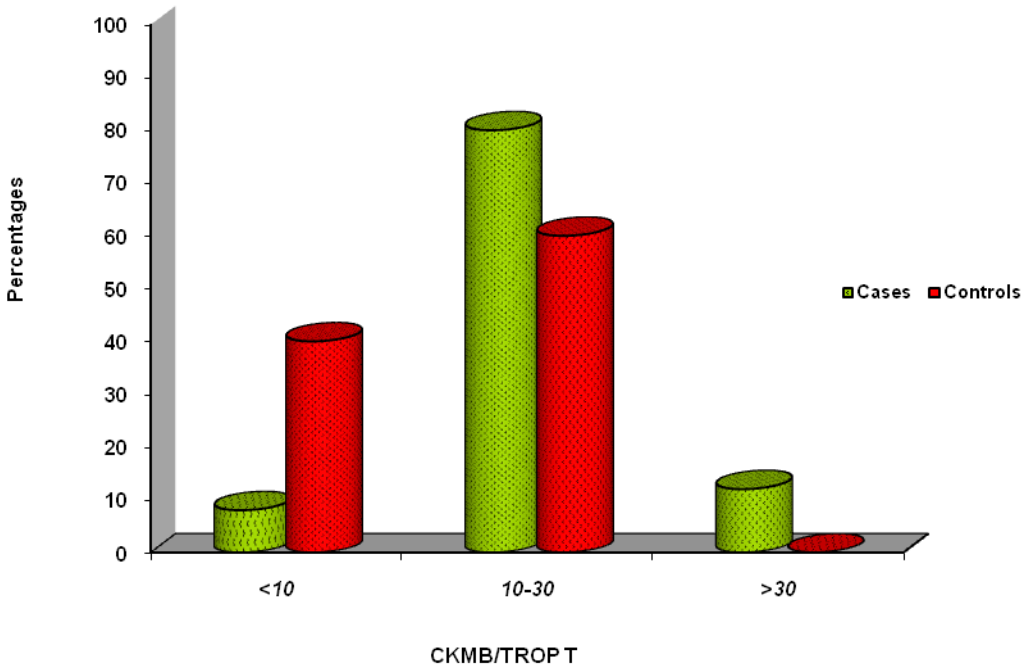


Graph 9: Depicting lipid parameters between 2 groups

Table 11: Distribution of CKMB/TROP T between 2 groups

CKMB/TROP T	Cases		Controls	
	No	%	No	%
<10	4	8.0	20	40.0
10-30	40	80.0	30	60.0
>30	6	12.0	0	0.0
Total	50	100.0	50	100.0
Mean ± SD	21.50±9.56		9.74±4.50	

CKMB /Trop is significantly more associated with cases with P = <0.001**

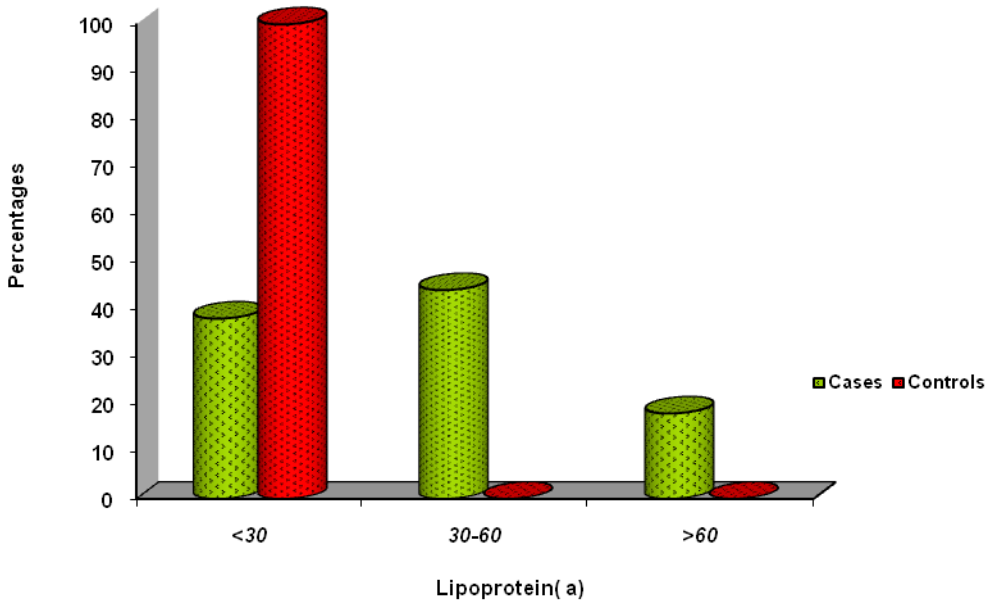


Graph 10: Depicting distribution of CKMB/TROP T between 2 groups

Table 12.Distribution of lipoprotein(a) in two groups of patients studied

Lipoprotein(a)	Cases		Controls	
	No	%	No	%
<30	19	38.0	50	100.0
30-60	22	44.0	0	0.0
>60	9	18.0	0	0.0
Total	50	100.0	50	100.0
Mean ± SD	39.80±24.85		9.24±5.06	

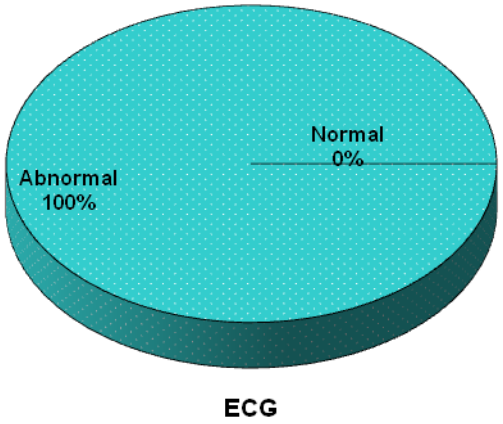
Lipoprotein (a) is significantly more associated with cases compared to controls with P = <0.001**

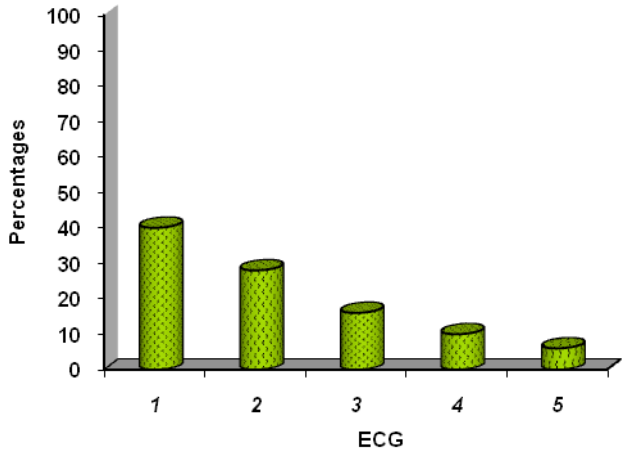


Graph11: Depicting Lipoprotein (a) between 2 groups

Table 13: Distribution of ECG in cases group

ECG	Number of patients (n=50)	%
Normal	0	0.0
Abnormal	50	100.0
• 1.ST depression in inferior leads	20	40.0
• 2.ST elevation in anterolateral leads	14	28.0
• 3.ST elevation in anterior leads	8	16.0
• 4.ST elevation in inferior leads with RBBB	5	10.0
• 5.ST -T depression in inferior leads	3	6.0

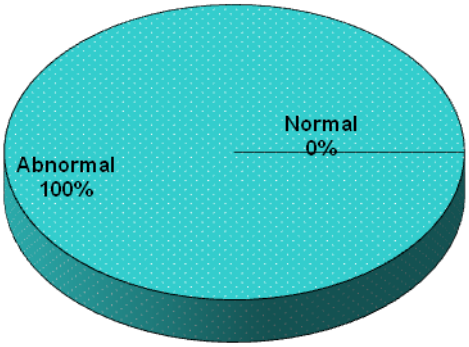




Graph12: Depicting ECG between 2 groups

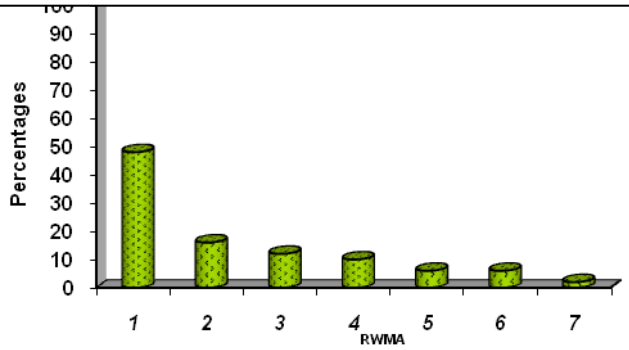
Table 14: Distribution of 2D ECHO in cases group

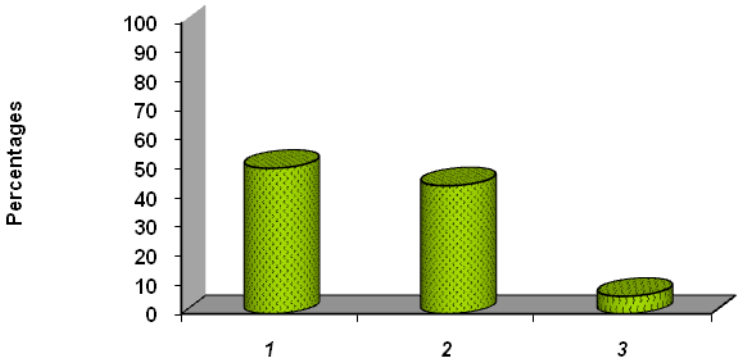
2D ECHO	Number of patients (n=50)	%
RWMA		
Normal	0	0.0
Abnormal	50	100.0
• 1.Inferior wall Hypokinesia	24	48.0
• 2.Anterior wall Hypokinesia	8	16.0
• 3.Antero lateral Hypokinesia	6	12.0
• 5.Global Hypokinesia	3	6.0
• 6.Inferolateral Hypokinesia	3	6.0
SYSTOLIC DYSFUNCTION		
• 1.Grade 1 systolic dysfunction	25	50.0
• 2.Normal LV systolic dysfunction	22	44.0
• 3.Grade 3 systolic dysfunction	3	6.0
DIASTOLIC DYSFUNCTION		
Normal	38	76.0
Abnormal	12	24.0
• Grade 1	12	24.0



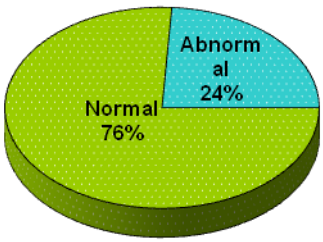
2D ECHO

Graph13: Depicting 2D ECHO in study group





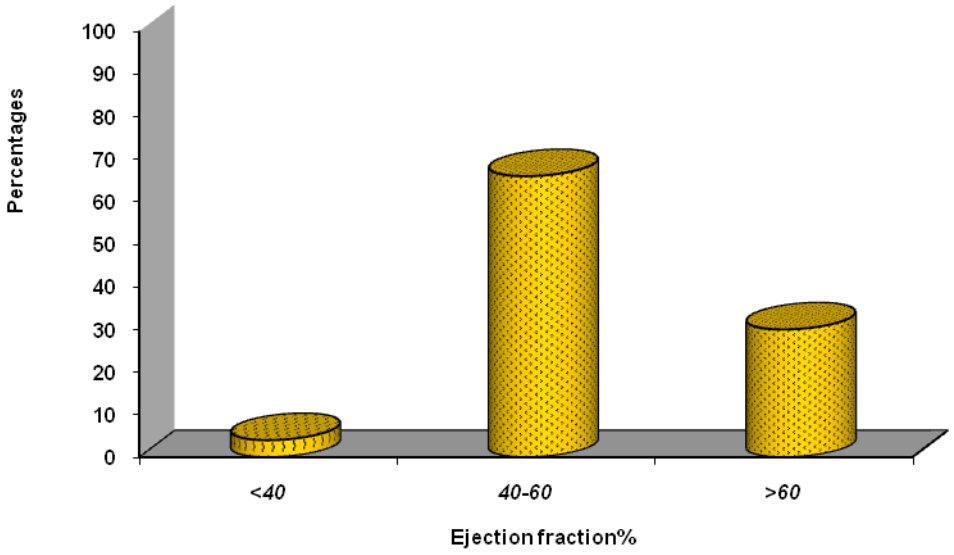
SYSTOLIC



DIASTOLIC

Table 15: Distribution of ejection fraction in cases group

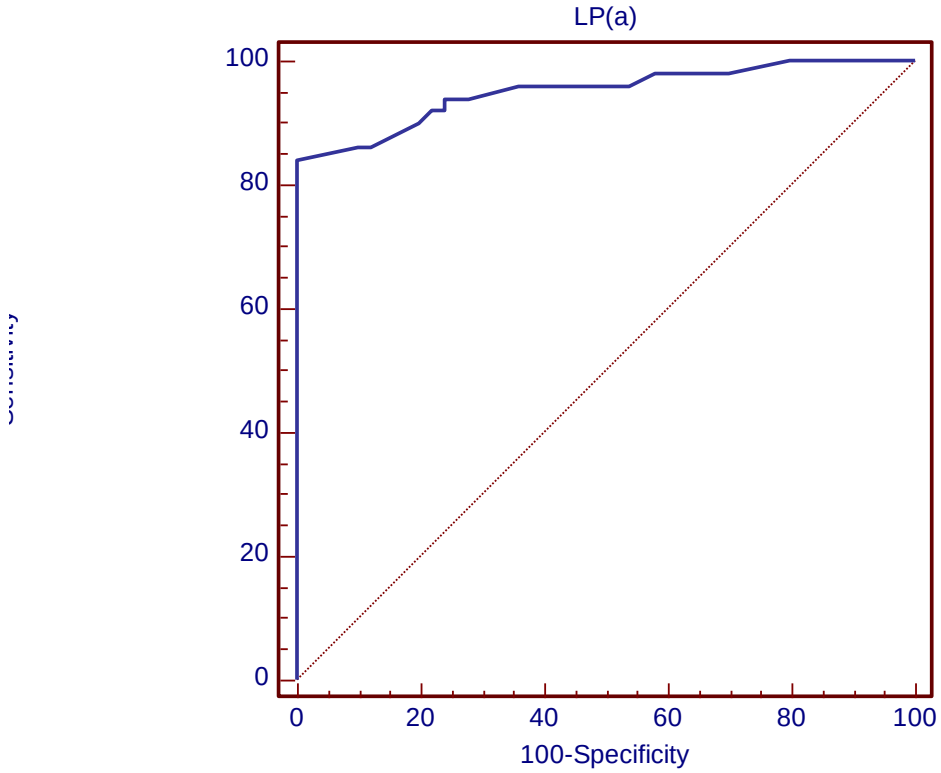
Ejection fraction%	Number of patients	%
<40	2	4.0
40-60	33	66.0
>60	15	30.0
Total	50	100.0



Graph 14: Depicting Ejection fraction in study group

Table 16: ROC curve analysis to study the role of LP(a) as a predictive marker

	Cut-off	Sensitivity	Specificity	AUC	P value
LP(a)	**>18.0**	**84.00**	**100.00**	**0.951**	**<0.001****



Graph 15: ROC curve analysis to study the role of LP(a) as a predictive marker

DISCUSSION

In the present study there were 50 cases and 50 age and sex matched controls. Out of 50 cases 26 were males 24 were females. The common presenting symptoms in cases of IHD were chest pain (100%), some patients with breathlessness. Common risk factor was smoking (88%), Diabetes mellitus (82%), Hypertension (88%) in majority of cases of IHD.

In this study 50 cases and 50 controls were age and sex matched, co morbid conditions were assessed .In assessing the blood pressure parameters P value were significantly high as shown in table no.4. In hematological parameters P value were found to be statistically significant in our study.

In this study lipid parameters showed statistically significant as shown in table number 9. In table number 11, cardiac biomarkers were estimated and found to be statistically significant (100%).In table number 12 comparisons of Lipoprotein (a) were estimated and found to be statistically significant. As in table number 13 ECG abnormalities were found 100%.In table number 14 ECHO estimation were done according to wall involvement and found to be statistically significant. In table number 15, Ejection fraction was estimated.

Nordestgaard BG et al (2010) did a study on Lipoprotein (a) as a cardiovascular risk factor current status. The aims of the study were, first, to critically evaluate lipoprotein (a) [Lp(a)] as a cardiovascular risk factor and, second, to advise on screening for elevated plasma Lp(a), on desirable levels, and on therapeutic strategies. The robust and specific association between elevated Lp(a) levels and increased cardiovascular disease (CVD)/coronary heart disease (CHD) risk, together with recent genetic findings, indicates that elevated Lp(a), like elevated

LDLcholesterol, is causally related to premature CVD/CHD.Finally recommend screening for elevated Lp(a) in those at intermediate or high CVD/CHD risk, a desirable level,50 mg/dL as a function of global cardiovascular risk, and use of niacin for Lp(a) and CVD/CHD risk reduction. [50]

Serban C et al (2011) conducted a study on Lipoprotein (a), an emerging cardiovascular risk factor in hypertensive patients. A significant correlation was found between Lp(a) and carotid intima media thickness. Lp(a) levels are related to early structural changes of the carotid arteries as shown by ultrasound measurements of IMT and to early functional changes evaluated by brachial FMD and can be considered an emerging risk factor for premature atherosclerosis. [51]

Colley KJ et al (2011) did a study on Lipoprotein associated phospholipase A2: role in atherosclerosis and utility as a biomarker for cardiovascular risk. Drug therapies to inhibit Lp-PLA2 are in development and show considerable promise, including darapladib, a specific molecular inhibitor of the enzyme. In addition to substantially inhibiting Lp-PLA2 activity, darapladib reduces progression of the necrotic core volume of human coronary artery atheromatous plaque. The growing body of evidence points to an important role and utility for Lp-PLA2 testing in preventive and personalized clinical medicine. [52]

Chandni R, Ramamurthy KP (2011) evaluated the Lipoprotein (a) in type 2 diabetic subjects and its relationship to diabetic micro vascular complications. Patients with diabetic nephropathy had higher Lp (a) levels. No association was found between Lp(a) levels and diabetic retinopathy or neuropathy. Longer duration of diabetes correlated with higher Lp (a) levels. [53]

Kwon SW et al (2012) conducted a study to evaluate whether elevated [Lp(a)] is associated with worse outcome in symptomatic patients with coronary artery disease (CAD), and to clarify the prognostic value of Lp(a) in the era of coronary artery revascularization. Elevated Lp(a) is an independent prognostic risk factor for cardiovascular events, and moreover, has incremental prognostic value in symptomatic patients with coronary artery disease, irrespective of coronary artery revascularization status. [54]

Farajzadeh S et al (2011), did a case control study on Serum lipoprotein (a) as an atherosclerosis risk factor in men with androgenic alopecia 45 male patients with androgenic alopecia who were aged from 20 to 50 years and 45 men with a normal hair status aged from 20 to 50 years were enrolled as the case and control groups, respectively. A significant difference in serum lipoprotein (a) was observed between case and control groups ($p< 0.001$). We noted that 47.1 percent of the patients and 17.96% of the controls had a lipoprotein (a) level more than 30 mg/dl which is a critical level for coronary artery disease. The family history of androgenic alopecia and coronary heart disease was significantly higher in the cases than the control. Considering the results of the study and the important role of lipoprotein (a) as a risk factor for atherosclerotic heart disease. [55]

Philip S et al (2011) performed a prospective study on Apo B/Apo A-I Ratio a better predictor of coronary artery disease in patients with or without type II diabetes mellitus and to analyse whether these parameters can be used as a more accurate lipid risk factor than the conventional ones. In the study, ratio of Apo B to Apo AI (Apo B/Apo AI) was found to be markedly high in CAD patients ($p<0.001$) when compared

to the control. As the ratio covers both atherogenic and antiatherogenic lipid risk factor, it can be used as a better predictor than conventional risk factor. [56]

Chen Q et al (2011) examined the association of antibodies against oxLDL (anti-oxLDL) with the severity of CAD in 558 Women's Ischemia Syndrome Evaluation (WISE) study samples (465 whites; 93 blacks) determined by coronary stenosis (<20%, 20%–49%, >50% stenosis). Data suggest that higher IgM anti-oxLDL levels may provide protection against coronary stenosis and that genetic variation in some candidate genes are determinants of anti-oxLDL levels. [57]

Kotani K et al (2012) studied a carotid intima thickness (CIMT) in asymptomatic patients with low lipoprotein (a) levels on 65 female patients with lipo (a) <30mg/dl. The median Lp(a) level was 18.6 mg/dL and the mean CIMT level was 0.8 mm. There was a significant and inverse correlation between the CIMT and Lp(a) ($r = -0.24$, $P \leq 0.05$), in addition to a significant and positive correlation between the CIMT and subject age and systolic blood pressure. They concluded the Lp(a) levels were inversely correlated with the CIMT in this population, suggesting that subjects with a low Lp(a) level may have a predisposition to carotid atherosclerosis. [58]

Albahrani A et al (2012) did a prospective study on Lipoprotein (a): an independent risk factor for ischemic heart disease that is dependent on triglycerides in subjects with type 2 diabetes mellitus. Lp (a) concentration was significantly lower and negatively correlated with triglycerides among Omani diabetic compared to non-diabetic subjects. [59]

Djordjevic VB et al (2011) conducted a research on lipoprotein (a) as a single best marker of unstable angina. Lp(a) is better in the evaluation of SAP and USAP patients, considering that Lp(a) showed the highest area under the curve (AUC). [60]

Tsimikas S et al (2012) did a research on effect of Mipomersen, an antisense apoB synthesis inhibitor, on lipoprotein(a) in patients with hypercholesterolemia across four phase III studies. In conclusion Mipomersen is the first pharmacological therapy to consistently and effectively reduce Lp(a) levels in patients with FH or severe hypercholesterolemia and high CVD risk. [61]

Boronat M et al (2012) conducted a cross-sectional study on High levels of lipoprotein (a) are associated with a lower prevalence of diabetes with advanced age. These results suggest that the age-related increase in the probability of having diabetes is significantly lower in subjects with Lp(a) levels >46 mg/dl. [62]

Pedersen TX et al (2012) did a research on uremic mice to find out the atherosclerotic effect of lipoprotein (a). In conclusion, expression of apo(a) or Lp(a) increased uremia-induced atherosclerosis. Binding of OxPL on apo(a) and Lp(a) may contribute to the atherogenicity of Lp(a) in uremia. [63]

Nicholls SJ et al (2012) observed the relationship between serum Lp(a) levels and both the extent of angiographic disease and 3-year incidence of major adverse cardiovascular events. Lp(a) levels correlate with the extent of obstructive disease and predict the need for coronary revascularization in subjects with suboptimal LDL-C control. [64]

Chapman MJ et al (2011) did a study on Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease. The Panel believes that therapeutic targeting of elevated triglycerides (≥1.7 mmol/L or 150 mg/dL), a marker of TRL and their remnants, and/or low HDL-C (1.0 mmol/L or 40 mg/dL) may provide further benefit. Treatment decisions regarding statin

combination therapy should take into account relevant safety concerns, i.e. the risk of elevation of blood glucose, uric acid or liver enzymes with niacin, and myopathy, increased serum creatinine and cholelithiasis with fibrates. [65]

Banerjee et al (2011) conducted a research on Racial and Ethnic Variation in Lipoprotein (a) Levels among Asian Indian and Chinese Patients. There are known racial/ethnic differences in Lp(a) levels. Asian Indian and NHW men have higher Lp(a) values than Chinese men, with a trend toward, similar associations in women. High Lp(a) may be more strongly associated with IHD in Asian Indians and Chinese.[66]

Eckardstein AV et al (2001) did a study on to assess the role of elevated lipoprotein(a) [Lp(a)] as a coronary risk factor. In conclusion Lp(a) increases the coronary risk, especially in men with high LDL cholesterol, low HDL cholesterol, hypertension and/or high global cardiovascular risk. [67]

Kamstrup PR et al (2007) conducted a prospective study on extreme lipoprotein(a) levels and risk of myocardial infarction in the general population on 9330 men and women from the general population in the Copenhagen City Heart Study. During 10 years of follow-up, 498 participants developed M.I. Various studies have confirmed as mentioned above the usefulness of measuring Lp(a) levels [1,3,4,5,6,50,53,54.]Lp(a) levels is an independent risk factor in IHD patients while other lipids lost their discriminative value in aged 52. In the present study Lp(a) is significantly associated with cases with p value <0.001. [68]

In our study Lipoprotein (a) as an independent risk factor for Ischemic heart disease were estimated with sensitivity of 84% and specificity of 100%. P value < 0.001 which is statistically significant.

CONCLUSION

Lipoprotein(a) excess is the strongest determinant of Lipoprotein(a) acts as a competitive inhibitor for the action of plasminogen and prevents fibrinolysis. Lipoprotein(a) there by acts as a dual pathogen which is both atherogenic due to its similarity with LDL and thrombogenic due to Apo(a)'s structural resemblance to plasminogen . Lipoprotein(a) is an LDL like molecule consisting of an apoprotein (Apo) B-100 particle attached by a disulphide bridge to Apo(a). Lipoprotein (a) is a predictor of many forms of vascular disease, including premature coronary artery disease.

Lipoprotein (a) levels were found to be independent risk factor in patients with Ischemic heart disease.

SUMMARY

This study is a hospital based study carried out from December 2011-November 2011.This study included 50 patients of Ischemic heart disease patients who were admitted in R.L.Jalappa hospital attached to SDUMC , Kolar.

1. There were 26 male patients and 24 female patients .The male to female ratio was approximately 2:1.
2. The maximum number of patients was in the age group of 51 to 60 years i.e., 46%.
3. Majority of the patients presented with chest pain (80%), breathlessness (40%).
4. Major risk factors being smoking (88%) and hypertension (88%), diabetes mellitus (80%).
5. Cardiac biomarker CK MB /Trop T were estimated and found to be significantly elevated in ischemic heart disease patients.
6. Lipoprotein (a) levels were estimated in 50 cases and 50 controls .Lp(a) levels were significantly more in cases compared to controls.

REFERENCES

1. Berg K. A new serum type system in man: the Lp system. Acta Pathol Microbiol Scand. 1963; 59: 369–82.
2. Tsimikas S, Witztum JL. Measuring circulating oxidized low-density lipoprotein to evaluate coronary risk. Circulation 2001; 103:1930-2.
3. Ehara S, Ueda M, Naruko T, et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. Circulation2001; 103:1955-60.
4. Holvoet P, Collen D, Van de Werf F. Malondialdehyde-modified LDL as a marker of acute coronary syndromes. JAMA 1999; 281:1718-21.
5. Nishi K, Itabe H, Uno M, et al. Oxidized LDL in carotid plaques and plasma associates with plaque instability. ArteriosclerThromb Vasc Biol 2002; 22:1649-54.
6. Tsimikas S, Bergmark C, Beyer RW, et al. Temporal increases in plasma markers of Oxidized low-density lipoprotein strongly reflects the presence of acute coronary syndromes. J Am Coll Cardiol 2003; 41:360-70.
7. Tsimikas S, Lau HK, Han KR, et al. Percutaneous coronary intervention results in acute increases in oxidized phospholipids and lipoprotein(a): short-term and long-term immunologic responses to oxidized low-density lipoprotein. Circulation 2004; 109:3164-7.
8. Utermann G. Lipoprotein(a). In: Scriver CR, Beaudet AL, Sly WS, Valle D, et al. The Metabolic and Molecular Bases of Inherited Disease. 2001ed. New York, NY: McGraw-Hill Publishing Co, Medical Publishing Division; 2006:2753–87.

9. Deb A, Caplice NM. Lipoprotein(a): New insights into mechanisms of atherogenesis and thrombosis. Clin Cardiol. 2004; 27:258 –64.
10. Nielsen LB, Nordestgaard BG, Stender S, Niendorf A, Kjeldsen K. Transfer of lipoprotein(a) and LDL into aortic intima in normal and in cholesterol-fed rabbits. Arterioscler Thromb Vasc Biol. 1995; 15:1492–1502.
11. Nielsen LB, Stender S, Jauhiainen M, Nordestgaard BG. Preferential influx and decreased fractional loss of lipoprotein(a) in atherosclerotic compared with non-lesioned rabbit aorta. J Clin Invest. 1996; 98:563–71.
12. Nielsen LB, Gronholdt ML, Schroeder TV, Stender S, Nordestgaard BG. In vivo transfer of lipoprotein(a) into human atherosclerotic carotid arterial intima. Arterioscler Thromb Vasc Biol. 1997; 17:905–11.
13. Nielsen LB, Juul K, Nordestgaard BG. Increased degradation of lipoprotein(a) in atherosclerotic compared with non-lesioned aortic intima–inner media of rabbits: In vivo evidence that lipoprotein(a) may contribute to foam cell formation. Arterioscler Thromb Vasc Biol. 1998; 18:641– 9.
14. Boffa MB, Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for atherosclerosis and thrombosis: mechanistic insights from animal models. Clin Biochem. 2004; 37:333–43.
15. Craig WY, Neveux LM, Palomaki GE, Cleveland MM, Haddow JE. Lipoprotein(a) as a risk factor for ischemic heart disease: metaanalysis of prospective studies. Clin Chem. 1998; 44:2301–6.
16. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease: meta-analysis of prospective studies. Circulation. 2000; 102:1082–5.

17. Von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol. 2001; 37:434–9.

18. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001; 104:1108 –13.

19. Luc G, Bard JM, Arveiler D, Ferrieres J, Evans A, Amouyel P, Fruchart JC, Ducimetiere P. Lipoprotein(a) as a predictor of coronary heart disease: the PRIME Study. Atherosclerosis. 2002; 163:377–84.

20. Ariyo AA, Thach C, Tracy R. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. N Engl J Med. 2003; 349:2108 –15.

21. Rifai N, Ma J, Sacks FM, Ridker PM, Hernandez WJ, Stampfer MJ, Marcovina SM. Apolipoprotein(a) size and (A) concentration and future risk of angina pectoris with evidence of severe coronary atherosclerosis in men: the Physicians' Health Study. Clin Chem. 2004; 50:1364 –71.

22. Danik JS, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. JAMA. 2006; 296:1363–70.

23. Rifai N, Ma J, Sacks FM, Ridker PM, Hernandez WJ, Stampfer MJ, Marcovina SM. Apolipoprotein(a) size and (a) concentration and future risk of angina pectoris with evidence of severe coronary atherosclerosis in men: the physicians' health Study. Clin Chem. 2004; 50:1364 –71.

24. Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, Witztum JL, Berger PB. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med. 2005; 353:46 –57.

25. Siekmeir R, Schmagl H, Kostner T, Grammer T, Maiz W. Variations of Lipoprotein (a) plasma concentrations in health and disease. The open clinical chemistry journal. 2010; 3:72-89.

26. Nordestgaard GM, Chapman MJ, Ray K, Jan B, Felicita A, Gerald FW. Lipoprotein (a) as a cardiovascular risk factor: current status. European heart journal. 2010; 10:1093-1105.

27. Vidosova BD, Vladen C, Ivana S, Slavica K, Lillka Z, Marina D. Lipoprotein (a) is the best marker in assessing unstable angina pectoris. Cardiology Research and Practice. 2011:10.

28. Banarjee D, Eric CW, Jessica S, Stephen PM, Latha P. Racial and ethnic variation in Lipoprotein (a) levels among asian indians and chinese patients. Journal of lipids. 2011:1-5.

29. Lippi G, Targher G. Optimal therapy for reduction of lipoprotein(a). Journal of pharmacy and therapeutics. 2012; 37:1-3.

30. Melvyn R, Deepthi V, Sangeetha MK,Robert LB,Elizibeth AJ,Donald G et al, Lipoprotein (a): Perspectives from a lipid-referral program. Journal of clinical lipidology . 2012; 6:66-73.

31. Paul MR, Lipoprotein(a), Ethnicity, and Cardiovascular risk in circulation 2012; 125:207-9.

32. Jemma C, Hopewell, Robert Clarke, Saral Parish, Jane Armitage, Mark Lathrop, Jane Hager and Rory Collins. Lipoprotein(a) Genetic Variants Associated With Coronary and Peripheral Vascular Disease but Not With

Stroke Risk in the Heart Protection Study. Cir Cardiovasc Genet 2011; 4; 68-73.

33. Sokhanvar1 S, Rezvan Rohi, R Mazaki2, Mousavinasab N, Zahra Golmohammadi Z. The Association between Serum Lipoprotein (a) and Other Cardiac Risk Factors with the Severity of Coronary Artery Disease. J Cardiovasc Thorac Res 2011; 3 (1): 35- 9.
34. Borge G, Nordestgaard, John CM, Kausik R, Jan B, Felicita A et al. Lipoprotein (a) as a cardiovascular risk factor :current status. European Heart Journal: 2010; 31, 2844–53.
35. Erqou S, Kaptoge S, Perry PL, Di AE, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009; 302: 412–23.
36. Siekmeier1 R, Scharnagl H, Kostner G M, Grammer T, Stojakovic2 and Marz W. Lipoprotein(a)–Structure, Epidemiology, Function and Diagnostics of a Cardiovascular Risk Marker. The Open Clinical Chemistry Journal, 2008; 1: 79-91.
37. **Kannel W.B. and Higgins M: Smoking and HTN as predictors of cardiovascular risk in population studies. J.Hypertens. Suppl. 1990; 8: 53.**
38. **MacMohan S, Reto R, Cutter J, et al: Blood pressure, stroke and coronary heart disease, part-2 short term reductions in blood pressure overviewing of randomised drug trials in their epidemiological context, Lancet. 1990; 5:827-32.**
39. **De Fronzo LA and Ferrannini E: A multifaceted syndrome responsible for NIDDM, obesity, HTN, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care. 1991; 14: 173.**

40. **Eaker E.D, Abbot R.D. and Kannel: Frequency or uncomplicated angina pectoris in type A compared with type B persons (the Framingham study) Am. J. Cardol.1989; 63: 1042.**

41. **Henry Ginsberg: Lipid Disorders, Lipoprotein metabolism and its relationship to Atherosclerosis. Medical Clinics of North America, Jan. 1994; 10:1-19.**

42. **Weatherall, Leadingham and Warnell. Oxford Text book Medicine 3rd edition.**

43. **Montgomery, Conway and Spector: Biochemistry A case oriented approach Lipoproteins and its metabolism 5th Edition. 1990.**

44. **Devlin TM. Lipid metabolism II. Text book of biochemistry with clinical correlations, 5th edn. New York: Wileyliss Co., 2002; 745-7.**

45. **Nader R, Warnick GR. Lipids, lipoproteins, apolipoproteins and other cardiovascular risk factors. In: Burtis CA, Ashwood ER and Bruns DA, eds. Tietz text book of clinical chemistry and molecular diagnostics, 4th edn. New Delhi: Elsevier Co., 2006; 916-52.**

46. **Ernst J Schafer, Shlomo Eisenberg. Robert Levy: Lipoprotein apoprotein metabolism: Journal of lipid research. 1979; 19:667-9.**

47. **a) Eugene Braunwald – Heart diseases, 3 rd edition.**

    b) Eugene Braunwald -Heart diseases, 4th edition.

48. **Pesach Segal, Basil Rifkind, Paul Bachorik, Robert Levy: Lipids and Dyslipoproteinemias. Todd, Sanford, and David Sohn: Clinical Diagnosis and Management by Laboratory Methods 17th Edition, 1989; 11: 180-95.**

49. **Joh J. Albers, W. Wahl. V.G. Cabana, Hazzard WR, JJ Hoover: Quantification of Apolipoprotein A1 of Human Plasma High Density Lipoprotein. Metabolism.1975; 25(6): 633-44.**

50. **Naresh Trehan, Anil Kumar. P. Sivaram: Lipoproteins and vessel walls, Implications of new research on our understanding of atherosclerosis. New developments in cardiology and cardiac surgery .1985: 1-9.**

51. **P. P. Jadhav, Taskar, A.P. Taskar., S.P.Taskar., and T.D. Dame: Evaluation of Apolipoprotein AI and Apo B are survivors of Myocardial infarction. JAPI - 1994; 42(9):703-5.**

52. **Ruben et al, Inhibition of early atherogenesis in transgenic mice by human Apo AI. Nature, 1991; 353:265-72.**

53. **Stephen G Young, M.D: Recent progress in understanding apolipoprotein B Circulation. 1990; 8:19-25.**

54. **Julie L Buring. S.D. Gerald T., O Connor, SCD: Sameul Z Goldhaber, M.D Peter N. Herbert. M.D: Decreased HDL2 and HDL3 Cholesterol, Apo A- I and Apo A-II and increased risk of M.l. Circulation. Jan 1992; 85.**

55. **Esko Nikkila: Metabolic regulation of plasma high density lipoprotein concentration. European Journal of Clinical Investigation 1989; 8: 111-3.**

56. **MacMohan S, Reto R, Cutter J, et al: Blood pressure, stroke and coronary heart disease, part-2 short term reductions in blood pressure overviewing of randomised drug trials in their epidemiological context, Lancet. 1990; 335: 827.**

57. **De Fronzo L.A, and Ferrannini E: A multifaceted syndrome responsible for NIDDM, obesity, HTN, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care. 1991; 14: 173.**

58. Marz W, Trommlitz M, Scharrer I, Gross W. Apolipoprotein (a) concentrations is not related to the risk of venous thrombosis. Blood Coagul. Fibrinolysis. 1991; 2: 595-9.

59. **Eaker E.D, Abbot R.D. and Kannel: Frequency or uncomplicated angina pectoris in type A compared with type B persons (the Framingham study) Am. J. Cardol. 1989; 63: 1042.**

60. **Djordjevic VB et al. Lipoprotein (a) is the best single marker in assessing unstable angina pectoris. Cardiology research and practice. December2011: 1-13.**

61. **Sotiris Tsimikas, Joseph Witztum, Alberico Catapano.Effect of Mifepristone on lipoprotein(a) in patients with hypercholesterolemia across four phase III studies. JACC March 1959; 13:1202-21.**

62. **Haffnner S.M, Stern M.P: Relationship of proinsulin and insulin to CVS risk factors in Non-diabetic subjects. Diabetes. 1993; 43: 1297-1301.**

63. **Report of the 1:1:1.Epert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Archives of Internal Medicine 1988; 148: 36-9.**

64. **Eugene Braunwald 5th edition.**

65. **Schwartz., A.J. Valente, E.A.Sprague: Pathogenesis of Atheroscerlorsis an overview, Clinical Cardiology. 1991; 14(1): 1-16.**

66. **Harrison's Text Book of principles of Internal Medicine 18th Edition. Atherosclerosis, 1108-9.**

67. **P Alaupovic et al. Apolipoproteins & Lipoproteins Atherosclerosis 1971; 13: 141-6.**

68. **R. Gupta, Bharati, Malhotra: Infections and atherosclerosis in the Indian context. JAPI 1999; 47:4.**

69. **John J Albers, Marian Cheung, WR Hazzard: High Density Lipoprotein in Myocardial Infarction Survivors. Metabolism, 1978; 27(4): 479- 85.**

70. **Viekko Salomaa, Nena Aleksic: Soluble thrombomodulin as a predictor of incident coronary heart disease and symptomless carotid artery atherosclerosis in the atherosclerosis risk in communities (ARIC) study a case - cohort study, the Lancet. 1999; 353-9.**

71. **Norman E Miller: Association of High Density Lipoprotein subclasses and apolipoprotein with Ischemic Heart Disease and Coronary Atherosclerosis. American Heart Journal. 1987; 18:589-97.**

72. **P Alaupovic., A Gustaffson, Sambar S.S, Furman: Protein Moieties of human serum lipoprotein a basis for classification Circulation. 1964; 30**

73. **Riesen WF, Mordasini R, Salzmann A, and Guntner HP: Apoproteins & Lipids as discriminators of severity of Coronary Heart Disease. Atherosclerosis. 1980; 37: 157-62.**

74. **James J Maciejko, Holmes D, Kottkc, Zinsmeister, Dinh, SJT Mao: Apolipoprotein AI as a market of angiographically assessed Coronary Artery Disease. NEJM. 1983; 309:385-9.**

75. **Ohta T, Hattori S, Masuji M, Nishiyama S and Matsuda C: Age and sex related differences in lipoproteins containing Apoprotein AI Arteriosclerosis. 1989; 9: 90-5.**

76. **Kottke B, Zinmnseistcr, Holmes J., Kneller. SJT Mao: Apoplipoproteins and Coronary Artery Disease. Mayo Clinic Proceedings 1986; 61:313-20.**

77. **Onitri AC, Jover E: Comparative serum apolipoprotein studies on IHD control subjects. Clin. Chem Acta. 1980; 108; 25-30.**

78. **Hester, Shepherd fasting specimen is not required for routine measurements of plasma apoplipoproteins A I and AB. Annals of clinical Biochemistry, 1989; 26: 374.**

79. **Cho JY et al. High lipoprotein (a) levels are associated with long term adverse outcomes in acute myocardial infarction patients in high Killip classes 2010. Korean Circ J 2010; 40:491-8.**

80. Ali A, Alkindi M, Marks E, and Shenkin A: Lipoprotein(a): an independent risk factor for ischemic heart disease that is dependent on triglycerides in subjects with type 2 diabetes mellitus. Lipids in Health and Disease 2007; 6:26.

81. **Sacks S, Salvini, Willett W, Hennckens C: A prospective study of Cholesterol. Apolipoproteins and the risk of myocardial infarction. New England Journal of Medicine.1991; 325:373-81.**

82. **De Becker., Rosseneu et al., Discriminative value of lipids and apoproteins in Coronary Heart Diseases. Atherosclerosis. 1982; 42:197-203.**

83. **Radhakrishnan Chandni, Kollengode Parameswaran Ramamurthy. Lipoprotein(a) in type 2 diabetic subjects and its relationship to diabetic microvascular complications. World J Diabetes; 3(5):105-9.**

84. **Nordestgaard BG et al. Lipoprotein (a) as a cardiovascular risk factor; current status. European heart journal-2010:31; 2844-53.**

85. **Serban C et al. Lipoprotein(a): An emerging cardiovascular risk factor in hypertensive patients: International journal of research on internal medicine and public health-2011; 3(10):733-42.**

86. **Kenneth J Colley, Robert l, wolfert, mechael e cobble. Lipoprotein(a) associated phospholipase A2: Role in atherosclerosis and utility as a biomarker for cardiovascular risk. EPMA Journal 2011; 2:27-38.**

87. Anthonia O, Ogbera, Alfred O, Azenabor. Lipoprotein (a), C-reactive protein and some metabolic cardiovascular risk factors in type 2 DM. Diabetology & Metabolic Syndrome 2010, 2:51.

88. **Kwon SW et al, Lipoprotein(a) as a cardiovascular biomarker for long-term clinical outcomes in symptomatic patients with coronary artery disease, irrespective of coronary artery revascularization status. JACC, March 2012; 59 (13): 1-6.**

89. **Farajzadeh S et al, Serum lipoprotein(a) as an atherosclerosis risk factor in men with androgenic alopecia. Iran J Dermatol 2011; 14:81-5.**

90. **Philip S, Abraham P, sheriff DS. Apo B/Apo AI ratio a better predictor of coronary artery disease in patients with or without type II diabetes mellitus. JABPT 2011; 2(3):153-8.**

91. **Chen Q et al. Association of anti-oxidized LDL and candidate genes with severity of coronary stenosis in the women's ischemia syndrome evaluation study. J lipid Res.2011; 52(4):801-7.**

92. **Kotani K, Sakane K. Carotid intima thickness in asymptomatic subjects with low lipoprotein(a) levels. J Clin Med Res 2012; 4(2):130-4.**

93. **Ali A, alkindi M, Marks E and Shenkin A. Lipoprotein (a): an independent risk factor for ischemic heart disease that is dependent on triglycerides in subjects with type 2 diabetes mellitus. December 2007; 6(26):1-5.**

94. **Djordjevic VB et al. Lipoprotein (a) is the best single marker in assessing unstable angina pectoris. Cardiology research and practice 2011: 1-13.**

95. **Tsimikas S, Witztum J, Catapano A. Effect of Mifepristone on lipoprotein(a) in patients with hypercholesterolemia across four phase III studies. JACC March; 59(13):1202-21.**

96. **Mauro Boronat et al. High levels of lipoprotein(a) are associated with a lower prevalence of diabetes with advancing age: Results of cross-sectional epidemiological survey. Cardiovascular Diabetology 2012; 11(81):1-8.**

97. **Pederson TX, McCormick SP, Tsimikas S, Susanne, Nielsen LB. Lipoprotein(a) accelerates atherosclerosis in uremic mice. Lipid Res 2010; 51(10):2967-75.**

98. **Nicholls SJ et al. Lipoprotein(a) levels and long-term cardiovascular risk in the contemporary era of statin therapy. J Lipid Res.2010 October; 51(10):3055-61.**

99. **Chapman JM et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Europian Heart Journal 2011; 32:1345-61.**

100. **Banerjee D, Eric C. Shin WJ, and Palaniappan L. Racial and ethnic variation in lipoprotein(a) levels among Asian Indian and Chinese patients. Journal of lipids 2011:1-6.**

101. **Eckardstein AV et al. The role of elevated lipoprotein(a) levels as coronary risk factor. American college of Cardiology 2001.**

102. **Kamstrup PR et al. Extreme lipoprotein(a) levels and risks of myocardial infarction in the general population: The Copenhagen city heart study. Circulation 2008; 117:176-84.**

PROFORMA

A) PATIENT PARTICULARS

NAME	:	CASE NO.	:
AGE	:	I.P.NO.	:
SEX	:	CASE/CONTROL	
OCCUPATION	:		
ADDRESS	:		
DATE OF ADMISSION	:		

B) PRESENTING COMPLAINTS:

1. Chest pain

Site	substernal/ left side /right side
Onset	sudden / insidious
Nature	heavy /squeezing/gripping/crushing/burning
Duration	----------
Radiation	L-arm/R-arm/back/neck/jaw/shoulder/ear
Severity	mild/moderate/severe
Aggravating factors	exertion/stress/heavy meals/others
Precipitating factors	exertion/stress/heavy meals/others
Relieving factors	rest/posture/drugs
Associated symptoms	sweating/giddiness/nausea/vomiting/cough/others

2. Dyspnoea

Duration	----------
Onset	sudden/insidious
Onset in relation to pain	----------
Aggravating factors	exertion/stress/heavy meals/others
Precipitating factors	exertion/stress/heavy meals/others
NYHA class	I/II/III/IV
PND	Yes/No
Orthopnoea	Yes/No

3. PALPITATION

Onset	sudden /insidious
Onset in relation to pain	----------
Nature	continuous /intermittent
Duration	----------
Precipitating factors	exertion/excitement/fear/drugs/others
Relieving factors	rest/drugs/others

4. SWEATING YES / NO

Duration

Onset associated with pain

5. OTHER SYMPTOMS

C) PAST HISTORY

SIMILAR COMPLAINTS	YES /NO
Anginal pain	Yes/No Duration
Diabetes mellitus	Yes/No Duration
Hypertension	Yes/No Duration
Dyslipidemia	Yes/No Duration
Ischemic heart disease	Yes/No Duration
Cerebrovascular accident	Yes /No
Rheumatic fever	Yes/No

D) PERSONAL HISTORY

Diet	vegetarian / non veg/mixed
Appetite	good /poor
Bowel habit	regular/constipation/diarrhea
Bladder	normal/polyuria/oliguria
Physical activity	sedentary/moderate/heavy

Habits:

Smoking: yes/No.Beedis / cigarettes: duration _____ yrs.

Number _____ day alcohol, duration _____ years, quantity

Tobacco chewing yes /No

Marital life single /married

C) FAMILY HISTORY

Ischemic heart disease	Yes / No
Diabetes	Yes / No
Hypertension	Yes / No
Dyslipidemia	Yes / No
Sudden deaths	Yes / No
Other illnesses	Yes / No

D) MENSTRUAL HISTORY

1. Age of menarche
2. Married life / no of children
3. Age of menopause

G) GENERAL PHYSICAL EXAMINATION

Appearance	normal / ill looking
Pallor	present / absent
Icterus	present / absent
Cyanosis	present / absent
Clubbing	present / absent
Signs of hyperlipidemia	xanthoma /xanthalesma /arcus senilis
Pedal edema	present / absent
Significant lymphadenopathy	present / absent
Height	----------cm
Weight	---------- kg
BMI	
Thyroid	normal /enlarged

VITALS

Pulse	----------/min	Peripheral pulses-felt/not felt
B.P	---------- mm Hg	
Respiratory rate	---------- /min	
Temperature	---------- Celsius	

H) SYSTEMIC EXAMINATION

1. CARDIOVASCULAR SYSTEM

INSPECTION

JVP

Shape of chest	normal / abnormal
Precordial pulsations	yes /no
Apical impulse	----------
Pulsations (Epigastric, parasternal)	yes /no

PALPATION

Apical impulse site	----------
Apical impulse character	normal / tapping /hyper dynamic/heaving
Parasternal heave	
Epigastric pulsations	
Thrill	
Other palpable sounds	

PERCUSSION

Cardiac borders	
Liver dullness	

AUSCULTATION

Heart sounds	normal /faint /accentuated
Added sounds	s3/s4/s3s4
Murmur	yes /no
Site	
Grade	
Position best heard	

2. RESPIRATORY SYSTEM EXAMINATION

Rate	----------/min
Rhythm	regular / irregular
Depth	normal /deep/shallow
Breath sounds	vescicular/bronchial/wheeze/crepitations/ Ronchi/others
Inspection	
Palpation	
Percussion	

3. ABDOMINAL EXAMINATION

Tenderness	Present / absent
Hepatomegaly	Present / absent
Splenomegaly	Present / absent
Ascites	Present / absent
Other findings	Yes / No

4. CENTRAL NERVOUS SYSTEM

Higher mental functions	orientation / memory
Speech	normal /abnormal
Cranial nerves	normal /abnormal
Motor system	normal /abnormal
Sensory system	normal /abnormal
Cerebellar system	normal /abnormal
Autonomic nervous system	normal /abnormal
Optic fundus	normal /abnormal

I) INVESTIGATIONS

DATE			
HB (gm %)		**LIVER FUNCTIONS**	
TC		S.T. BILIRUBIN	
DC(N,L,E)		S.D.BILIRUBIN	
ESR		SGOT	
PLATELET COUNT		SGPT	
RBS		ALK.PHOS	
B.UREA		T.PROTEIN	
S.CREAT		ALBUMIN	
SODIUM		GLOBULIN	
POTASSIUM		A/G RATIO	

LIPID PROFILE		GAMMA GT	
S.CHOL			
TRIGLYCERIDES		**LIPOPROTEIN (a)**	
S.CHOLESTROL			
TRIGLYCERIDES		CPK	
LDL		CKMB	
HDL			
URINE R/M		CHEST X RAY	
ECG			
2D ECHO			

OTHER INVESTIGATIONS (if any)

J) TREATMENT GIVEN

K) TOTAL DURATION OF HOSPITAL STAY:

L) FINAL DIAGNOSIS:

M) OUTCOME OF THE PATIENT: Discharge / Death / ----------

N) REMARKS OF GUIDE:

SIGNATURE SIGNATUE

PROF.DR.V.LAKSHMIAH DR.PAVITHRA.L

DATE:

KEY TO MASTER CHART

Hb% Hemogram

TLC Total leucocyte count

DLC Differential leucocyte count

ESR Erythrocyte sedimentation rate

Rbs Random blood sugar

Fbs fasting blood sugar

Ppbs Post prandial blood sugar

Na Sodium

K Potassium

HDL High density lipoprotein

LDL Low density lipoprotein

STB Serum total bilirubin

SDB Serum direct bilirubin

SGOT Liver enzymes

ALP Alkaline phosphatase

TP Total protein

A/G Albumin /Globulin

GGT Gamma glutamyl transferase

CK MB Creatinine kinase –Muscle brain

Trop T Troponin T

RWMA Regional wall motion abnormality

EF Ejection fraction

2 D ECHO 2D Electrocardiography

N Normal