CHAPTER - V

LIPID PROFILE AND KIDNEY FUNCTIONS IN
ATHEROSCLEROSIS AND IN MYOCARDIAL DISEASES

Introduction:

Thomas et al, observed that the important clinical presentations of atherosclerosis are:

a) Acute coronary syndrome

b) Cerebrovascular accidents

c) Peripheral vascular episodes. So, atherosclerosis is an multifactorial illness. The concept of risk factors in the genesis of atherosclerosis was initially developed by Framingham study investigations.¹³⁷

WHO’s goal is “Health for all by 2000 AD” (now extended upto 2020 AD) seems a distant dream despite the huge advancement in western medical technology.²⁵

Cardiovascular disease (CVD), is the 50% of the mortality in developed countries caused by Cardiovascular diseases. Over the next 25 years, there may be about 60 million deaths from Cardiovascular diseases. By the year 2010, this group of diseases may also be responsible for a quarter of deaths in the 3rd world.²⁵
Among the Cardiovascular diseases, the coronary heart disease (CHD) remains the most important cause for early invalidity, professional inactivity and premature deaths (Age – 15-64 yrs.).\textsuperscript{(10)}

Cook R. (2000) showed that the ischemic heart disease (IHD) is a consequence of impeded blood supply to the myocardium. Oxygen starvation (resultant from this) sets up a series of metabolic changes in the myocardium at the cellular level. These metabolic changes are at the direct result of deficient in high energy phosphate compounds and consequent changes in the internal pH and glycolysis.\textsuperscript{(13)}

Heart failure (HF) is a devastating disease with increase prevalence in elderly populations. HF occurs when heart cannot maintain adequate output to the peripheral tissues or can do so only at increased filling pressure. HF is a complex clinical syndrome manifested by signs and symptoms of cardiac output and pulmonary and/or systemic congestion.

Symptoms of heart failure include fatigue, cough, nocturia, exertional dyspnoea, arthopenea, paroxysmal nocturnal dyspnea and wheezing. Abnormalities in left ventricular function and neurohormonal regulation are a major characteristic of this condition.\textsuperscript{(7,10)}
Patients history and clinical examination may fail to provide a definitive diagnosis and additional testing such as chest radiography, electrocardiography, complete blood count, chemistries, urinalysis and electrocardiogram and TSH values are use to aid in diagnosis.

The annual cost of treating heart failure patients is more than $20 billions, which is estimated to be greater than the myocardial infarction and all concerns combined. Given the complex pathophysiology and varied manifestations of HF interest has intensified in developing biological markers to predict susceptibility and aid in the early diagnosis and management of this disease.\textsuperscript{[23]}

i) Role of Lipid Profile in Atherosclerosis and in Myocardial Diseases:

The present chapter describes results obtained on the study of lipid profile and kidney function in myocardial diseases such as CHD, IHD and AMI.

Chaudhari and Das, showed that the patients with myocardial infarction had hypercholesterolemia, decreased HDL-C and hypertriglyceridemia (dislipidemia). This dislipidemia has been associated with high plasma levels of tissue plasminogen
activator inhibitor and may thereby play an important factor underlying the pathogenesis of coronary artery disease.\textsuperscript{138}

The unifying hypothesis, considering the all data available today, suggests that combined effects of nature and nurture in the development of accelerated atherosclerosis in Asian Indians. The nurture is contributed by affluence, mechanization and urbanization. Affluence leads to consumption of foods rich in calories and fats, whereas the later results in sedentary living. These lifestyle factors lead to abdominal obesity, insulin resistance and atherogenic dislipidemia character by elevated serum triglyceride, borderline /high LDL and low high density lipoprotein (HDL). This combined with predominantly genetically determined elevated levels of Lp(a) decreases the threshold for pathological effects of LDL and Lp(a) and potentiates their adverse effects.

Joseph L. Witzum and Cannel Steinberg (1990), showed that today there is no any longer doubt about the causative relationship between hypercholesterolemia and premature atherosclerosis.\textsuperscript{53}

Mohan and Premlatha observed that, the prevalence of coronary artery disease is higher for adults with diabetes mellitus as compared to the prevalence in general population. The prevalence of angina, myocardial infarction and sudden death are more common in diabetes.\textsuperscript{139}
Hyperlipidemia has been found in approximately 50%. In diabetic patient the lipid abnormalities includes low HDL elevated VLDL and triglyceride, which contributes, to the cardiovascular risks. In addition, there are often alterations in the composition of the apolipoprotein. It has been also observed that the pathogenic features include:

Myocardial enlargement, myocardial hypertrophy and fibrosis, increase basement membrane thickness, microaneurysms, microvascular narrowing leading to microangiopathy. Abnormal calcium uptake by sarcoplasm.

Cross Mary observed that, lipid abnormalities are of importance because of their relation to atherosclerotic vascular diseases especially coronary heart disease (CHD), attributed due to abnormalities in the levels and metabolism of plasma lipids and lipoprotein (Hyperlipidemia means increase in cholesterol or triglyceride). Hypercholesterolemia is most clearly associated with increase risk for coronary artery disease. The elevation of LDL cholesterol can result from single defects. Polygenic disorders and secondary effects of other disease states.\(^{(65)}\)

In homozygous form is associated with cholesterol \(>500\) mg/dl. Cholesterol levels between 240-350 mg/dl is polygenic in origin, multiple genes interact, with environmental factors to contribute to hypercholesterolemia and both overproduction and
reduced catabolism of LDL are thought to play a role in pathophysiology. In which triglyceride and HDL are normal.

The hypertriglyceredemia, due to decrease catabolism of triglyceride rich lipoprotein and overproduction of VLDL. Fasting hypertriglyceridemia does not appear to increase risk factors for CHD.\textsuperscript{(65)}

Vitzum and Steinberg observed the \textbf{oxidative modifications increase the atherogenesity of LDL}. The original theory is based on the concept that the oxidative modifications promote the uptake and retention of circulating LDL, in the arterial wall. The other causes, includes the oxidation of membrane lipids of platelets as well as arterial wall endothelial cells and smooth muscle cells. These effects could enhance the intercellular interactions that promote atherogenesis.\textsuperscript{(53)}

Krishnaswamy and Prasad (1989), coronary artery disease is present in Indians with relatively low cholesterol level and Framingham Cohort is often very not prominent among Indians with coronary artery disease. Hyperinsulinemia, impaired gastrointestinal tract (GIT), hypertri-glyceridemia, abdominal obesity, hypertension etc are much more prevalence in Indians.\textsuperscript{(140)}

In the study of CAD risk factors in Indians, a significant correlationship has been demonstrated between
**hypercholesterolemia (< 200 mg%).** Even though the levels were below 150 mgs% the incidence of coronary artery disease had been reported. These data suggest correlation between atherogenic lipids and presence of coronary artery disease. The National Cholesterol Education Program (NCEP) guidelines may be too liberal in the Indian context.(140)

Cooke R. observed that myocardial ischemia can be prevented by correction of the patients risk factor profile using combination of diet, lifestyle changes and drug therapy.(13)

Choosing appropriate treatment for stable angina patients can turn into a real challenge for clinicians. Haemodynamic treatment such as ca-antagonists, β-blockers or nitrates have long been used either in monotherapy or in combination.(13)

The health professional follow up study found that high intakes of vit. ‘E’ was associated with decrease rates of coronary heart disease only.(141)

Opie L.H. showed the major metabolic substrates of the normal well-oxygenated myocardium are FFA in the fasted state and glucose in the fed state. In general the normal myocardium uses whichever fuel is available. During ischemia, there is a swing towards glucose metabolism and it is proposed that glycolysis provides beneficial glycolytic ATP, which has many protective
actions including prevention of sodium pump activity. Hypothetically, when sodium pump activity stops, cytosolic Ca$^{++}$ increase and ischemic contracture, often an irreversible event occurs. The rise in internal sodium may alter sodium/calcium exchange, thus precipitating contracture.\textsuperscript{(142)}

Guizg A. showed in cardiovascular system (CVS), association of diabetes with risk factors such as hyperlipidemia, hypertension. LDL oxidant causes atherosclerosis, releases EDRF (NO) (Same findings as previous qutori quote).\textsuperscript{(143)}

Lee Goldman \textit{et al} states that \textbf{prevention is better than cure}. In their studies they suggest that primary and secondary risk factor reductions explain about 50\% of the striking decline in coronary mortality and more than 70\% of overall decline mortality has occurred among patients in coronary disease.\textsuperscript{(144)}

Sainani G.S. described in his observations that hypercholesterolemia whether familial or otherwise is associated with atherosclerosis because there is increase in LDL cholesterol. Other risk factor includes hypertension; Smoking and decrease HDL-C are less atherogenic if lipids and liporotein are low. These findings suggest that intimal lipid deposition in the initial inciting even in atherosclerosis. triglycerides rich lipoprotein, chylomicrons, VLDL and cholesterol rich lipoprotein.\textsuperscript{(145)}
HDL (via one of its apo-lipoprotein, apo A-1) mediated removal of cholesterol called reverse cholesterol transport, so decrease HDL-C is associated with increase risk of atherosclerosis due to impaired clearance of cholesterol from tissues such as arterial wall. Hence deposition of lipoprotein in arterial tissues may occurs through:

1) Accumulation of excessive amount of lipoprotein in plasma (plasma hyperlipidemia).

2) Increase permeability to endothelial cell wall damage either by oxidative damage or hemodynamic stress.

3) Defective removal of lipoprotein from arterial tissue due to low HDL-C levels.\(^{(145)}\)

Dupis et al showed that in atherosclerosis, there is increase in total cholesterol and LDL-C levels. Total and LDL-C levels were similar at admission and before randomization in both groups. Responses to nitroglycerin and pravastatin therapy in 6 weeks shows that reduction in cholesterol levels after therapy rapidly improves the endothelial functions. Cholesterol reducing agent reduces the risk of mortality and myocardial infarction (Sacks et al (1996))\(^{(147)}\). Although cholesterol lowering effectively induces regression and delays the progression of coronary atherosclerosis.\(^{(146)}\)
Other mechanisms of which plaques regression may represent a phenomenon, have therefore have been postulated to explain these findings. Thus cholesterol lowering may stabilize the vulnerable plaques by modifying its content, mostly through a reduction of the oxidized lipids in core, which renders its susceptible to rupture. Cholesterol reduction also improves both coronary and systemic endothelial functions.\(^{(146)}\)

Christoph Bickel et al showed showed risk factors of death and it’s not necessarily associated with other traditional/common risk factors.\(^{(148)}\)

Lancet showed that based on presumption that the likelihood of benefit outweighs any low probability of harm with daily supplementation of vitamin E.\(^{(149)}\)

Mohan V. and Deepa R. observe the coronary artery disease is already a major killer disease followed by infectious diseases like tuberculosis, diarrhea or other respiratory diseases.\(^{(10)}\)

They describe the common risk factor for coronary artery diseases are – Diabetes, obesity, dislipidemia, hypertension, contributes to coronary artery disease. Coronary risk factors like hypertension, physical inactivity, obesity and truncal obesity, hypercholesterolemia, hypertriglyceridemia, insulin resistance, are highly prevalent among Indians. Plasma HDL level is inversely
related to coronary artery disease, its role in coronary artery disease and the role of niacin in elevating low HDL levels.\(^{10}\)

Tillman Cyrus et al showed that it is now a known hypothesis that oxidative stress-mediated mechanisms play a central role in early atherogenesis. According to him the nitrous oxide increases, vitamin E supplementation may prevent the progression of atherosclerosis by suppressing oxidative and inflammatory reaction and increase nitrous oxide levels.\(^{150}\)

They also showed that in hypertension uric acid level are more strongly associated with adverse events in women than in men. Uric acid is also associated with diastolic blood pressure, glucose intolerance, and the risk factors that contribute greater relative risk for cardiovascular diseases in women. Among the men, elevated serum uric acid levels was associated with decrease incidence of coronary heart disease.\(^{150}\)

Daniel Steinbergh et al, described the pathophysiology of atherosclerosis, the progression of the disease the basic cause of the disease.\(^{65}\)

**ii] Role of Lipid Profile in CHD :**

Ravanoskovl V. showed lowering serum cholesterol levels did not reduce the mortality and is unlikely to prevent CHD.\(^{151}\)
Rifai N. *et al* also regarded that lipoprotein A as a biological marker for familial CAD. High LP(a) levels are equally important as history of **premature CAD** in patients.\(^{(152)}\)

CAD in Indians study shown that LDL-C levels in Indians does not differ in patient with / without coronary artery disease. Achari *et al* have reported no significant difference in LDL-C level among patient with CHD and normal subjects. The desirable levels for Indians are suggested by certain authorities C=80 mg% for secondary prevention).\(^{(153)}\)

The relationship of triglycerides concentration and risk for CHD has been an issue of great interest and controversy. However emerging evidence at the epidemiologic, clinical, cellular, genetic and molecular level constitutes a compelling case for triglycerides to be an independent risk factor for coronary artery disease.

The lipid profile including triglycerides in the evaluation of a patient risk for coronary artery disease. A measurement of fasting triglycerides and its assessment in conjunction with LDL-C and HDL-C concentration and other risk factors would seems to be the most practical way of assessing any additional risk proposed by hypertriglyceredemia.\(^{(153)}\)

The desired level for triglycerides in Indians is suggested as less than 150 mg% and TC/HDL-C ratio is below 4.5
Low plasma HDL-C is a powerful risk factor for CHD. High levels of HDL-C protects from coronary artery disease both in men and women. Each 1 mg% increase in HDL-C concentration is estimated to decrease coronary artery disease events by 2% in men and 3% in women.\textsuperscript{(153)}

According to Mechens M. et al National Cholesterol Educatin Program (NCEP) has defined 3 levels of HDL-C

Low \ (< 35 Mg%)

Normal \ (35-60 mg%)

High \ (> 60 mg%)

Apart from its role in reverse cholesterol transport, HDL has anti-inflammatory and antiatherogenic property. TC/HDL-C ratio (> 4.5%) which is considered to be most powerful predictor of coronary artery disease is prevalent in 42% of urban Indian hypertensive.\textsuperscript{(153)}

\textbf{iii] Role of Lipid Profile in AMI :}

Corvette (2001), coronary artery disease in Indians commonly manifest with an AMI with or without prior angina. Indians in the age group of 30-39 years are at 10 times greater risk of MI than Caucasians of the same age.\textsuperscript{(17)}

The abnormal lipid profile levels characterised by increase in LDL also their inherent atherogenicity and also markedly increase
triglycerides and decrease in HDL along with many other risk factors such as smoking, diabetes truncal obesity etc. by the year 2015, it is predicted that CVDs in India would replace infectious diseases as the major killer. An increase in mortality by 103% in males and 90% in female is expected from 1985-2015. Coronary artery disease will account for 34% of all male deaths and 32% of all female deaths in India. WHO predicts that by 2025 cardiovascular diseases will become more prevalent and that will be largely due to adoption of western lifestyle and their accompanying risk factors.(17)

Isser et al observed the study group consist of lipid profile level below 45 years with MI.(154)

There was no significant difference in Total-C and LDL-C among the three group. HDL-C levels significant low in MI and their relatives versus ‘C’ group. triglycerides was significantly increased in MI as compared to controls. Since young MI and their first-degree relatives have significant (statistically) higher levels of triglycerides and lower levels of HDL-C as compared to ‘C’, thus Sr.triglycerides may be an important risk factors than TC and LDL-C.(154)

Increase rates of delivery of FFA are potentially harmful to the ischemic myocardium. Fatty acids has “oxygen-waiting” potential in the aerobic, ischemic or reperfused myocardium, and
provision of glucose rather than FFA promotes the recovery in the post ischemic reperfusion period.\textsuperscript{154}

Sainani G.S. showed both HDL-C and apo E play role in removal of cholesterol from plaques. Both macrophages and smooth muscle cells in culture secrete apo-E. Synthesis of apo-E by macrophages in plaques particularly lipid laden foam cell macrophages, has been documented.\textsuperscript{145}

In a recent epidemiological study, prevalence of coronary artery disease 96.7/1000 (urban) and 27.1/1000 (Rural). Prevalence of other risk factors was also lower in this rural center as compare to urban population.\textsuperscript{152}

Collertan \textit{et al} showed the association with risk for cardiovascular disease and death. The findings and results of these studies suggested that a positive association between uric acid and cardiovascular outcomes.\textsuperscript{155}

Nigam P.K. \textit{et al} observed that in patients with AMI during acute phase (day 1,2 and 3), predischarge and after 3 months. Total lipids, cholesterol and LDL-C showed no significant change in levels during the hospital stay and three months of follow-up. While the HDL-C started falling after two days and remained till three months. So it is concluded that the optimum time for
assessment of serum lipid profile in patients with AMI seems to be within 24 hours of the acute episode.\cite{156}

Thus we have progressed substantially the work that cause of coronary heart disease (CHD) is a multifactorial, a concept that lead to the use of a term ‘risk factor” rather than “Cause”. Also an expanded research effort has resulted in significantly greater knowledge about the atherogenesis processes and risk for coronary heart diseases much work remains. We must develop approaches that will allow more rapid, rigorous evaluation of these emerging markers.\cite{156}

Hamesten A. showed that the relation of triglycerides concentration to mortality from CHD in women was present at all body mass indices. The increase concentration of triglycerides affects the hemostatic system through their positive correlation both with the coagulant activity of factor VII and with plasminogen activator inhibitor.\cite{157} Triglycerides concentration is also related to the presence of small low-density lipoprotein particles now considered being genetically influenced risk factors for coronary heart disease. Hypertriglyceridemic very low density lipoprotein may affect endothelial cells and turn macrophages into foam cells and postprandeal hypertriglyceredemia with delayed clearance of chylomicrons remnants also increase atherosclerosis.\cite{157}
The diet used in western societies favors the development of decrease glucose tolerance, increase triglycerides concentration, and decrease HDL-C, hypertension and abdominal obesity. Peoples with a clustering risk factors, the insulin resistance. Syndromes are at high risk of developing coronary heart disease. Similar observations were reported by Folsom et al.(158)

Stensvold Inger et al showed initial screening of lipid profile and other risk factors like hypertension, obesity, body weight etc. They found that the high triglycerides concentration is an independent risk factor for mortality from coronary heart disease, cardiovascular disease and any cause of mortality particularly in women. The association between triglycerides concentration with increase cholesterol is discussed.(159)

Klag M.J. the prospective study was designed to determine the link between serum cholesterol levels and risk for CVD have generally involved middle aged subjects.(160)

Brown et al observed the consequences of evidence from angiographic trials demonstrates both coronary artery and clinical benefits of lowering lipids by a variety of regimens.(161)

Grekh K.F. et al described the role of β carotene as a protective role in CHD. In their studies they observed that the mortality from
cardiovascular diseases was correlated to the baseline concentration of carotene.\(^{(162)}\)

Seeman et al observed his findings do not support cholesterol as a risk factor with a graded and continuous association with all cause mortality, CHD mortality or hospitalization for ischemic event among very elderly subjects (more than 70 years of age). The higher cholesterol, lower HDL and higher risk ratio were not associated with CHD is elder patients.\(^{(163)}\)

Sacks et al showed in normal cholesterolemic patient of atherosclerotic coronary artery disease, with the raised LDL concentration. The intensive pharmacological treatment of normal cholesterolemic patient has significant effect on plasma lipid concentration but no angiographically measurable benefit on the coronary arteries. Information is needed from secondary prevention trials that measure clinical event rates, to form conclusions about the benefits of cholesterol lowering treatment in coronary heart disease (CHD) patients who do not have hyperlipidemia.\(^{(147)}\)

La-Jolla et al showed when plasma cholesterol rises above 4.1 mmol/L, the chances of development of coronary artery disease increase and also increase in the plasma LDL-C. There is a great diversity in the extent of these levels and in the expression of clinical disease. Stenberighs hypothesis states that oxidative LDL-C (or other lipoprotein) is important and obligatory in the
pathogenesis of the atherosclerotic lesion. A corollary is that inhibiting the oxidized LDL will decease or prevent atherosclerosis with proximal sequelae could a significant reduction in coronary artery disease could achieved by augmented intake of antioxidant vitamins or similar compound?.[164]

Opie L.H. observed the major focus in research on blood lipids and coronary artery disease is now and the role of oxidized LDL. There is strong evidence that such oxidation occurs, that is promoted by various factors that increase the rate of formation of oxygen free radical and that oxidised LDL is more noxious to the vascular intima. Further more oxidised LDL may provoke monocytes to produce cytokine, interleukin-I, which together with other cytokines such as tumor necrosis factor – alpha may participate in atherogenesis. This coincides with current concepts that damaged endothelium promotes coronary atheroma and that various risk factors chronic hypertension, smoking act to promote endothelial damage.[165]

Another important findings were lower plasma β-carotene and tocopherol in men. The relevance of these findings is supported by a recent study showing that Swedish men with had decrease serum concentration of tocopherols. However, Reimersma et al found that plasma concentration with vit. ‘E’ was independently and inversely related to the risk of angina.
Chopra and Wasir described the role lipid profile in coronary artery disease patients.\textsuperscript{[166]}

Salonen \textit{et al} showed that there is a significant change in serum HDL-C level (increase) among men who received vitamin ‘C’ supplement, whereas vitamin ‘E’ has effect on serum HDL-C in men. In women neither ‘C’ nor ‘E’ had any effect on HDL-C level. These results are of greater significance because it is found that the basal levels of vit. ‘C’ plus ‘E’ are less in men as compared to women so which might responses strongly than women. The possible mechanism responsible for antiatherogenic effect of vit.C plus vit.E in combination would be entirely or in part other than inhibition of lipid peroxidation. After discovery of $\alpha$-tocopherol binding protein with possible receptors functions, it’s observed that vit. ‘E’ exerts a more functions in the human body than antioxidative actions and these other properties may be as a antiatherogenic properties. Similar findings were also observed by Tribble D.L., 1999\textsuperscript{[117]} and Yasunariik, 1999.\textsuperscript{[118]} The $\alpha$-tocopherol may increases protein phosphatases 2A\textsubscript{1} activity and inhibits protein kinase C and smooth muscle cell proliferation, cell adhesion and platelet aggregation and enhances nitric oxide bioavailability. It also counteracts inflammation and also improves endothelium dependent vasodilator function. $\alpha$-Tcopherol exert these pleiotrophic effects only in its reduced form, thus a co-
antioxidant vit ‘C’ is necessary pre-requisite for antiatherogenic effects of vitamin. ‘E’ and vitamin ‘C’ is also known as scavenging action/scavenger for vitamin ‘E’.\(^{(99)}\)

Manindar Kaur et al observed that patients suffering from mild to moderate degree of hypertension having hyperlipidemia followed by felodipine therapy. After 2-4 months significant falls in the levels of cholesterol, triglycerides and total lipids though no significant variations observed in HDL and LDL-C levels.\(^{(167)}\)

Regina C.B. et al showed in their training program on lipid profile and myocardial oxidative stress. Reactive oxygen species (ROS) and free radicals are mediators of several forms of tissue damage, such as ischemic injuries and cardiac damage. Antioxidant defense cell systems protect against or minimized oxidative damage induced by ROS, but there is a conflicting information on the effects of exercise and training in these antioxidant defenses.\(^{(168)}\)

Baskaran S. and Lakshmi S. showed the increase activity of these antioxidamt enzyme also increase the utilization of glutathione hence there was a concomitant decrease in the level of glutathione in these tissues.\(^{(33)}\)

Landmesser et al, during the past decade, numerous experimental and clinical studies have demonstrated that many
common condition predisposing to atherosclerosis, such as hypercholesterolemia, hypertension, DM, smoking are associated with reduced vascular availability of nitric oxide (No). No is not only produces vasodilation but also as a potent antiatherogenic properties. These properties are – inhibition of platelet aggregation, prevention of smooth muscle cell proliferation, and reduction of lipid peroxidation and inhibition of adhesion molecule expression.\(^{169}\)

The loss of nitrous oxide, observation in these various conditions not only alters vascular tone but also may explain in part why these conditions are risk factors for atherosclerosis.

Main cause of impairing endothelial functions by the risk factors due to increase production of reactive oxygen species within the vessel. In particular super oxide (\(\text{O}_2^\cdot\)) reacts rapidly with No, resulting in the formation of a peroxynitrite anion and the loss of No bioactivity. Recently it is found that peroxinitrite can oxide tetrahydrobiopterin, a critical co-factor required for nitric oxide synthase.

Vaccarino \textit{et al} observed risk factors for CVD : one down, many more to evaluate. In this Framingham Heart study, resolve the long standing controversy surrounding the role of uric acid as a risk factor for CVDs.\(^{170}\)
Mehrotra et al observed serum lipids i.e. triglycerides, cholesterol and free fatty acids were found to be raised significantly in all cases of diabetes mellitus. In vascular diseases, the values are much higher than diabetes mellitus. Values of cholesterol and triglycerides are higher significantly than who have only diabetes mellitus and no vascular complications or evidence of were higher as compared to controls. Still higher values are observed in patients with diabetes mellitus with vascular complications.\(^{(171)}\)

Similar observations were also reported in earlier studies by Lawy A.D. and Barch J.W.\(^{(172)}\) and Carrison L.A. and Bottinger L.E.\(^{(173)}\)

Salonen J.T. showed the autoantibodies to MDA – modified LDL in base line serum sample is an independent predictor of progression of carotid atherosclerosis over 2 years. Present study and other have reported that autoantibody against oxidized LDL exists in serum of patients with coronary artery disease and controls showed results for progression of CAD.\(^{(174)}\)

Gale et al showed that the mortality from stroke was highest in those with the lowest vit. ‘C’ intake had a relative risk of 0.5% compared to those with the lowest third. The relation between vit. ‘C’ intake and stroke was independent of social class and other dietary variables. A similar gradient risk was present for plasma
ascorbic acid concentration. No association was found between vit. ‘C’ status and risk of death from CHD.\(^{(141)}\)

A striking finding in our study was the lower resistance of LDL to oxidation in men. Several studies suggested that low LDL might be oxidized in the arterial wall and thus initiate and promote atherosclerosis. A short lag phase for the oxidation of LDL is associated with coronary atherosclerosis in patients with coronary heart disease. Susceptibility of low LDL to oxidation has been related to progression of atherosclerosis in carotid and femoral arteries and higher proportion of partially oxidized LDL was found in patients with progression of atherosclerotic plaques.\(^{(141)}\)

Trivedon (1995) a group of Cipla Pharmaceutical Publications published a review purpose for myocardial ischemia.\(^{(80)}\)

Elevated total cholesterols are a risk factor for death from CHD in older, adults, and the apparent adverse effects associated with low cholesterol levels are secondary to co morbidity and frailty. This suggests that the excluding older persons from cholesterol screening is in appropriable, but interpretation of screening results in older persons requires along with clinical judgment.\(^{(175)}\)

The prevalence of coronary artery disease has been consistently observed to be high in Indians. The excess risk ranges from 2.5-5 for AMI and 1.5-3 for coronary artery disease mortality.
Resistance to insulin mediated glucose uptake and consequent hyperinsulinemia (insulin resistance syndrome) (IRS) has been considered as the most important cluster of metabolic risk factors and early and extensive CAD in Indians. It provides a base on which low HDL-C, high triglycerides, and impaired glucose tolerance and finally atherosclerosis occurs.\(^{176}\)

Basu \textit{et al} describe the risk factors for ischemia showed complete hemogram, BSL F, PP, KFT, lipid profile, L(a) homocysteine etc were identified as a risk factors. 87.5% risk factors followed by IHD, (35% diabetes). Dislipidemia were also found in cases.\(^{177}\)

**II] Role of Kidney Function in Atherosclerosis and Myocardial Diseases:**

This topic describes the role of kidney function tests and atherosclerosis and myocardial diseases. Here the uric acid serve both as kidney function parameters and secondary antioxidant.

i) Hyperuricemia (IHD):

Beard J.T. observed that present study does not support an independent role for hyperuricemia in the pathogenesis for arterial damage.\(^{178}\)

Selby \textit{et al} describe that in hypertension without complications (essential hypertension) elevated serum uric acid
level have been noted. The uric acid – hypertension association did not appear to be due to an effect of attained blood pressure level on uric acid metabolism at baseline. Serum creatinine also an important correlate of the uric acid level. Increase in serum triglycerides – uric acid association, because a triglycerides level is a predictive developing hypertension. Serum cholesterol levels remained predictive of developing hypertension. This association even through may not strong but is of interest in line of recent hypothesis linking hypertension and dislipidemia.\textsuperscript{(54)}

Wald N.J. observed that lowering serum cholesterol concentration in a population is critical in reducing mortality from IHD. Appropriate action is needed, including wider health education. Labeling of foods in supermarkets and provision of information on the content of restaurant meals. Most important, though more difficult is to implement national and international policies on food subsides those are linked to health priorities. Actions need to be taken to reach this target.\textsuperscript{(179)}

Williamson D.F. observed that although several investigators have found that elevated uric acid levels to be an independent predicting risk factor for IHD and total mortality.\textsuperscript{(180)}

Stronger associations were seen with IHD mortality among women. Each 1 mg/dl increase in uric acid increase the fully adjusted mortality rate (95%) with a uric acid levels > 7.0 mgs%.
They also observed hyperuricemia is frequently found among persons with IHD. In women, serum uric acid level was a predictive of mortality from all causes and from IHD.

Recent studies also suggest that increase insulin resistance, which can decrease the renal clearance of uric acid, may leads to hyperuricemia. Persons with prevalence IHD and high diastolic blood pressure along with those who reported using diuretics or antihypertensive medications had higher levels of uric acid than did other persons.

Because uric acid levels are associated with several risk factors ischemic heart disease, the importance of hyperuricemia in the development of clinical disease has been difficult to assess.

Hypercholesterolemia is found in their study with hyperuricemia has been associated with various dislipoproteinemias and a high fat diet.(180)

Similar observation was also reported in earlier studies.(53)

\textbf{ii) Role of Kidney Function in CHD}

Virtamo J. et al shows the mechanism of increase deaths in previous history of MI in patients the probable reason is that the antioxidant effect of $\alpha$-tocopherol limits or abolishes the protection of the myocardium against by short periods of ischemia and reperfusion while $\beta$-carotene is easily incorporated not the
atherosclerotic plaques and whether its presence may render the plaques more susceptible to rupture is not known. A decrease in spontaneous thrombolysis and electrical or mechanical instability of the injured myocardium are also possible mechanism.\textsuperscript{(181)}

**iii] Role of Kidney Functions in AMI**

Wannamethe \textit{et al} observed the relationship between serum urate and the risk of coronary heart disease depends heavily upon the presence of pre-existing myocardial infarction and widespread underlying atherosclerosis as well as the clustering of risk factors. Thus serum urate is not a truly independent risk factor for coronary heart disease. Raised serum urate appears to be an integral part of the cluster of risk factors associated with the insulin resistance syndrome that includes DM, obesity, raised serum cholesterol and triglycerides levels.

In his study, serum urate was significantly and positively associated with risk of CHD, even after adjustment for the life style factors and disease indicators including pre-existing CHD and use of antihypertensive treatment. While several studies found risk to be related to the pre-existing coronary heart disease.\textsuperscript{(56)}

The hypercholesterolemia exceeds the concentration with hyperuricemia. The more correlation exists with serum cholesterol and uric acid is in primary hypertension. In chronic patients
revealed changes seen in gouty kidneys, these changes includes glomerular capillary thickening and sclerosis, tubular atrophy, pigment deposit and degeneration especially n loops of Henle and extensively interstitial deposits of uric acid in renal medullary tissue.\(^{54}\)

William \textit{et al} observed hyperuricemia in both types of hypertension results from diminished renal excretion of urate. Altered lactic acid metabolism in hypertension may account in part for the altered transport of uric acid. This also results the possibility that increase in serum uric acid is established in turn contribute to the renal insufficiency frequently seen in hypertensive patients. Hyperuricemia in hypertensive disease may results from overproduction of uric acid and occurs in gout and familial hyperuricemia. It may also leads to impair uric acid excretion and secondary to deranged kidney functions associated with hypertension.\(^{182}\)

Law M.R. and Wald N.J. showed the results from Cohort studies, international comparisons and clinical trials are remarkably consistent.\(^{179}\)

Dixon \textit{et al} describe the role of nitrous oxide in myocardial diseases.\(^{183}\)
The association of uric acid and atherosclerosis, uric acid increases platelet adhesiveness (Newland H, 1975)\textsuperscript{[66]} and urate crystals may be associated with increase platelet lysis. Uric acid may also play an important role in the formation of free radicals and oxidative stress. Hyperinsulinemia may cause increase sodium resorption at the proximal tubule, hyperuricemia and hypertension.

Therefore the role of uric acid is critical where it is an independent risk factor of atherosclerosis or hyperuricemia is merely an indirect marker of adverse outcome by reflecting the association between uric acid and cardiovascular risk factors. Increase uric acid levels have also been perforated to be a predictor of stroke.

Mechanism by which uric acid associated with atherosclerosis is uncertain. A large body of evidence links uric acid with metabolic syndrome of insulin resistance, obesity, hypertension and dislipidemia. Uric acid may also be an indicator for increase in oxidative stress. Xanthine oxidase, a critical enzyme in the degradation of purines to uric acid has been shown to an important source of superoxide free radicals. An activity of xanthine oxidase increases during ischemia and intensifies during reperfusion in coronary endothelial cells. The allopurinol limits
infarction size and enhances recovery of stunned myocardium perhaps the limiting the generation of toxic free radicals.\textsuperscript{(66)}

Collerton and colleagues found that elevated uric acid level was strongly associated with higher age associated risk for CHD, death from DVD in women and not in men. However adjustment with other risk factors (body mass index, diabetes, cholesterolemia, smoking alcohol consumption, hypertension etc.). They found no association between uric acid level and any of the outcomes in men and women.\textsuperscript{(155)}

Still the study is important beyond the resolution of uric acid controversy. It is another example of rigorous methods used by Framingham investigators to expand our knowledge and understanding of risk factors for CVD. The development of new diagnostic methods to detect sub-clinical disease has also expanded the number of potential risk factors. Because of such risk factors are introduced with increase frequency, the example of uric acid study is particularly relevant. It’s clear that the challenge of evaluating risk factors will increase the pace of scientific inquiry accelerates.
Experimental Design: Study Groups

This chapter deals with the study serum lipid profile and kidney function tests in atherosclerosis and myocardial diseases (IHD, CHD and AMI).

(For graphical presentation the kidney function parameters are expressed in percentage).

In this group of studies that 50 patients were selected from the ICCU and General Medicine Wards of Government Medical College, Aurangabad who receive the treatment for their diseases. There diagnosis is confirmed by ECG and 2-D Echocardiography basis. All patients were under regular treatment.

Their family history period for existence of the disease, treatment portion, were considered and the blood chemistries performed to help for the diagnostic and prognostic purpose.

The blood sugar levels were recorded for ruling out diabetes mellitus. The details of methods described in Chapter II – Material and Methods.
Results and Discussion:

In the present group of study, estimation of lipid profile and kidney function test were studied in atherosclerotic subjects suffering from various myocardial diseases. This myocardial disease were diagnosed and classified into three types:

I) Ischemic heart disease (IHD),

II) Coronary heart disease (CHD)

III) Acute myocardial diseases. All the above-mentioned parameters of each group were estimated and the levels were studied.

Table V and Fig. 5 describe the abnormal lipid profile is characterized by increased in LDL-c and also their inherent atherogenacitv and markedly increased triglyceride along with decrease in HDL-c levels. With many other risk factors such as smoking, diabetes, truncal obesity etc observed in present study. The maximum levels of TG with high LDL-c were observed with vascular complications like coronary artery disease. Hypercholesterolemia and hypertriglyceridemia were found in cases of myocardial diseases. This data also suggest that hypertriglyceridemia support the significance of risk factor with NIDDM.
### TABLE – V

**Serum lipid profile in atherosclerosis and myocardial diseases**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>Myocardial Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IHD</td>
</tr>
<tr>
<td>Sr. Total cholesterol</td>
<td>177.33±20.80</td>
<td>251.30±29^a</td>
</tr>
<tr>
<td>(mgs%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sr. Triglycerides</td>
<td>116.87±36.10</td>
<td>178.8±14.6^b</td>
</tr>
<tr>
<td>(mgs%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sr. HDL-cholesterol</td>
<td>53.28±9.3</td>
<td>33.40±5.66^a</td>
</tr>
<tr>
<td>(mgs%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sr. LDL-Cholesterol</td>
<td>100.63±2.02</td>
<td>214.9±20.74^c</td>
</tr>
<tr>
<td>(mgs%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sr. VLDL-C (mgs%)</td>
<td>23.37±7.23</td>
<td>35.77±2.93^c</td>
</tr>
</tbody>
</table>

Values are mean±SD,

(a) p<0.001,
(b) p<0.01,
(c) p<0.05,
Low plasma HDL-c is powerful risk factor for coronary heart disease. Total cholesterol / HDL-c ratio were $\geq 4.5\%$ is considered to be the most powerful predictor of coronary heart disease in 58% population in the present study. Higher the LDL-c level in the present study group suggestive of the role of oxidized LDL-c on blood lipids and coronary artery disease which is more noxious to the vascular intima.

The cholesterol levels were significant higher in myocardial diseases as compared to control. Similarly the TG levels were also moderately on higher side in myocardial diseases. This study also point out the serum cholesterol levels and the risk of cardiovascular disease have general involved in the middle aged subjects. Similar highly abnormal pattern of lipid profile in IHD was reported by Robert Cooke,(13) and Corvette et al,(17) which were in correlation with the present study. Law M.R. et al (179) observed high level of serum cholesterol from IHD falling in various age groups. In above 40 years of age group, the levels of serum cholesterol in IHD group were relatively highly in correlation with the present study group.

In the second group of the present study i.e. coronary heart disease (CHD), similar type of abnormal levels of lipid profile was observed. Serum cholesterol levels were significantly found to be elevated with levels ($p<0.001$) compared with IHD and AMI group
Triglyceride levels were low compared to IHD group, but raised were observed in AMI which were highly significant with p<0.001. Serum HDL-C levels was significantly lowered with mean values $31.0 \pm 9.83$ mgs% in CHD compared with IHD and control group. But more reduction with mean values of $30.0 \pm 4.12$ mgs% was observed in AMI group. Similar correlating abnormal pattern of lipid profile was observed and studied by Jacolyn Dupius et al (146) in which they had observed rapid improvement of coronary arterial diseases with six weeks of therapy. Rovanoskovl V. et al (151) reported hypercholesterolemia in CHD cases, which were statistically correlated with the present study of CHD group. They also reported that, reduction in cholesterol levels might reduce the prevention and mortality rate of CHD. Also Lee Goldman et al, (144) studied and reported abnormal lipid profile pattern in CHD, which were correlated with the present group study. They had suggested that about 50% coronary mortality and primary and secondary risk factors of CHD could be reduced. Maria-Chiara et al (175) also observed similar correlating elevated levels of cholesterol in CHD. Serum LDL-C levels were found to be increased significantly in all the three groups of present study. The levels in IHD group study were highly elevated with mean values $214.97 \pm 20.74$ mgs%. The increase was highly significant compared with other groups such as CHD (mean values $196.29 \pm 11.66$ mgs%) and AMI (mean values
139.92±6.89 mgs%) compared with control group. similar to resembling elevated levels of LDL-C were reported.\textsuperscript{(146,166)}

**Table VI and Figure 6 describes the levels of kidney function studies**

Significant increase blood urea, serum creatinine and uric acid levels were found in all the groups compared with control. The levels were found more increased in CHD with mean urea levels 33.31±1.91 mgs%, serum creatinine 1.14±0.01 mgs% and serum uric acid levels 6.40±0.25 mgs% which were highly significant compared other two groups.

The levels of uric acid in a low risk groups with coronary artery disease indicates that uric acid is an independent predictor of traditional or common risk factors. Other than uric acid serum creatinine level is also shows significant higher in hypertensive patients. Raised serum uric acid appears to be in cluster of risk factor associated with insulin resistance syndrome that includes diabetes mellitus, obesity, raised serum cholesterol and TG levels.

Uric acid may also be an indicator for increased oxidative stress. Xanthine oxidase, a critical enzyme responsible for degradation of purines – uric acid has been shown to an important source of superoxide free radicals. Similar observation of
TABLE – VI

kidney functions in atherosclerosis and myocardial diseases

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>Myocardial Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IHD</td>
<td>CHD</td>
</tr>
<tr>
<td>Blood Urea (mg%)</td>
<td>19.21±2.2</td>
<td>31.4±1.7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sr. Creatinine (mg%)</td>
<td>0.71±0.15</td>
<td>1.19±0.07&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sr. Uric acid (mg%)</td>
<td>3.20±0.32</td>
<td>5.86±0.29&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are mean±SD,

(a) p<0.001,
(b) p<0.01,
(c) p<0.05,
hyperuricemia also correlates with the studies of Christoph B.K. et al (2002).\textsuperscript{148}

The free radical stress and antioxidant status in myocardial diseases and atherosclerosis is discussed in Chapter VI.