A PROSPECTIVE COMPARATIVE CLINICAL STUDY OF ATORVASTATIN AND ATORVASTATIN WITH VITAMIN D3 ON LIPID PROFILE IN VARIOUS PATIENT POPULATION

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Madurai

.09.2014

CERTIFICATE

This is to certify that the dissertation entitled **"A PROSPECTIVE COMPARATIVE CLINICAL STUDY OF ATORVASTATIN AND ATORVASTATIN WITH VITAMIN D3 ON LIPID PROFILE IN VARIOUS PATIENT POPULATION"** is a bonafide record of work done by **DR.M.VIJAYALAKSHMI**, under the guidance and supervision of **DR.R.SAROJINI M.D.**, Professor, in the Institute of Pharmacology, Madurai Medical College, Madurai during the period of her postgraduate study of M.D Pharmacology from 2012-2015.

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DECLARATION

I, **DR.M.VIJAYALAKSHMI** solemnly declare that the dissertation titled **"A PROSPECTIVE COMPARATIVE CLINICAL STUDY OF ATORVASTATIN AND ATORVASTATIN WITH VITAMIN D3 ON LIPID PROFILE IN VARIOUS PATIENT POPULATION"** has been prepared by me under the able guidance and supervision of **DR.R.PARAMESWARI M.D,** Director and Professor, Institute of Pharmacology, Madurai Medical College, Madurai , in partial fulfillment of the regulation for the award of M.D Pharmacology degree examination of the Tamilnadu Dr.MGR Medical University, Chennai to be held in April 2015. This work has not formed the basis for the award of any degree or diploma to me, previously from any other university to anyone.

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CONTENTS

ABSTRACT

OBJECTIVE

To compare the effect of Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in various patient population

METHODOLOGY

The study was conducted in outpatient department of General Medicine, Nephrology, Madurai Medical College, Madurai, between February 2013 to August 2014. 120 patients with Dyslipidemia were selected based on measurement of lipid profile. Out of 120 patients, 60 patients were treated with atorvastatin 10 mg/day orally and the remaining 60 patients were treated with atorvastatin 10mg and vitamin D3 1000IU/day orally. In atorvastatin group, 30 were Hypertensive and 30 had chronic kidney disease (CKD). In atorvastatin vitamin D3 group 30 were Hypertensive and 30 had CKD.The plasma lipid profile was assessed at the beginning, third month and at the end of sixth month. The results were tabulated and analyzed statistically

RESULTS

All the patients were followed up till the end of the study. There were no dropouts. At the end of sixth month the mean total cholesterol was significantly reduced in atorvastatin vitamin D3 group than in atorvastatin

group with ‘p’ value <0.001. The mean Low Density Lipoproteins, Triglycerides, and very Low Density Lipoproteins were significantly reduced in atorvastatin vitamin D3 group than in atorvastatin group with ‘p’ value <0.001. The mean High Density Lipoproteins in atorvastatin vitamin D3 group was- 45.32 and in atorvastatin group was-44.28 with ‘p’ value <0.001.

CONCLUSION

Fasting plasma lipid profile improved significantly in both groups. However the improvement was very high in the atorvastatin vitamin D3 group. The Atorvastatin and vitamin D3 treated group showed good response compared to atorvastatin treated group

Key words- Atorvastatin, Dyslipidemia, lipid profile, vitamin D3

INTRODUCTION

Dyslipidaemia and atherosclerosis are closely linked to cardiovascular diseases like hypertension, coronary artery disease[1]. Dyslipidaemia is an independent risk factor for cardiovascular diseases (CVD). In India the most common cause of morbidity and mortality includes CVD[2]. Dyslipidaemia is a disorder of lipoprotein metabolism. This includes either lipoprotein overproduction or deficiency[3]. Dyslipidaemia can be diagnosed by doing plasma lipid profile. This is manifested by elevation of the total cholesterol, the low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a reduction in the high-density lipoprotein (HDL) cholesterol concentration in the blood[3]. A large proportion of individuals in the society have dyslipidaemia, often associated with modifiable risk factors.

The global prevalence of hypercholesterolemia among adults in the year 2008 was 39% (37% males-37% and females- 37%). The most common lipid abnormalities observed in Tamilnadu as per the ICMR-INDIAB study are hypercholesterolemia-18.3%, high LDL-15.8%, low HDL-72.3%[4]. The risk factors for dyslipidaemia include diabetes, hypertension, chronic kidney disease, physical inactivity. The prevalence of dyslipidaemia in India

is increasing, that calls for urgent lifestyle modification strategies. This is aimed to prevent and manage this important cardiovascular risk factors.

Vitamin D deficiency affects more than one billion population worldwide[5]. This pandemic of vitamin D deficiency can mainly be attributed to lifestyle changes (for example reduced physical activity, fast food) and environmental factors(air pollution due to various causes) .This result in inadequate exposure to sunlight. Ultraviolet –B (UVB) rays in the sunlight induce vitamin D synthesis in the skin.

The increasing prevalence of vitamin D deficiency is an important health problem in the community. Vitamin D deficiency is an independent risk factor for mortality in general population[6]. Various research supporting the role of vitamin D against many diseases including heart disease, hypertension, dyslipidaemia, type 2 diabetes ,autoimmune diseases, tuberculosis, cancer and mental illness. It is also observed that there is a strong correlation between low vitamin D level and fibromyalgia[7]. Many physicians have suggested oral supplementation of vitamin D -1000 IU/day[8].

Adequate vitamin D levels are necessary for good vascular health[9]. Vitamin D deficiency is associated increased incidence of CVD[10]. Seasonal variation in vitamin D levels - deficiency in winter leads to peripheral insulin resistance in type 2 diabetes mellitus patients which in turn alters the

lipid profile contributing to metabolic syndrome[11]. Serum levels of vitamin D are inversely correlated with very low density lipoprotein and triglyceride levels. Low serum 25 (OH) vitamin D levels are associated with reversible myalgia in statin treated patients. Normalization of low serum 25 (OH) vitamin D by oral vitamin D supplementation reverses myalgia, which otherwise might cause satin intolerance.

Atorvastatin is the most effective drug for treating Dyslipidaemia. Atorvastatin acts by inhibiting HMG-CoA reductase enzyme. This enzyme involved in rate limiting step in biosynthesis of cholesterol in the body. Atorvastatin is effective in reducing high LDL-C levels in patients with dyslipidaemia. It is also effective in reducing triglyceride levels.

There is a strong relationship between elevated levels of plasma cholesterol and atherosclerotic vascular disease. By reducing the total cholesterol and LDL cholesterol to below critical levels, there is a marked reduction in cardiovascular mortality.

Hence this clinical study was undertaken to compare efficacy of the fixed dose combination of Atorvastatin with vitamin D and Atorvastatin alone on lipid profile in patients with chronic kidney disease and hypertension.

AIMS

&

OBJECTIVES

AIM AND OBJECTIVE

To compare the effect of Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in various patient population.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Hypercholesterolemia is defined as high levels of cholesterol in the blood which is by itself not a disease but a metabolic derangement that can be secondary to many diseases and can affect any system of body, particularly cardio vascular system. There are 2 types of hypercholesterolemia-primary & secondary hypercholesterolemia. Dyslipidaemia includes Hyperlipidaemia (hypercholesterolemia) and low levels of HDL-C. Hypercholesterolemia is a leading etiological factor for atherosclerosis and atherosclerosis induced conditions like ischemic heart disease, ischemic cerebrovascular disease, and peripheral vascular disease[12].

The prevalence of dyslipidaemia among adults -37.5% in our country.[3] This prevalence depends on various factors such as socioeconomic status, area of residence, age, diet, physical activity and genetic factors.

LIPOPROTEIN METABOLISM

Lipoproteins are macromolecular substances formed by the combination of proteins with lipids .They are spherical complexes[13]. Triglycerides, Phospholipids, free cholesterol and Esterified cholesterol forms the lipid content. The protein part is called as apoprotein or apolipoproteins. It may function as ligand or as cofactor which regulates lipoprotein metabolism. The protein components provide the structural stability to lipoproteins.

Hydrophobic lipids (Triglycerides and cholesteryl esters) form the core of lipoproteins, which is surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins. Lipids are transported by lipoproteins. Lipoproteins play an important role in the absorption of fatty acids, cholesterol and fat soluble vitamins. The amount of lipid and protein per particle determines the density of the lipoproteins.

Chylomicrons

Chylomicrons are synthesized from the dietary triglycerides and cholesterol absorbed from the small intestinal epithelial cells. After absorption from the enterocytes fat-soluble vitamins are incorporated into chylomicron molecules.

Chylomicrons are the largest plasma lipoproteins and float to the top of plasma when allowed to stand undisturbed for 12 hours. The buoyancy of Chylomicrons are due to their high fat content (98-99%), of which nearly 85% is from fatty acids of dietary triglycerides. In chylomicrons, ratio of triglycerides to cholesterol is 10 or greater. In individuals with normal lipid profile, after a fat-containing meal, chylomicrons are found in plasma for 3-6 hours. Chylomicrons are not found in plasma after 10- 12 hours of fasting. Niemann-Pick C1–Like 1 protein (NPC1L1) mediates absorption of Intestinal cholesterol and plant sterol, which appears to be the target of ezetimibe, a cholesterol absorption inhibitor[14]. Plant sterols, unlike

cholesterol, are not normally esterified and incorporated into chylomicrons. ABCG5 and ABCG8 are located on the apical plasma membrane of intestinal epithelial cells and are called ATP-binding cassette (ABC) half-transporters, and they transport plant sterols back into the intestinal lumen, preventing their assimilation into the body. Sitosterolemia, a disorder with mutations in either of the genes that encode ABCG5 and ABCG8[15]. Leading to abnormal absorption large amounts of plant sterols, failure to excrete dietary sterols into the bile, and thus leads to accumulation of plant sterols in the blood and tissues leading to subcutaneous and tendon xanthomas and also substantially increases the risk of premature CHD. This is an autosomal recessive disease.

Triglyceride synthesis is regulated by diacylglycerol transferase in many tissues. In the endoplasmic reticulum, triglycerides are transferred by microsomal triglyceride transfer protein (MTP) to the site where apoB-48 is available to form chylomicrons.

The apolipoproteins of chylomicrons derived from enterocytes. These include apoB-48, apoA-I, and apoA-IV. Others acquired from HDL apoE and apoC-I, C-II, and C-III. From the enterocytes Chylomicrons have been excreted into the lymph and enter the systemic circulation. The apoB-48 of chylomicrons is one of the two forms of apoB present in lipoproteins. ApoB-48, synthesized by enterocytes. In the liver Apoprotein B-100 is

synthesized. Apo B-100 is incorporated into VLDL and intermediate-density lipoproteins (IDL) and LDL, which are products of VLDL catabolism. The apparent molecular weight of apoB-48 is 48% that of apoB-100, which accounts for the name "apoB-48." The amino acid sequence of apoB-48 is identical to the first 2152 of the 4536 residues of apoB-100. An RNA-editing mechanism unique to the intestine accounts for the premature termination of the translation of the apoB-100 mRNA. ApoB-48 lacks the portion of the sequence of apoB-100. Apo B-48 is an important structural component of chylomicrons.

Dietary cholesterol is esterified by the type 2 isoenzyme of acyl coenzyme A:cholesterol acyl transferase (ACAT-2)[16]. Type 2 isoenzyme is found in the intestine and in the hepatocytes. Here cellular free cholesterol is esterified before triglyceride-rich lipoproteins like chylomicrons and VLDL are assembled. In the absorption of dietary cholesterol in the enterocytes is regulated by type 2 isoenzyme. Thus for reducing blood cholesterol levels this type 2 isoenzyme act as a therapeutic target.

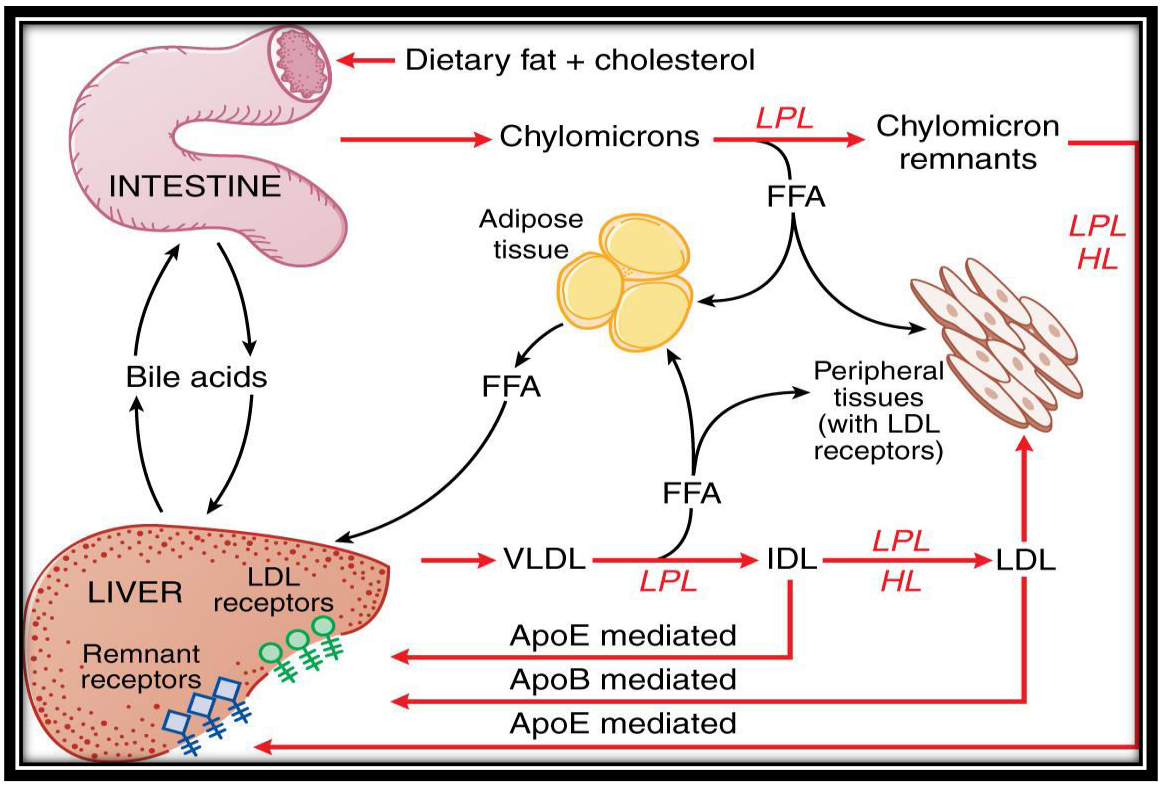
Another isoenzyme is ACAT-1, which is expressed in

- Macrophages include foam cells
- adrenocortical cells
- sebaceous glands.

Chylomicrons enter into the systemic circulation through thoracic duct. The capillary endothelial surface contains lipoprotein lipase (LPL)[17]. Triglycerides of Chylomicrons are degraded by this enzyme. It is also called as triglyceride hydrolase.

These tissues include adipose tissue, skeletal and cardiac muscle, and breast tissue of lactating women. The triglycerides are hydrolyzed by LPL. The free fatty acids are released. These free fatty acids are taken up by the adjacent cells. It will be used for energy production. The interaction of chylomicrons and LPL needs apoC-II as a cofactor. The absence of functional LPL or functional apoC-II prevents the hydrolysis of triglycerides in chylomicrons and results in severe hypertriglyceridemia and pancreatitis during childhood or even infancy (chylomicronemia syndrome)[18]. Potentially atherogenic roles for LPL have been identified that affect the metabolism and uptake of atherogenic lipoproteins by the liver and the arterial wall and that impact the dyslipidaemia of insulin resistance .

Figure -1 Fate of chylomicrons



Chylomicrons are converted to chylomicron remnants by the hydrolysis of their triglycerides by LPL. Chylomicron remnants are rapidly cleared from the plasma by the liver. "Remnant receptors" include LDL receptor–related protein (LRP), LDL receptors, and perhaps other receptors. Free fatty acid (FFA) released by LPL is used by muscle tissue as an energy source or taken up and stored by adipose tissue.

Chylomicron Remnants

From the chylomicron 90% of triglycerides are removed. This decreases the size of the chylomicron. Thus chylomicron remnants are formed from the chylomicron. They are transported to liver through systemic circulation.

Apo E content of the remnants interact with the heparin sulfate which is located on liver cells. They are further degraded by the hepatic lipase. This decreases the triglyceride content. They are taken up by the hepatocytes via LRP receptors (LDL receptor related protein). This is known as LDL receptor mediated endocytosis. LRP not only recognizes apo E but also interact with other ligands not related to lipid [19].

In plasma lipid metabolism, the LRP interact with apoE of remnants of chylomicrons and VLDL. Mutation or Inherited absence of either HL or functional apoE will reduce the clearance of remnant by the LDL receptor and the LRP. This result in elevated triglyceride content of the plasma leads to familial type III hyperlipoproteinemia or familial dysbetalipoproteinemia.

Within the lysosomes of liver cells most of the remnants are hydrolyzed to glycerol, fatty acids and free cholesterol. Some of the remnants of chylomicron are degraded to PL-rich lipoprotein termed as remnant remnants. The fate of remnant remnants is not well known. The catabolism of chylomicron is very rapid. The half life is 60 minutes.

Very Low Density Lipoproteins (VLDL)

Major quantity of plasma VLDL is synthesized by hepatic parenchymal cells. Minor quantity is synthesized by mucosal cells of small intestine. The diameter of VLDL particles are 40-100 nm. As compared to

chylomicrons, VLDL has more density because it contains higher percentage of protein content. It Is composed of lipids-95%, protein- 5%.

The lipid components are

- Triglyceride- 60%
- Phospholipids- 15%
- Cholesterol- 20%

The protein components are[20]

- ApoB-100- major lipoprotein
- ApoE - obtained from HDL
- ApoC- obtained from HDL

From the liver cells VLDL is secreted into the circulation by reverse pinocytosis. The nascent VLDL contains only apo B100. Apo E and apo C are obtained from the circulating HDL. VLDL is the carrier of endogenous triglycerides. They transport endogenous triglycerides from liver parenchymal cells to peripheral tissues like adipose tissue and skeletal muscles for energy needs. This is the main function of VLDL.

In adipose tissues and skeletal muscles, VLDL is hydrolyzed by lipoprotein lipase. Free fatty acids released due to hydrolysis, are taken up by these tissues for energy production. Hydrolysis of VLDL results in removal of triglyceride that reduces the diameter of particles and increases

the density of VLDL. Thus VLDL remnants are formed. The VLDL remnants then release their apoproteins – apo E and apo C, which are transferred back to circulating HDL and the VLDL remnants are transformed into Intermediate Density Lipoprotein (IDL) then to Low Density Lipoprotein (LDL). This is known as lipoprotein cascade pathway.LDL thus produced retains apoprotein B 100, and contains more cholesterol and less triglycerides.

Low Density Lipoproteins

LDL is derived from the metabolism of VLDL. It is neither synthesized in the hepatocytes nor by the mucosal cells of intestine. The density of LDL is more compared to VLDL. The protein content of LDL is high compared to VLDL. The composition of LDL includes lipids - 80% and protein -20%[21].

The lipid components are

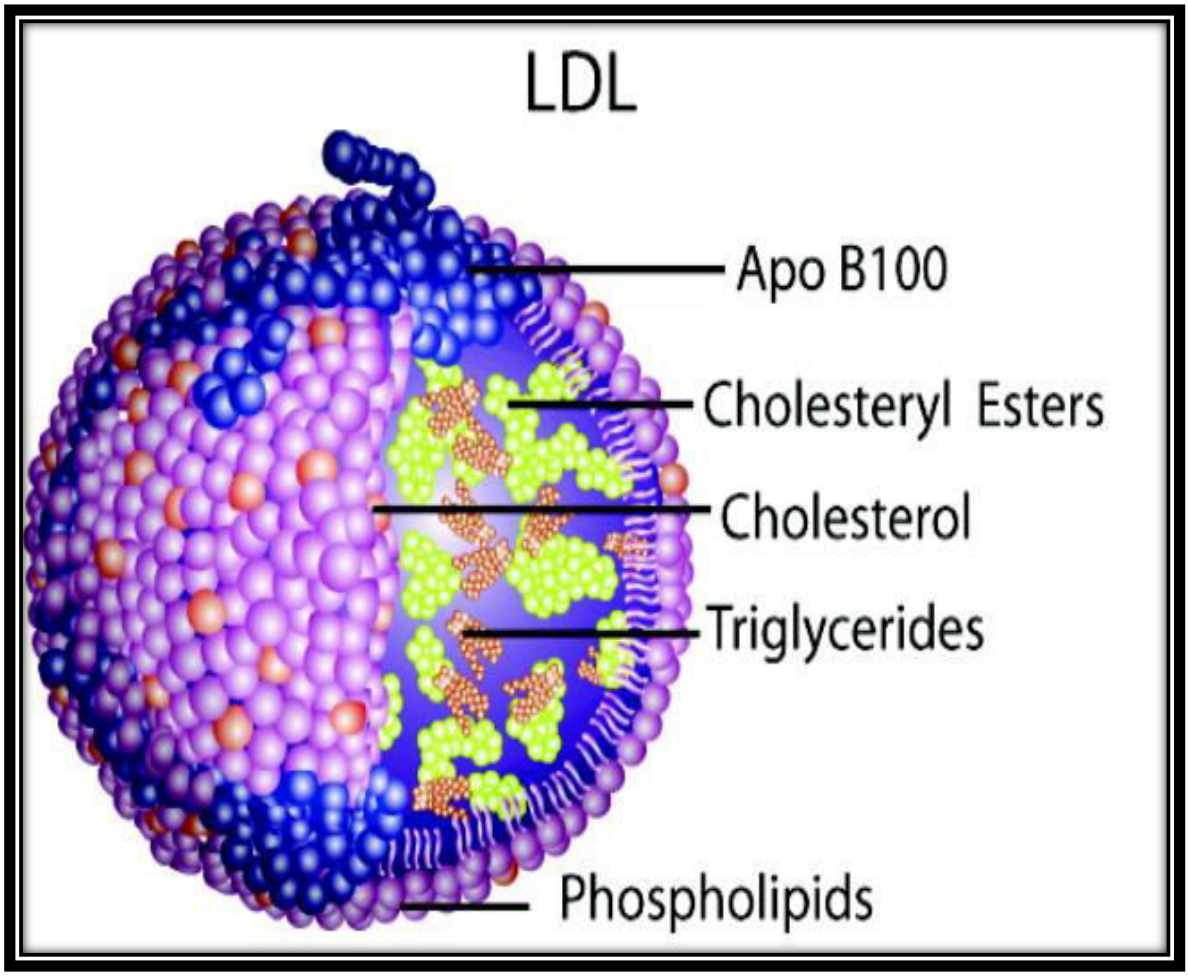
- Cholesterol- 50%
- Phospholipid- 22%
- Triglyceride- 8%

The protein component

- Apo B 100

The plasma half life of LDL is about 36-48 hours. LDL transports cholesterol from hepatocytes to peripheral tissues.

Figure-2 Structure of LDL



Metabolism of LDL and its receptors

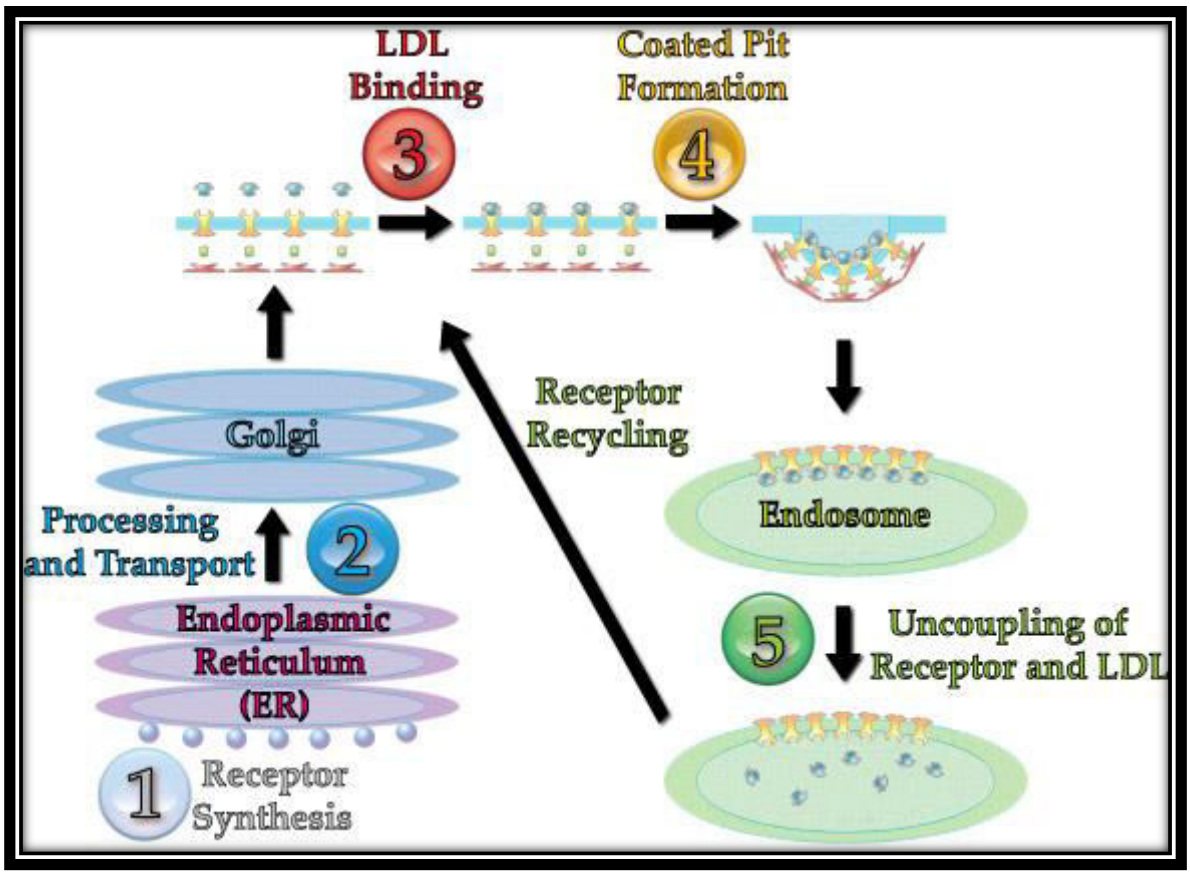
The LDL is rich in cholesterol. LDL helps to transport cholesterol from liver to extrahepatic tissues. It is taken up by the peripheral tissues like skeletal muscles and adipocytes etc through receptor mediated process .LDL

binds to its receptors which are located on the cell surface of the target tissues. This receptors recognize apoprotein B 100 [22]. After binding, the receptor and LDL complex is taken up by receptor mediated endocytosis. Binding of LDL to its receptor and uptake of cholesterol from LDL is a highly regulated process.

LDL receptors are located on all cells. But they are abundant in liver cells. They are situated in a highly specialized location called Clathrin coated pits. The LDL receptor is a polypeptide. It contains 839 amino acids.apo B100 and apoE bind to the extra cellular domain of the receptor. The intracellular domain of the receptor is responsible for the clustering of LDL receptors into regions of the plasma membrane termed coated pits. When apo B100 binds to the apo B 100 receptor, the receptor –LDL complex is internalized by endocytosis. The internalized LDL is then degraded by lysosomal hydrolases yielding free fatty acids, phospholipids, cholesterol, glycerol and amino acids.

The free receptors are recycled and return to the surface of the cell membrane to bind further LDL molecules. 70% of LDL is degraded in the hepatocytes. The rest 30% is degraded in the extra hepatic tissues. In 1985 Michael Brown and Joseph Goldstein were awarded Nobel Prize for their work on LDL receptors.

Figure- 3 Uptake and Fate of LDL



The free cholesterol derived intracellularly from LDL is utilized for the synthesis of vitamin D3 in skin, bile acids in liver and steroid hormones in renal cortex and gonads It is also incorporated into plasma membranes or esterified by ACAT and stored within the cell.

The level of intracellular cholesterol is regulated through cholesterol induced suppression of LDL receptor synthesis and cholesterol induced inhibition of cholesterol synthesis. The increased level of intracellular cholesterol that results from LDL uptake activates ACAT, thereby allowing

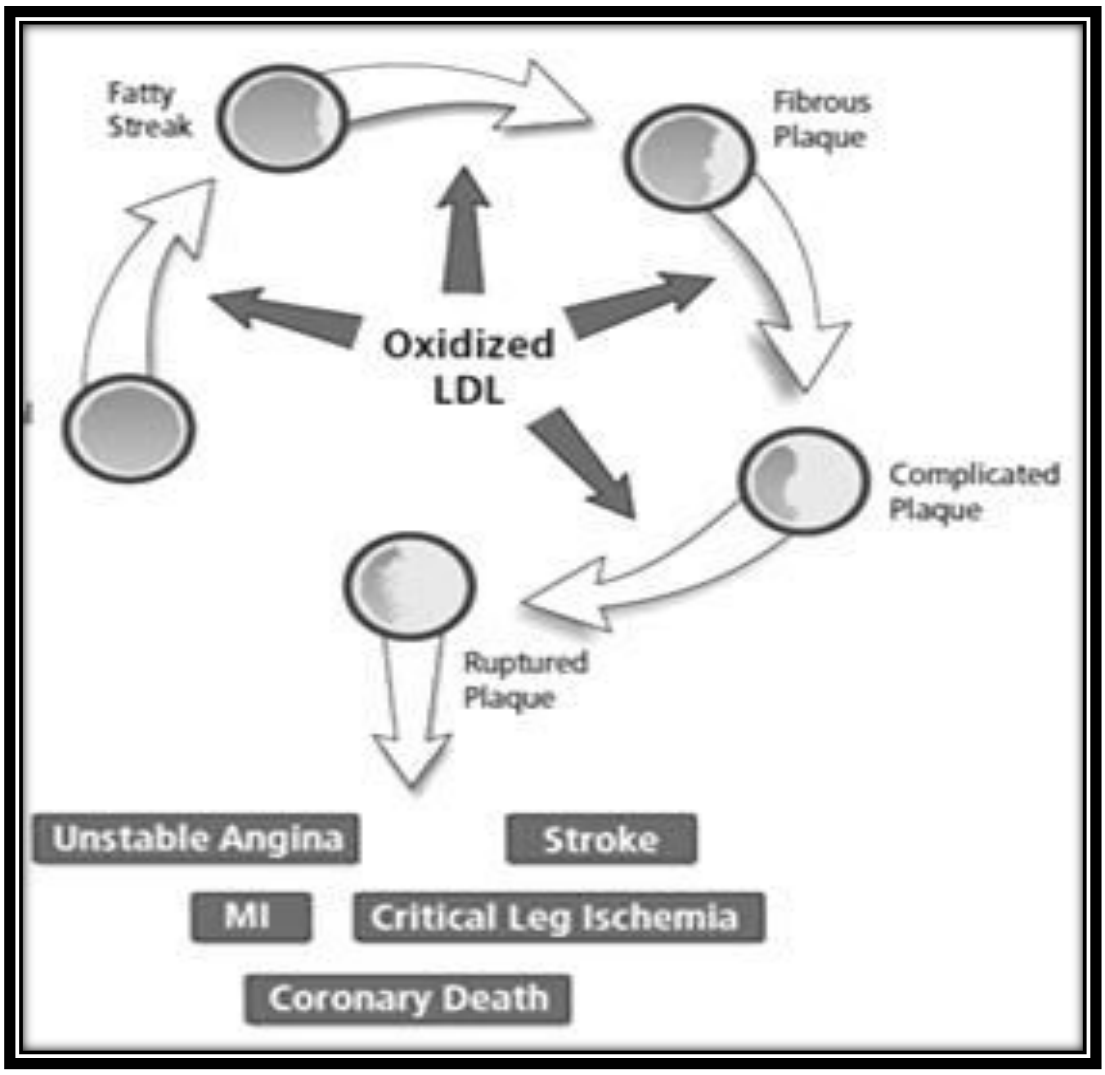
the storage of excess cholesterol within cells. However, the effect of cholesterol induced suppression of LDL receptor synthesis is to reduce the rate at which LDL and IDL are removed from the serum. This can lead to excess circulating levels of cholesterol. The excess cholesterol tends to be deposited within the arterioles, leading to atherosclerosis.

PCSK9, a serine protease that destroys LDL receptors in the liver[23.] Estrogen and Thyroxin increase the expression of LDL receptor gene[12]. These hormones have LDL-C–lowering effects through regulation of gene expression.

Regulation of LDL receptor expression is part of a complex process by which cells regulate their free cholesterol content. This regulatory process is mediated by transcription factors called sterol regulatory element binding proteins (SREBPs) and its cleavage activating protein-Scap. Scap is a sensor of cholesterol content in the endoplasmic reticulum.

LDL becomes atherogenic when modified by oxidation[24] . This process leads to foam-cell formation in arterial lesions. At least two scavenger receptors (SRs) are involved (SR-AI/II and CD36). Knocking out either receptor in transgenic mice retards the uptake of oxidized LDL by macrophages.

Figure - 4



LDL Receptor- Related Protein (LRPs)[25]

LRPs, represent a group of structurally related transmembrane proteins. This proteins involved in a wide range of biological activities. The activities of this group of proteins include nutrient transport, lipid metabolism and protection against atherosclerosis.

LDL receptor related protein family include

- LRP 1 also known as α 2 macroglobulin receptor.
- LRP 1b
- LRP 2 also known as megalin
- LRP 4
- LRP 5/6
- LRP 8 also called apo E receptor 2
- VLDL Receptor

LRP 1 is expressed in numerous tissues. This receptor involved in

- Modulation of platelet derived growth factor receptor-β signaling
- Transport of lipoprotein
- Regulation of cell surface protease activity
- The control of cellular entry of viruses and bacteria

Regulation of platelet derived growth factor receptor-β (PDGFR β) activity mediates the protective effects of LRP 1 in development of atherosclerosis.

LRP 2 is located on the surfaces of epithelial cells and in endosomes. LRP 2 is involved in the reabsorption of variety substances from the renal tubules. This protein interacts with lipoproteins, vitamins, vitamin binding proteins, hormones, proteases and protease inhibitor complexes.

LDL and its clinical application

Positive correlation exists between plasma LDL concentration and the incidence of CVD. A small fraction of cholesterol is taken up by the macrophages. This is not a normal regulated pathway. Elevated levels of modified LDL, that is oxidized LDL increases the fraction of cholesterol taken up by macrophages. LDL crosses the endothelial layer of arterial walls, and are taken up by the scavenger cells and macrophages. This is the starting point of atherosclerosis. This increases the risk of Myocardial infarction. These cells become engorged with cholesterol, and form foam cells. They get deposited in the sub endothelial space. This will trigger the formation of atheromatous plaque. These procoagulant changes increases the risk of thrombosis and coronary artery disease.

Insulin and T_3 triiodo thyronin enhance the binding of LDL to hepatocytes. Corticosteroids have the opposite effects. This is the reason for elevated serum LDL level, and increased risk of atherogenic vascular disease in patients with uncontrolled diabetes and hypothyroidism. Defect in LDL receptor synthesis leads to familial hypercholesterolemia.

High Density Lipoproteins

HDL transport cholesterol from extra hepatic tissues to the hepatocytes. Lipoprotein particles may be distinguished by their electrophoretic mobilities. Mature HDL particles have α mobility; LDL particles show β mobility. It has highest density among all lipoproteins. The composition of HDL includes lipids - 60% and protein -40%.

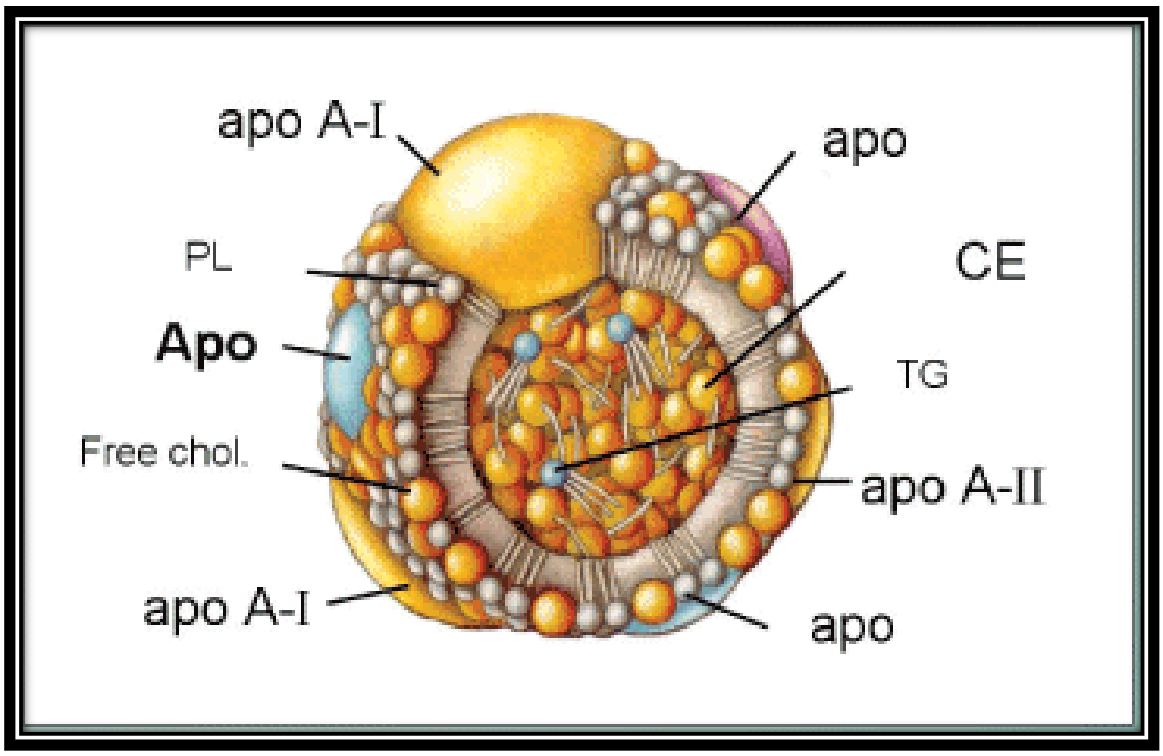
The lipid components are

- Cholesterol- 25%
- Phospholipid-30%
- Triglyceride- 5%

The protein component

- Apo A1, A2
- Apo C
- Apo E

Figure – 5 Structure Of HDL



HDL serves as a plasma reservoir of apo E and apo C. These apoproteins are transferred to Chylomicron and VLDL. HDL is synthesized in liver cells and also in intestinal mucosal cells. Hepatic HDL- apo A and apo C are synthesized by polysomes on the rough endoplasmic reticulum. They are assembled with lipids to form the nascent HDL, which is released into the circulation. Intestinal HDL – apo A is synthesized by polysomes on the rough endoplasmic reticulum. It is assembled with lipids to form nascent HDL which is released into the circulation from mucosal cells of intestine[26]. Apo C, apo E are only synthesized in the liver. The nascent HDL is also known as discoidal HDL. This nascent HDL contains discoid phospholipid bilayer and free cholesterol.

Metabolism of HDL

The free cholesterol derived from peripheral cells are taken up by the HDL. The apo A 1 of HDL activates lecithin cholesterol acyl transferase [LCAT]. The LCAT binds to the discoidal HDL. From the cells, the cholesterol is transported by an efflux pump called cholesterol efflux regulator protein which is an ABC transporter.

LCAT of plasma binds with nascent HDL discs and gets activated by apo A 1 and apo C II of HDL. This will transfer acyl groups from HDL – Phospholipids to the free cholesterol. Thus lysophospholipids and cholesteryl esters are produced. The cholesterol esters are hydrophobic, moves to the interior of the HDL disc.

This reaction continues till HDL becomes spherical with lot of cholesterol esters are formed. This HDL particle is called as HDL 3 or spherical HDL or mature HDL.

Mature HDL are taken up by hepatocytes by apo A 1 mediated receptor mechanism. HDL is taken up by hepatic scavenger receptor B1[SR- B 1]. Phospholipids and triglycerides of HDL are hydrolyzed by hepatic lipase. So that cholesterol esters are released into liver cells. The cholesterol within the hepatocytes is utilized for the synthesis of bile acids or excreted as such in bile. Androgens increase HL activity, which accounts

for the lower HDL-C values observed in men than in women. Estrogens reduce HL activity, but their impact on HDL-C levels in women is substantially less than that of androgens on HDL-C levels in men.

When HDL 3 remains in circulation, the cholesterol ester from HDL is transferred to VLDL, IDL, and LDL by a cholesterol ester transfer protein (CETP). Triacyl glycerol from VLDL, IDL, and LDL is transferred to HDL in exchange for cholesterol ester. The HDL particles which are rich in triacyl glycerol and spherical are called HDL 2. These particles are acted upon by hepatic triglyceride lipase (HTGL) before being taken up by the scavenger receptors in liver. The reverse cholesterol transport needs the activity of LCAT, CETP, and apo D.

Clinical significance of HDL

There is an inverse relationship between the level of HDL in plasma and the incidence of myocardial infarction. As it is anti atherogenic or protective in nature, HDL is known as good cholesterol. HDL also may protect against atherogenesis by mechanisms not directly related to reverse cholesterol transport. These functions include putative anti-inflammatory, anti-oxidative [27]activities. Increased fish and reduced carbohydrate consumption both are associated with higher HDL-C.

Lipoprotein (a)

LP(a) is a special type of lipoprotein . It is not present in all person. It is elevated only in some persons. It may be present in 20% of normal individuals. In remaining 80% of population, LP(a) is not present in the serum in detectable amounts. It is attached to apo B 100 by a disulphide bond. It is highly atherogenic. It inhibits fibrinolysis. It is strongly associated with myocardial infarction. It is sometimes called as little rascal.

In 20% of population , LP(a) concentration in plasma is found to be more than 30 mg/dl. These individuals are more susceptible for heart attack at a younger age. Indians have a higher concentration of LP(a) than western population.

Clinical importance

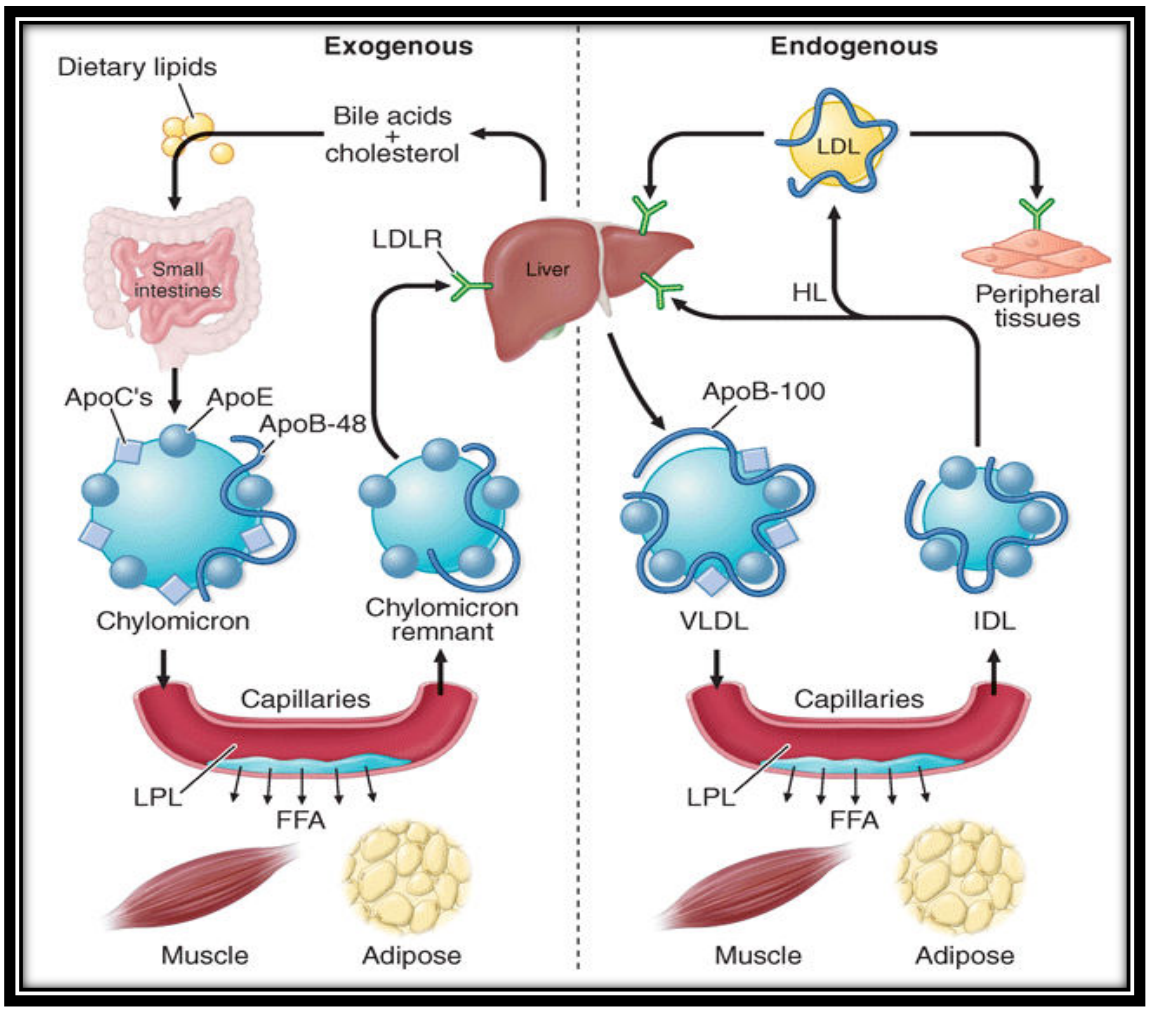
- The person having LP(a) are more susceptible to heart attack at the younger age group of 30- 40 years.
- Serum levels > 30mg/dl increases the risk of myocardial infarction by 3 times.
- When the increased LP(a) level is associated with increased LDL, the risk of myocardial infarction increases further.

Transport of dietary (Exogenous) lipids [28]

Dietary triglycerides are hydrolyzed by the pancreatic lipase, then emulsified with bile acids to form micelle. Chylomicrons formed from the dietary triglycerides and cholesterol. It also contains fat soluble vitamins. Chylomicron are absorbed from the intestinal epithelial cells into the lymph and finally enters the systemic circulation.

Lipoprotein lipase is an enzyme which is located on the capillary endothelium of heart, adipose tissue and skeletal muscles. Lipoprotein lipase requires apo CII as a cofactor for its optimal functioning. Lipoprotein lipase hydrolyzes chylomicron into triglycerides and release free fatty acids. Free fatty acids are taken up by the adjacent myocytes and adipocytes. The free fatty acid is either oxidized to generate energy or esterified and stored. Some of the free fatty acid binds with albumin. Free fatty acid albumin complex are transported to various organs, especially liver. Chylomicron becomes chylomicron remnant, which are cleared from the circulation by hepatocytes through apo E receptors.

Figure- 6 Llipoprotein Metabolic Pathway



Transport of hepatic (Endogenous) lipids

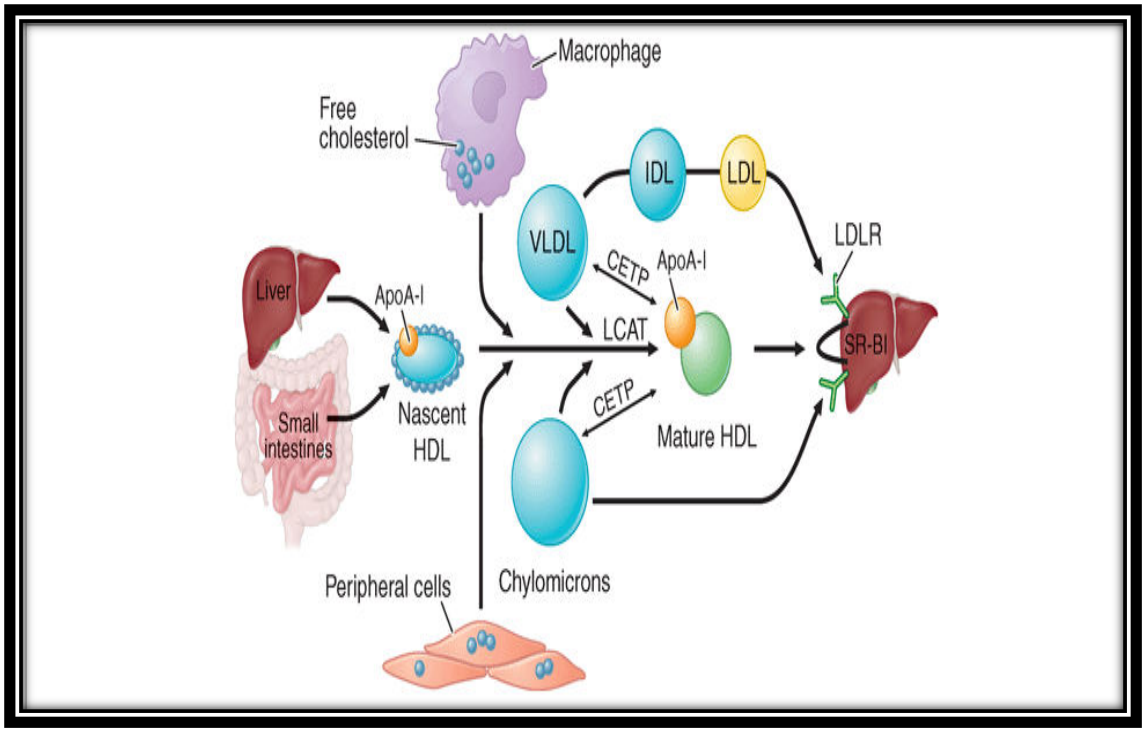
Transport of apo B containing lipoprotein from the liver to peripheral tissues. VLDL is secreted from the liver to plasma. VLDL is hydrolyzed by lipoprotein lipase in heart, skeletal muscle, adipocyte. VLDL is converted to IDL, 40-60% of IDL is cleared by the hepatocytes via LDL receptor mediated endocytosis.LDL is formed from IDL by hepatic lipase.LDL contain apo B100 which is the only lipoprotein and cholesteryl ester which is the main core lipid in LDL. LDL contains greater than half of plasma

cholesterol. Three fourth of circulating LDL is removed by hepatocytes. LDL receptor gene expression is enhanced by hormone such as thyroxin, estrogen. Hence thyroxin and estrogen have LDL lowering effect.

Reverse cholesterol transport[29]

The scavenging action of HDL play a role in the removal of cholesterol from peripheral extra hepatic tissues to liver. Free cholesterol from macrophages are removed by this transport. Thereby reduces the risk of atherosclerosis. HDL has antiatherogeneic and antioxidant properties. HDL cholesterol is also known as good cholesterol. LDL cholesterol is also known as bad cholesterol.

Figure-7 Reverse Cholesterol Transport



Cholesterol is transported from the peripheral cells to liver and intestine. In contrast to atherogenic apoB 100, the apo A1 containing HDL appears to be antiatherogenic. Other apoproteins on HDL are apo A11, apo C, apo E. HDL acquires free cholesterol from peripheral tissues including arterial wall foam cells. ABC-1 which is a cholesterol transport protein facilitates the important step in reverse cholesterol transport. The acquired free cholesterol is then esterified by the circulating enzyme lecithin cholesterol acyl transferase (LCAT). The esterified cholesterol then moves into the core of HDL. Apo C1 in HDL activates LCAT and thus facilitates free cholesterol esterification. Cholesteryl ester transport protein is responsible for transfer of cholesteryl ester of HDL to VLDL, IDL, LDL, chylomicron remnant. This is thought to be a primary mechanism by which HDL protects from atherosclerosis.HDL enhances antioxidant enzyme activity which protects LDL from oxidative stress .Low level of HDL is associated with increased risk atherosclerosis. The elevation of apo B containing lipoprotein including lipoprotein (a) which deliver cholesteryl ester to the vessel wall, and increases the risk of atherosclerosis.

Table-1

				Apolipoproteins		
Lipoprotein	Density, g/mL[a]	Size, nm[b]	Electrophoretic Mobility[c]	Major	Other	Other Constituents
Chylomicrons	0.930	75–1200	Origin	ApoB-48	A-I, A-IV, C-I, C-II, C-III, E	Retinyl esters
Chylomicron remnants	0.930–1.006	30–80	Slow pre-β	ApoB-48	A-I, A-IV, C-I, C-II, C-III, E	Retinyl esters
VLDL	0.930–1.006	30–80	Pre-β	ApoB-100	A-I, A-II, A-V, C-I, C-II, C-III, E	Vitamin E
IDL	1.006–1.019	25–35	Slow pre-β	ApoB-100	C-I, C-II, C-III, E	Vitamin E
LDL	1.019–1.063	18–25	β	ApoB-100		Vitamin E
HDL	1.063–1.210	5–12	α	ApoA-I	A-II, A-IV, A-V, C-III, E	LCAT, CETP paroxonase
Lp(a)	1.050–1.120	25	Pre-β	ApoB-100	Apo(a)	

Causes of Dyslipidemia[30]

Primary causes

1.Familial or genetic due to single gene defect

2.Multifactorial or polygenic which have multiple genetic, dietary and physical activity related causes.

Table-2

Table – **Fredrickson-Levy-lees classification of hyperlipoproteinemia**	
Type	Lipoprotein elevation
I	Chylomicrons
IIa	LDL
IIb	LDL+VLDL
III	IDL
IV	VLDL
V	VLDL+ Chylomicrons

Secondary causes

1. Hypothyroidism
2. Chronic kidney disease
3. Diabetes mellitus
4. Obstructive liver disease
5. Obesity
6. Cushing's syndrome
7. Alcohol
8. Drug induced

Table-3

SECONDARY CAUSES	
DISORDER	**MAJOR LIPID EFFECT**
Diabetes mellitus	Triglycerides
Nephrotic syndrome	Triglycerides
Alcohol use	Triglycerides
Oral OC Pill use	Triglycerides
Estrogen	Triglycerides
Glucocorticoid excess	Triglycerides
Hypothyroidism	Cholesterol
liver disease	Cholesterol

Dyslipidaemia in thyroid disease

Hypothyroidism is associated with reduction in the function of LDL receptors[31]. Reductions in the hepatic LDL receptors are associated with delayed clearance of LDL that results in increased LDL cholesterol. Hyperthyroidism is associated with decreased LDL cholesterol level. All patients with elevated LDL Cholesterol should be screened for hypothyroidism. Treatment of thyroid disease usually corrects the hypercholesterolemia.

Dyslipidaemia associated with chronic kidney disease

In chronic kidney disease increased triglyceride rich lipoprotein is due to decreased lipoprotein lipase and hepatic lipase activity. There is increased apolipoprotein C-III in the setting of renal insufficiency. Lipoprotein lipase activity is inhibited by apoC-III. Thus elevated triglyceride is associated with increased apoC-III levels. apoC-III appears to increase plasma triglyceride by

1.Modulates the affinity to bind triglyceride rich lipoproteins to receptors on hepatocytes and proteoglycans.

2.Decreases the lipolysis of triglyceride by lipoprotein lipase.

The effects of chronic kidney disease are mediated via increased oxidative stress, chronic inflammation, other toxic components of uremia. This results in changes in the structure and function of lipoproteins. In chronic kidney disease HDL is contaminated by serum amyloid. Normally HDL has antioxidant activity. In chronic kidney disease antioxidant activity of HDL is decreased[32], and HDL becomes dysfunctional. This dysfunctional HDL is less efficient in reverse cholesterol transport from peripheral tissues such as macrophages to hepatocytes.

Lipoprotein abnormalities in chronic kidney disease include increased triglyceride, LDL, VLDL, and decreased HDL. Dyslipidaemic triad include increased triglycerides and VLDL and decreased HDL. Postprandial clearance of triglyceride is also reduced in chronic kidney disease. There is impaired catabolism of chylomicron remnants and VLDL remnants.

Dyslipidaemia in diabetes mellitus

Insulin resistance is the cause for abnormalities in lipoprotein metabolism which include elevated triglyceride. There is reduced hydrolysis of triglyceride in VLDL by lipoprotein lipase, reduced free fatty acid trapping, increased influx of free fatty acid to the hepatocytes due to decreased inhibition of hormone sensitive lipase by insulin, resulting in increased synthesis of VLDL in the liver. Type 1 diabetes mellitus patients are usually not dyslipidaemia if their glycemic control is good . Diabetic keto acidosis is commonly associated with hypertriglyceridemia. This is because of increased influx of free fatty acids from adipose tissues to liver. Here the lipid abnormalities respond well to the administration of insulin. Dyslipidaemia is common in patients with type 2 diabetes mellitus though their glycemic control is good. Type 2 diabetes mellitus is frequently associated with high level of insulin and insulin resistance. The Insulin resistance has multiple effects on lipid metabolism.

Effects of Insulin resistance on lipid metabolism

1. Reduced catabolism of chylomicrons and VLDL due to reduced lipoprotein lipase activity.
2. Increased synthesis of fatty acids in the hepatocytes
3. Increased VLDL production in the liver
4. Increased release of free fatty acid from the adipocytes.

Patients with diabetes typically have higher triglycerides and lower HDL. Triglyceride levels are positively correlated with the level of insulin resistance. Three characteristic lipid abnormalities in diabetes are[33]

1. Hyper triglyceredemia
2. Low HDL
3. Elevated small dense LDL particles

Increased serum LDL levels are generally not a feature of type 2 diabetes. If there is an elevation in serum LDL level, suspect - underlying lipoprotein abnormalities or renal involvement. Atherosclerosis is the common cause of mortality in patients with diabetes. Hence it is essential to treat dyslipidaemia. The various trials of cholesterol reducing measures show that HMGCoA reductase inhibitors are highly efficacious in the prevention of cardiovascular disease in diabetes.

Dyslipidaemia and Obesity

Obesity is frequently associated with Hyperlipidaemia. Excessive caloric intake causes hypertrophy of adipocytes and increased visceral adipose tissue. Adipose tissue is an endocrine organ which secretes many pro inflammatory cytokines and adipokines. The proinflammatory cytokines are tumor necrosis factor alpha (TNF α), interleukin IL- 1, IL- 4, IL- 6, Monocyte Chemo tactic Protein (MCP-1), Interferon γ (INF - γ) and nitric oxide synthase 1 (NOS- 1)[34]. These proinflammatory cytokines initiate inflammation and causes insulin resistance and finally dyslipidaemia.

Patients with obesity have increased adipocyte mass and decreased insulin sensitivity. Excessive fatty acids are released from the adipose tissue and delivered to the liver. The free fatty acids in the hepatocytes are re esterified to form triglycerides and they are packaged into VLDL and secreted into the systemic circulation. Intake of simple carbohydrates also increases the production of VLDL. In obese patients plasma HDL is low. Physical activity is associated with increased plasma HDL and reduced apoB containing lipoproteins.

Normal adipocytes (smaller and not hypertrophied) secrete increased amount of adiponectin. Adiponectin helps to prevent insulin resistance, inflammation and Dyslipidaemia. Under the influence of adiponectin macrophage secrete anti-inflammatory substances such as interleukin IL-10.

Since obesity is a risk factor for cardiovascular diseases, and negatively affecting levels of total cholesterol, LDL, HDL, and Triglyceride, a strong focus of a cardio protective dietary recommendation is- to achieve ideal body weight.

Waist- to-hip ratio (WHR) and waist circumference measure abdominal adiposity. This is an indicator of cardiovascular risk events..

Dyslipidaemia and Cushing syndrome

Dyslipidaemia seems to be less frequent metabolic complication in Cushing's syndrome. Insulin resistance plays an important role in determining lipid abnormalities[35]. Excess glucocorticoid increases VLDL production. There by increases triglyceride level. These Patients may have mild elevation of serum LDL cholesterol.

Dyslipidaemia and chronic alcoholism

Hypertriglyceridemia is the most common lipoprotein abnormality in alcoholism. Regular alcohol consumption inhibits oxidation of free fatty acids in liver. Increased free fatty acids in liver promote the synthesis of hepatic triglyceride and secretion of VLDL. Alcohol intake may be classified into 'light', 'moderate' and 'heavy' consumption. This classification is based on the quantity of alcohol intake that is in the form of daily intake of pure ethanol.

'Light–moderate' consumption- 1 to 2 drinks /day or <30 g of alcohol/day

'Heavy consumption'- ≥3 drinks /day or >30 g alcohol /day [36].

Regular moderate consumption of alcohol is associated with light to moderate increase in plasma HDL cholesterol. However regular consumption of alcohol is associated with many side effects like hypertension, gastritis, malabsorption, pancreatitis, fatty liver, hepatitis, cirrhosis, deficit in cognitive function and judgment, dementia, tolerance, dependence hence it is not recommended.

Dyslipidaemia and estrogen

Estrogen decrease serum LDL level and raises HDL and triglyceride. The ratio of HDL: LDL is raised. Plasma lipid profile should be monitored when oral contraceptive pills or hormone replacement therapy with estrogen is started. Administration of low dose estrogen containing preparations or transdermal patch can reduce the effect of externally administered estrogen on lipid profile.

Drugs causing dyslipidemia[34]

Thiazide diuretics

Cyclosporine

Niacin toxicity

Estrogen

Anabolic steroids

Bêta blockers

Bile acid binding resins

Retinoic acid

HIV protease inhibitors

Growth hormone

Isotretinonin

Complications of Dyslipidaemia

Atherosclerosis

Stroke

Myocardial infarction

Coronary artery disease

Peripheral vascular disease

Dyslipidaemia and atherosclerosis[12]

Dyslipidaemia contributes to the pathogenesis of atherosclerosis and atherosclerosis-induced conditions. These include coronary artery disease (CAD), ischemic stroke, and peripheral vascular disease

Cardiovascular and cerebrovascular ischemic diseases are the leading causes of morbidity and mortality all over the world. A major cause for the development of ischemic disease is associated with the development of atherosclerosis as a complication of Dyslipidaemia.

Increased LDL cholesterol, decreased HDL cholesterol, Smoking, Systemic hypertension, Type II diabetes mellitus, Increase in age and a positive history of premature coronary artery disease events (men<55yrs, women<65 yrs) in a first degree relative are important risk factors for

cardiovascular disease. The important measure to prevent premature coronary heart disease is to control the modifiable risk factors like diet, smoking habit etc , which account for 85% of excess risk for premature coronary events.

National Cholesterol Education Program (NCEP) Guidelines for Assessing Risk

In 2001, the existing National Cholesterol Education Program, Adult Treatment Panel (ATP) III guidelines were formed and it was updated in 2004.

The key features of the update are

1. Abandoning the concept of a threshold LDL-C level that must be exceeded before initiating cholesterol-lowering therapy in CHD or CHD equivalent patients;
2. Adopting a new target LDL-C level (<70 mg/dl) for very high-risk patients;
3. Employing a "standard statin dose" (a dosage sufficient to lower LDL-C by 30-40%) as a minimum therapy when initiating cholesterol-lowering therapy with Statins.

Table – 4[37]

LDL Cholesterol Lowering Treatment Guidelines[a]			
Risk category	**LDL-CH goal (mg/dl)**	**LDL CH level for initiation of lifestyle changes**	**LDL CH level for initiation of drug therapy (mg/dl)**
Very high risk CAD/CAD equivalent[b] + one[c]	**<** 70[e]	All subjects	All subjects
High risk CAD or CAD equivalent	**<** 100[e]	All subjects	All subjects
Moderately high risk ≥2 CAD risk factors + 10 year CAD risk[d] 10-20%	< 130 (optimal < 100[f])	≥ 100[g]	≥ 130 (100-129[f])
Moderate risk ≥2 CAD risk factors + 10 year CAD risk[d] < 10%	< 130	≥ 130[g]	≥ 160
Low risk 0-1 CAD risk factor	< 160	≥ 160[g]	≥ 190 (0ptional 160-189[f)]

a) Adopted from the US National Cholesterol Education program (NCEP) ;2004 Revision of adult treatment panel III (ATP III)

b) CAD equivalent include – diabetes mellitus; 10 yr CAD risk >20%; peripheral vascular disease; abdominal aortic aneurysm; symptomatic carotid artery disease.

c) One additional feature from (a) ≥2 CAD risk factors (b) single uncontrolled CAD risk factors (c) diabetes mellitus (d) metabolic syndrome (e) acute coronary syndrome.

d) As per risk assessment tables from the Framingham Heart Study

e) When LDL cholesterol is near or below the goal value, then a statin dose to lower LDL CH by 30-40% should be employed.

f) Patients with severe or multiple risk factors.

g) Any subject who has life style related risk factors, such as obesity, physical inactivity, smoking, etc. is a candidate for life style change of the risk factors regardless of LDL CH level.

Risk Assessment

Severity of a patient's risk determines the intensity of treatment of Dyslipidemia. 66% of men and 50% women are affected. This high prevalence rates mandate that all adults of age ≥ 20 years and children with high risk, an assessment of their risk of developing CVD.

Risk factors for of developing an ischemic stroke include,

1. Patients with previous history of CAD, or TIA

2. Patients with Type II DM.

These patients are at increased risk. They have to be managed intensively to improve plasma lipid profile. Others who have not had a prior CVD event need monitoring of plasma lipid profile and assessment of risk factors for CVD to determine whether the treatment to decrease lipid-related risk is necessary.

Fasting Lipid levels (total cholesterol, triglycerides, LDL-C, HDL-C, and non-HDL-C) and blood sugar should be measured . The LDL-C is not measured by direct method. The LDL-C is calculated by using this formula:[total cholesterol – (HDL-C) – (triglycerides/5) = LDL-C] [38]. Non-HDL-C is calculated as follows: total cholesterol – HDL-C = non-HDL-C. The classification of plasma lipid values is shown in Table.

Table- 5

Classification of plasma lipid levels (mg/dl)[a]		
Profile	Values	Inference
Total cholesterol	< 200 200-239 ≥ 240	Desirable Borderline High
HDL-CH	< 40 > 60	Low (< 50 for women) high
LDL-CH	< 70 < 100 100-129 130-159 160-189 ≥190	Optimal for very high risk Optimal Near optimal Borderline high High Very high
TGL	<150 150-199 200-499 ≥500	Normal Borderline high High Very high

[a]2001 National Cholesterol Education Program guidelines.

Measurement of apoA-I and apoB afford better risk prediction of lipid-related risk than LDL-C and HDL-C. However, lack of an established national reference laboratory for quality control of these apolipoprotein assays has precluded formal adoption of apoA-I and apoB measurements by

the NCEP thus far. Despite this, targets for apoB levels have been established by the American Diabetes Association for the management of patients with type 2 diabetes mellitus.

Risk Factors for coronary artery disease[39]

1. Men >45 yrs, women >55yrs
2. Hypertension
3. Smoking
4. Low HDL-CH (<40 in men, ,50 in women)
5. High LDL CH ≥160 or total CH ≥240
6. Family history of MI, before 55yrs (Men), 65 yrs (women)
7. Diabetes
8. Obesity

Diabetes is regarded as CAD-equivalent and hence the lipid management of diabetes patients is important in as in persons with established vascular disease .

Management of Dyslipidemia

Nonpharmacological treatment

Pharmacological treatment

Other approaches like surgeries

Nonpharmacological treatment[40]

Dietary modification

Weight loss

Aerobic exercise

Increased physical activity

Lifestyle modification

Table- 6

Macronutrient Recommendations for the TLC(therapeutic lifestyle change) diet	
Component	Recommended intake
Total fat	25-35% of total calories
Saturated fat	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrates	50-60% of total calories
Cholesterol	<200 mg/day
Dietary fiber	20-30 gram/day
Plant sterols	2 gram/day
Proteins	Approximately 15% of total calories
Total calories	To achieve and maintain desirable body weight

Pharmacological treatment[41]

1. HMG-CoA reductase inhibitors (statin)

   Atorvastatin

   Rosuvastatin

   Simvastatin

   Pravastatin

   Lovastatin

   Pitavastatin

2. Bile acid sequestrants (resins)

   Cholestyramine

   Colestipol

3. Lipolysis and triglyceride synthesis inhibitors

   Nicotinic acid

4. Lipoprotein lipase activators (PPARα activators,Fibrates)

   Clofibrate

   Bezafibrate

   Fenofibrate

Gemfibrozil

5. Sterol absorption inhibitor

Ezetimibe

6. Cholesteryl ester transfer protein (CETP) inhibitors

Torcetrapib

Anacetrapib

7.Omega 3 fatty acids

Eicosopentae noic acid (EPA)

Docosahexaenoic acid (DHA)

Drug therapy of Dyslipidemia

HMG-CoA Reductase inhibitors

Statins are the most efficacious hypolipidaemic drugs. They act by competitively inhibit HMG-CoA reductase enzyme. 3-Hydroxy-3methyl glutaryl coenzyme A is converted to mevolanate by HMG-CoA reductase enzyme which is the rate limiting step in de novo cholesterol biosynthesis. They reduce cholesterol synthesis, which results in compensatory increase in LDL receptor expression on hepatocytes. There is increased uptake and degradation of LDL and IDL.

Statins were obtained from a mold, Penicillium citrinum[42]. In 1976 Endo and colleagues identified that statins are inhibitor of cholesterol biosynthesis. They named the drug as Mevinolin which was isolated from Aspergillus terreus. Now it is known as Lovastatin. Chemically modified derivatives of Lovastatin include Pravastatin and Simvastatin.

Lovastatin , Pravastatin and Simvastatin are fungal derivatives while Atorvastatin ,Fluvastatin ,Rosuvastatin, Cerivastatin and Pitavastatin are synthetic compounds. The side group of statin is structurally similar to HMG-CoA. Lovastatin , Pravastatin and Simvastatin contain a hexahydronaphthalene ring. Heptanoic acid side chain of Atorvastatin ,Fluvastatin ,Rosuvastatin and Pitavastatin have similar structure with that of HMG-CoA intermediate.

Monacolin K- HMG-CoA reductase enzyme inhibitor. It is chemically identical to Lovastatin. It is obtained from the yeast, known as Monascus purpureus which grows on red rice.

Pharmacokinetics

Lovastatin and simvastatin are lactone prodrugs. They are less soluble in water than other statin. They are enzymatically hydrolyzed into active hydroxy acid forms[43].

Atorvastatin, rosuvastatin, pravastatin, fluvastatin and pitavastatin are administered in the active, hydroxyl acid form. All statins are given by oral route. The absorption is enhanced by food except Pravastatin. All statins undergo extensive first-pass metabolism in the hepatocytes.

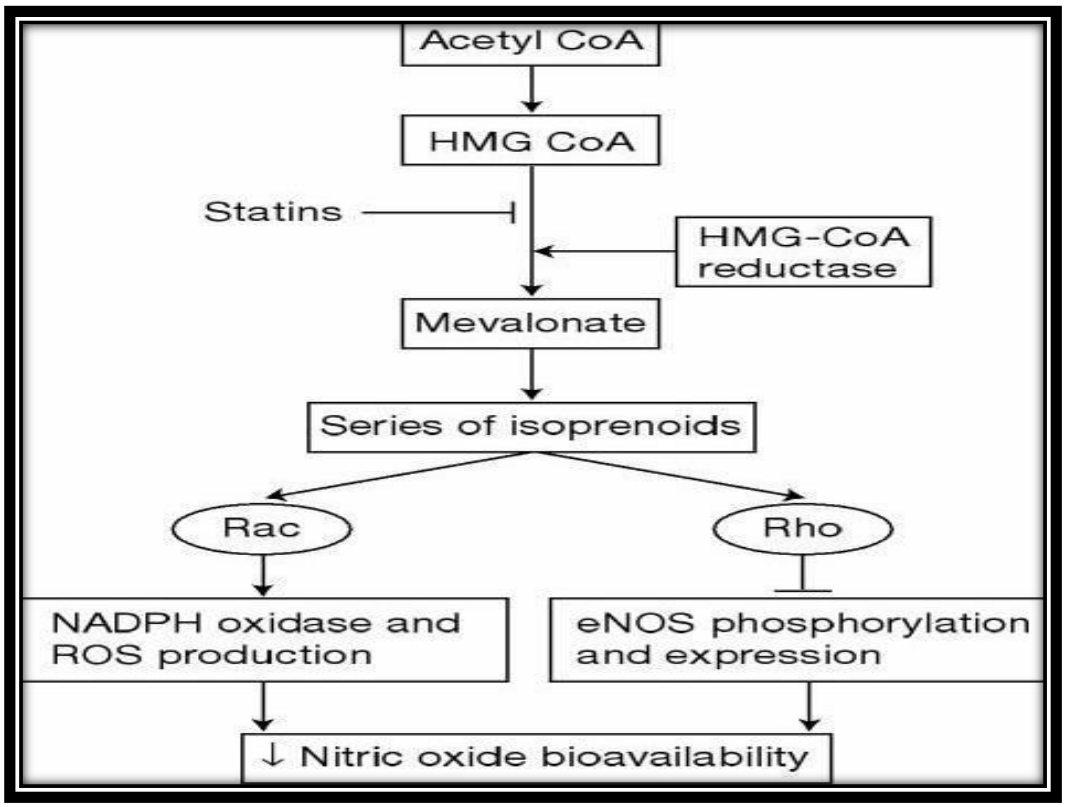
Oral bioavailability varies between 5% and 60% of administered doses. They are metabolized in the liver by CYP enzyme and eliminated through bile[44]. Plasma concentration of statins increase in liver failure. Under steady-state conditions, small amounts of the parent drug and its metabolites produced in the liver can be found in the systemic circulation. About 90-95% is bound to plasma proteins. Pravastatin is 50% bound to proteins

Peak plasma concentration will be achieved within 4 hours. The rate and extent of absorption of Atorvastatin is affected by time of administration[45,], while pharmacokinetic properties of Rosuvastatin are unaffected[46]. However for both drugs, the lipid lowering effects are similar whether given in the morning or evening

Mechanism of action of statins[47]

Statins exert their effect by inhibiting HMG-CoA reductase enzyme. The major effect of statin is the reduction of LDL levels. The reduction of HMG-CoA to mevalonate is catalyzed by HMG-CoA reductase. It is the rate limiting step.

Figure- 8



Regulation of Cholesterol biosynthetic pathway.

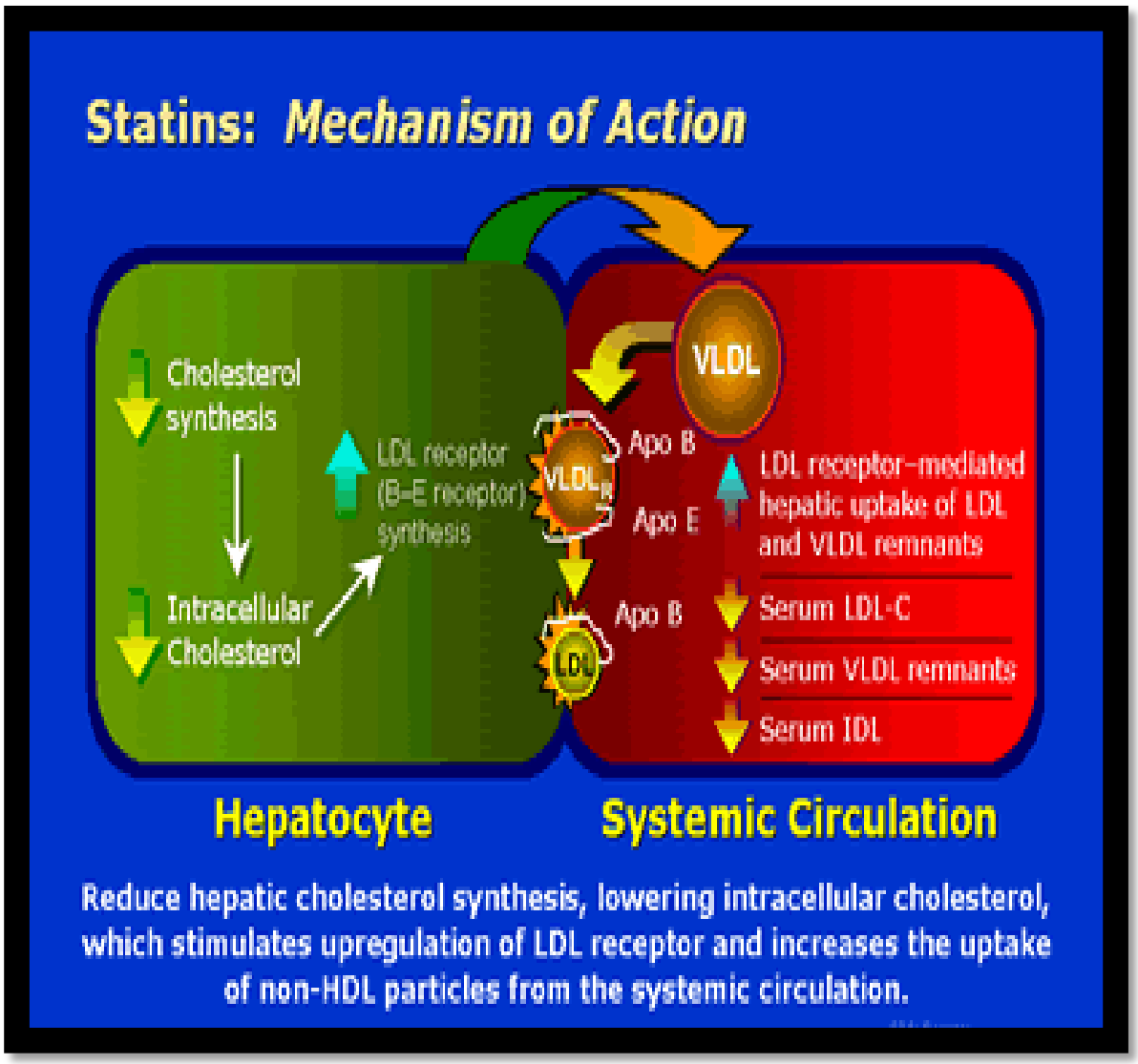
In 1940 Konrad Bloch described that all carbon atoms of cholesterol are derived from acetyl CoA. He got Nobel Prize in 1964. The cholesterol

biosynthetic pathway was described by Sir John Cornforth and Vladimir Prelog. They got Nobel Prize in 1975. Liver, adrenal cortex, testis, ovaries and intestine are the major sites of synthesis of cholesterol.

Statins lower plasma lipid levels by inhibiting cholesterol biosynthesis. Reduced plasma cholesterol levels causes increased expression of LDL receptor gene. Intracellular reduction in free cholesterol content within the hepatocytes result in cleavage of membrane bound SREBPs by protease. It is translocated to the nucleus, which enhances transcription of LDL gene and increases the number of LDL receptors. Decreases the number of LDL receptor destruction. The number of LDL receptors on parenchymal cells of liver are increased that result in enhanced clearance of LDL from the plasma, thereby reducing LDL cholesterol.

Various studies support that statin induces LDL receptors that interact with both apoB-100, apoE. This results in increased clearance of LDL precursors VLDL, IDL. Statins also reduce synthesis of VLDL from the liver. This is secondary to reduced cholesterol synthesis. The cholesterol is an important content of VLDL. Statin also reduces triglycerides and LDL in patient with homozygous familial hypercholesterolemia.

Figure- 9 Mechanism Of Action Of Statins



Triglyceride Reduction by Statins

Triglyceride levels >250 mg/dl are reduced substantially by statins, and the percent reduction achieved is similar to the percent reduction in LDL-C. Accordingly, the patients with hypertriglyceridemia who are treated with the maximum doses of the most potent statins showed, reduction in LDL-C and

triglycerides upto 35-45%. The efficacy of triglyceride lowering by Pitavastatin in patients with baseline triglyceride levels >250 mg/dl is currently unknown.

Effect of Statins on HDL-C Levels

Most studies of patients treated with statins have systematically excluded patients with low HDL-C levels. In studies of patients with elevated LDL-C levels and gender-appropriate HDL-C levels (40-50 mg/dL for men; 50-60 mg/dl for women), an increase in HDL-C of 5-10% was observed, irrespective of the dose or statin employed. However, in patients with reduced HDL-C levels (<35 mg/dL), statins may differ in their effects on HDL-C levels. Simvastatin, at its highest dose of 80 mg, increases HDL-C and apoA-I levels more than a comparable dose of atorvastatin (Crouse et al., 2000). In preliminary studies of patients with hypertriglyceridemia and low HDL-C, rosuvastatin appears to raise HDL-C levels by as much as 15-20% . More studies are needed to ascertain whether the effects of statins on HDL-C in patients with low HDL-C levels are clinically significant.

Effects of Statins on LDL-C Levels

Statins lower LDL-C by 20-55%, depending on the dose and statin used. In large trials comparing the effects of the various statins, equivalent doses appear to be

5 mg of simvastatin = 15 mg of lovastatin

15 mg of lovastatin = 15 mg of pravastatin

15 mg of pravastatin = 40 mg of fluvastatin

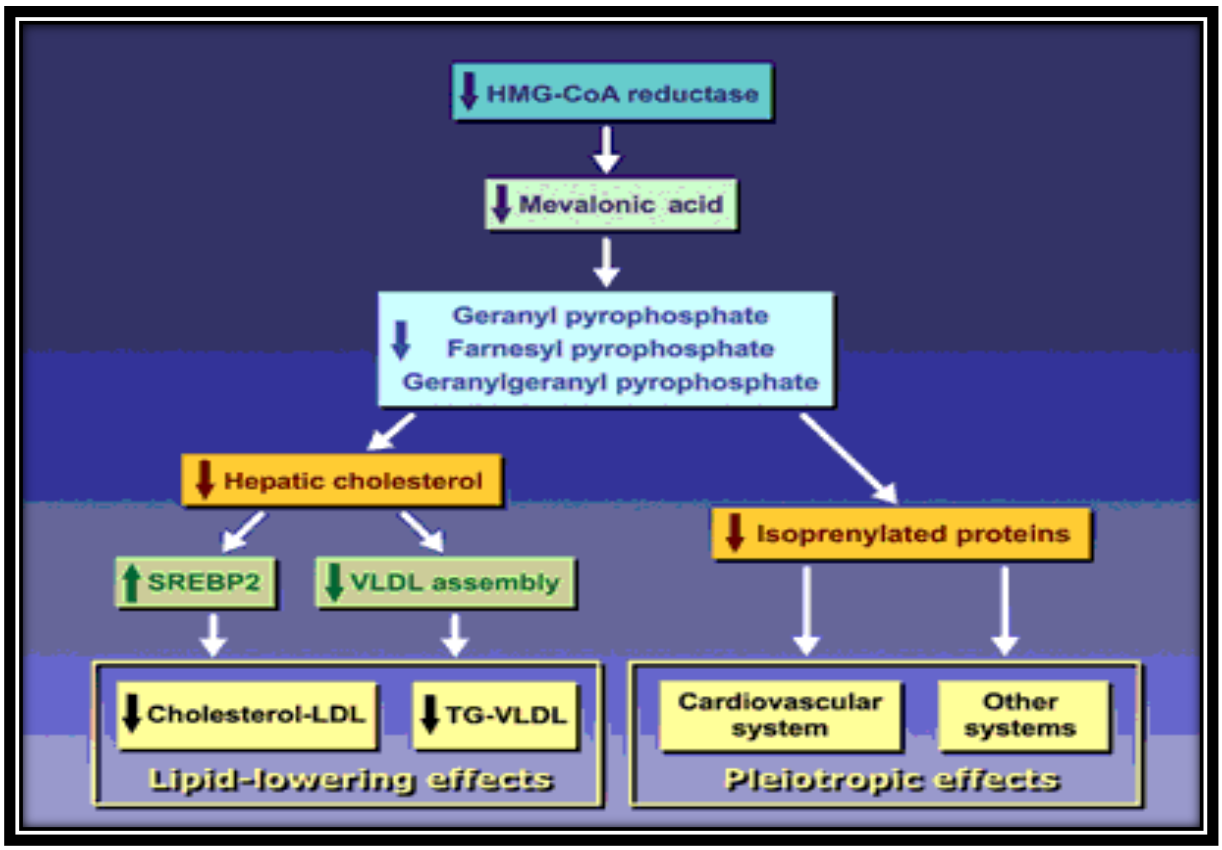
20mg of simvastatin = 10 mg of atorvastatin

20 mg of atorvastatin = 10 mg of rosuvastatin .

LDL-C reducing effect of statins showed, log-linear relationship on dose- response curve. LDL-C is lowered by nearly 6% (from initial value) with each doubling of the dose. Maximal therapeutic benefits on plasma cholesterol levels are seen within 7-10 days.

Statins improve lipid profile by reducing LDL –C and increasing HDL-C. These effects of statins on lipid profile have favorable effect in reducing CVD events. In addition to lipid lowering effect it also exert other effects , that protects individual from ischemic vascular events. This is referred to as pleiotropic effect that is not related to their effect on plasma lipid levels.

Figure- 10 Pleiotropic Effects Of Statin



Other actions of statins[48]

Improved endothelial function

Reduced vascular inflammation

Reduced platelet aggregability

Increased neovascularisation of ischemic tissue

Increased circulating endothelial progenitor cells

Stabilization of atherosclerotic plaque

Antithrombotic actions

Enhanced fibrinolysis

Inhibition of germ cell migration during development

Statins and Endothelial Function

Dyslipidemia can cause endothelial dysfunction by increasing the level of free radicals and reducing nitric oxide synthases activity. Hypercholesterolemia depresses acetylcholine induced vasodilatation in coronary arteries. Treatment with statins stabilize nitric oxide synthase mRNA , leading to improved endothelial function. This action is not related to plasma lipid lowering effect.

Statins and Plaque Stability

Atheromatous plaque stability is very important than the extent of narrowing due to plaque. Atheromatous plaque may rupture and cause serious vascular events. Statins reduces the formation of atheromatous plaque and decreases the chance to rupture by following mechanism

1. They inhibit infiltration of macrophages into the intima of vessel wall.

2. They inhibit release of matrix metalloproteinase from inflammatory cells[49].

This enzyme destroys the extracellular matrix. This results in destabilization fibrous cap of atheromatous plaques.

Statins reduce the recruitment of inflammatory cells. They also reduce smooth muscle hyperplasia by increasing their cell death and reduces its multiplication. Reduced proliferation of smooth muscle cells and enhanced apoptosis can regress initial hyperplasia and restenosis. Their role on inhibition of proliferation of cells and enhanced rate of apoptosis has beneficial effects on malignant tumors.

Statins and Inflammation

Inflammatory cells and processes involved in the pathogenesis of atherogenesis. Statins showed an anti-inflammatory activity in animal models. Statins reduce baseline plasma C-reactive protein content. CRP is an inflammatory marker and also considered as marker for CHD . The reduction in CRP level is independent of cholesterol lowering effect of statin. Patients with morbid obesity and insulin resistance have high level of CRP. Secondary preventive measures have to be adopted in patients with serum CRP level >3 mg/ lit

Statins and Lipoprotein Oxidation

Oxidized LDL plays an important role in the process of atherogenesis. This modified LDL is taken up by the macrophages. This increases the recruitment of other inflammatory cells into the vessel wall. Statins decrease the oxidative modification of lipoproteins.

Statins and Coagulation

Statins reduce platelet aggregation and reduce the deposition of platelet thrombi. In addition, statins decrease the plasma fibrinogen levels. Elevated plasma fibrinogen levels are associated with an increase in the incidence of CHD.

Adverse Effects and Drug Interactions

The satins are devoid of adverse effects and very rarely cause side effects.

1. Gastro intestinal disturbances[50]
2. Mild head ache
3. Skin rashes
4. Muscular cramps
5. Sleep disturbances
6. Hypersensitivity reaction
7. Hepatotoxicity
8. Myopathy

Hepatotoxicity

Elevation of serum aminotransferases can occur in < 1% of patients under treatment [51]. But liver damage is rare. So liver function tests should be done before starting therapy and monitored during therapy.

Observational studies and a prospective trial suggest that transaminase elevations in patients with nonalcoholic fatty liver disease and hepatitis C are not at risk of statin-induced liver toxicity .This is important, as many insulin-resistant patients are affected by nonalcoholic fatty liver disease and have elevated transaminases. Patients with type 2 diabetes mellitus, benefit from lipid-lowering therapy with statins. It is reassuring that these patients with elevated transaminases can safely take statins.

Myopathy

The major adverse effect associated with statin use is myopathy. The incidence is less than 1 per 1000. It can progress to rabdomyolysis. So monitor CPK while on therapy.

The risk factors for of myopathy and rhabdomyolysis

1. Increased statin dose and plasma concentrations. including
2. Elderly patients
3. Renal failure
4. Hepatic failure
5. perioperative periods
6. diabetes mellitus
7. Low BMI
8. Hypothyroidism

9. Concurrent use of cyclosporine, gemfibrozil, macrolide, warfarin, , antibiotics, digoxin and azole antifungals.

Drug interactions

Refers to alteration of response of one drug by another when they are administered simultaneously. It can be divided into pharmacokinetic or pharmacodynamic interaction.

Gemfibrozil, the drug most commonly associated with statin-induced myopathy, due to its inhibitory effect on hepatic OATP1B1 . Gemfibrozil nearly doubles the plasma concentration of the statin hydroxy acids. Other fibrates, especially fenofibrate, do not interfere with the glucuronidation of statins and pose less risk of myopathy when used in combination with statin therapy.

Concomitant therapy with simvastatin, 80 mg daily, and fenofibrate, 160 mg daily, results in no clinically significant pharmacokinetic interaction. Similar results were obtained in a study of low-dose rosuvastatin, 10 mg daily, plus fenofibrate, 67 mg three times a day. Myopathy is more common when nicotinic acid is given concurrently.

Drugs that interfere with statin oxidation are those metabolized primarily by CYP3A4 and include erythromycin, itraconazole, cyclosporine; nefazodone, (phenylpiperazine antidepressant); HIV protease inhibitors; and

amiodarone. These pharmacokinetic interactions are associated with increased plasma concentrations of statins and their active metabolites.

Atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYPs 3A4 and 3A5. Fluvastatin is mostly (50-80%) metabolized by CYP2C9 to inactive metabolites, but CYP3A4 and CYP2C8 also contribute to its metabolism. Pravastatin, however, is not metabolized to any appreciable extent by the CYP system and is excreted unchanged in the urine. Pravastatin, fluvastatin, and rosuvastatin are not extensively metabolized by CYP3A4.

Pravastatin and fluvastatin may be less likely to cause myopathy when used with one of the predisposing drugs. However, because cases of myopathy have been reported with both drugs, the benefits of combined therapy with any statin should be carefully weighed against the risk of myopathy. Although rosuvastatin is not transformed to any appreciable extent by oxidation, cases of myopathy have been reported, particularly in association with concomitant use of gemfibrozil. Experience with pitavastatin is limited. There are no data regarding myopathy and rhabdomyolysis that might be associated with its use.

Despite the rarity of 10-fold elevations of CK, many patients complain of muscle aches (myalgias) while taking statins. It is unclear if such myalgias are caused by taking a statin. In one clinical trial involving 20,000

subjects randomized to simvastatin (40 mg daily) or placebo, it was observed over the 5 years of the study that one-third of patients complained of myalgia at least once, whether the active drug or the placebo was being taken (Heart Protection Study Collaborative Group, 2002).

There are few reports of statin induced thrombocytopenia[52,53]. The miscellaneous pathophysiologic mechanisms of statin induced thrombocytoprnia can be divided into two major categories.

1. Decreased platelet production via bone marrow suppression.
2. Peripheral platelet clearance by immune mechanisms.

Replacing vitamin D in patients with a vitamin D deficiency reportedly reduces statin-associated myalgias and improves statin tolerance (Ahmed et al., 2009). The observation needs to be confirmed, but it is potentially significant because vitamin D deficiency is associated with myopathy, insulin resistance, and increased incidence of CVD.

Pregnancy

Statins cross placental barrier and reaches the fetus. It will affect cholesterol synthesis in the fetal tissues. Cholesterol is essential for fetal development. Hence Statins are contraindicated during pregnancy and lactation[54].

Therapeutic Uses

1. Patients with Familial Hypercholesterolemia[55]
2. Patients with myocardial infarction
3. Patients with ischemic stroke
4. Patients with DM

Hepatic cholesterol synthesis is maximal between midnight and 2:00 A.M. Thus, statins with $t_{1/2}$ 4 hours (all but atorvastatin and rosuvastatin) should be taken in the evening.

The initial recommended dose of lovastatin is 20 mg and is slightly more effective if taken with the evening meal than if it is taken at bedtime, although bedtime dosing is preferable to missing doses. The dose of lovastatin may be increased every 3-6 weeks up to a maximum of 80 mg/day. The 80-mg dose is slightly (2-3%) more effective if given as 40 mg twice daily.

The approved starting dose of simvastatin for most patients is 20 mg at bedtime unless the required LDL-C reduction exceeds 45% or the patient is a high-risk secondary prevention patient, in which case a 40-mg starting dose is indicated. The maximal dose is 80 mg, and the drug should be taken at bedtime. In patients taking cyclosporine, fibrates, or niacin, the daily dose

should not exceed 20 mg. Pravastatin therapy is initiated with a 20- or 40-mg dose that may be increased to 80 mg. This drug should be taken at bedtime. Because pravastatin is a hydroxy acid, bile-acid sequestrants will bind it and reduce its absorption. Practically, this is rarely a problem because the resins should be taken before meals and pravastatin should be taken at bedtime. should be weighed against the disadvantages inherent in fixed-dose combinations.

The starting dose of fluvastatin is 20 or 40 mg, and the maximum is 80 mg/day. Like pravastatin, it is administered as a hydroxy acid and should be taken at bedtime.

Atorvastatin has a long $t_{1/2}$, which allows administration of this statin at any time of the day. The starting dose is 10 mg, and the maximum is 80 mg/day. Rosuvastatin is available in doses ranging between 5 and 40 mg. It has a $t_{1/2}$ of 20-30 hours and may be taken at any time of day. Because experience with Rosuvastatin is limited, treatment should be initiated with 5-10 mg daily, increasing stepwise, if needed, until the incidence of myopathy is better defined. If the combination of gemfibrozil with rosuvastatin is used, the dose of rosuvastatin should not exceed 10 mg.

Pitavastatin ≥ is available in doses of 1, 2, and 4 mg. There is very limited post-marketing experience with this drug. Gemfibrozil reduces clearance of pitavastatin and raises blood concentrations.

The selection of statins will be based on effects and the economic status of the patients. Three drugs (lovastatin, simvastatin, and pravastatin) have been used safely in clinical trials involving thousands of subjects for 5 or more years. The documented safety records of these statins should be considered, especially when initiating therapy in younger patients. Once drug treatment is initiated, it is almost always lifelong.

Baseline determinations of ALT and repeat testing at 3-6 months are recommended. If ALT is normal after the initial 3-6 months, then it need not be repeated more than once every 6-12 months. Measurements of CK are not routinely necessary unless the patient also is taking a drug that enhances the risk of myopathy. Because myopathy may develop months to years after the start of combined therapy, it is unlikely that routine monitoring for the accompanying rise in CK will consistently herald the onset, even if monitoring is performed every 3-4 months.

Statin Use by Children

Some statins have been approved for use in children with heterozygous familial hypercholesterolemia. Atorvastatin, lovastatin, and simvastatin are indicated for children ≥ 11 years. Pravastatin is approved for children ≥ 8 years.

Statins in Combination with Other Lipid-Lowering Drugs

1. Statins can be combined with cholestyramine, colestipol and colesevelam for (type II a) familial hypercholesterolemia.
2. Nicotinic acid can be combined with statins for familial combined hyperlipidaemia (type II b). This .combination increase the risk of myopathy
3. Statins can be combined with ezetimibe for treating primary hypercholesterolemia
4. Statins can be combined with fibrates for treating hypertriglyceridemia

The combination of a fibrate (clofibrate, gemfibrozil, or fenofibrate) with a statin is particularly useful in patients with hypertriglyceridemia and high LDL-C levels. This combination increases the risk of myopathy but usually is safe with a fibrate at its usual maximal dose and a statin at no more than 25% of its maximal dose. Fenofibrate, which is least likely to interfere with statin metabolism, appears to be the safest fibrate to use with statins. Triple therapy with resins, niacin, and statins can reduce LDL-C by up to 70%. Vytorin, a fixed combination of simvastatin (10, 20, 40, or 80 mg) and ezetimibe (10 mg), decreased LDL-C levels by up to 60% at 24 weeks.

Vitamin D

History of Vitamin

As early as second century AD there are reports of symptoms of rickets from historians. In 1650 Francis Glisson wrote a classical account of infantile rickets. In 1919 McCollum produced experimental model of rickets induced by dietary deficiency. In 1931 Angus and coworkers isolated Vitamin D and named it as calciferol. It was later identified as Vitamin D3. The structural elucidation was done independently by Otto Diels and Kurt Alder. In 1950 both were awarded Nobel prize[56].

Vitamin D can be synthesized in the skin. It is the major source of Vitamin D hence it is not strictly a vitamin. Dietary source is required only when sunlight exposure is inadequate. Vitamin D plays an important role in the regulation of calcium absorption and homeostasis. It also has a role in controlling cell differentiation and proliferation. The actions of vitamin D are mediated by interacting with the nuclear receptors that regulate gene expression. There is evidence that intake considerably higher than are required to maintain calcium homeostasis reduce the risk of insulin resistance, obesity, cardiovascular diseases and the metabolic syndrome, as well as various cancers. Sunlight exposure is inadequate in northern latitudes. That results in vitamin D deficiency leading to rickets in children and osteomalacia in adults.

Table-7

Vitamin D and its major metabolites and analogs

Chemical and generic names	Abbreviation
Vitamin D3; Cholecalciferol	D3
Vitamin D2;ergocaciferol	D2
25-Hydroxyvitamin D3;calcifediol	25(OH)D3
1,25-Dihydroxyvitamin D3;calcitriol	$1,25(OH)_2D3$
24,25-Dihydroxyvitamin D3;secalciferol	$24,25(OH)_2D3$
Dihydrotachysterol	DHT
Calcipotriene(calcipotriol)	None
1α-Hydroxyvitamin D2;doxercalciferol	1α(OH)D2
19-nor-1,25-Dihydroxyvitamin D2;paricalcitol	19-nor-1,25(OH)D2

Formation of Vitamin D

Vitamin D is a secosteroid. It is produced in the skin from 7-dehydrocholesterol or ergosterol by the action of ultraviolet radiation ranging from 290-315nm[57]. 7-dehydrocholesterol is an intermediate product

of minor pathway of cholesterol biosynthesis. It is available in the Malpighian layer of epidermis. In the skin , ultraviolet rays break the bond between position 9 and 10 of the steroid ring. The steroid ring is opened to form secosterol which is a provitamin.The cis double bond between 5^{th} and 6^{th} carbon atoms, is then isomerised to a trans double bond to give rise to vitamin D3 or cholecalciferol, hence vitamin D is called **sun-shine vitamin.**

Vitamin D production in the skin is directly proportional to the exposure to sunlight and inversely proportional to the skin pigmentation. Skin is the largest organ in the body. It makes about 16% of body weight. It receives quarter of the body blood supply. An increase in solar zenith angle during November to March shifts the wavelength of Ultraviolet rays to longer wavelengths which will not produce the vitamin, hence vitamin deficiency is seen in winter.

Vitamin D is a fat soluble vitamin. Its action is similar to steroid hormones. Calcitriol synthesis is subjected to feed back regulation.

Source of vitamin D and normal serum level

The major source (80% to 90%) of vitamin D in humans is derived from synthesis of vitamin D3 in the skin from sunlight exposure. The dietary supply of vitamin D is minor compared to cutaneous formation. Total-body sun exposure to 1 minimal erythemal dose provides the equivalent of 250 to

500 mcg (10,000 to 20,000 IU) of vitamin D per day. The dietary supply contributes to minor sources.

Dietary sources

Fatty fish, fish liver oil, egg yolk,Butter, milk[58.]

25(OH) D is the major circulating form of vitamin D which is used to diagnose vitamin D insufficiency, deficiency, or toxicity. Estimation of vitamin D is used to monitor the patients receiving vitamin D therapy. Immunoassays include RIAs, electrochemiluminometric assays, and immunochemiluminometric assays are available to estimate serum 25(OH) D level. Liquid chromatography tandem mass spectroscopy measures circulating 25(OH) vitamin D and is considered the "gold standard."

The serum concentration at which beneficial effects are observed is ≥ 30ng/ml, serum level between 21 to 29ng/ml is considered insufficient, serum level < 20 ng/ml is considered as vitamin D deficiency state. High serum 25(OH)D concentration were associated with a favorable serum lipid profile. Inconsistent with this, high serum 25 (OH) D were associated with a significant decrease of serum triglyceride and LDL level . In the absence of adequate sun exposure, at least 800–1000 IU vitamin D_3/d may be needed to achieve this in children and adults.

Activation of vitamin D

Vitamin D is a prohormone. The cholecalciferol is transported to liver, where hydroxylation at 25th position occurs, to form 25 hydroxy cholecalciferol. The hepatic 25 –hydroxylase is a microsomal monooxygenase and product of gene CYP27A1. It requires cytochrome P450 and NADPH. 25-hydroxy cholecalciferol is the major storage form. In plasma, 25-hydroxy cholecalciferol is bound to vitamin D binding protein , an alpha -2 globulin.

In the kidney, it is further hydroxylated at the 1st position. The 1α hydroxylase is located in mitochondria of proximal convoluted tubules and a product of the gene CYP27B1. It requires cytochrome P450, NADPH and ferrodoxin. Thus 1, 25 –dihydroxy cholecalciferol is generated .Since it contains three hydroxyl groups at 1,3 and 25 positions, it is also called calcitriol. The calcitriol is the active form of vitamin. It is a hormone. 24, 25 –dihydroxy cholecalciferol may be formed by hydroxylation of 25 hydroxy cholecalciferol at the 24th position, a relatively inactive product.

Vitamin D receptors are located on nucleus and plasma membrane. The calcitriol binds to vitamin D receptors on nucleus and form heterodimeric complex with retinoid X receptor (RXR). This heterodimeric

complex bind to vitamin D response element on DNA. This results in modulation of transcriptional activity of gene which is responsible for the vitamin D response. Vitamin D receptors are located on the nucleus of various cell types. Vitamin D receptors regulate the expression of more than 500 genes. This action occurs in minutes. In brain and immune cells vitamin D is essential for signal transduction.

Actions of vitamin D

Vitamin D regulates calcium homeostasis

Action on bone

Vitamin D activates osteoblast, thereby increases bone mineralization, regulates remodeling

Vitamin D and innate immunity

Vitamin D acts as an immune modulator. Syntheses of vitamin D receptor, 1 alpha hydroxylase are stimulated by binding of tuberculous pathogen to macrophage receptors. This results in up regulation of specific gene which is responsible for the production of antimicrobial protein in the cell. Vitamin D also effective in childhood asthma and steroid resistant asthma.

Vitamin D and metabolic syndrome

There is increased risk of hypertension, obesity, glucose intolerance, insulin resistance, impaired synthesis and secretion of insulin, type 2 diabetes mellitus, metabolic syndrome, myocardial infarction, stroke, peripheral vascular disease and asthma. Vitamin D concentration positively correlates with HDL cholesterol and negatively with serum triglyceride levels and LDL cholesterol. Supplementation with Vitamin D is found to be beneficial in all these clinical conditions.

Vitamin D and Blood pressure

Various clinical studies have shown that vitamin D deficiency is associated with hypertension. Supplementation with vitamin D has beneficial effect on blood pressure. Vitamin D reduces rennin synthesis.

Vitamin D and cancer

Vitamin D decreases cell proliferation and increases cell differentiation, stops the growth of new blood vessels, and has significant anti-inflammatory effects. Many studies have suggested a link between low vitamin D levels and an increased risk of cancer, with the strongest evidence for colorectal cancer. There is some evidence that vitamin D intake reduces breast cancer risk.

Vitamin D and depression

Vitamin D intake is associated with significant improvement in depressive symptoms.

Vitamin D and cognition

Deficiency of vitamin D

In children , vitamin D deficiency results in failure to mineralize newly formed bone and cartilage matrix, causing defect in growth known as Rickets. In adults, vitamin D deficiency causes generalized accumulation of under mineralized bone matrix known as Osteomalacia.

Hypervitaminosis D

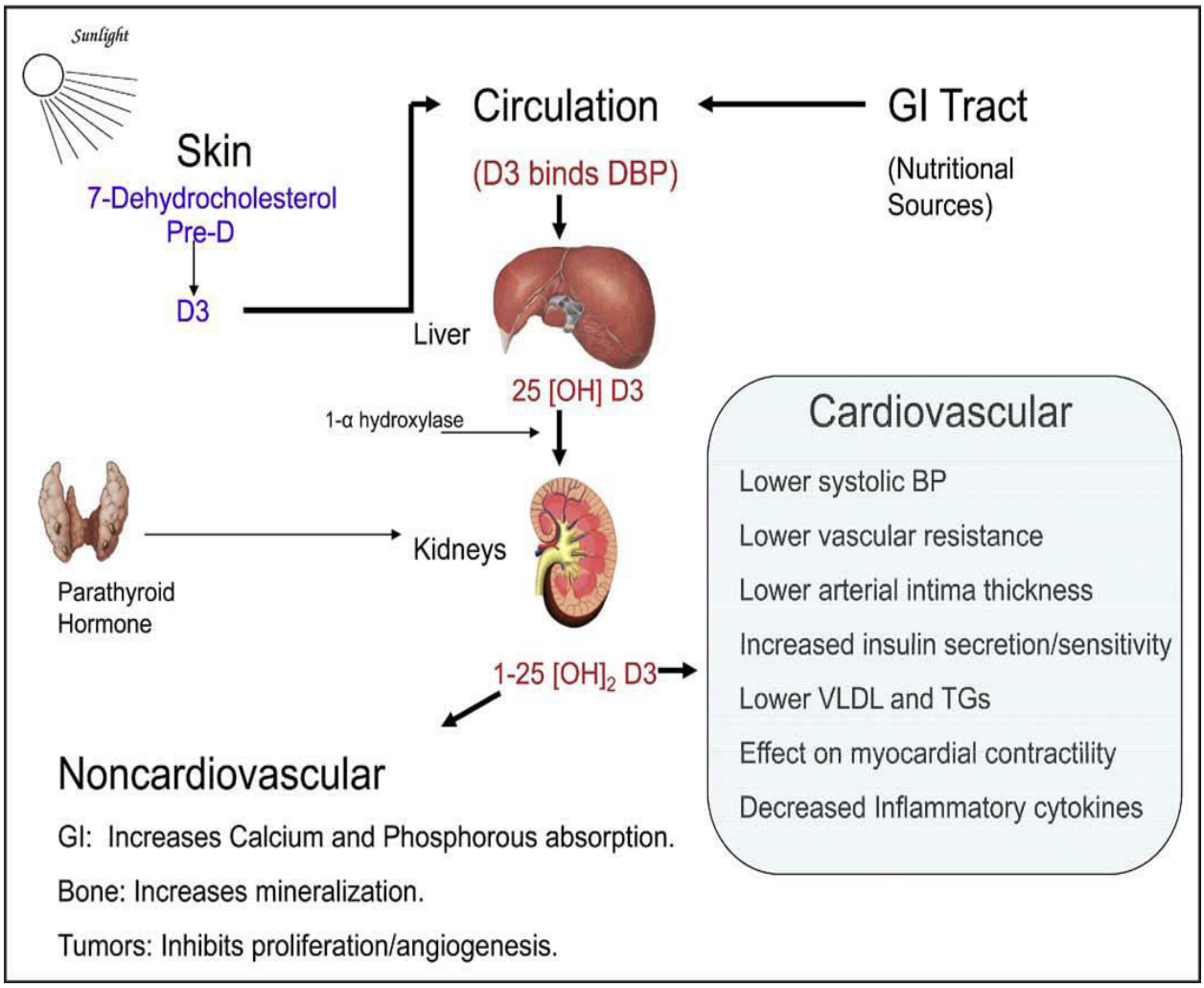
The dose of vitamin D necessary to cause Hypervitaminosis varies widely among patients. Daily ingestion of ≥ 50,000 units per day by a person with normal sensitivity to vitamin D and normal parathyroid function is associated with poisoning. Signs and symptoms of toxicity are related with hypercalcemia.

Clinical manifestations of vitamin D toxicity include: hypercalcemia, hypercalciuria, kidney stones, hyperphosphatemia, polyuria, polydipsia, ectopic calcification of soft tissues (kidney and lung), nausea, vomiting, anorexia, constipation, headache, and hypertension[59] .

Potential mechanisms through which vitamin D deficiency may affect cardiovascular disease

Pathology	Proposed Mechanism of Action
Hypertensive vascular disease	• Increased intracellular calcium leading to decreased renin activity • Calcitriol suppression of renin promoter gene • Alteration of the sensitivity of vascular smooth muscle cells
Peripheral vascular disease	• Increased calcification
Diabetes mellitus	• Immunomodulatory effects by reducing tumor necrosis factor–α, parathyroid hormone, and interleukin-10 • Decreased insulin receptor expression, leading to peripheral resistance of insulin • Effect on intracellular calcium levels leading to decreased insulin secretion
Lipid metabolism	• Increase peripheral insulin resistance, contributing to high lipid profile • Statins may increase vitamin D levels by increasing 7-dehydrocholerterol • Increased vessel free radicals lead to oxidation of low-density lipoprotein and increased engulfment by macrophages, an early sign of atherosclerosis
Coronary artery disease	• Indirect effect through risk factor modification • Altering endothelial function • Increased coronary artery calcification
Heart failure	• Direct effect on myocardial contractility • Regulation of brain natriuretic peptide secretion • Reduction of left ventricular hypertrophy with effects on extracellular remodeling • Regulation of inflammatory cytokines • Secondary hyperparathyroidism, which leads to vasodilatation and positive inotropic stimulation
Arrhythmias	• Direct myocardial substrate modification • Indirectly via calcium levels and metabolism at a cellular level

Figure- 11 Metabolism And Biologic Actions Of Vitamin D



Metabolism and biologic actions of vitamin D. The major biologic form of vitamin D, vitamin D3, is synthesized in the skin from the precursor(pre-D) under direct sunlight. Vitamin D from cutaneous synthesis and nutritional sources enters the circulation and is bound to vitamin D–binding protein (DBP). A series of enzymatic hydroxylation in the liver and kidneys transform vitamin D to biologically active 1,25(OH)2 vitamin D.

Parathyroid hormone regulates the hydroxylation in kidney. Activated vitamin D exerts multiple cardiovascular and non cardiovascular actions. BP - blood pressure; GI -gastrointestinal; TG -triglyceride; VLDL -very low density lipoprotein

Requirement of vitamin D

Children- 10 mcg (400IU)/ day[60]

Adults -5 to 10 mcg (200IU)/ day

Pregnancy and lactation- 10 mcg (400IU)/ day

Age above 60years – 600 IU/ day.

MATERIALS

&

METHODS

MATERIALS AND METHODS

STUDY CENTRE

The present study was carried out in the outpatient department of General Medicine and Department of Nephrology, Government Rajaji Hospital, Madurai after obtaining clearance from Institutional Ethical Committee , Government Rajaji Hospital, Madurai.

STUDY POPULATION

Patients attending the Outpatient department of Medicine and Nephrology , Government Rajaji Hospital, Madurai

SAMPLE SIZE

Total sample was 120 (60+60) cases, those who satisfied the inclusion and exclusion criteria.

COLLABORATING DEPARTMENTS

This study was carried out in collaboration with

- Institute of pharmacology, Madurai medical college, Madurai
- Department of Medicine, Govt. Rajaji Hospital, Madurai.
- Department of Nephrology, Govt. Rajaji Hospital, Madurai.

- Department of Biochemistry, Madurai medical college, Madurai.

STUDY DESIGN

It was a single centre, open labeled, prospective, interventional study in patients with Dyslipidemia.

STUDY PERIOD

This study was conducted from February 2013 to August 2014 for a period of 19 months.

1. Literature collection: 6 months

2. Designing the study: 1 month

3. Case selection and follow-up : 9 months

4. Analysis: 1 month.

5. Interpretation: 1 month.

6. Discussion: 1 month.

STUDY DURATION

6 months for every patient

STUDY MATERIALS

Drugs 1.Atorvastatin 10 mg

2. Atorvastatin 10 mg and Vitamin D3 1000 IU

DETAILS OF DRUG

Atorvastatin and vitamin D3

Brand name - Atorsave D10

Batch no – ASDH12013

Manufacturing date - AUG.2012

Expiry date – JUL.2014

Drug formulation and strength -Atorvastatin calcium

equivalent to Anhydrous Atorvastatin 10 mg

Cholecalciferol 1000 IU

Route of administration – oral

Dosage – 1 tablet / day at bedtime.

ETHICAL APPROVAL

Ethical clearance was obtained from Institutional ethical Committee, Government Rajaji Hospital, Madurai. Ref.Letter No .990/E4/3/2012.

INCLUSION CRITERIA

1. **Age – from 30 yrs to 60 yrs**

Patients can be made to understand easily

Better cooperation from the patients

Economical independence

2. **Sex-both male and female**

To monitor the response to treatment in both gender

3. **Patients with hypertension with hypercholesterolemia**

4. **Patient with chronic kidney disease with hypercholesterolemia**

5. **Subjects willing for the study**

Subjects were explained about the proposed study and need for follow up. Only those who were willing were included for the study**.**

EXCLUSION CRITERIA

1. Patients with liver disease

Those with chronic liver disease are excluded as atorvastatin can cause hepatic damage.

2. Patients with hypothyroidism- treatment of hypo/hyperthyroidism will correct lipid abnormalities

3. **Patients with history of allergy / hypersensitivity to the drugs**

4. Patients with H/o Excessive alcohol intake

Alcohol intake can alter the lipid profile

5. Patient who are already on Atorvastatin

6. Pregnancy

7. Lactation

8. Children

9. Previous participation

Those who have participated in similar drug trials elsewhere were excluded

DISCONTINUATION

1. Patients were given the freedom to quit the study at any time.

2. Subjects were withdrawn from the study, if they develop any adverse effects to drugs.

METHODOLOGY

120 patients with Dyslipidemia were taken into the study. The patients were diagnosed to have Dyslipidemia as per laboratory data. Out of 120 patients, 60 patients were treated with atorvastatin 10 mg/day orally and the remaining 60 patients were treated with atorvastatin 10mg and vitamin D3 1000IU/day orally. In atorvastatin group 30 were Hypertensive and 30 had chronic kidney disease (CKD). In atorvastatin vitamin D3 group 30 were Hypertensive and 30 had CKD.

Patients satisfying the eligibility criteria were included in this study. Patients were informed both verbally and in writing by the investigator about the nature, significance, implications and the risks of study prior to enrollment. These were explained by the investigator in a language and terms that were easy to understand by the patient. Informed consent was obtained from all the patients personally, dated and signed both by the patient and the investigator. The details of the investigator (name, phone

number and contact address) were given to each and every patient, to enable them to contact for any ailments at any time during the study period.

The socio- demographic data, age, sex, address, educational qualifications, smoking and alcohol intake were collected at initial visit. Clinical examination and lab investigations were done.

Patients attended the medicine and nephrology OPD fortnightly to procure drugs. During these visits, compliance was checked by counting empty drug packs and patients with poor compliance were given counseling to adhere to therapy. Adverse drug reactions to drugs were assessed.

The treatment efficacy was monitored by doing lipid profile at first, third and sixth month of therapy. Other biochemical parameters like liver function tests ,thyroid function test , complete hemogram, blood sugar, renal function test and urine test were also monitored during their visits. The results were tabulated and analyzed statistically.

Statistical analysis

Data were entered in Microsoft excel sheet and analyzed by paired t test and independent t test.

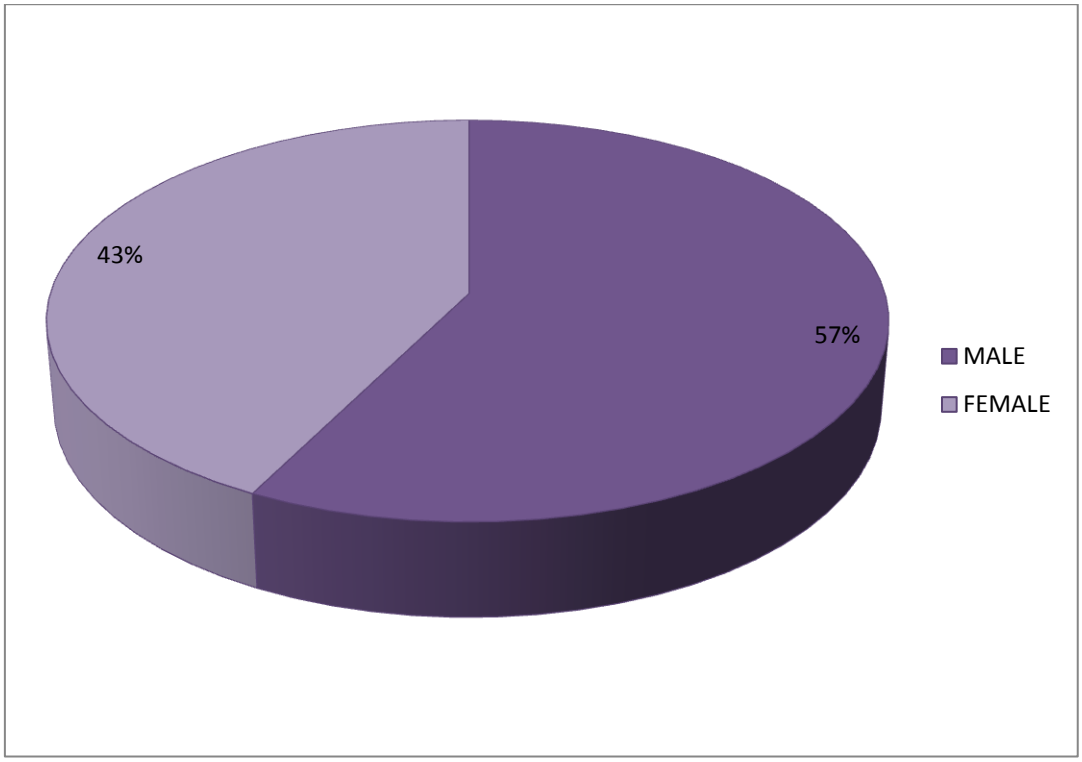
RESULTS

RESULTS

120 patients were recruited for the study. All the patients were followed up till the end of the study. There were no dropouts. Among the 120 patients analyzed, 57% were male and rest were female (43%). The age ranged from 30 to 60 years in both the groups.

Figure- 12

Gender distribution of patients with Dyslipidemia



Among the 120 patients included in the study, the age related distribution were as follows, 11 patients were in the age group 30-39 years, 53 belonged to the age group 40-49 years, and 56 belonging to age group 50-59 years. The distribution in relation to age and gender is as follows.

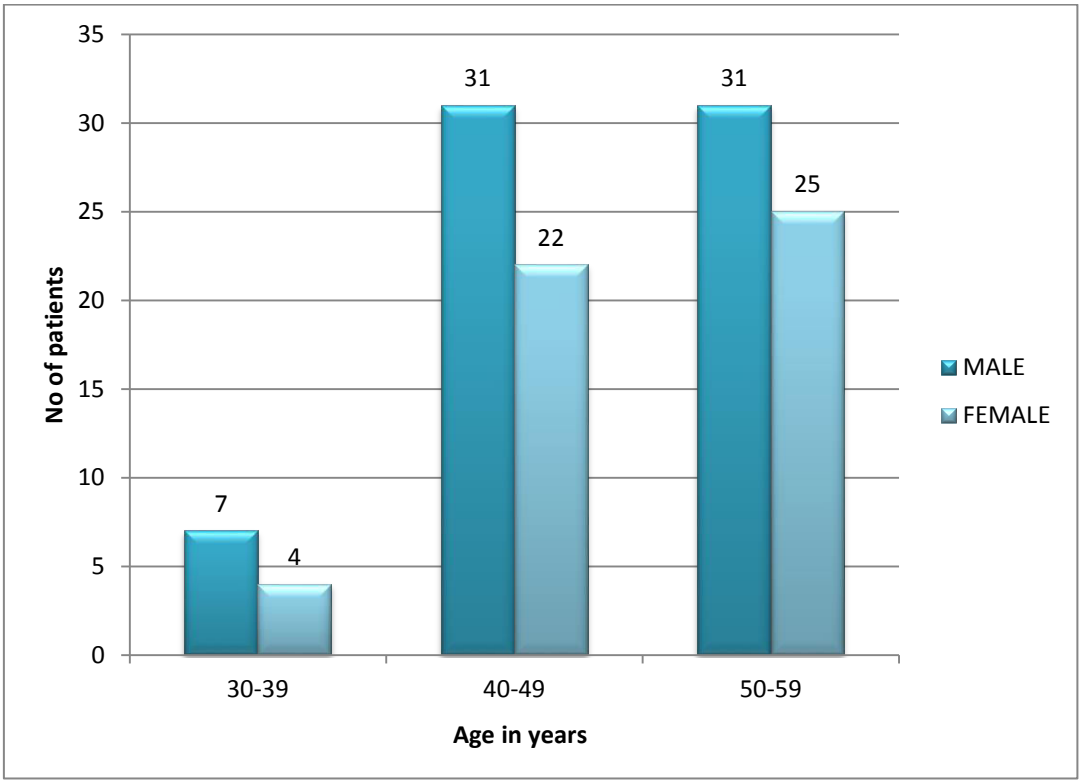
Table- 8

Age and Gender distribution of patients with Dyslipidemia

Age (years)	**Male**	**Female**	**No of patients**
30- 39	7	4	11
40- 49	31	22	53
50- 59	31	25	56
TOTAL	69	51	120

Figure- 13

Age and Gender distribution of patients with dyslipidemia



Efficacy parameters

Lipid profile – total cholesterol, LDL, HDL, TG, VLDL were evaluated at the base line, third month and 6th month.

Table- 9

Effect of Atorvastatin on lipid profile in various patient population (N=60)

Lipid profile	Before Atorvastatin (n=60)		After Atorvastatin (n=60)	
	Mean	SD	Mean	SD
Total cholesterol	238.63	18.627	199.62	18.302
LDL	159.41	17.840	123.78	14.330
HDL	40.93	2.253	44.28	2.805
TG	193.98	49.498	165.23	44.577
VLDL	38.80	9.900	32.71	9.022

P<0.05

Figure- 14

Effect of Atorvastatin on lipid profile in various patient population (N=60)

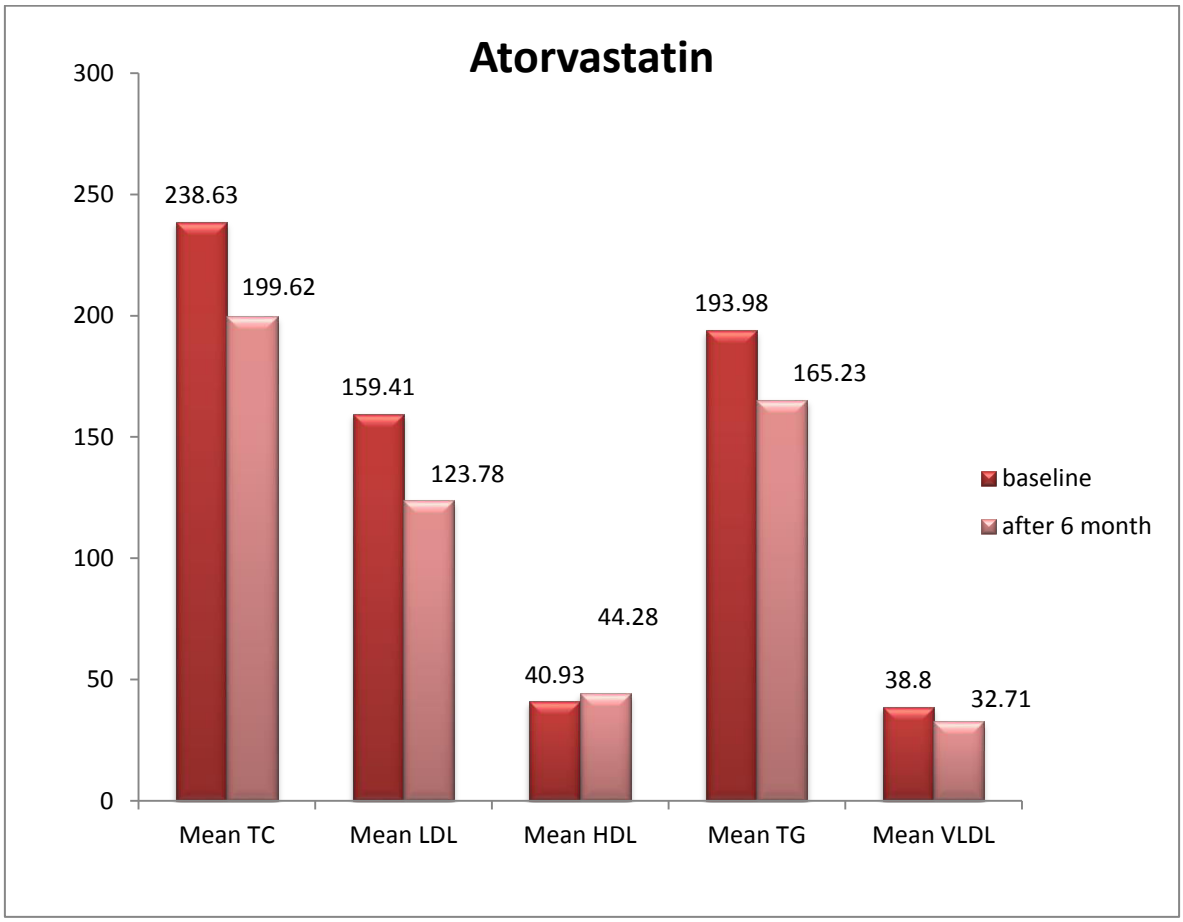


Table- 10

Effect of Atorvastatin and vitamin D3 on lipid profile in various patient population (N=60)

Lipid profile	Before Atorvastatin and vitamin D3 (n=60)		After Atorvastatin and vitamin D3 (n=60)	
	Mean	SD	Mean	SD
Total cholesterol	243.85	18.062	169.32	10.772
LDL	166.71	17.358	98.20	9.176
HDL	40.33	2.070	45.32	2.943
TG	186.57	49.244	129.57	35.999
VLDL	37.31	9.849	25.80	7.189

$P<0.05$

Figure- 15

Effect of Atorvastatin and vitamin D3 on lipid profile in various patient population (N=60)

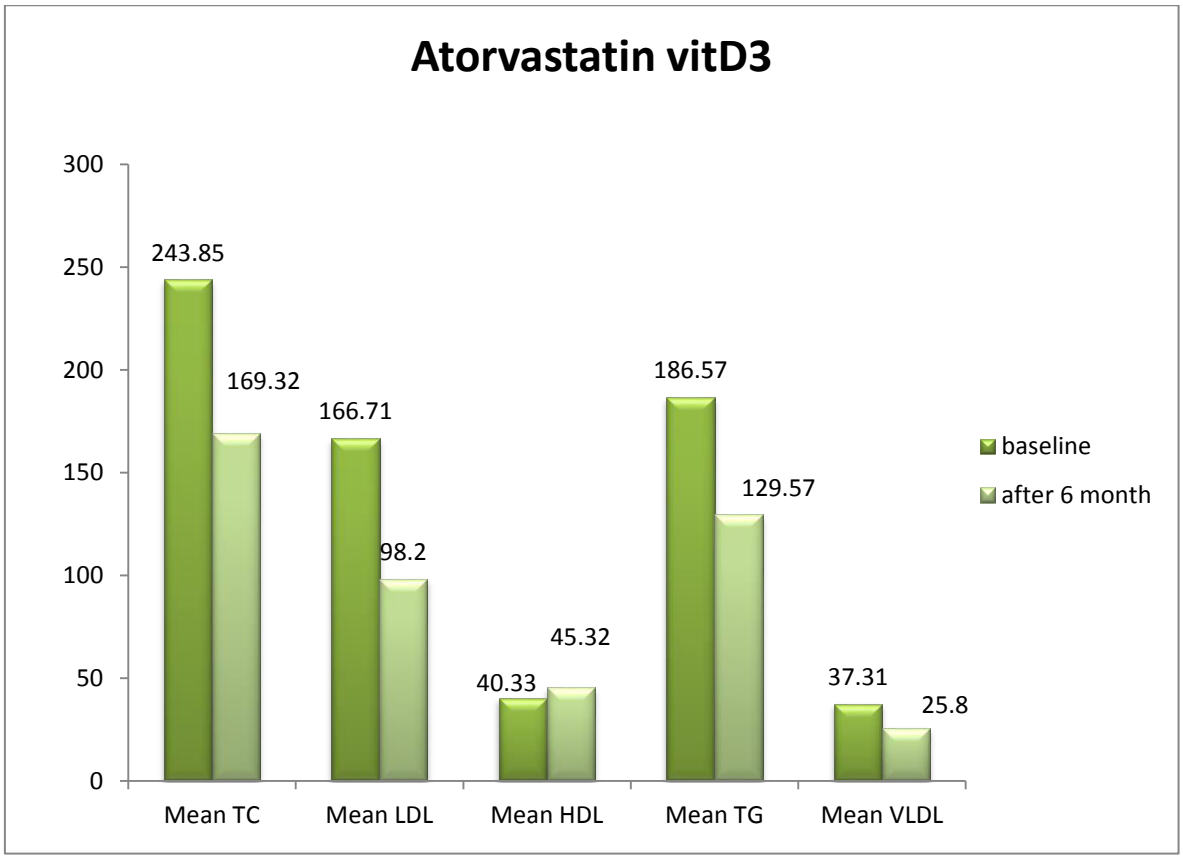


Table- 11

***t-test* Results comparing Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile (at the end of 6th month) in various patient population**

Lipid profile	Atorvastatin and vitaminD3(N=60)		Atorvastatin (N=60)		t test	df
	Mean	SD	Mean	SD		
Total cholesterol	169.32	10.772	199.62	18.302	11.052	118
LDL	98.20	9.176	123.78	14.330	11.642	100
HDL	45.32	2.943	44.28	2.805	-1.969	118
TG	129.57	35.999	165.23	44.577	4.821	113
VLDL	25.80	7.189	32.71	9.022	4.641	112

P<0.05

In order to compare the effect of Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in various patient populations an **independent-samples t-test** was conducted.

1. The test indicated that serum total cholesterol levels were significantly lower for patients on atorvastatin and vit D3 (M = 169.32, SD = 10.772) than patients on atorvastatin (M = 199.62, SD = 18.302), t (96) = 11.05,

$p < .001$. Levene's test indicated unequal variances ($F = 19.35$, $p = .0001$), so degrees of freedom were adjusted from 118 to 95.

2. The test indicated that serum LDL levels were significantly lower for patients on atorvastatin and vit D3 (M =98.20, SD =9.176) than patients on atorvastatin (M =123.78, SD =14.330), t (100) = 11.64, $p < .001$. Levene's test indicated unequal variances (F = 14.13, p = .0001), so degrees of freedom were adjusted from 100-118.

3. The test indicated that serum HDL levels were significantly higher for patients on atorvastatin and vit D3 (M =45.32, SD =2.943) than patients on atorvastatin (M =44.28, SD =2.805), t (118) = -1.96, $p < .001$.

4. The test indicated that serum TG levels were significantly lower for patients on atorvastatin and vit D3 (M =129.57, SD =35.99) than patients on atorvastatin (M =165.23, SD =44.57), t (113) = 4.821, $p < .001$. Levene's test indicated unequal variances (F = 4.75, p = .0001), so degrees of freedom were adjusted from 113-118.

5. The test indicated that serum VLDL levels were significantly lower for patients on atorvastatin and vit D3 (M =25.80, SD =7.18) than patients on atorvastatin (M =32.71, SD =9.022), t (112) = 4.64, $p < .001$. Levene's test indicated unequal variances (F =5.29, p = .0001), so degrees of freedom were adjusted from 112-118.

Figure- 16

Comparing Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile (at the end of 6th month) in various patient population

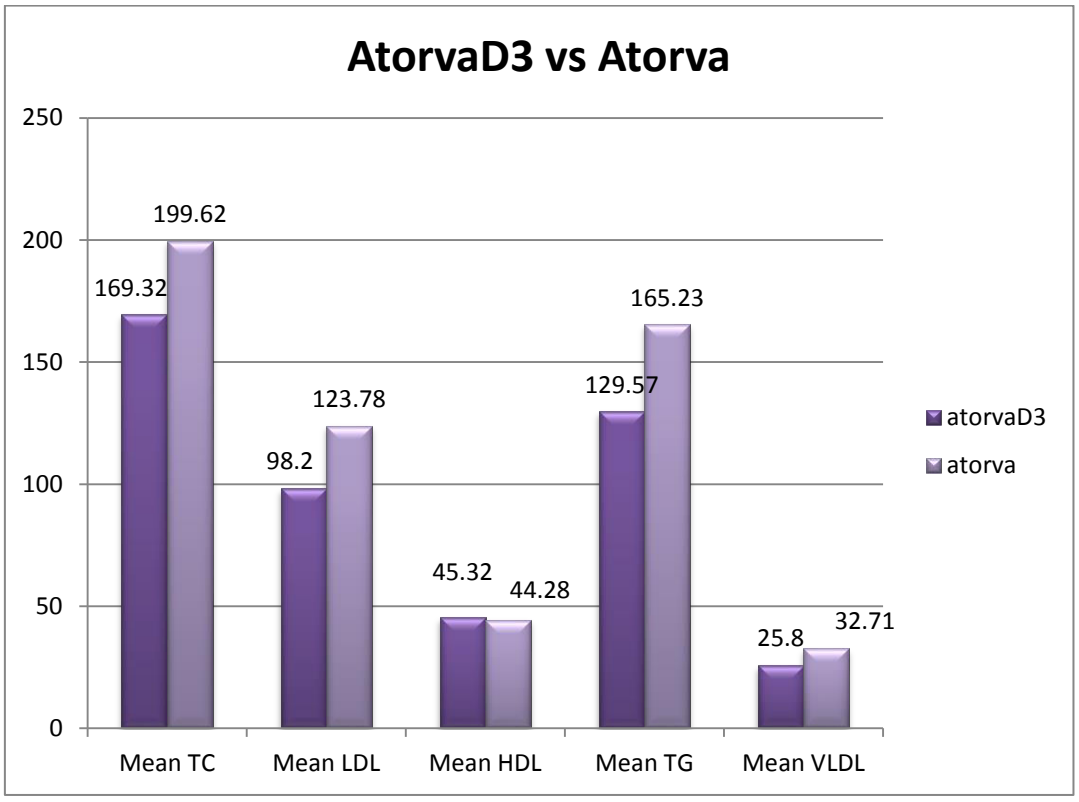


Table- 12

t-test **Results comparing Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in Hypertensive patients**

Lipid profile	Atorvastatin and vitaminD3(N=30)		Atorvastatin (N=30)		t test	df
	Mean	SD	Mean	SD		
Total cholesterol	164.10	9.484	188.17	10.175	9.477	58
LDL	96.87	10.143	115.10	11.839	6.406	58
HDL	47.60	2.191	46.70	1.557	-1.834	53
TG	99.33	19.286	135.20	39.660	4.451	42
VLDL	19.63	3.409	26.37	7.636	4.410	40

P<0.05

In order to compare the effect of Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in Hypertensive patients an **independent-samples t-test** was conducted.

1. The test indicated that serum total cholesterol levels were significantly lower for patients on atorvastatin and vit D3 (M =164.10, SD=*9.484*) than patients on atorvastatin (M = 188.17, SD = 10.175), t (58) =9.47, $p < .001$

2. Serum LDL levels were significantly lower for patients on atorvastatin and vit D3 (M =96.87, SD =10.143) than patients on atorvastatin (M =115.10, SD =11.839), t (58) = 6.406, $p < .001$.

3. Serum HDL levels were significantly higher for patients on atorvastatin and vit D3 (M =47.60, SD =2.191) than patients on atorvastatin (M =46.70, SD =1.557), t (53) = -1.83, $p < .001$. Levene's test indicated unequal variances (F =4.653, p = .0001), so degrees of freedom were adjusted from 52.3-58

4. Serum TG levels were significantly lower for patients on atorvastatin and vit D3 (M =99.33, SD =19.286) than patients on atorvastatin (M =135.20, SD =39.660), t (42) = 4.451, $p < .001$. Levene's test indicated unequal variances (F = 10.06, p = .0001), so degrees of freedom were adjusted from 41.9-58.

5. Serum VLDL levels were significantly lower for patients on atorvastatin and vit D3 (M =19.63, SD =3.409) than patients on atorvastatin (M =26.37, SD =7.636), t (40) = 4.41, $p < .001$. Levene's test indicated unequavariances (F =8.52, p = .0001), so degrees of freedom were adjusted from 40.1-58.

Figure- 17

Comparing Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in Hypertensive patients

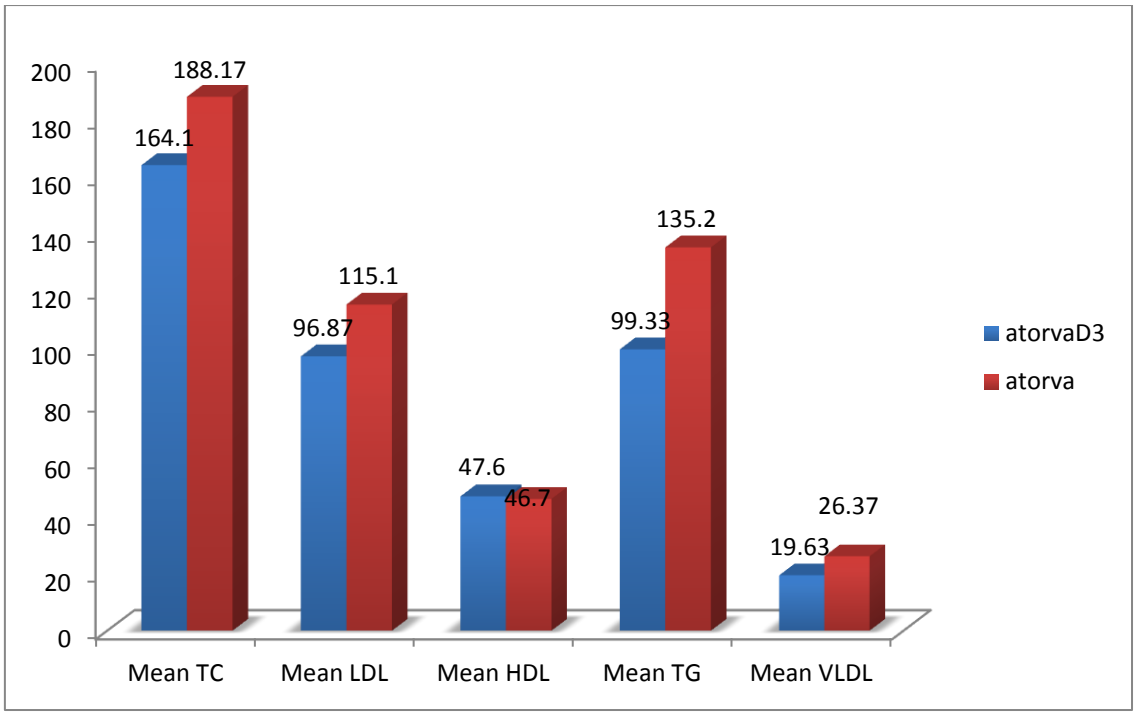


Table-13

***t-test* Results comparing Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in Chronic Kidney Disease patients**

Lipid profile	Atorvastatin and vitamin D3 (N=30)		Atorvastatin (N=30)		t test	df
	Mean	SD	Mean	SD		
Total cholesterol	174.54	9.472	211.07	17.509	10.052	58
LDL	99.53	8.046	132.45	11.043	13.196	58
HDL	43.03	1.426	41.87	1.224	-3.400	58
TG	159.80	19.324	195.26	24.517	6.221	58
VLDL	31.96	3.865	39.05	4.906	6.218	58

P<0.05

In order to compare the effect of Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in patients with Chronic Kidney Disease an **independent-samples t-test** was conducted.

1. The test indicated that serum total cholesterol levels were significantly lower for patients on atorvastatin and vit D3 (M =174.54, SD=9.472) than patients on atorvastatin (M =211.07, SD =17.509), t (58) =10.052,

p<.001.Levene's test indicated unequal variances (F =2.953, p = .001), so degrees of freedom were adjusted from 44.6-58

2. Serum LDL levels were significantly lower for patients on atorvastatin and vit D3 (M =99.53, SD =8.046) than patients on atorvastatin (M =132.45, SD =11.043), t (58) = 13.196, p < .001. Levene's test indicated unequal variances (F =1.898, p = .001), so degrees of freedom were adjusted from 53-58.

3. Serum HDL levels were significantly higher for patients on atorvastatin and vit D3 (M =43.03, SD =1.426) than patients on atorvastatin (M =41.87, SD =1.224), t (58) = -3.400, p < .001. Levene's test indicated unequal variances (F =0.415, p = .0001), so degrees of freedom were adjusted from 56.7-58

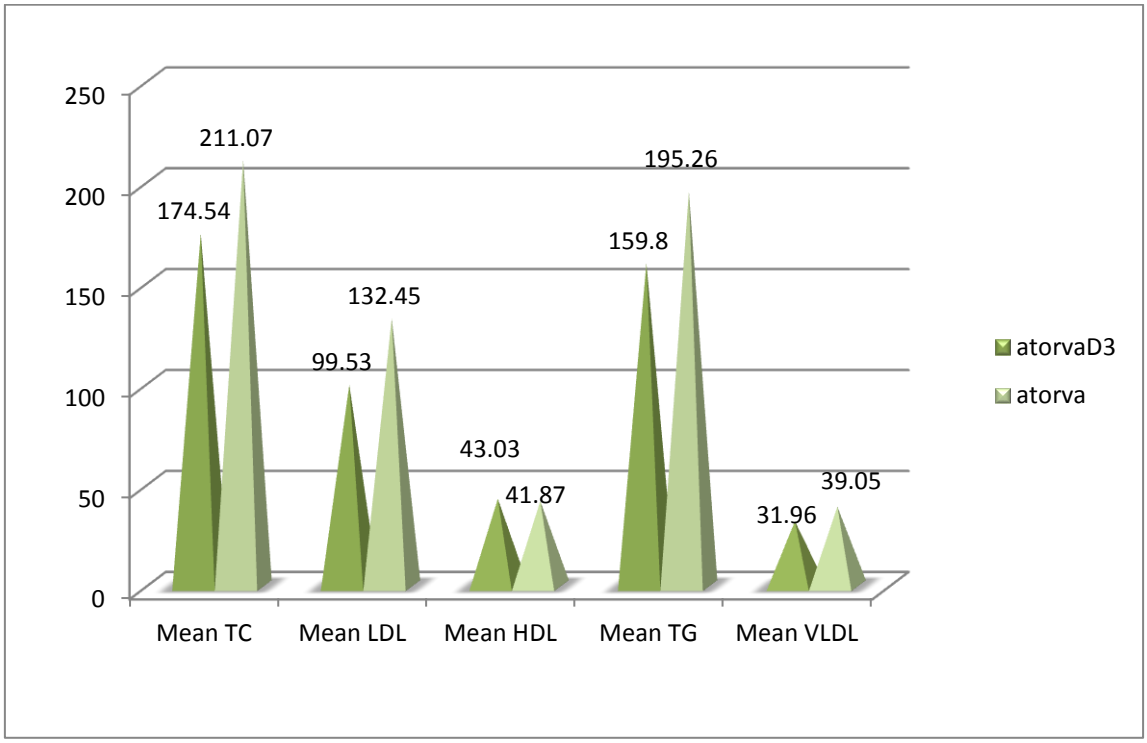
4. Serum TG levels were significantly lower for patients on atorvastatin and vit D3 (M =159.80, SD 19.324=) than patients on atorvastatin (M =195.26, SD =24.517), t (58) = 6.221, p < .001. Levene's test indicated unequal variances (F = 2.915, p = .0001), so degrees of freedom were adjusted from 54.9-58.

5. Serum VLDL levels were significantly lower for patients on atorvastatin and vit D3 (M =31.96, SD =3.865) than patients on atorvastatin (M =39.05, SD =4.906), t (58) = 6.218, p < .001. Levene's test indicated unequal

variances (F =2.925, p = .0001), so degrees of freedom were adjusted from 54.9-58.

Figure- 18

Comparing Atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in Chronic Kidney Disease patients



DISCUSSION

DISCUSSION

Dyslipidemia is an important predictor of cardiovascular disease. Dyslipidemia represents the elevation of plasma cholesterol and /or triglycerides or a low level of HDL. Multiple genetic abnormalities and environmental factors are involved in clinical lipid abnormalities and routinely used laboratory measurements do not define the underlying abnormalities.

Most patients with Dyslipidemia are asymptomatic for many years. It can be diagnosed on the basis of measurement of fasting lipid profile.

Initial therapy for Dyslipidemia is therapeutic life style changes with restricted intake of total and saturated fat along with regular physical activity. This is followed by pharmacological therapy. Lipid lowering drugs should be selected on the basis of specific lipoprotein disorder and plasma concentration of each lipoprotein.

Statins are the most potent and effective drug for the treatment of Dyslipidemia. Statins are the drug of choice for the management of Dyslipidemia because of their proven efficacy and safety profile. They also have a role in managing cardiovascular risk in patients with relatively normal levels of plasma cholesterol. They are highly efficacious at lowering LDL-C, with reduction ranges from 20%- 55% [49]. Atorvastatin acts by

inhibiting HMG-CoA redutase enzyme which is the rate limiting step for cholesterol biosynthesis.

Vitamin D3 has favorable effects on plasma lipid profile. It has TG lowering effects especially in patients with CKD. Two mechanisms have been proposed for TG lowering effect of vitamin D. First, vitamin D may reduce serum TG by reducing hepatic TG formation and secretion via an effect on hepatocellular calcium. Second, vitamin D has suppressive effect on serum parathyroid hormone (PTH) levels. The reduction in serum PTH may decrease serum TG via increased peripheral removal. It also has pleiotropic effect. Many physicians have increased their recommendations for vitamin D3 supplementation to at least 1000IU. Meta analytical studies from various sites have substantiated that supplementation with vitamin D has markedly reduced the mortality.

Statin and vitamin D have synergistic actions in preventing CVD. Addition of vitamin D3 improved statin tolerance by reducing the incidence of myalgia. Hence the study was undertaken to explore the effects of atorvastatin vitamin D3 combination on lipid profile in various patient population.

After the institutional ethical clearance and informed consent, a single blind open label, comparative trial was attempted among 120 patients with Dyslipidaemia.

120 patients with Dyslipidaemia were selected from outpatient department of general medicine and Nephrology. Their socio demographic, clinical and lab data were collected. They were explained about the study and were given the drugs orally.

Fasting plasma lipid profile, liver function tests were done before starting drug therapy. Treatment efficacy in both groups was assessed at the end of third and sixth month.

At the end of sixth month the mean total cholesterol was significantly reduced in atorvastatin vitamin D3 group than in atorvastatin group with 'p' value <0.001. The mean LDL-C, TG, VLDL were significantly reduced in atorvastatin vitamin D3 group than in atorvastatin group with 'p' value <0.001. The mean HDL-C in atorvastatin vitamin D3 group was- 45.32 and in atorvastatin group was-44.28 with 'p' value <0.001. The significant reduction in total cholesterol, TG, LDL, VLDL could be due to reduction in hepatic TG formation and suppressive effect on parathyroid hormone levels.

Fasting plasma lipid profile improved significantly in both groups. However the improvement was very high in the atorvastatin vitamin D3 group and also Myalgia was less common in atorvastatin vitaminD3 treated group compared to atorvastatin treated group[12].

JB Schwartz, division of Clinical pharmacology, Department of Medicine, University of California, San Francisco, California, USA. showed that atorvastatin and vitaminD3 have synergistic effects on cholesterol concentration.

Ahmed et al, from the cholesterol center, Jewish hospital of Cincinnati, Cincinnati, Ohio showed that vitamin D3 improved statin tolerance by reducing myalgia.

SUMMARY

&

CONCLUSION

Conclusion and summary

Dyslipidaemia is associated with disturbance in lipoprotein metabolism. Elevated LDL and low HDL are unequivocally linked to increased risk for cardiovascular and cerebrovascular morbidity and mortality. LDL is the primary target. Reduction in total cholesterol and LDL-C with increase in HDL-C will reduce the cardiac events. More than half of individuals at borderline risk remain unaware that they have Dyslipidaemia. Unfortunately, the identification of patients at high risk because of Dyslipidemia is too frequently overlooked, because blood lipid levels are not always evaluated, even after an event such as Myocardial infarction.

120 patients with Dyslipidaemia were selected from outpatient department of general medicine and Nephrology. Out of 120 patients, 60 patients were treated with atorvastatin 10 mg/day orally and the remaining 60 patients were treated with atorvastatin 10mg and vitamin D3 1000IU/day orally.

Both groups were followed for a period of 6 months. The compliance was checked and efficacy was monitored by doing lipid profile.

The Atorvastatin and vitamin D3 treated group showed good response compared to atorvastatin treated group.

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ANNEXURES

PROFORMA

Name OP/IP No.

Age

Sex

Occupation

Address

Socio economic status

Phone no.

H/o presenting illness :

Past history :

H/o Comorbid Illness.

Family h/o:

Occupational H/o:

Menstrual history:

Personnel History:

H/o Smoking

H/o alcoholism.

Dietary Habits.

Treatment History :

Drug History

H/O about drug compliance:

H/O any adverse Effect to drugs:

General examination

HEIGHT: WEIGHT: BMI:

O/E

Conscious

Oriented

Pallor

Cyanosis

Clubbing

Pedal edema

Generalized lymphadenopathy

VITALS

Pulse :

B.P

R.R

Temp

Examination of neck :

Any Carotid Bruit, Elevated JVP, Any signs of Thyroid swelling,

Skin examination :

Face

CVS

RS

P/A

CNS

Investigations

Baseline Investigations

Complete hemogram

Liver function tests

Bilirubin (total,direct,indirect), SGOT, SGPT, Total Proteins, Albumin, Globulin.

Lipid Profile

Parameter	Baseline	3 Months	6 Months
Total Cholesterol			
VLDL			
LDL			
HDL			
TG			

INFORMED CONSENT FORM IN ENGLISH

Full name of the patient(in capital letters): _____

Address:_____

_____Date of Birth:_____

Patient no:_____ Sex :_____ I freely agree to participate in the above – mentioned clinical study.

My doctor_____ informed me in a personal counseling interview about the study drug, possible side effects and risks, the nature, objective and significance of this clinical study and my responsibilities resulting thereof. In addition, I read and understood the contents of the Patient Information Sheet and Informed Consent Form. The doctor answered all questions in an adequate and comprehensible manner. I had sufficient time to decide on my participation in this clinical study.

I will follow the instruction of my doctor, which are essential for the performance of this clinical study. I have the right to withdraw from the study at any time without giving any reason and without any disadvantage for me.I confirm that I have not participated in this study and I have not taken part in another study within the last 30 days prior to the start of the study.

I received one original of the Patient Information Sheet together with the signed Information Consent Form.

_____

(Place, Date & Signature of the Patient)

_____

(Place, Date & Signature of the Doctor)

PATIENT INFORMATION SHEET

Who can be contacted for further questions?

For further questions regarding this clinical study or your rights as patient and participant in the study, please contact your doctor who will always be ready to provide you the necessary information.

If you have experienced any health related problems as well as in case of hospitalization please contact your doctor.

Name and Address of the Contact Person:

_____

_____

Phone number: _____

Please take a copy of this information sheet home with you.

<u>பல்வேறு வகை நோயாளிகளில் ரத்தகொழுப்பு அளவினை அட்டார்வாஸ்டாட்டின் மற்றும் விட்டமின் டி 3 யை அட்டார்வாஸ்டாட்டின் உடன் ஒப்பீட்டு ஆய்வு.</u>

நோயாளி அடையாளப்படுத்துதல் :

பங்கேற்பாளர் எண் :

ஒரு ஆராய்ச்சி ஆய்வில் பங்கேற்கும்படி நீங்கள் கேட்டுக்கொள்ளப்படுகிறீர்கள்.பங்கு பெற உங்களுக்கு விருப்பமா ,என்பதை முடிவு செய்ய உங்களுக்கு உதவ இந்தப்படிவம் தகவல்களைக் கொண்டுள்ளது.நேரம் எடுத்துக்கொண்டு ,இந்த படிவத்தை கவனமாக படித்து உங்களுக்கு இருக்கும் ஐயப்பாடுகளை ஆய்வு மருத்துவரையோ அல்லது ஏதுனும் ஊழியர்களையோ கேட்கவும்.

இந்த ஆய்வை பற்றி :-

இரத்தத்தில் கொழுப்பு அதிகமாக இருப்பவர்களுக்கு இரத்தத்தில் கொழுப்பு அளவைக் குறைக்க அட்டார்வாஸ்டாட்டின் மற்றும் விட்டமின் டி 3 யை அட்டார்வாஸ்டாட்டின் உடன் ஒப்பீட்டு ஆய்வு.

இந்த ஆய்வில் பங்கேற்க நீங்கள் அனுமதிக்கப்படுவதற்கு இந்த காரணங்கள் இருக்கக்கூடும் .உங்களுக்கு இரத்தத்தில் கொழுப்பு அதிகமாகஇருப்பதினால்.**நான் என்ன செய்யுமாறு கேட்டுகொள்ளப்படுவேன்** .

சாப்பிடும்போது உப்பு குறைவாகவோ அல்லது முற்றிலுமாக உப்பு சேர்க்காமலோ இருப்பது.

இரண்டு வாரத்திற்கு ஒரு முறை வந்து மாத்திரைகளை வாங்கிக்கொள்வது .

முறையாக உடற்பயிற்சி செய்வது.

நேரத்திற்கு சரியாக துங்குவது.

மருத்துவர் அறிவுரை இல்லாமல் எந்த ஒரு புதிய மருந்தோ மாத்திரையோ உட்கொள்ளாமல் இருப்பது .

நீங்கள் ஒவ்வொரு முறை வரும்பொழுதும் நீங்கள் எடுத்தமருந்தின் காலிஅட்டைகளை கொண்டுவருவது .

வருகையின் இடையில் உங்களுக்கு ஏதேனும் பக்கவிளைவுகள் இருக்கிறதா என்பதை அறிந்து கொள்வதற்காக, ஆய்வு

ஊழியர்களிடமிருந்து வரும் தொலைபேசி அழைப்புகளை பெற்றுகொள்வது.

நீங்கள் உங்கள் ஆய்வு வருகைகளுக்கு வரும்போது ஆய்வு மருத்துவரால் அல்லது ஆய்வு ஊழியர்களால் பின்வருபவைகளில் ஏதுனும் ஒன்றோ இல்லை முழுவதுமாகவோ உட்படுத்தபடுவீர்கள்.

உங்கள் மருத்துவ வரலாற்றை மறுஆய்வு செய்வது.

ஆய்வு மருந்துகளையும் அறிவுரைகளையும் வழங்குவது.

உங்களது இதயத்துடிப்பு ,இரத்தஅழுத்தம் ,உடல்எடை,உயரம் ,வயிற்றின் சுற்றளவு, ஆகியவற்றை அளப்பது .

இரத்தம் மற்றும் சிறுநீர் மாதிரிகள் பரிசோதனை.

எலெக்ட்ரோ கார்டியோக்ராம் (இருதய சுருள் படம்).

மருந்துகள் எப்பொழுதாவது கீழ்க்கண்ட பின்விளைவுகளையோ அல்லது பக்கவிளைவுகளையோ உண்டாக்கலாம்.

வாந்தி, மருந்து ஒவ்வாமை, .

கை கால் தசை வலி.

ஆய்வின் போது பின்விளைவுகள் ஏற்ப்பட்டால் ஆய்வு மருந்து உட்கொள்வதை நிறுத்திவிட்டு உடனடியாக மருத்துவரை அணுகவேண்டும்.உங்கள் மருத்துவர் வேறு மருந்து கொடுத்து பின்விளைவுகளை நிறுத்த முயற்சிப்பார்.

இரத்தப் பரிசோதனை செய்வதால் உண்டாகும் எதிர்விளைவுகள்

பெரும்பாலானவர்களுக்கு இரத்தம் எடுப்பதற்காக ஊசி குத்துவது எவ்வித மோசமான பிரச்சனைகளையும் ஏற்படுத்துவதில்லை.ஆயினும் , சில நேரங்களில் இரத்தம் எடுக்கப்பட்ட இடத்தில் , இரத்தக் கசிவு , இரத்தம் கன்றிப் போதல் ,அசௌகரியம் , நோய்தொற்றுக்கள் மற்றும் /அல்லது வலி ஆகியவை உண்டாகலாம். நீங்கள் தலைசுற்றுவதாகவும் உணரலாம்

எலட்ரோகார்டியோக்ராம் / ஈ . சி . ஜி

எலட்ரோகார்டியோக்ராம் / ஈசிஜி பரிசோதனை இதயத்துடிப்பு அல்லது இதய தாளத்தின் மின்சார தடமறிதல்.அவை ஈகேஜி பரிசோதனை எனவும் அழைக்கபடுகின்றன. ஈசிஜி

பரிசோதனை செய்து கொள்வதற்கு , உங்கள் உடலின் பல்வேறு பகுதிகளில் ஒட்டுக்கள் வைக்கப்படும்.

உலகளாவிய தரவுகள் பாதுகாப்பு அறிக்கை

இந்த ஆய்வை நடத்துவதன் ஒரு பகுதியாக ,உங்கள் மருத்துவத் தகவல்களை ஆய்வு மருத்துவர் தவிர பிறருடன் பகிர்ந்து கொள்வது அவசியமாகிறது .உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்கள் எவ்வாறு பயன்படுத்தப்படும் மற்றும் இந்த ஆராய்ச்சி ஆய்வுக்காக அவை யாருக்குத் தரப்படும் (வெளிப்படுத்துதல்) என்பவை பற்றி , தரவுகள் பாதுகாப்பு அறிக்கை விளக்கமளிக்கிறது. உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களைப் பார்வையிட உங்கள் உரிமைகள் உட்பட உங்களது பாதுகாப்பு உரிமைகளையும் இது விவரிக்கிறது.

நீங்கள் யார் என்று கண்டறியப் பயன்படுத்தபடும் உங்களைப் பற்றிய தகவல்களே உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களாகும். இந்த ஆய்விற்குத் தேவைப்படும் தற்போதைய உங்கள் மருத்துவப் பதிவேடுகளில் உள்ள தகவல்கள் இந்த ஆய்வின்போது உருவாக்கப்படும் அல்லது சேகரிக்கப்படும் புதிய

தகவல்கள் ஆகியவற்றை உள்ளடக்கியவையே இந்த ஆய்விற்குத் தேவையான தகவல்களாகும்.

இந்த ஆய்விற்கான ஒப்புதல் படிவத்தில் கையொப்பமிடுவதன் வாயிலாக , இந்த தரவுகள் பாதுகாப்பு அறிக்கையில் விவரிக்கப்பட்டுள்ள உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களை பயன்பாட்டுக்கும் வெளிப்படுத்துதலுக்கும் நீங்கள் அனுமதி (“அங்கீகாரம் “) அளிக்கிறீர்கள் . இப்பயன்பாடுகளை நீங்கள் அனுமதிக்க விரும்பவில்லை என்றால், இந்த ஆய்வில் நீங்கள் பங்கேற்கக் கூடாது.

இந்த ஆய்வில் பங்கேற்க நீங்கள் ஒப்புக் கொண்டால், உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்கள் கீழ்க்கண்ட வழிகளில் பயன்படுத்தப்படும் மற்றும் வெளிப்படுத்தப்படும்.

- ஆய்வின் போது ,ஆய்வை நடத்துவதற்காக , உங்கள் மருத்துவப் பதிவேடுகளையும் ,உருவாக்கப்பட்ட அல்லது சேகரிக்கப்பட்ட தகவல்களையும் ஆய்வு மருத்துவர் மற்றும் ஊழியர்கள் பயன்படுத்துவார்கள்.

- ஒப்புதல் படிவத்தில் விவரிக்கப்பட்ட ஆய்வின் அறிவியல் நோக்கங்களுக்கு ஆதரவளிக்கும் ஆராய்ச்சிக் காரணங்களுக்காகவும் ,ஆய்வில் சேர்க்கப்பட்ட மருந்து அல்லது சிகிச்சையின் பாதுகாப்பு மற்றும் பலன்களை மதிப்பீடு செய்யவும் , ஆய்வில் சேர்க்கப்பட்டுள்ள நோய்(கள்) பற்றி சிறப்பாக புரிந்து கொள்ளவும் அல்லது எதிர்கால ஆய்வுகளை வடிவமைத்து மேம்படுத்தவும் இந்த ஆய்வுத் தரவுகள் பயன்படும்.

- உங்களை அடையாளம் காணாத ஆய்வுத் தரவுகள் மருத்துவ இதழ்களில் வெளியிடப்படலாம் அல்லது அறிவியல் விவாதங்களின் ஒரு பகுதியாக மற்றவர்களுடன் பகிர்ந்து கொள்ளப்படலாம்.

- உங்கள் மருத்துவ பதிவேடுகள் மற்றும் ஆய்வுத் தரவுகள் கணினிகளில் வைக்கப்பட்டு செயல்முறைப்படுத்தப்படலாம்.

ஆய்வு தொடர்பான உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்கள் ,ஆய்வு மருத்துவரிடம் இருக்கும்வரை ,அவற்றை நீங்கள் பார்வையிடவும் அவற்றின் நகலைப் பெறவும் ,உங்களுக்கு

உரிமையுண்டு. இருப்பினும் ,ஆய்வின் அறிவியல் ஒருமைப்பாட்டை உறுதிசெய்யும் பொருட்டு,ஆய்வு முடிவடையும் வரை சில ஆய்வுத் தகவல்களை நீங்கள் மறுஆய்வு செய்ய முடியாது.

ஆய்வு மருத்துவருக்கு எழுத்து மூலம் அறிவிப்பை அளித்து உங்கள் அங்கீகாரத்தை எப்போது வேண்டுமானாலும் நீக்கி விடலாம். நீங்கள் உங்கள் அங்கீகாரத்தை நீக்கிக் கொண்டால் ,ஆய்வின் அறிவியல் ஒருமைப்பாட்டை பாதுகாப்பதற்காக , ஆய்வு மருத்துவர் அல்லது ஊழியர்கள் இந்த ஆய்வுடன் தொடர்புடைய உங்கள் தனிப்பட்ட மருத்துவத் தகவல்கள் சிலவற்றை பயன்படுத்தும் அல்லது உரிமை வழங்கல் தேவை இல்லாதவரை , உங்கள் ஆய்வு மருத்துவர் அல்லது ஊழியர்கள் உங்கள் தனிப்பட்ட ஆரோக்கியத் தகவல்களைப் பயன்படுத்தவோ அல்லது வெளிப்படுத்தவோ மாட்டார்கள்.

நோயாளி தகவல் மற்றும் ஒப்புதல் படிவம் இணைப்பு 2

ஆய்விடத் தகவல் மற்றும் தொடர்பு விவரங்கள்.

வெவ்வேறு வகை நோயாளி மக்களில் அட்டார்வாஸ்டாட்டின் மற்றும் விட்டமின் டி 3 யை அட்டார்வாஸ்டாட்டின் உடன் ஒப்பீட்டு ஆய்வு.

ஆய்வு குறித்த ஐயப்பாடுகள் மற்றும் விவரங்களைப் பற்றி கேட்பதற்கான ஆய்வு மருத்துவர்களின் தொடர்பு விவரங்கள்.

ஆய்வு மருத்துவரின் பெயர் .

முகவரி .

தொடர்பு எண்

ஓர் பங்கேற்பாளராக உங்கள் உரிமைகளைப் பற்றி கேட்பதற்கான ஈஆர்பி தொடர்பு விவரங்கள்

ஐஆர்பி தொடர்பு நபரின் பெயர்

தொடர்புஎண்

MASTER CHARTS

									Pre treatment					Post treatment				
S.NO	**Patient ID**	**Age**	**Sex**	**Height**	**Weight**	**BMI**	**Disease**	**Drug**	**Total cholesterol**	**LDL cholesterol**	**HDL cholesterol**	**Triglyceride**	**VLDL**	**Total cholesterol**	**LDL Cholesterol**	**HDL cholesterol**	**Triglyceride**	**VLDL**
1	39876	56	F	1.6	60	23.43	HT	Atorva	233	166	41	130	26	193	123	46	120	24
2	36543	48	M	1.54	58	24.47	HT	Atorva	227	155	42	150	30	185	115	46	120	24
3	76089	38	M	1.62	62	23.62	HT	Atorva	218	135	40	215	43	165	100	45	100	20
4	70014	39	M	1.48	60	27.39	HT	Atorva	214	148	40	130	26	176	111	45	201	20
5	65509	45	M	1.44	56	27	HT	Atorva	215	145	40	150	30	174	110	44	100	20
6	23409	52	F	1.61	58	22.37	HT	Atorva	220	146	44	150	30	179	105	48	130	26
7	33008	53	M	1.58	66	26.43	HT	Atorva	235	168	40	135	27	197	128	46	115	23
8	45076	57	F	1.52	65	28.13	HT	Atorva	228	145	46	185	37	188	110	48	150	30
9	34778	58	M	1.42	65	32.23	HT	Atorva	216	144	40	160	32	184	110	46	140	28
10	45787	48	F	1.66	68	24.67	HT	Atorva	255	180	45	150	30	204	130	48	130	26
11	56609	47	F	1.5	70	31.11	HT	Atorva	220	160	40	140	28	196	124	48	120	24
12	88700	49	F	1.4	75	38.26	HT	Atorva	261	190	46	125	25	205	134	50	105	21
13	680099	50	M	1.41	66	33.19	HT	Atorva	240	178	40	110	22	190	126	46	90	18
14	25564	60	M	1.35	69	37.86	HT	Atorva	215	155	40	100	20	196	133	47	80	16
15	35564	57	F	1.38	78	40.95	HT	Atorva	241	166	45	150	30	185	112	48	125	25
16	30657	48	M	1.7	66	22.83	HT	Atorva	251	191	40	100	20	174	110	46	90	18
17	47095	49	M	1.62	72	27.43	HT	Atorva	220	150	40	150	30	201	130	46	125	25
18	42006	48	F	1.58	80	32.04	HT	Atorva	215	145	45	125	25	180	110	48	110	22
19	50608	47	F	1.56	58	23.83	HT	Atorva	258	185	45	140	28	207	135	49	115	23

20	71123	48	M	1.57	62	25.15	HT	Atorva	210	140	40	150	30	181	108	47	130	26
21	57077	54	F	1.6	60	23.43	HT	Atorva	224	146	44	170	34	182	109	45	140	28
22	43007	53	F	1.6	60	23.43	HT	Atorva	238	150	40	240	48	200	112	48	200	40
23	54861	57	M	1.55	56	23.3	HT	Atorva	210	110	45	275	55	182	90	44	240	48
24	70098	47	F	1.58	67	26.83	HT	Atorva	220	140	40	200	40	193	110	48	175	35
25	55765	45	F	1.64	78	29	HT	Atorva	233	160	45	140	28	195	125	46	120	24
26	65007	54	M	1.68	84	29.76	HT	Atorva	207	120	40	235	47	185	98	45	210	42
27	54006	56	M	1.7	80	27.68	HT	Atorva	228	156	40	160	32	185	114	45	130	26
28	33765	55	M	1.8	64	19.75	HT	Atorva	212	140	40	160	32	182	110	46	130	26
29	65743	48	F	1.38	72	37.8	HT	Atorva	241	168	45	140	28	195	125	48	110	22
30	45588	49	F	1.44	70	33.75	HT	Atorva	212	120	45	235	47	186	96	49	205	41
31	11034	46	M	60	1.5	26.66	CKD	Atorva	220	130	40	250	50	153	104	42	225	45
32	14584	48	M	55	1.7	19.03	CKD	Atorva	279	191	40	240	48	237	152.5	42	212.5	42.5
33	10345	52	M	70	1.8	21.6	CKD	Atorva	227	150	40	185	37	193	120	42	157.25	31.4
34	13440	44	F	54	1.6	21.09	CKD	Atorva	257	161	44	260	52	219	128.8	46	221	44.2
35	11254	38	M	80	1.54	33.73	CKD	Atorva	241	166	38	185	37	174	133	40	157	31.4
36	14832	49	M	56	1.55	23.3	CKD	Atorva	210	132	40	190	38	180	106	42	162	32.4
37	18360	51	F	58	1.6	22.65	CKD	Atorva	240	162	40	190	38	204	130	42	162	32.4
38	11442	48	M	64	1.63	24.08	CKD	Atorva	254.5	161.1	40.6	264	52.8	217	130	42	225	45
39	11340	39	M	66	1.7	22.83	CKD	Atorva	250.5	162.5	40	240	48	211	129	42	204	40.8
40	11534	47	F	67	1.58	26.83	CKD	Atorva	241.8	150.8	40	255	51	215.4	130	42	217	43.4
41	12134	52	M	70	1.54	29.51	CKD	Atorva	253.8	162.5	40.2	255.5	51.1	206.2	120.8	42	217	43.4
42	13544	55	M	72	1.54	30.35	CKD	Atorva	260.4	171.4	40	245	49	216	129	42	225	45
43	13324	53	M	74	1.46	34.71	CKD	Atorva	241.8	166.8	38	185	37	213	141.4	40	158	31.6
44	10123	49	M	63	1.48	28.76	CKD	Atorva	258.4	190.41	38	262	52.4	217.6	133	40	223	44.6
45	10233	55	M	70	1.52	30.29	CKD	Atorva	246.7	160.2	39	237.5	47.5	233.4	152	41	202	40.4
46	12098	50	M	74	1.6	28.9	CKD	Atorva	260	172	40	240	48	210.8	128	42	204	40.8

47	13324	46	F	75	1.58	30.04	CKD	Atorva	256	164	40	260	52	216	129	43	220	44
48	14221	48	M	66	1.6	25.78	CKD	Atorva	248	170	40	190	38	206.4	132	42	162	32.4
49	11001	50	F	58	1.53	24.77	CKD	Atorva	269	180	40	245	49	227.8	144	42	209	41.8
50	11324	38	F	56	1.55	23.3	CKD	Atorva	264	178	40	230	46	224.2	143	42	196	39.2
51	11846	48	M	45	1.6	17.57	CKD	Atorva	240	157	38	225	45	204.4	126	40	192	38.4
52	23111	56	M	62	1.7	21.45	CKD	Atorva	248	168	38	210	42	211.8	135	41	179	35.8
53	11007	55	F	64	1.66	23.22	CKD	Atorva	260	180	40	200	40	222	144	44	170	34
54	13280	52	F	63	1.65	23.14	CKD	Atorva	250	170	41	195	39	214	136	43	166	33.2
55	14327	58	M	62	1.64	23.05	CKD	Atorva	248	169	38	205	41	210	135	40	175	35
56	13528	45	M	65	1.63	24.46	CKD	Atorva	238	155	40	215	43	202.6	124	42	183	36.6
57	11473	48	F	66	1.61	25.46	CKD	Atorva	254	167	40	235	47	217	135	42	200	40
58	17655	44	F	63	1.5	28	CKD	Atorva	260	168	40	260	52	222	136	42	221	44.2
59	11098	52	F	62	1.6	24.21	CKD	Atorva	258	172	40	230	46	223.2	142	42	196	39.2
60	11065	50	M	61	1.5	27.11	CKD	Atorva	266	175	40	255	51	230.4	145	42	217	43.4
61	22332	39	F	1.54	80	33.73	HT	Atorva+vit D3	248	180	40	140	28	165	100	45	100	20
62	54321	43	M	1.7	78	26.98	HT	Atorva+vit D3	280	214	38	140	28	184	119	44	105	21
63	35045	45	F	1.55	76	31.63	HT	Atorva+vit D3	260	182	38	200	40	181	110	45	130	26
64	28745	56	M	1.56	55	22.6	HT	Atorva+vit D3	230	156	40	170	34	175	106	46	150	23
65	29020	57	F	1.6	54	21.09	HT	Atorva+vit D3	260	190	38	160	32	169	104	44	105	21
66	53468	48	M	1.62	48	27.43	HT	Atorva+vit D3	270	202	40	140	28	165	100	46	95	19
67	48152	49	M	1.59	52	20.56	HT	Atorva+vit D3	240	172	38	150	30	155	90	45	100	20
68	39660	39	M	1.53	60	25.63	HT	Atorva+vit D3	240	175	40	125	25	152	88	46	90	18
69	53766	55	F	1.52	65	28.13	HT	Atorva+vit D3	260	195	38	135	27	158	95	44	95	19
70	48054	57	F	1.7	67	23.18	HT	Atorva+vit D3	250	182	38	150	30	153	90	43	100	20
71	36213	56	F	1.6	80	31.25	HT	Atorva+vit D3	233	166	41	130	26	167	100	49	90	18
72	35689	52	F	1.54	75	31.64	HT	Atorva+vit D3	227	155	42	150	30	163	93	50	100	20
73	86008	53	M	1.53	66	28.18	HT	Atorva+vit D3	218	135	40	215	43	151	75	48	140	28
74	83221	54	M	1.56	63	25.88	HT	Atorva+vit D3	214	148	40	130	26	156	90	48	90	18

75	78034	57	M	1.5	70	31.11	HT	Atorva+vit D3	215	145	40	150	30	156	87	49	100	20
76	51112	54	F	1.61	74	28.54	HT	Atorva+vit D3	220	146	44	150	30	158	88	50	100	20
77	43545	47	F	1.7	72	24.91	HT	Atorva+vit D3	235	168	40	135	27	168	100	50	90	18
78	58347	43	F	1.6	80	31.25	HT	Atorva+vit D3	228	145	46	185	37	165	87	50	140	28
79	38453	46	M	1.5	76	33.77	HT	Atorva+vit D3	216	144	40	160	32	155	86	48	105	21
80	20876	46	F	1.6	70	27.34	HT	Atorva+vit D3	255	180	45	150	30	173	104	49	100	20
81	30098	55	M	1.4	82	41.83	HT	Atorva+vit D3	220	160	40	140	28	163	96	49	90	18
82	45087	50	F	1.62	81	30.86	HT	Atorva+vit D3	261	190	46	125	25	178	112	50	80	16
83	34354	38	F	1.58	88	35.25	HT	Atorva+vit D3	240	178	40	110	22	171	106	48	85	17
84	87767	44	F	1.6	65	25.39	HT	Atorva+vit D3	215	155	40	100	20	155	93	49	65	13
85	76001	58	F	1.7	60	20.76	HT	Atorva+vit D3	241	166	45	150	30	168	99	49	100	20
86	46377	48	M	1.56	62	25.47	HT	Atorva+vit D3	251	191	40	100	20	174	113	48	65	13
87	65011	51	M	1.58	64	25.63	HT	Atorva+vit D3	220	150	40	150	30	158	90	48	100	20
88	34476	58	F	1.6	65	25.39	HT	Atorva+vit D3	215	145	45	125	25	152	87	49	80	16
89	30098	54	F	1.5	66	29.33	HT	Atorva+vit D3	258	185	45	140	28	178	110	50	90	18
90	26678	50	F	1.6	70	27.34	HT	Atorva+vit D3	210	140	40	150	30	157	88	49	100	20
91	11033	45	M	58	1.41	29.17	CKD	Atorva+vit D3	240	157	38	225	45	170	95	44	158	31.6
92	11543	48	M	65	1.44	31.34	CKD	Atorva+vit D3	248	168	38	210	42	172.4	101	42	147	29.4
93	10365	57	F	59	1.5	26.22	CKD	Atorva+vit D3	260	180	40	200	40	179	108	43	140	28
94	13442	54	F	70	1.6	27.34	CKD	Atorva+vit D3	250	170	41	195	39	172.4	102	43	137	27.4
95	11235	52	M	72	1.52	31.16	CKD	Atorva+vit D3	248	169	38	205	41	170.8	102	40	144	28.8
96	11453	60	M	80	1.6	31.25	CKD	Atorva+vit D3	238	155	40	215	43	167.2	93	44	151	30.2
97	14382	47	M	62	1.7	21.45	CKD	Atorva+vit D3	254	167	40	235	47	177	101	43	165	33
98	18630	49	M	63	1.6	24.6	CKD	Atorva+vit D3	260	168	40	260	52	181.4	101	44	182	36.4
99	14142	46	M	71	1.5	31.55	CKD	Atorva+vit D3	258	172	40	230	46	180.2	104	44	161	32.2
100	12131	38	M	72	1.54	30.35	CKD	Atorva+vit D3	266	175	40	255	51	184.8	105	44	179	35.8
101	10055	39	M	76	1.52	32.89	CKD	Atorva+vit D3	220	130	40	250	50	156	78	43	175	35

102	14322	48	M	66	1.6	25.78	CKD	Atorva+vit D3	279	191	40	240	48	191.6	115	43	168	33.6
103	10978	44	M	64	1.56	26.29	CKD	Atorva+vit D3	227	150	40	185	37	159	90	43	130	26
104	12003	36	F	63	1.58	25.23	CKD	Atorva+vit D3	257	161	44	260	52	180.4	97	47	182	36.4
105	13426	48	M	58	1.5	25.77	CKD	Atorva+vit D3	241	166	38	185	37	168	100	42	130	26
106	11968	53	M	60	1.5	26.66	CKD	Atorva+vit D3	210	132	40	190	38	150.6	80	44	133	26.6
107	10654	52	M	54	1.6	21.09	CKD	Atorva+vit D3	240	162	40	190	38	167.6	98	43	133	26.6
108	12341	48	F	60	1.7	20.76	CKD	Atorva+vit D3	254.5	161.1	40.6	264	52.8	177	97	43	185	37
109	10342	47	M	48	1.58	19.22	CKD	Atorva+vit D3	250.5	162.5	40	240	48	174.6	98	43	168	33.6
110	14432	45	M	58	1.6	22.65	CKD	Atorva+vit D3	241.8	150.8	40	255	51	169.8	90	44	179	35.8
111	16243	56	F	55	1.52	23.8	CKD	Atorva+vit D3	253.8	162.5	40.2	255.5	51.1	176.8	98	43	179	35.8
112	15332	54	M	56	1.6	21.87	CKD	Atorva+vit D3	260.4	171.4	40	245	49	181.4	103	43	172	34.4
113	11398	55	M	74	1.48	33.78	CKD	Atorva+vit D3	241.8	166.8	38	185	37	167	100	41	130	26
114	11324	54	M	63	1.5	28	CKD	Atorva+vit D3	258.4	190.41	38	262	52.4	190.8	114	40	184	36.8
115	10067	43	M	60	1.51	26.31	CKD	Atorva+vit D3	246.7	160.2	39	237.5	47.5	169.2	96	40	166	33.2
116	13328	46	M	72	1.6	28.12	CKD	Atorva+vit D3	260	172	40	240	48	181.6	104	44	168	33.6
117	15422	48	F	56	1.45	26.63	CKD	Atorva+vit D3	256	164	40	260	52	178.4	99	43	182	36.4
118	10303	50	M	58	1.5	25.77	CKD	Atorva+vit D3	248	170	40	190	38	171.6	102	43	133	26.6
119	11748	46	F	54	1.4	27.55	CKD	Atorva+vit D3	269	180	40	245	49	186.4	108	44	172	34.4
120	10568	44	M	55	1.4	28.06	CKD	Atorva+vit D3	264	178	40	230	46	183.2	107	44	161	32.2

ABBREVIATIONS

ABC- ATP-binding cassette

ACAT- Acyl coenzyme A: Cholesterol acyl transferase

ALT- alanine transaminase

ATP- Adult Treatment Panel

CAD- Coronary Artery Disease

CETP- cholesterol ester transfer protein

CK- creatine kinase

CRP- C-reactive protein

CVD- Cardio Vascular Disease

CYP- Cytochrome P

DM- Diabetes Mellitus

FFA- Free fatty acid

HDL- High Density Lipoproteins

HL-Hepatic lipase

HMG- CoA- 3-Hydroxy-3methyl glutaryl coenzyme A

IDL- Intermediate Density Lipoproteins

IL- interleukin

LCAT- lecithin cholesterol acyl transferase

LDL- Low Density Lipoproteins

LP (a)- Lipoprotein (a)

LPL- Lipoprotein lipase

LRP- LDL receptor-related protein

MTP- Microsomal triglyceride transfer protein

NCEP- National Cholesterol Education Program

OATP- organic anion- transporting polypeptide

PTH- parathyroid hormone

RNA- Ribonucleic acid

Scap- SREBP and its cleavage activating protein

SR- Scavenger receptor

SREBP- sterol regulatory element binding proteins

TG- Triglycerides

TNF- tumor necrosis factor

UVB- Ultraviolet-B

VLDL- Very Low Density Lipoproteins

ETHICAL CLEARANCE LETTER

Ref. No. 990/E4/3/2012 **Govt. Rajaji Hospital, Madurai.20. Dated: 12.03.2013**

Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College &
Govt Rajaji Hospital, Madurai 625020.
Convenor

Dept of Pharmacology
MMC

Sub: Establishment-Govt. Rajaji Hospital, Madurai-20-
Ethics committee-Meeting Minutes- approval -regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 10.00 am to 12.00.pm on 25.02.2013 at the Surgery Seminar Hall, Govt. Rajaji Hospital, Madurai. The following members of the committee have attended the meeting.

1.Dr. V. Nagarajan, M.D., D.M (Neuro) Ph: 0452-2629629 Cell.No 9843052029	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2. Dr.Mohan Prasad , M.S M.Ch Cell.No.9843050822 (Oncology)	Professor & H.O.D of Surgical Oncology(Retired) D.No.72, West Avani Moola Street, Madurai -1	Member Secretary
3. Dr.L. Santhana Lakshmi,MD Cell.No 9842593412	Associate Professor of Physiology/V.P Madurai Medical College	Member
4. Dr. Parameswari M.D (Pharmacology) Cell.No.9994026056	Director of Pharmacology Madurai Medical College	Member
5. Dr.Moses K.Daniel MD(Gen.Medicine) Cell.No 09842156066	Professor & H.O.D of Medicine Madurai Medical College	Member
6. Dr.D. Soundara Rajan,MS(Gen.Surgery) Cell.No 9842120127	Professor & H.O.D of Surgery Madurai Medical College	Member
7. Dr.Angayarkanni MD(O&G) Cell.No 9443567724	Professor & H.O.D of O&G Madurai Medical College	Member
8. Dr.P.V. Pugalenthi M.S, (Ortho) Cell.No 9443725840	Professor & H.O.D Ortho Madurai Medical College	Member
9. Dr. M. Sundarajan M.S., Mch Cell.No 9994924369 (Neuro Surgery)	Professor (Neuro Surgery) Madurai Medical College	Member
10 Thiru..Pala. .Ramasamy , BA.,B.L., Cell.No 9842165127	Advocate, D.No.72.Palam Station Road, Sellur, Madurai -2	Member
11. Thiru. P.K.M. Chelliah ,B.A Cell.No 9894349599	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

Following Project was approved by the committee

Name of P.G.	Course	Name of the Project	Remarks
Dr. M. Vijayalakshmi	PG in MD (Pharmacology) Govt. Rajaji Hospital & Madurai Medical College, Madurai.	A Prospective comparative clinical study of atorvastatin and atoravastatin with vitamin D3 on lipid profile in various patient population.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.

She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.

4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary **Chairman** **DEAN/Convenor**
Govt. Rajaji Hospital,
Madurai- 20.

12/3/13

To
The above Applicant
-thro. Head of the Department concerned.

Dept. of Pharmacology

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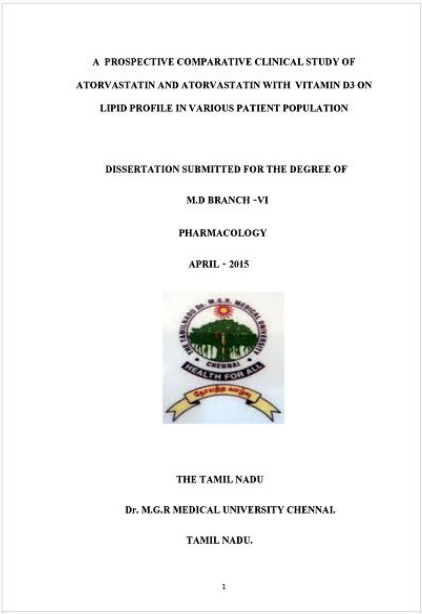

A PROSPECTIVE COMPARATIVE CLINICAL STUDY OF ATORVASTATIN AND ATORVASTATIN WITH VITAMIN D3 ON LIPID PROFILE IN VARIOUS PATIENT POPULATION

DISSERTATION SUBMITTED FOR THE DEGREE OF

M.D BRANCH -VI

PHARMACOLOGY

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THE TAMIL NADU

Dr. M.G.R MEDICAL UNIVERSITY CHENNAI

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