A STUDY OF LIPID PROFILE IN CHRONIC RENAL FAILURE PATIENTS ON CONSERVATIVE MANAGEMENT, HEMODIALYSIS AND AFTER RENAL TRANSPLANTATION

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BRANCH - I

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CERTIFICATE

This is to certify that this dissertation titled **"A STUDY OF LIPID PROFILE IN CHRONIC RENAL FAILURE PATIENTS ON CONSERVATIVE MANAGEMENT, HEMODIALYSIS AND AFTER RENAL TRANSPLANTATION"** is the bonafide original work of **Dr.LAVANYA S.** in partial fulfillment of the requirement for MD (Branch I) General Medicine examination of the Tamil Nadu Dr.MGR Medical University to be held in March 2008.

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DECLARATION

I, **Dr.LAVANYA S.,** solemnly declare that this dissertation **"A STUDY OF LIPID PROFILE IN CHRONIC RENAL FAILURE PATIENTS ON CONSERVATIVE MANAGEMENT, HEMODIALYSIS AND AFTER RENAL TRANSPLANTATION"** is a bonafide record of work done by me in the Department of Medicine, Government Stanley Medical College and Hospital, Chennai under the guidance of **Prof.Dr.S.RAMASAMY, M.D.,** Prof. of Medicine, Government Stanley Medical College and Hospital, Chennai – 600 001.

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ABBREVIATIONS

CRF	-	Chronic renal failure
ESRD	-	End stage renal disease
TG	-	Triglyceride
TC	-	Total cholesterol
HDL	-	High density lipoprotein
LDL	-	Low density lipoprotein
VLDL	-	Very low density lipoprotein
HD	-	Hemodialysis
LPL	-	Lipoprotein lipase
LCAT	-	Lecithin cholesterol acyl transferase
ACAT	-	Acyl CoA cholesterol acyl transferase
SRB-1	-	Scavenger Receptor class B type 1
CETP	-	Cholesteryl ester transfer protein
ABCA1	-	ATP binding cassette transporter type 1

INTRODUCTION

Chronic renal failure (CRF) results in profound lipid disorders, which stem largely from dysregulation of high-density lipoprotein (HDL) and triglyceride-rich lipoprotein metabolism .Together, these abnormalities may contribute to the risk of arteriosclerotic cardiovascular disease and may adversely affect progression of renal disease and energy metabolism in CRF.

Cardiovascular disease (CVD) is the leading cause of death among patients with chronic and end-stage renal disease (ESRD). There is growing evidence that cardiovascular damage begins as soon as the kidney loses function and increases in severity during the progression of kidney disease. Hypertension and diabetes mellitus, known risk factors for the development of CVD in the general population, are also the most common causes for the development of CVD in patients with CRF and ESRD. It is known that patients with type 2 diabetes who require dialysis are about 30 times more likely to die of CVD, including heart attacks and strokes, than the general population.

There are several other important risk factors, such as smoking, proteinuria and dyslipidemia that independently or in combination with elevated blood pressure, can cause deterioration in renal function. Abnormalities in lipid metabolism and dyslipidemia are known to contribute to glomerulosclerosis and are common in renal disease. In addition, post-transplant dyslipidemias have been associated with an increased risk of ischemic heart disease and have been shown to increase risk of chronic rejection, altered graft function and mortality. However, only recently, trials are

starting to evaluate if reversal of dyslipidemia can actually lead to a decreased risk of CVD in patients with chronic renal conditions.

Various studies have been done to describe the characteristic features of lipoprotein metabolism during different stages of renal insufficiency and to describe the possible links between the underlying lipid transport abnormalities and the pathophysiology of lipoprotein abnormalities in patients with chronic renal failure. Similar abnormalities of lipid profile are found in chronic renal failure patients when they are on regular dialysis, but several other factors have been found to contribute to them. After renal transplantation, the addition of immunosuppressive treatment and the presence of renal rehabilitation causes other abnormalities of lipid transport .

Since hyperlipidemias become more pronounced as renal failure advances and can be modulated by therapeutic intervention it is worthwhile to study and compare lipid profile abnormalities in renal failure patients on different modes of management.

A prospective study was taken up, to study the lipid profile in patients of chronic renal failure

a. on conservative management
b. on regular haemodialysis
c. after renal transplantation and to compare with healthy controls.

AIM OF THE STUDY

1. To estimate the levels of

   Serum triglycerides,

   Serum total cholesterol,

   High density lipoprotein cholesterol,

   Low density lipoprotein cholesterol,

   Ratio of total cholesterol to HDL cholesterol level in patients of chronic renal failure,

   a. On conservative management
   b. On regular hemodialysis
   c. Following renal transplantation

2. To compare the lipid profile of the above mentioned patients with that of healthy controls.

REVIEW OF LITERATURE

PLASMA LIPIDS AND LIPOPROTEIN METABOLISM

Plasma Lipids

Lipids exist in the following forms:

a. Fatty acids are straight chain compounds of varying lengths.

b. Triglycerides consist of glycerol and three fatty acids.

c. Phospholipids are complex lipids, resembling triglycerides but containing phosphate and a nitrogenous base. The major phospholipids in plasma are lecithin and sphingomyelin.

The phosphates and nitrogenous bases are water soluble, a fact that is important in lipid transport. Cholesterol has a steroid structure, and other steroids are derived from it. About 2/3rd of the plasma cholesterol is esterified with fatty acids to form cholesterol esters.

Lipoproteins

Lipids are relatively insoluble in water but are carried in the body fluids as soluble protein complexes known as lipoprotein : the water soluble (polar) group of protein, phospholipids and free cholesterol enclose a core of insoluble (non polar) cholesterol esters and triglycerides. They may be classified according to their densities using ultracentrifugation into four main classes.

Two classes are important for cholesterol transport :

- HDL (High density lipoprotein) transports cholesterol from peripheral cells.
- LDL (Low density lipoprotein) transports cholesterol to peripheral cells.

Two classes are most important for triglyceride transport :

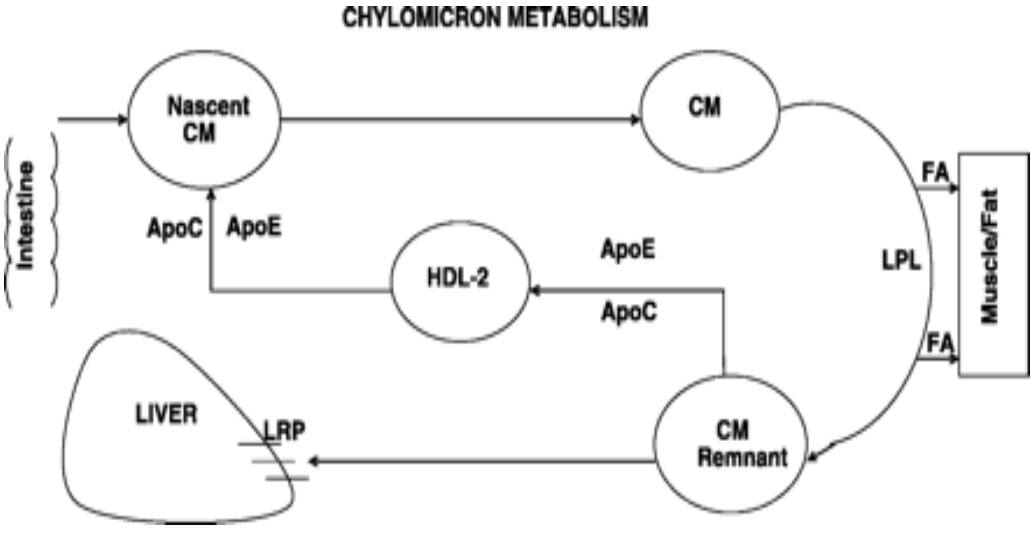
- VLDL (Very Low Density Lipoproteins) - transport endogenous triglyceride from the liver to the cells.
- Chylomicrons transport exogenous (dietary) triglycerides from gut.

A 5th Class, IDL (Intermediate Density Lipoprotein) is usually a transient intermediate in the metabolism of VLDL to LDL and contains both cholesterol and endogenous triglycerides. Plasma taken from a fasting subject contains HDL, LDL and VLDL.

Chylomicrons

Chylomicrons serve as the vehicle for the transport of dietary lipids in the plasma. They are produced within the enterocytes from the packaging of fat droplets (containing triglycerides, cholesterol ester, and phospholipids) with a number of apolipoproteins including apoB-48, apoA-I, apoA-II, and apoA-IV. The nascent chylomicrons are then released into the circulation via the lymphatic system. In the circulation, the nascent chylomicrons acquire apoE, apoC, and additional cholesterol from HDL-2 in exchange for apoA-I, apoA-II, and phospholipids. This transaction with HDL is essential for subsequent

lipolysis of chylomicrons by lipoprotein lipase (LPL) because apoE is necessary for chylomicron binding to the endothelial surface and apoC-II is required for activation of LPL. On reaching the capillary networks perfusing the muscle and adipose tissues, mature chylomicrons form a transient binding to the endothelial surface via their constituent apoE. The endothelium binding accommodates interaction of chylomicrons with the endothelium-bound LPL and its activation by apoC-II. This is followed by hydrolysis of the triglyceride content of chylomicrons and release of free fatty acids within the capillaries. The majority of fatty acids released diffuse into the adjacent myocytes for energy production or into adipocytes for energy storage. The remaining fatty acids are carried to distant sites by albumin and various lipoproteins. This results in formation and release of chylomicron remnants and return of the borrowed apoC and apoE to HDL before their eventual removal by the liver and other tissues via LDL receptor-related protein (LRP).



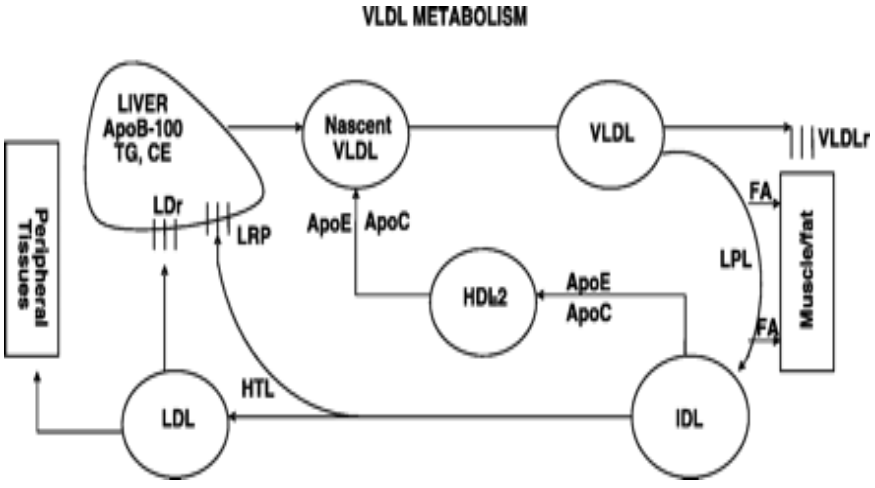
VLDL, IDL, and LDL

VLDL particles are produced by the liver and serve as the vehicle for delivery of endogenous lipids to the peripheral tissues. Nascent VLDL is formed within the hepatocyte from the fusion of partially lipidated, newly synthesized apoB-100 with a triglyceride-rich lipid droplet, followed by addition of apoE, apoA-I, and apoA-II. The triglycerides and cholesterol ester used by hepatocytes for incorporation into VLDL are generated by the enzymes acyl-CoA diglycerol acyltransferase (DGAT) and acyl-CoA cholesterol acyltransferase (ACAT), respectively. The fatty acids and cholesterol supplies used for these processes by the hepatocyte are derived from a combination of de novo synthesis and uptake from the circulating blood. After being released into the circulation, nascent VLDL acquires apoC and apoE from HDL-2 in exchange for apoA-I, apoA-II, and phospholipids.

As with chylomicrons, this transaction with HDL-2 is critical for subsequent metabolism of VLDL by LPL and the VLDL receptor. On reaching the capillary beds perfusing the muscle and adipose tissues, mature VLDL particles bind to the endothelial surface via their constituent apoE. This process facilitates interaction of VLDL with LPL and the VLDL receptor. LPL, which is attached to the endothelial surface through its heparin-binding domain, is enzymatically activated by the apoC-II content of the adjacent VLDL. This is followed by hydrolysis of VLDL triglycerides by the activated enzyme, leading to release of two fatty acids. Most of the fatty acids released in this manner diffuse into the adjacent myocytes or adipocytes for energy production or storage, respectively. The remaining fatty acids bind to albumin and lipoproteins and are transported to the liver and other tissues.

Lipolysis of VLDL by LPL results in a 70% reduction in their triglyceride content and detachment and release of a remnant particle, commonly known as IDL. In the circulation, IDL particles return the borrowed apoE and apoC to HDL and donate part of their remaining triglyceride cargo to HDL in return for cholesterol ester. The latter exchange is catalyzed by cholesteryl ester transfer protein (CETP). Most of the IDL particles undergo further lipolysis via hepatic triglyceride lipase. This leads to extraction of nearly all remaining triglycerides from IDL by the liver and formation of cholesterol-rich LDL, which are normally devoid of triglycerides. LDL particles are then removed via the LDL receptor by the liver, as well as extrahepatic tissues. The remaining IDL particles are removed by the liver (and other tissues) via LRP. The latter pathway is commonly referred to as the shunt pathway.

An alternative pathway for clearance of VLDL has been recently identified, in which LDL is removed in its entirely by myocytes and adipocytes via binding to the novel VLDL receptor.[1]



HDL

The primary function of HDL is retrieval and transport of surplus cholesterol from the extrahepatic tissues for disposal in the liver[2]. This process which is commonly known as reverse cholesterol transport, is critical for cellular cholesterol homeostasis and protection against atherosclerosis, renal disease, and other complications. In addition, HDL plays a major role in metabolism of triglyceride-rich lipoproteins by serving as a donor and acceptor of apoC and apoE for the nascent and remnant chylomicrons and VLDL, a process which is vital in triglyceride metabolism. Moreover, HDL serves as a potent endogenous inhibitor of inflammation, platelet adhesion, and LDL oxidation[3].

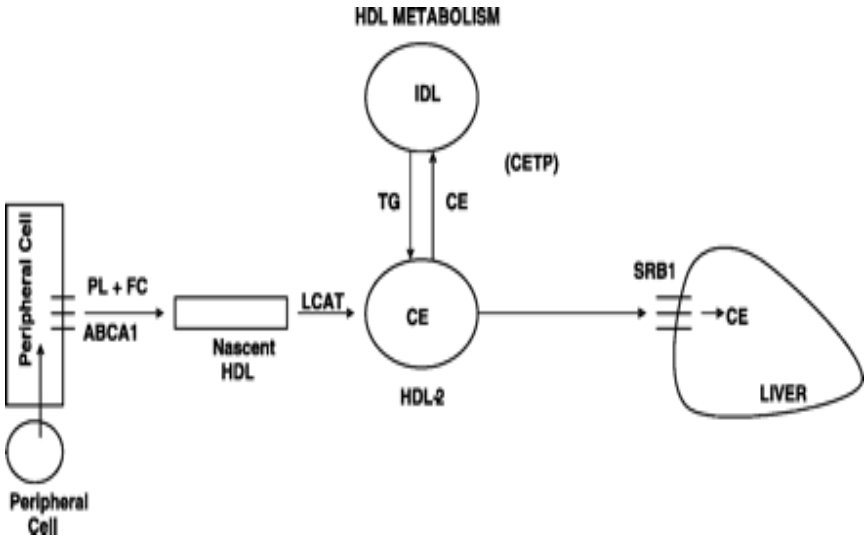
The principal apolipoprotein constituents of HDL are apoA-I and apoA-II, which are produced by the liver and intestine and secreted with VLDL and chylomicrons, respectively. On reaching the extracellular space, apoA-I and apoA-II dissociate from VLDL and chylomicrons (as phospholipid complexes) and coalesce to form nascent HDL. apoA-I constitutes 70% of HDL protein content. In addition to serving as the main structural constituent of HDL, apoA-I serves as the activator of LCAT, which is essential for the HDL-mediated cholesterol retrieval from extrahepatic tissues. The second most abundant apolipoprotein constituent of HDL is apoA-II, which represents 20% of HDL protein content. In addition to its role as a major structural constituent of HDL, apoA-II serves as an activator of hepatic lipase, which plays a central role in the removal of HDL-borne triglycerides by the liver. Once formed, nascent HDL acquires apoE-phospholipid and apoC-phospholipid complexes from either the available pool in the plasma or from chylomicron and VLDL remnants. The

assembly of these components leads to formation of a small cholesterol-poor discoid particle known as HDL-3.

HDL-mediated removal of surplus cholesterol from extrahepatic tissues requires attachment of nascent HDL to the ATP binding cassette transporter type I (ABCA1) [4,5,6] binding to ABCA1 appears to trigger active transfer of phospholipids to nascent HDL, a step which is necessary for efficient translocation of free cholesterol from adjacent caveolae to the surface of HDL[4]. Free cholesterol reaching the surface of HDL is promptly esterified by LCAT. Due to its intense hydrophobicity, cholesterol ester formed on the surface of HDL immediately moves to the core of HDL, thus sustaining the favorable gradient for maximal cholesterol uptake by the maturing HDL.

These observations illustrate the critical role of LCAT in the maturation of cholesterol-poor HDL-3 to spherical, cholesterol ester-rich HDL-2 and, hence, HDL-mediated reverse cholesterol transport. Once fully loaded, HDL-2 dissociates from the binding site and returns to the bloodstream. While in transit, HDL-2 participates in a series of elaborate exchanges of apoproteins and lipids with the apoB-containing lipoproteins before reaching the liver. In the liver, HDL-2 forms a reversible binding with the HDL receptor (SRB-1), which facilitates simultaneous unloading of its cholesterol ester content, as well as hydrolysis and extraction of its fatty acid cargo by hepatic lipase. These events lead to transformation of HDL-2 to HDL-3, its detachment from SRB-1, and its return to the blood stream for recycling[7]. These observations highlight the critical role of SRB-1 in HDL-mediated reverse cholesterol transport and hepatic lipase-dependent disposal of HDL-borne triglycerides in the liver.

Another significant pathway of cellular cholesterol efflux is the facilitated and passive diffusion of free cholesterol followed by its binding to albumin and subsequent transfer to HDL in the circulation. This phenomenon highlights the important role of albumin in reverse cholesterol transport[4].



APOPROTEINS

The route of metabolism of lipoprotein is determined by the apoproteins they carry. These proteins not only make the lipids water soluble, but are necessary for lipoproteins secretion by hepatic and intestinal cells and for recognition by the cell surface receptors. They also activate the enzymes involved in lipoprotein metabolism.

The functions of the main group of apoproteins are summarized in the table below:

The main Apoproteins

Apoproteins	Occurrence	Known function
A	Chlomicrons/HDL	Cofactor for LCAT(A-I)
B	Chylomicrons,VLDL,IDL,LDL	Secretion of chylomicrons,VLDL/ binding of LDL to receptors
C	HDL,VLDL,IDL,Chylomicrons (from HDL)	Cofactor for lipoprotein lipase(C-II)
D	HDL	Cholesterol ester transfer
E	HDL,VLDL,IDLchylomicrons (HDL)	Binding of IDL and remnant particles to receptors

SUMMARY OF LIPOPROTEIN METABOLISM

Lipids are derived from food (exogenous) or are synthesised in the body (endogenous).

The fate of exogenous (dietary) lipids

Fatty acids and cholesterol released by digestion of dietary fat are absorbed into the intestinal mucosal cells where they are reesterified to form triglycerides and cholesterol esters.

These, together with phospholipids and apoproteins B(essential for secretion from the cell), and A, are secreted as chylomicrons into lymphatics and pass through the thoracic duct into the systemic circulaton.

In the lymphatics and the blood, apoproteins C&E originating from HDL, are added to the chylomicrons. Most of the chylomicrons are metabolized by adipose and muscle tissue.

The enzyme lipoprotein lipase, located in capillary wall, is activated by apoproteins C-II and triglycerides in the chylomicrons are hydrolyzed to glycerol and fatty acids. The fatty acids are taken up by the fat on muscle cells or are bound to albumin in the plasma, and the glycerol enters the hepatic glycolytic pathway. As the chylomicron shrinks surface apoprotein A, and some apoprotein C, and phospholipids, are reincorporated into HDL . The short lived particles are compounds mainly of cholesterol and apoproteins B,C &E. They bind to specific receptors in the liver and are taken by hepatocytes where the protein is catabolised and the cholesterol released into the cells. At the end of this process dietary triglycerides have been delivered to adipose tissue and muscle and cholesterol to the liver.

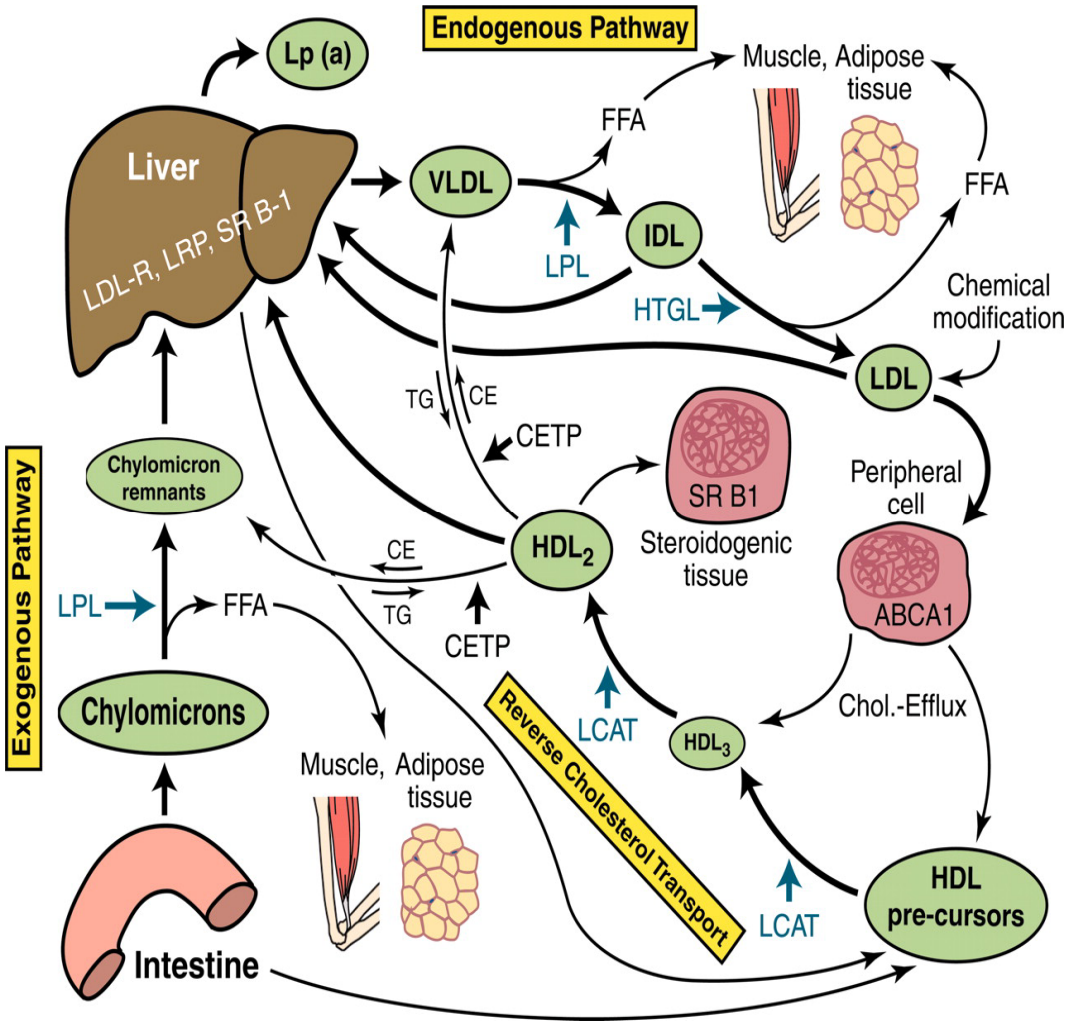
The fate of endogenous lipids

Triglycerides are synthesized in the liver from FFA derived from adipose tissue , if carbohydrate intake is high , FFA may be synthesized from excess glucose. These triglycerides, together with cholesterol synthesized in the liver or derived from chylomicron remnants, combine with apoproteins B&C to form VLDL, After Secretion into the blood, the VLDL takes up more apoproteins C, from HDL. This activates lipoprotein lipase on the capillary walls and the triglycerides like the exogenous triglycerides in chylomicrons are hydrolysed and removed from the plasma, leaving IDL. Some IDL is taken up

by the receptors in the liver, but the rest is converted to LDL, which consists almost entirely of cholesterol and apoprotein B. The mechanism and site of this conversions are not known.

The further metabolism of LDL is only partly understood but is of great importance in the development of atheroma. LDL is probably removed from the plasma by two pathways. In the first, after binding to specific receptors found on most cell membranes LDL is taken up by the cells and releases cholesterol which can be incorporated in the membranes. This cholesterol by feed back inhibition of early steps in cellular cholesterol synthesis and by reduction of the synthesis of LDL receptors on the surface, regulates the cell content of cholesterol. Probably most of the cholesterol needed by peripheral cells is derived from the liver. Some LDL, specially if plasma levels are high may also enter some cells by an unregulated, passive route. Some LDL may be taken up by hepatocytes.

Thus at the end of this process endogenous triglycerides have been delivered to peripheral cells for local energy requirements and endogenous cholesterol for membrane synthesis.



Lipoprotein Metabolism

PLASMA LIPIDS AND LIPOPROTEIN PROFILE IN CRF

Hypertriglyceridemia is the most common abnormality in adults and children with renal failure although the reported prevalence varies considerably in different populations.[10,11,12,13,17,19]

Triglycerides are usually elevated to moderate degree[20]. The plasma cholesterol level is normal except condition where there is pronounced hypertriglyceridemia. Since enrichment of triglycerides is seen in VLDL, IDL, LDL, HDL[12,14], progression of renal insufficiency leads to marked increase in total triglycerides with increase in VLDL,LDL,HDL lipoprotein triglycerides.[16]

Redistribution of cholesterol from HDL to VLDL and IDL occurs even when the plasma cholesterol level are within normal limits[11,12]. Total cholesterol is slightly elevated due to increase in VLDL Cholesterol. The decreased level of HDL cholesterol indicates reduction in the HDL2 and HDL3 sub-fractions (8). It has been reported in the recent past that patients with chronic renal failure have increased concentration of lipoproteins.[15, 22]

In cases of less advanced renal failure (but significant) the plasma triglyceride and cholesterol are normal, but minor changes in the lipid profile might be seen including an increase in LDL triglyceride level and decrease in HDL.

APOLIPOPROTEIN PROFILE IN CRF

The abnormalities of lipid metabolism has also been observed in the protein moieties of lipoprotein, the apolipoproteins. In advanced renal failure, the plasma protein profile shows decreased concentration of apolipopotein A-I

and A-II, normal or slightly increased levels of apo-B and normal or decreased levels of apo E.[12,22] The most important feature of plasma apolipoprotein profile is significant increase in concentration of apo C-III, together with less marked increase of apo C-I and apo C-II.[11,12,17] Though the apo C-III levels usually correlate with triglyceride levels, increased concentration of apo C-III is also seen in normotriglyceridemic patients. The above mentioned alterations in renal failure results in decreased ratio of apo A-I/apo C-III, apoA-I/apo-B and an increased ratio of apoD-III/apoE. [11,22,17]

The apoC-III ratio is a useful means of evaluating the efficiency of processes responsible for the degradation of triglyceride rich lipoprotein [12]. The low ApoC-III ratio found in CRF is more pronounced in hypertriglyceridemia than in normolipidemic patients. [11]

Studies in the distribution of apolipoprotein in major lipoprotein density classes has shown a shift in the distribution of apolipoprotein B,C and E from HDL to VLDL and LDL with three fold increase of the apolipoprotein in VLDL and two fold increase in LDL.[14] In addition to apo C and apo E the levels of apo A-I and apo A-II are also found to be reduced in HDL.[12]

Studies in the recent past have emphasized the importance of apolipoprotein as marker of dyslipoproteinemia showing that one can observe significant changes in the apolipoprotein profile of plasma and major lipoprotein density classes in early stages of renal insufficiency[12].

There is a marked reduction in the levels of apo A-I and apo A-II and elevation in the levels of apo C-III in patients with glomerular filtration rate of 15-60 ml/min.

Redistribution of apoB, apoC-III and apoE, which is characteristic feature of advanced renal failure could also be detected in early renal insufficiency [11] Guitz macher et al[12] found that increased levels of apo C-III are found in patients with near normal renal function and that levels of apolipoprotein increase as renal function deteriorates.

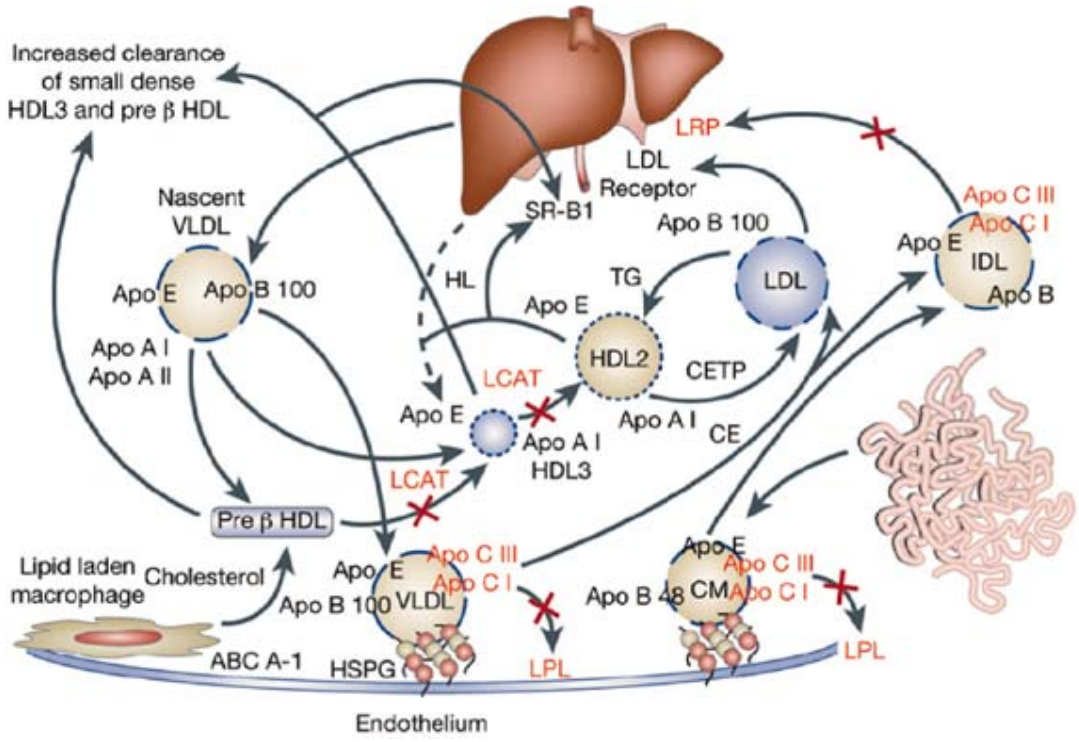
Summary of lipoprotein profile abnormality

1. Increase in Total Triglycerides.
2. Increase in VLDL and LDL, HDL triglycerides
3. Slight increase of total cholesterol.
4. Decrease in HDL Cholesterol

Summary of apolipoprotein profile abnormality

1. Decreased Apo A-I, Apo A-II
2. Increased Apo C-III
3. Decreased Apo –E
4. Normal or increased levels of Apo B

Pathogenesis of Uremic Dyslipidemia



Enzymes and pathways that are adversely affected in CKD are indicated in red

PATHOGENESIS OF URAEMIC DYSLIPIDEMIA

Abnormalities in triglyceride metabolism

I. DECREASED CATABOLISM

A. Decreased activity of lipolytic enzymes

1. Lipoprotein lipase due to

    - Insulin deficiency
    - Inhibitors in uraemic plasma
    - Reduced apo C-II/apo C-III ratio

2. Hepatic Triglyceride lipase.

3. Lecithin cholesterol acyl transferase (LCAT)

B. Alteration of lipoprotein substrate

C. Decreased carnitine level.

D. Decreased beta oxidation of free fatty acids.

E. Triglyceride enriched LDL

F. Altered apolipoprotein composition

G. Increased apo C-III/apo E in IDL,LDL.

H. Modification of lipoproteins.

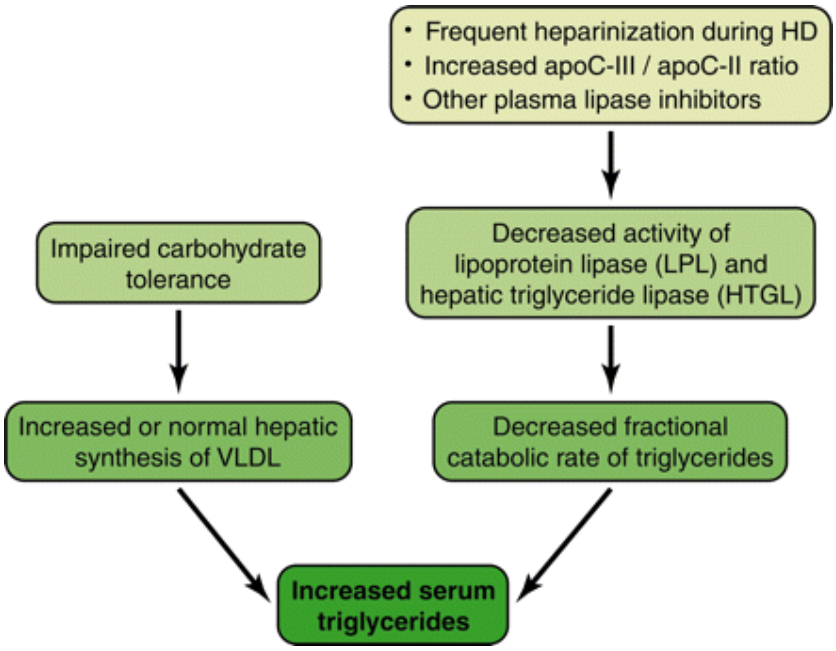
I. Decreased receptor and non-receptor mediated uptake of lipoprotein.

II. INCREASED TRIGLYCERIDE PRODUCTION

a. Increased dietary carbohydrates

b. Uptake from glucose due to immune resistance insulin

c. Hyperinsulinemia



Abnormalities in HDL Metabolism

CRF is consistently associated with reduced plasma HDL cholesterol concentration, impaired maturation of cholesterol ester-poor HDL-3 to cholesterol ester-rich HDL-2, increased HDL triglycerides, and depressed plasma apoA-I. These abnormalities are primarily due to CRF-induced dysregulation of several important proteins, which are briefly described below.

LCAT: LCAT plays an important role in HDL-mediated cholesterol uptake from the extrahepatic tissues and, as such, serves as a main determinant of HDL maturation and plasma HDL cholesterol level. Thus LCAT deficiency can potentially account for diminished plasma HDL cholesterol and impaired HDL maturation in CRF. Plasma LCAT activity is consistently diminished in patients with ESRD.[9,18,21]

This is accompanied by a significant elevation of plasma-free cholesterol and a marked reduction in plasma esterified cholesterol concentration, providing functional evidence for diminished LCAT-dependent cholesterol esterification . The reduction in plasma LCAT activity is associated with a parallel reduction in plasma concentration of immunodetectable LCAT and downregulation of hepatic LCAT gene expression. [24,40,46]

CETP: CETP mediates transfer of cholesterol ester from HDL to IDL in exchange for triglycerides. Thus a potential increase in plasma CETP can contribute to the CRF-associated reduction in HDL cholesterol ester and elevation of HDL triglycerides. In fact, according to a recent study, more than 34% of hemodialysis-dependent patients were found to have high plasma CETP levels.[41] The mechanism responsible for the reported elevation of CETP in ESRD patients is unknown and requires future investigation. The effect of CRF is amplified by proteinuria, which has been shown to increase synthesis and markedly raise plasma concentration of CETP.[60] Thus plasma CETP is expectedly elevated in patients with heavy proteinuria and mild to severe renal insufficiency.

Hepatic lipase: Hepatic lipase catalyzes hydrolysis and removal of the triglyceride content of HDL. Thus hepatic lipase deficiency can potentially contribute to increased HDL triglyceride content. CRF results in pronounced hepatic lipase deficiency in humans and experimental animals. [26]

apoA-I and apoA-II: apoA-1 and apoA-II constitute the main structural constituents of HDL. In addition, apoA-I serves as the LCAT activator as well as ligand for the SRB-1 and HDL binding protein (ABCA1 transporter), whereas apoA-II serves as the hepatic lipase activator. Plasma concentrations of apoA-I and apoA-II are significantly reduced in patients with ESRD.[61] Studies in animals with experimental CRF have demonstrated that the CRF-induced reduction in plasma apoA-I is due to downregulation of hepatic apoA-I gene expression.[44] The reduction in plasma concentration of these important constituents can, therefore, contribute to both diminished plasma HDL concentration and impaired HDL function in CRF.

SRB-1*:* Hepatic SRB-1 is the primary pathway for disposal of HDL-borne cholesterol ester and triglycerides.[7] Therefore, potential dysregulation of this protein can impact HDL metabolism. Heavy glomerular proteinuria has been shown to significantly reduce hepatic SRB-1 protein expression in experimental animals.[25] In contrast, CRF per se, without heavy proteinuria, induced by nephrectomy, does not significantly change SRB-1 mRNA or protein abundance in the liver.[44] However, concomitant heavy proteinuria and renal insufficiency may affect SRB-1 expression and hence, HDL-mediated reverse cholesterol transport.

ACAT:HDL-mediated cholesterol uptake from the extrahepatic tissues depends on deesterification of cholesterol esters contained in the intracellular vesicles and the resultant release of free cholesterol. This process is opposed by ACAT, which is the main enzyme for intracellular esterification of cholesterol. Therefore, a relative increase in ACAT activity can potentially limit HDL-mediated cholesterol uptake and hence, contribute to the reduction in plasma HDL cholesterol and impaired maturation of HDL. Although the effect of CRF on ACAT expression and activity in the extrahepatic tissues is not known, CRF has been recently shown to markedly raise hepatic ACAT-2 mRNA and protein abundance, as well as total ACAT activity.[30] The potential contribution of ACAT to the CRF-induced dysregulation of HDL metabolism was illustrated by a recent study which revealed that pharmacological inhibition of ACAT results in a dramatic shift in plasma cholesterol from apoB-containing lipoproteins to HDL with virtually no change in plasma total cholesterol in CRF animals. [34]

Abnormalities in Cholesterol Synthesis and Catabolism

Plasma total cholesterol is usually normal or reduced and only occasionally elevated in patients with ESRD. However, plasma cholesterol is consistently, albeit mildly, elevated in the CRF rats. Plasma cholesterol concentration is primarily a function of its biosynthesis, catabolism (cholesterol conversion to bile acids), and tissue uptake. The effects of CRF on regulation of these pathways have been investigated in a very limited number of studies. The findings of these studies are summarized here.

Hydroxy-3-methylglutaryl-CoA reductase and cholesterol 7α-hydroxylase :

HMG-CoA reductase is the rate-limiting enzyme for cholesterol biosynthesis. In a study Pandak and associates[36] found elevated hepatic HMG-CoA reductase activity and 7α-hydroxylase activity, the rate-limiting enzyme for cholesterol catabolism and conversion to bile acids.[36] CRF results in posttranscriptional upregulation of these hepatic enzymes.

The LDL receptor*:* LDL receptor-mediated cholesterol uptake plays an important role in cholesterol homeostasis. Chronic renal insufficiency in the absence of heavy proteinuria does not alter hepatic LDL receptor gene expression or protein abundance.However, heavy proteinuria alone or in combination with chronic renal insufficiency results in acquired LDL receptor deficiency, which plays a central role in the genesis of the associated hypercholesterolemia. [32,46]

Low-Density Lipoprotein in CRF

Elevated plasma LDL cholesterol concentration is common in nephrotic syndrome but is not a typical feature of patients with advanced CRF. There are, however, qualitative changes in LDL in patients with CKD and dialysis patients. The proportions of sdLDL and IDL, which are considered to be highly atherogenic, are increased. IDL and sdLDL have high affinity for macrophages, which promote their entry into the vascular wall to participate in the formation of foam cells and atherosclerotic plaques .

DYSLIPIDEMIA IN CRF PATIENTS ON HEMODIALYSIS

The distinctive features of the lipid profile in dialysis patients appear to be the presence of low concentrations of HDL cholesterol and increased triglycerides, but without, or slight elevations of LDL cholesterol. A low HDL cholesterol concentration imparts additional risk of coronary heart disease. Hypertriglyceridemia is due to decreased lipase which is due to depletion of enzyme pool induced by frequent heparinisation. Plasma residence time of LDL and IDL is more than twice as long in HD patients as in nonuremic individuals . This reduced catabolism, however, is masked by the decreased production of LDL, resulting in near-normal plasma levels of LDL. These changes are due to diets with high carbohydrate and lipid content, decrease in lipoprotein lipase, metabolic acidosis, use of high rather than low molecular weight heparin, medications, high glucose content of dialysate and L-Carnitine deficiency.

HYPERLIPIDAEMIA AFTER RENAL TRANSPLANTATION

Hyperlipidaemia is a well-recognized complication of renal transplantation. Risk factors in the transplant population for hyperlipidaemia include age, male sex, diabetes, hypertension,prednisone dose, graft impairment, obesity and anti-hypertensive therapy. Reported changes of serum lipids include an increase in triglycerides[23], total cholesterol, as well as an increase in VLDL and LDLCholesterol contents . Kasiske and Umen[27] found that the serum cholesterol concentration was raised in 27% of patients at 1 to 2 years after transplantation, which occurred within 3-6 months after

transplantation in 82% of patients. They further found that hypertriglyceridemia occurred later in the post transplantation course than hypercholesterolemia and was present in only 15% of the patients.

Serum high density lipoprotein- cholesterol content has been reported to be low by some authors.[23,27] However, when analysing HDL subfractions, HDL2 Cholesterol was actually lower in female , but not in male transplant recipients.[33]

Serum total apolipoprotein A levels –have been reported to be decreased[28] or normal[23] and serum total apo B level increased.[31] Plasma lecithin cholesterol acyl transferase (LCAT) activities have been measured by Chan et al in allograft recipients before and after transplantation.[13] He found that when LCAT activities were decreased in uremic state, they were fully corrected after successful transplantation. Elevated concentration of this enzyme after transplant probably increases the turnover of triglyceride rich lipoprotein. As to VLDL triglycerides removal kinetics, most renal transplant patients have an impaired capacity to remove these lipoprotein particles and therefore develop an increase in serum triglycerides.[42] At the same time, serum total cholesterol and HDL cholesterol levels are also increased. The defect for the cause of hypertriglycerdemia has been reported to be less severe in kidney transplant recipients than that of chronically uremic patients. Surprisingly, circulating lipase activities have not been found diminished in patients after renal transplantation.

Post-transplant hypercholesterolaemia is probably multifactorial in origin. Corticosteroids have almost certainly been implicated above all.[8,48] But

since immunosuppressive therapy generally relies on several medication, it is difficult to incriminate corticosteroids alone . It must be however pointed out that hypercholeterolemia was observed in most renal transplant recipients in earlier series when high does prednisone regimes were used (37,38). Gokal et al[38] and Tiergan et al[39] found that when the maintenance does of oral prednisone was progressively reduced to 10mg daily or less, serum total cholesterol levels returned to normal values in the majority of patients. Steroid thereapy by providing insulin resistance has been attributed to contribute to these abnormalities [38,39,49]. These abnormalities are also caused by increased hepatic secretions of VLDL triglyceride and decreased removal of triglyceride in peripheral tissue. Human studies have demonstrated diminished clearance rates for infused synthetic triglycerides after transplantation[13] Whilst studies of endogenous VLDL triglyceride turnover have indicated, over production[8] or a range of defective removal and over production[42] as a cause for the hypertriglyceridemia.

Chan et al[13] have found that the cumulative steroid dose is high in hyperlipidemic than in normlipaemic renal allograft recipients. They also demonstrated a significant positive correlation between serum triglycerides concentration and plasma immunoreactive insulin levels.

In this regard, it is interesting to note that in acute experiments in rats, the rate limiting enzyme of lipogenesis, acetyl co-A caboxylase and free fatty acid synthetase, increase after steroid administration.[8] The rise in immune reactive insulin concentrations precedes the rise the concentration of these rate limiting enzymes and in alloxan diabetic rats no rise in acetyl Co.A carboxylase activity can be demonstrated.

Chan at al have also shown in 19 renal allograft recipients that K2 (fractional clearance rate of intralipid) correlated inversely with plasma immunoreactive insulin levels and that at a given K2 renal allograft recipient have higher serum triglyceride concentration than do normal subjects, probably reflecting increased triglyceride production. Although triglyceride production has not been measured directly, the finding of high free fatty acid concentration and positive correlation between serum triglycerides and insulin would indicate that increase hepatic production of triglycerides is the predominant factor.

The immunosuppressive agent cyclosporine may also adversely influence plasma lipids, since both serum TG and cholesterol levels decrease after conversation to azathioprine therapy, eventhough HDL concentration does not change[49] and hypertriglycerdemia was more severe under cyclosporine-prednisone treatment than under azathioprine-prednisone therapy.[43] However, reduction or cessation of cyclosporine is often accompanied by a fall in serum creatinine which itself has been found to positively correlate with serum Cholesterol or TG level.[29] The later observation does not exclude an effect of cyclosporine by its own as strongly suggested by the prospective study done by Raine et al[43]. The mechanism of this effect of cyclosporine is presently unknown. It may relate to its high liophilicity[49] since upto 80% of the drug is transportated in plasma by binding to lipoproteins, especially LDL and HDL.

Anti-hypertensive agents may also play a role in the increase of serum cholesterol levels. Thus the beta blocker propanolol leads to a rise of HDL cholesterol and also of VLDL-TG[37] such effects are shared less by cardioselective beta-blockers. The body weight gain which is often observed

after successful renal transplantation could at least theoretically be implicated in the hypertriglyceridemia of graft-recipients, even if no direct correlation exists between weight gain and plasma lipids in the general population[28] Increased food intake leads to increased hepatic triglyceride production. This mechanism appears to predominate over decreased peripheral triglyceride metabolism in such patients[39] Interestingly, increased serum triglyceride levels correlated with an extensive relative body weight in renal transplant patients and also with serum creatinine, but not with steroid or cyclosporine dose.

Summary of Lipid Profile Changes after Transplantation

1. Increase in total cholesterol with increase in VLDL, and LDL cholesterol.
2. Increase in Triglycerides.
3. Decrease in HDL cholesterol

DYSLIPIDEMIA IN INDIANS

Asian Indians have the highest rates of mortality and morbidity from CAD amongst all Ethnic groups. In Indian population CAD is often premature and runs a malignant course. CAD in Indians is present with relatively lower levels of lipids and lipoproteins. Raised levels of triglyceride-low HDL, apo B and Lp(a) occur commonly. Low levels of apo A-I have also been found.

Lipid levels in Indians : (Kaul et al)35

Category	LDL-C (mg/dl)	Cholesterol (mg/dl)	Triglycerides(mg/dl)
Desirable	<100	<150	<150
Borderline	100-130	150-200	150-170
High	>130	>200	>170

MANAGEMENT OF DYSLIPIDEMIA IN CRF

The appropriate management of dyslipidemia plays an important role in the overall care of the patient with chronic and ESRD, and renal transplantation. It is important to recognize that dyslipidemia in the patient with chronic and ESRD, and renal transplantation require a different screening and management approach than other populations,[47] as dyslipidemia may be secondary to different conditions, such as proteinuria, diabetic hyperglycemia, or drug-induced, all of which require a distinctive management approach.[47] Additionally, patients who have progressed to advanced renal disease may have altered metabolism and elimination of lipid lowering medications, which would increase their risk for adverse effects to these agents.

The United States (US) National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease - Pharmacotherapy Recommendations:

Patients with chronic renal disease should be considered to be in the high risk category
Evaluation of dyslipidemias should occur at presentation with chronic renal disease , following a change in kidney therapy modality and annually
Drug therapy should be used for LDL levels of 100-129 mg/dl after 3 month of therapeutic life style change
Initial drug therapy should be with a statin
Fibrates may be used in stage 5 CRF patients with triglyceride levels of >/=500mg/dl and for patients with triglyceride>/==200mg/dl and LDL>/==130mg/dl who do not tolerate statins.

Starting at a low dose and then titrating the dose of the statin upward to the goal minimizes adverse effects. Elevated transaminases occur in some patients on statin therapy and baseline values should be obtained. The risk of rhabdomyolysis from statins is low in general but it is increased in patients with chronic renal disease and those taking immunosuppressive agents, macrolide antibiotics, and fibric acid derivatives.[50]

For patients with elevated triglycerides (>500 mg/dL), fibric acid derivatives and niacian may be used. Fibrates may increase the levels of stains; when used in combination an increased risk of rhabdomyolysis has been reported.[50] Blood levels of a number of fibrates are increased in renal patients (e.g., bezafibrate, and fenofibrate), but levels of gemfibrozil are not increased. Elevations of BUN and creatinine have been reported with many fibrates. Since

this occurs only rarely with gemfibrozil, it has been recommended by some as the fibrate of choice in renal disease. Niacin reduces lipids only to a moderate degree and may be associated with flushing and other untoward side effects. Bile acid sequestrants are effective in cholesterol lowering, but may interfere with the absorption of other medications. The potential benefit of combination therapy must be closely weighed against the increased risk of adverse effects.

The pharmacotherapy management of posttransplant dyslipidemia is similar; however, another alternative which must be considered is the modification of the immunosuppressive regimen[51] Examples of such modifications include switching from cyclosporine to tacrolimus, lowering doses of sirolimus, and corticosteroid withdrawal. Although studies that have examined these approaches have found no increased risk of graft rejection or dysfunction, it is important to keep in mind that many of these studies were not powered to detect such risk, and any modification in immunosuppressive therapy must be undertaken carefully and monitored closely.[51]

Another important consideration in the pharmacotherapy management of posttransplant dyslipidemia is the potential drug interactions of lipid-lowering agents with immunosuppressants. Overall, statins have little effect on cyclosporine concentrations; however, cyclosporine has been shown to inhibit the metabolism of statins and a resultant increase in the risk of myopathy or rhabdomyolysis. [50,51] It has been suggested that fluvastatin, simvastatin and atorvastatin are the safest statins to be used with cyclosporine. Whereas fibrates may be especially valuable in patients treated with sirolimus, but should be carefully used in renal transplant patients taking cyclosporine or tacrolimus.

The Role of Statins

Statin therapy has been found to rapidly improve vasomotor response, enhance coronary blood flow, and reduce the levels of adhesion molecules. This is due in part to the ability of the statins to increase endothelial nitric oxide production.[52] The antioxidant effects of statins may also contribute to their ability to improve endothelial function. In addition, statins have been shown to exert positive effects on the fibrinolytic profile in the vascular endothelium[54] and anti-inflammatory effects by several pathways, including the reduction of inflammatory markers such as C-reactive protein, modification of fibrosing factors such as TGF-beta, and a favorable effect on coagulation and plaque stability.[52,53,55] Thus, theoretically, statins' anti-inflammatory and immunomodulatory effects and also their effects on endothelial function may be beneficial in renal hemodynamics. In addition, many large clinical trials have confirmed the beneficial effect of lipid-lowering agents on preservation of kidney function.[57] The protective effect on loss of renal function amounted to 1.9 ml/min/year, an effect whose magnitude was related to the length of treatment. Therapy with newer lipid lowering agents, such as the statins, is relatively safe in patients with chronic renal disease.

In the management of dyslipidemia after renal transplantation statins may have an additional benefit in the prevention of acute and chronic rejection. In the placebo-controlled ALERT (Assessment of Lescol in Renal Transplantation) study, 41 a total of 1050 patients were followed up for a mean of 5.1 years to evaluate the effect of fluvastatin on cardiovascular events. Fluvastatin proved to reduce the combined endpoint of cardiac death and nonfatal myocardial infarction by 35% ($p = 0.005$). However, fluvastatin did not show a significant effect on noncardiovascular death or graft loss.

MATERIALS AND METHOD OF STUDY

The study of lipid profile in patients of chronic renal failure was undertaken in The Department of Nephrology, Government Stanley Hospital, Chennai.

SUBJECTS FOR THE STUDY

- The study group constituted patients of

  a) Chronic renal failure on conservative management

  b) Chronic renal failure on regular hemodialysis.

  c) Post Renal Transplantation with normal renal function.

- The control group constituted twenty healthy adults – 10 males and 10 females of different age groups whose ages compared well with that of study group.

SELECTION OF CASES

STUDY GROUP

a. Patients with chronic renal failure on conservative management for a period of at least 6 months comprising of 10 males and 10 females within the age group of 15-50 years with none of them having diabetes were taken up.

b. Patients presenting with end stage renal failure on maintenance hemodialysis for period of 3 months comprising of 11 males and 9 females, all falling within the age group of 15 years to 50 years were taken up and none of them had Diabetes .

c. Post transplant patients with normal renal functions comprising of 10 males and 10 females within the age group of 15- 50 years and none of them had Diabetes.

CONTROL GROUP

This group consisted of 10 males and 10 females whose age group compared well with that of the study group. It was ascertained that none of them had hypertension, diabetes mellitus, renal or liver disease or any other metabolic disorder.

METHOD OF STUDY

Estimation of lipid profile

The various parameters analysed were :

- Serum total cholesterol (TC)
- Serum high density lipoprotein cholesterol (HDL)
- Serum low density lipoprotein cholesterol (LDL)
- Serum triglycerides (TG)
- Ratio of serum total cholesterol to high density lipoprotein cholesterol (TC/HDL).

Samples were collected after a 12 hour fast to avoid post prandial rise in serum triglyceride level.

Analysis of total cholesterol, triglycerides and HDL was done by use of an autoanalyser. Serum LDL cholesterol was calculated by Frederickson Friedwald's formula according to which LDL=total cholesterol – (HDL+VLDL). VLDL was calculated as $1/5^{th}$ of triglycerides. The results were statistically analysed.

OBSERVATIONS AND RESULTS

TABLE – 1

SERUM TOTAL CHOLESTEROL LEVEL IN DIFFERENT GROUPS AND THEIR COMPARISON (mg/dl)

Group	No.of cases	Mean	Standard deviation	'p' Value	Significance
Control	20	151.4	34.98	-	-
Conservative management	20	155.2	31.4	0.72	NS
Hemodialysis	20	159.3	38.8	0.503	NS
Post transplant	20	192.2	46.6	0.003	Significant increase

NS – Not significant

The table shows that the mean total cholesterol of the post transplant group is significantly high compared to other groups.

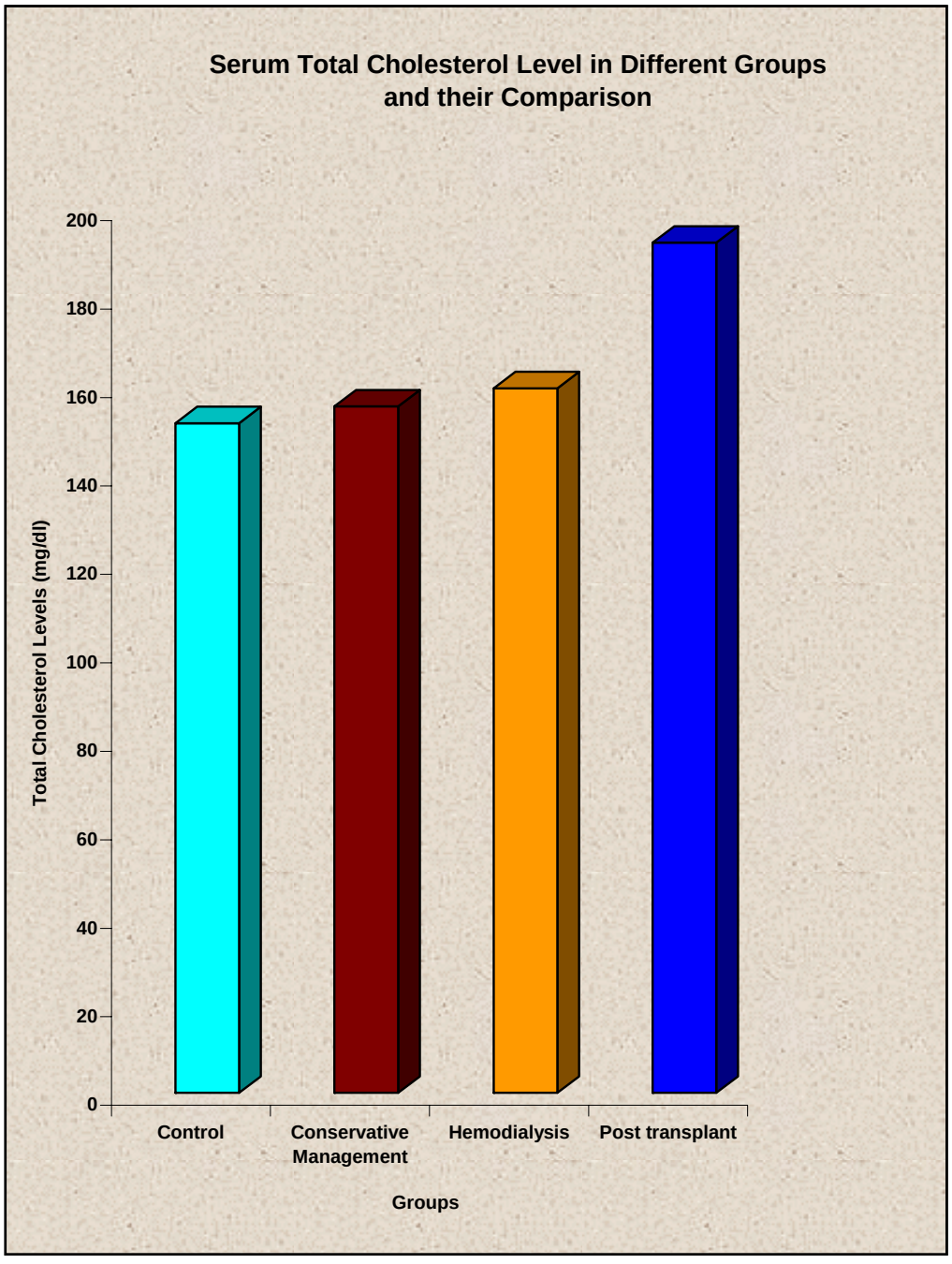

Serum Total Cholesterol Level in Different Groups and their Comparison
Total Cholesterol Levels (mg/dl)
200
180
160
140
120
100
80
60
40
20
0
Control
Conservative Management
Hemodialysis
Post transplant
Groups

TABLE -2

SERUM TRIGLYCERIDE LEVEL IN DIFFERENT GROUPS AND THEIR COMPARISON (mg/dl)

Group	No.of cases	Mean	Standard deviation	'p' value	Significance
Control	20	113.9	43.3	-	-
Conservative management	20	149.9	55.9	0.029	Significant increase
Hemodialysis	20	145.40	52.3	0.045	Significant increase
Post transplant	20	158.4	48.3	0.004	Significant increase

NS – Not significant

The table shows that the serum triglyceride level is significantly high in all the three study groups when compared to controls.

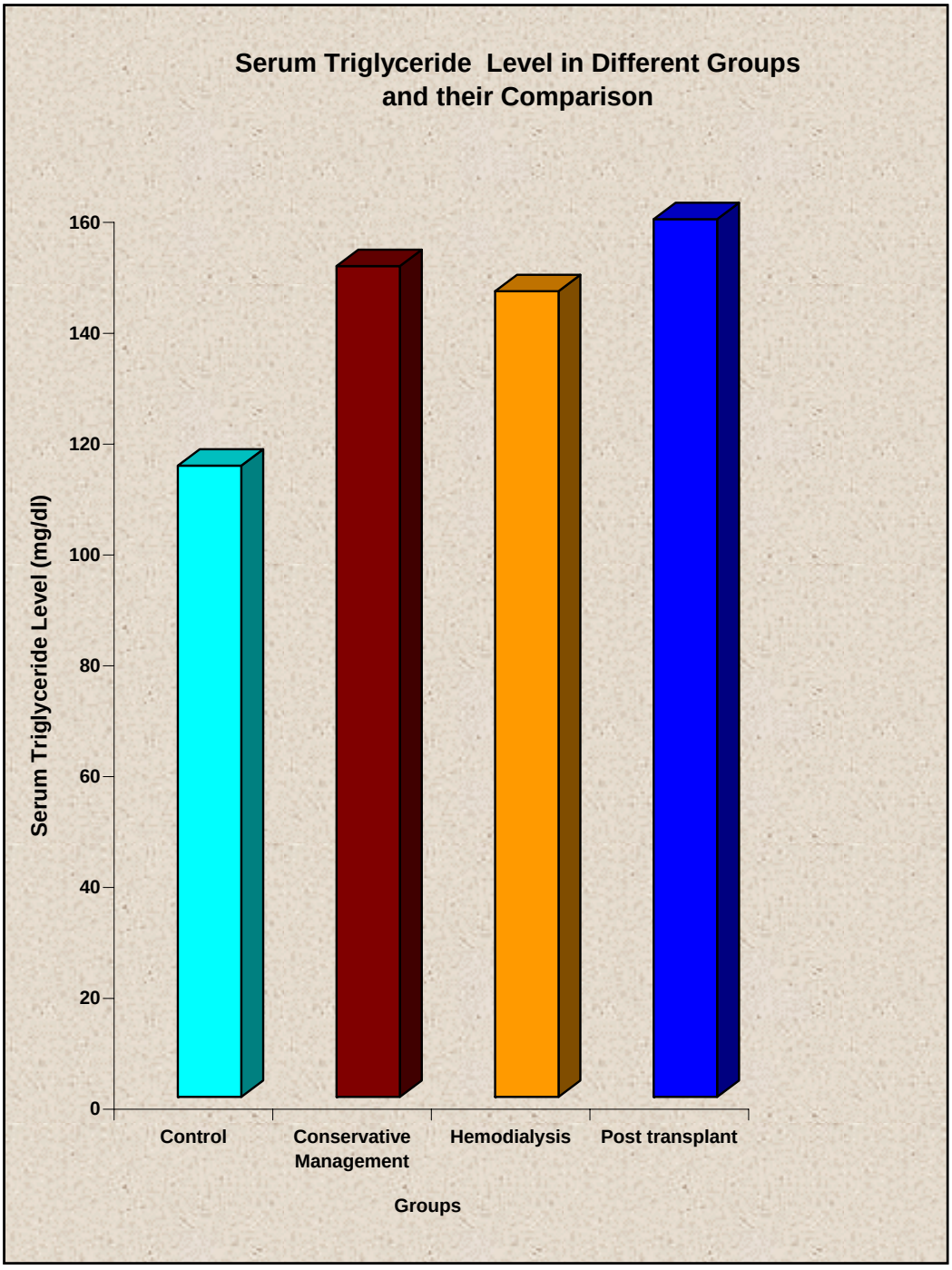

Serum Triglyceride Level in Different Groups and their Comparison
Serum Triglyceride Level (mg/dl)
160
140
120
100
80
60
40
20
0
Control
Conservative Management
Hemodialysis
Post transplant
Groups

TABLE – 3

SERUM HDL CHOLESTEROL LEVEL IN DIFFERENT GROUPS AND THEIR COMPARISON (mg/dl)

Group	No.of cases	Mean	Standard deviation	'p' value	Significance
Control	20	48.8	4.9	-	-
Conservative management	20	37.5	3.0	0.001	Significant decrease
Hemodialysis	20	40.1	6.2	<0.001	Significant decrease
Post transplant	20	39.2	4.4	<0.001	Significant decrease

The table shows that the mean HDL cholesterol is significantly decreased in all the three study groups.

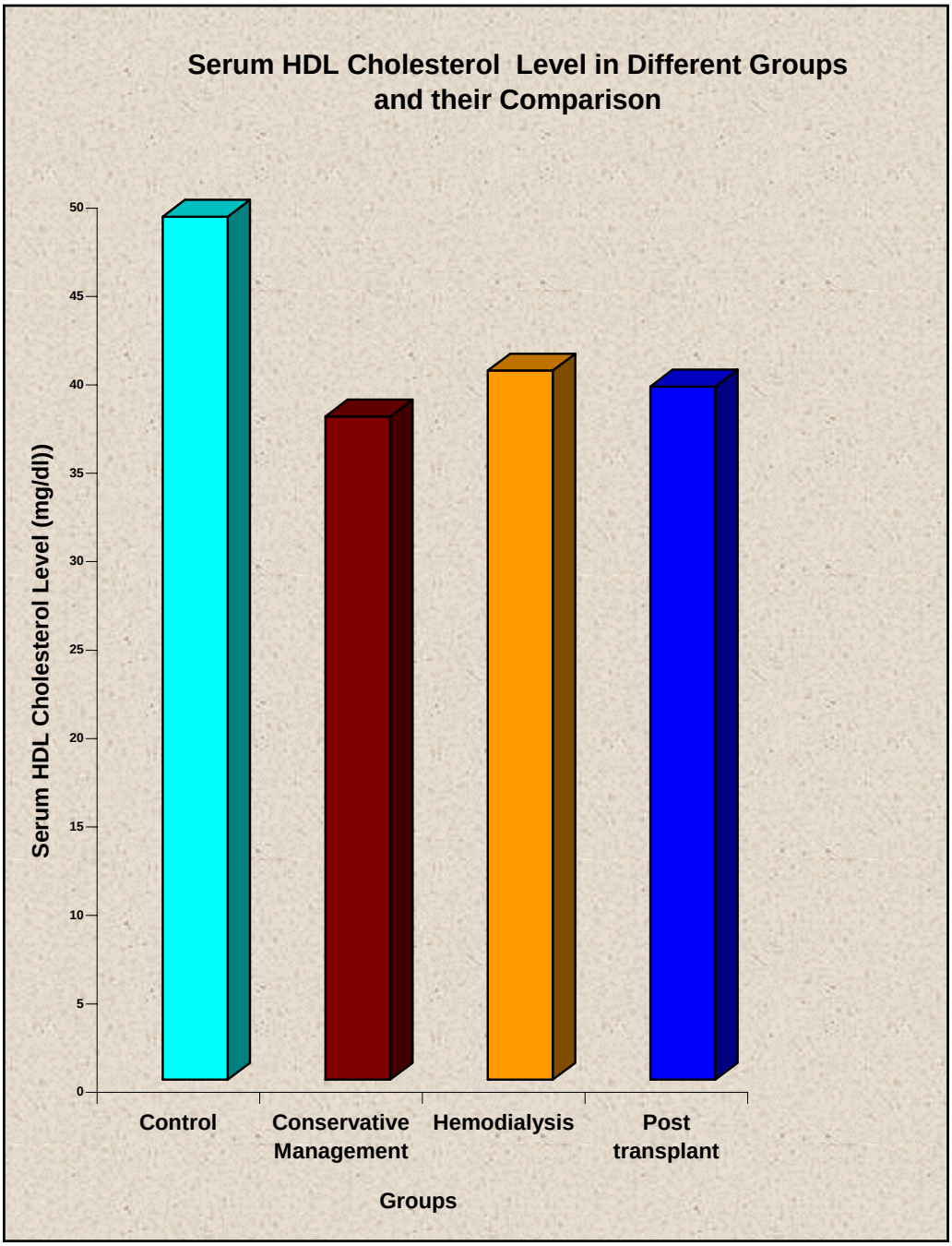

Serum HDL Cholesterol Level in Different Groups and their Comparison
Serum HDL Cholesterol Level (mg/dl))
50
45
40
35
30
25
20
15
10
5
0
Control
Conservative Management
Hemodialysis
Post transplant
Groups

TABLE – 4

SERUM LDL CHOLESTEROL LEVEL IN DIFFERENT GROUPS AND THEIR COMPARISON (mg/dl)

Group	No.of cases	Mean	Standard deviation	'p' value	Significance
Control	20	79.86	30.07	-	-
Conservative management	20	87.8	34.92	0.44	NS
Hemodialysis	20	90.1	40.78	0.371	NS
Post transplant	20	121.3	45.02	0.001	Significant increase

NS – Not significant

The table shows that the mean LDL cholesterol of the post transplant group is significantly high compared to other groups.

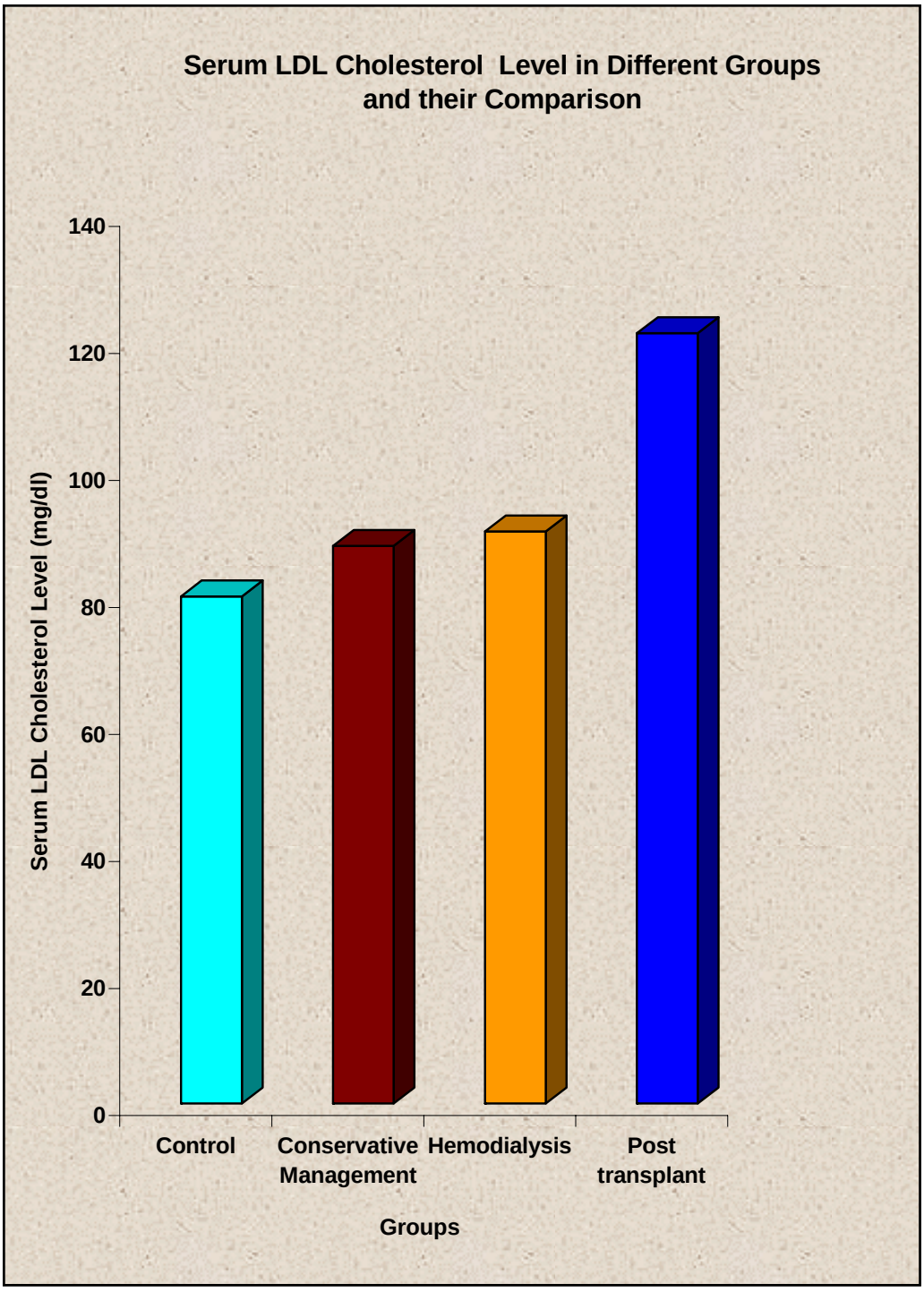

Serum LDL Cholesterol Level in Different Groups and their Comparison
Serum LDL Cholesterol Level (mg/dl)
140
120
100
80
60
40
20
0
Control
Conservative Management
Hemodialysis
Post transplant
Groups

TABLE – 5

RATIO OF SERUM TOTAL CHOLESTEROL TO HDL CHOLESTEROL IN DIFFERENT GROUPS AND THEIR COMPARISON

Group	No.of cases	Mean	Standard deviation	'p' value	Significance
Control	20	3.15	0.909	-	-
Conservative management	20	4.2	1.1	0.002	Significant increase
Hemodialysis	20	4.01	1.0	0.007	Significant increase
Post transplant	20	4.94	1.23	<0.001	Significant increase

NS – Not significant

The table shows that the ratio of total cholesterol to HDL Cholesterol is significantly high in all the three study groups.

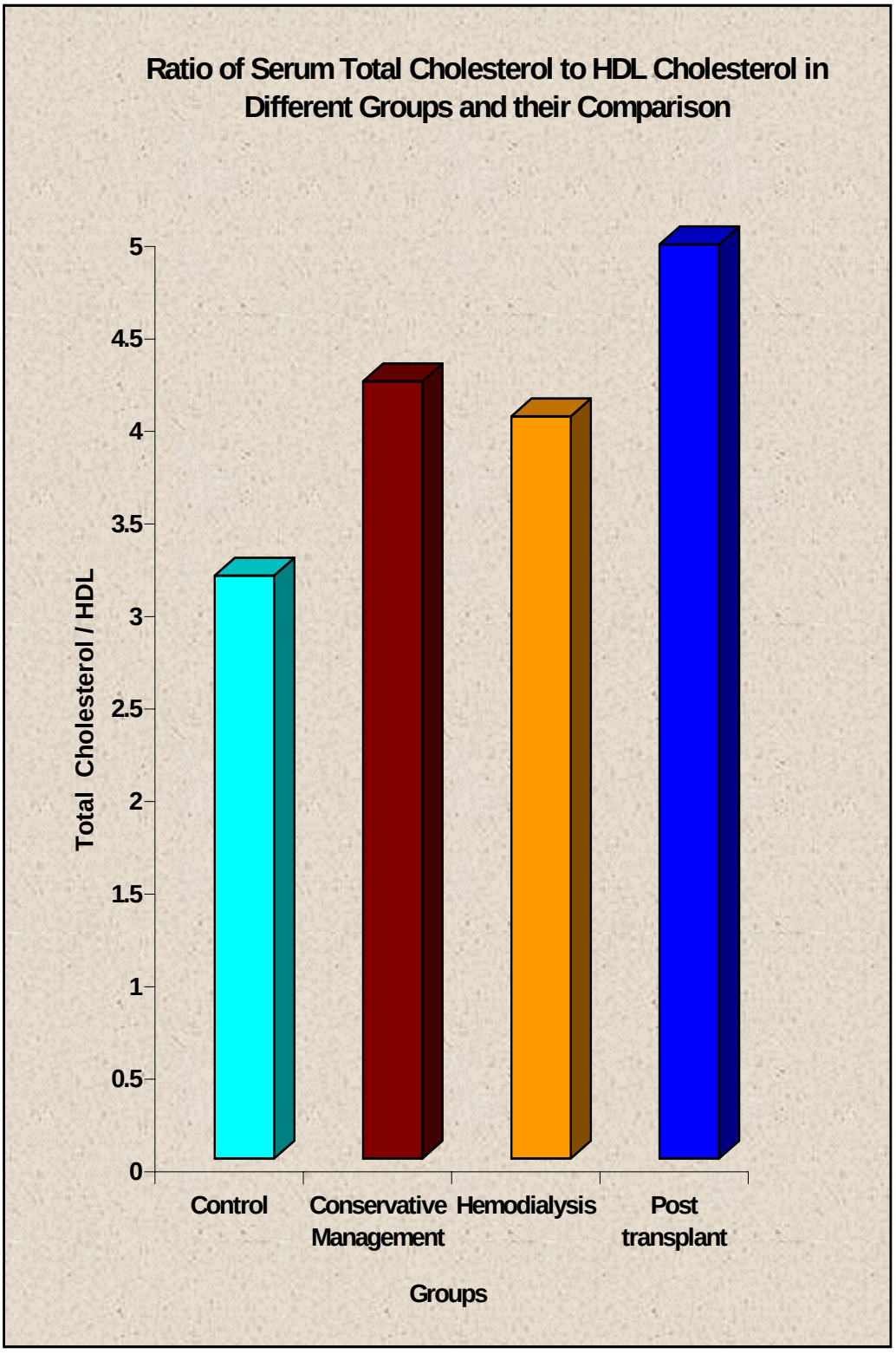

Ratio of Serum Total Cholesterol to HDL Cholesterol in Different Groups and their Comparison
Total Cholesterol / HDL
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Control
Conservative Management
Hemodialysis
Post transplant
Groups

TABLE – 6

VALUES OF LIPID PROFILE IN DIFFERENT GROUPS

Total cholesterol	**Upto 200mg/dl (normal)**	**200-239mg/dl (borderline-high)**	**>240mg/dl (elevated)**
Control	18	1	1
Conservative management	18	2	-
CRF - HD	16	3	1
Post transplant	12	5	3
HDL	**<40 mg/dl (high risk)**	**40-59mg/dl (moderate risk)**	**>60mg/dl (low risk)**
Control	-	19	1
Conservative management	14	6	-
CRF - HD	11	8	1
Post transplant	10	10	-
LDL	**<100 mg/dl (normal)**	**100-129mg/dl (borderline-high)**	**>129mg/dl (elevated)**
Control	18	-	2
Conservative management	14	5	1
CRF - HD	13	4	3
Post transplant	8	5	7

TABLE – 6 (CONTD.)

VALUES OF LIPID PROFILE IN DIFFERENT GROUPS

Serum triglycerides	**<150 mg/dl (normal)**	**150-199mg/dl (borderlinehigh)**	**>200mg/dl (elevated)**
Control	18	1	1
Conservative management	11	5	4
CRF - HD	14	1	5
Post transplant	7	8	5
TC/HDL RATIO	**<4 (normal)**	**4-6 (low risk)**	**>6 (high risk)**
Control	18	2	-
Conservative management	9	9	2
CRF - HD	13	6	1
Post transplant	4	11	5

COMPARISON OF LIPID PROFILE BETWEEN MALES AND FEMALES

TABLE – 7

CONTROL GROUP

Lipid profile	Males	Females	Inference
Total cholesterol	150.5	152.4	Not Significant
Triglycerides	113.8	114.1	Not Significant
HDL	48.9	48.8	Not Significant
LDL	78.9	80.8	Not Significant
TC/HDL	3.1	3.02	Not Significant

TABLE - 8

CONSERVATIVE MANAGEMENT GROUP

Lipid profile	Males	Females	Inference
Total cholesterol	154.6	155.9	Not Significant
Triglycerides	156.2	143.7	Not Significant
HDL	38	37	Not Significant
LDL	85.7	74.4	Not Significant
TC/HDL	4.13	4.28	Not Significant

The above two tables show that there is no significant difference in the lipid profile between males and females in the control and the conservative management group.

COMPARISON OF LIPID PROFILE BETWEEN MALES AND FEMALES

TABLE – 9

HEMODIALYSIS GROUP

Lipid profile	Males	Females	Inference
Total cholesterol	156	162	Not Significant
Triglycerides	149	142	Not Significant
HDL	40.3	40	Not Significant
LDL	85.7	93	Not Significant
TC/HDL	3.8	4	Not Significant

TABLE – 10

POST TRANSPLANT GROUP

Lipid profile	Males	Females	Inference
Total cholesterol	193.2	191.3	Not Significant
Triglycerides	148.2	168.6	Not Significant
HDL	41	37.4	Not Significant
LDL	122.5	120.1	Not Significant
TC/HDL	4.7	5.1	Not Significant

The above two tables show that there is no significant difference in the lipid profile between males and females in the hemodialysis and the post transplant group.

SUMMARY OF THE OBSERVATION

The lipid profile study of chronic renal failure patients on conservative management, on regular hemodialysis and post transplantation showed the following changes.

1. SERUM TOTAL CHOLESTEROL

The total cholesterol levels were normal in 18 (90%) and borderline high in 2(10%) patients in the conservative management group. The levels were normal in 16(80%), borderline high in 3(15%) and elevated in 1(5%) in the hemodialysis (CRF – HD) group . In the post transplant group the levels were normal in 12(60%), borderline high in 5(25%) and elevated in 3(15%) patients. The mean total cholesterol in the control group was 151.45mg/dl, the conservative management group was 155.2mg/dl, CRF – HD group was 159.3mg/dl and the post transplant group was 192.2mg/dl. The mean cholesterol was significantly increased in the post transplant group when compared to the other groups.

2. LDL CHOLESTEROL

The LDL cholesterol levels were normal in 14(70%) and borderline high in 5(25%) and elevated in 1(5%) patient in the conservative management group. The levels were normal in 13(65%), borderline high in 4(20%) and elevated in 3(15%) in the CRF – HD group. In the post transplant group the levels were normal in 8(40%), borderline high in 5(25%) and elevated in 7(35%) patients. The mean LDL cholesterol of the control group was 79.86mg/dl, the conservative management was 87.81mg/dl, CRF – HD group was 90.12mg/dl

and the post transplant group was 121.37mg/dl. The mean LDL cholesterol was significantly increased in post transplant group when compared to the other groups.

3. HDL CHOLESTEROL

The HDL cholesterol levels were decreased in 14 (70%) and normal in 6(30%) patients in the conservative management group. The levels were decreased in 11(55%) , normal in 9(45%) in CRF – HD group. In the post transplant group the levels were decreased in 10(50%) and normal in 10(50%) patients. The mean HDL cholesterol of the control group was 48.8mg/dl, conservative management group was 37.45mg/dl, CRF – HD group was 40.15mg/dl and the post transplant group was 39.2mg/dl. HDL cholesterol was significantly decreased in all study groups when compared to controls.

4. SERUM TRIGLYCERIDES

The triglycerides levels were normal in 11 (55%) and borderline high in 5(25%) patients and elevated in 4(20%) in conservative management group. The levels were normal in 14(70%), borderline high in 1(5%) and elevated in 5(25%) in CRF – HD group . In the post transplant group the levels were normal in 7 (35%) , borderline high in 8(40%) and elevated in 5(25%) patients. The mean triglyceride of the control group was 113.9mg/dl, the conservative management group was 149.9mg/dl, CRF – HD group was 145.4mg/dl and the post transplant group was 158.4mg/dl. The mean triglycerides level was significantly increased in all study groups when compared to controls.

5. RATIO 0F TOTAL CHOLESTEROL/HDL CHOLESTEROL

The total cholesterol/HDL ratio were normal in 9 (45%) and borderline high in 9(45%) patients and high 2(10%) in conservative management group. The levels were normal in 13(55%) , borderline high in 6(30%) and elevated in 1(5%) in CRF – HD group . In the post transplant group the levels were normal in 4(10%) , borderline high in 11(55%) and elevated in 5(25%) patients. The total cholesterol/HDL ratio of control group was 3.15, conservative management group was 4.21, CRF – HD group was 4.01 and the post transplant group was 4.94. The TC/ HDL ratio was significantly increased in all study groups when compared to controls.

DISCUSSION

Serum lipid changes are encountered in a majority of patients with chronic renal failure. This is attributed due to abnormalities in lipoprotein metabolism. The major defect lies in the apoproteins which are the determinants of lipoprotein metabolism. The apoproteins have three major functions in lipoprotein metabolism. 1. They make the lipids water soluble. 2. They are necessary for lipoprotein secretion by hepatic and intestinal cells. 3. They activate the enzymes (lipolytic enzymes) involved in lipoprotein metabolism. Hence the abnormality in apoprotein leads to decreased catabolism of apo-B containing lipoprotein and altered lipoprotein composition. Another factor which also plays a role is the changes in the action of insulin on lipolytic enzymes, possibly mediated via increased levels of parathyroid hormone in CRF.

The clinical consequences of defective lipoprotein transport which leads to renal dyslipoproteinemia may contribute to the development of atherosclerotic vascular disease and progression of glomerular and tubular lesions with subsequent deterioration of renal function. Dietary and/or pharmacologic intervention may ameliorate the uremic dyslipoproteinemia but the long term clinical effects of such treatment have yet to be established. Therapeutic interventions such as dialysis and renal transplantation seem to substantially modify the renal dyslipoproteinemia with several other factors contributing to the dyslipoproteinemia.

This study was conducted to determine the lipid profile changes in chronic renal failure patients on conservative management, on regular hemodialysis and post renal transplant patients with normal renal function and to compare them with healthy controls.

The study population was 60 patients with 20 patients in each group and 20 healthy controls. Each group had 10 males and 10 females to compare the sex variation, but there were 9 males and 11 females in the CRF –HD Group.

All the persons involved in the study were between 15-50 years. It was ensured that none of the control group had diabetes mellitus, hypertension, renal, liver or any metabolic disorder. It was also ensured that none of the patients in the study group had diabetes.

Serum total cholesterol , HDL cholesterol, LDL cholesterol , Triglycerides, Total cholesterol /HDL cholesterol ratio were measured using an autoanalyser, after a 12 hour fast. The results were statistically analysed.

Lipid changes in CRF patient on conservative management : reported studies

1. The characteristic plasma lipid abnormality in CRF patients is moderate hypertriglyceridemia - this is due to impaired carbohydrate tolerance leading to increased hepatic synthesis of VLDL and decreased activity of lipoprotein lipase and hepatic triglyceride lipase leading to decreased fractional catabolic rate of triglycerides.

2. Decrease in HDL cholesterol level - this is due to the deficiency of LCAT which is essential for esterification of cholesterol. LCAT plays an important role in HDL mediated cholesterol uptake from the extra hepatic tissues and serves as a main determinant of HDL maturation and plasma HDL cholesterol level. Decrease in HDL level is also contributed by elevation of CETP.

3. Normal or slightly increased total cholesterol level.

4. Normal or slightly increased LDL cholesterol level.

Observation on lipid profile changes of CRF patients on conservative management showed the following results:

The mean age of the control group was 30.85 yrs and the conservative management group was 36.75 yrs**.** There was no significant difference in the lipid profile between the males and the females in the conservative management group.

The total cholesterol levels were normal in 90% and borderline high in 10% of cases. The mean total cholesterol in the conservative management group was 155.2mg/dl and control was 151.4 mg/dl. This was not statistically significant. The triglyceride levels were borderline high in 25% and elevated in 20%.The mean triglyceride level in the conservative management group was 149.95mg/dl and was significantly increased when compared to a mean of 113.95mg/dl in the control group.

The LDL levels were normal in 70% and borderline high in 30% and HDL was <40mg/dl in 70%.The mean LDL cholesterol in the conservative management group was 87.81mg/dl and control was 90.12mg/dl. This difference was not significant. The mean HDL cholesterol in conservative management group was 87.81mg/dl and was significantly decreased when compared to the controls. The mean TC/HDL cholesterol ratio in conservative management group was 4.21 and was significantly increased compared to control .

The final results revealed a (1) significant decrease in HDL cholesterol (2) significant increase in triglyceride levels (3) significant increase in TC/HDL cholesterol ratio (3) non significant changes in serum total cholesterol and LDL cholesterol when compared to the control group. The significant decrease in HDL could be due to various reasons mentioned earlier (decrease in LCAT, hepatic lipase activity, increase in ACAT, decrease in apoA-I and apoAII) and the cause for hypertriglyceridemia has been mentioned earlier. Though the results were consistent with earlier studies the mean triglycerides and TC/HDL ratio were not as elevated as would be expected. According to Bagdade et al[10] there was moderate hypertriglyceridemia and decrease in HDL levels in CRF patients.

Indian studies on lipid profile abnormalities in chronic renal failure (CRF) have varied from no abnormalities at all to significant abnormality (hypertriglyceridemia and reduced HDL) as described in the Western literature. Sharma et al[62] and Kunde et al[63] observed no hyperlipidemia in patients of CRF. On the other hand, Gupta and Das et al[64] observed lipid abnormalities similar to those reported in Western studies. Though there is a significant increase in

triglycerides and TC/HDL ratio when compared to the controls, the mean level of triglycerides was < 150mg/dl and TC/HDL ratio was <6. This may be due to the study being conducted in low socioeconomic group whose dietary intake is low in both calories and fat and also due to the poor appetite in CRF patients.

Lipid changes in CRF patients on Hemodialysis : Reported studies

1. Moderate increase in triglyceride levels
2. Decrease in HDL levels
3. Normal / slightly elevated total cholesterol, LDL cholesterol
4. Increased Lp(a)
5. Increased apoB and apoA-IV and decreased apo A-I

In addition to factors responsible for renal dyslipoproteinemia the other contributing factors in a CRF-HD patient are

1. Reduced lipolytic activity following repeated heparinisation. The exact reason is not understood but may be due to functional insulin deficiency or insulin resistance, and also due to the presence of non dialyzable factor of lipolytic enzyme (lipoprotein lipase), in the plasma of CHF-HD patients. The changes are more pronounced with the use of conventional heparin than low molecular weight heparin.

2. The presence of Acetate in the dialysate which gets converted to long chain fatty acids and later to cholesterol in the liver.

3. Carnitine deficiency where carnitine is necessary for fatty acid oxidation.

Observation on lipid profile changes of CRF- HD showed the following results

The mean age of the hemodialysis group was 29.5 yrs. There was no significant difference in the lipid profile between males and females in this group.

The total cholesterol levels were normal in 80% and elevated in 20% of cases. The mean total cholesterol in the CRF – HD group was 159.3mg/dl and control was 151.4mg/dl. This difference was not significant. The triglyceride levels were normal in 70% and elevated in 25%. The mean triglyceride level in the CRF – HD group was 145.50 and was significantly increased when compared to the controls.

The LDL cholesterol levels were normal in 65% and borderline high in 35% of patients in this group. The mean LDL cholesterol in the CRF – HD group was 90.12mg/dl and in the control was 79.86mg/dl. This difference was not significant. The HDL cholesterol levels were below 40 mg/dl in 55%.The mean HDL cholesterol in the CRF – HD group was 40.15mg/dl and was significantly decreased when compared to 48.8mg/dl in the control group. The TC/HDL ratio was elevated in 1 (5%) patient. The mean TC/HDL cholesterol ratio in CRF – HD group was 4.21 and was significantly increased when compared to 3.15 in the control group.

The final results revealed a (1) significant decrease in HDL cholesterol (2) significant increase in triglyceride levels (3) significant increase in TC/HDL cholesterol ratio (4) non significant changes in serum total cholesterol and LDL

cholesterol but the elevation in the mean triglyceride level and TC/HDL ratio was not as high as reported in Western and in some Indian studies. Variation in lipid profile in hemodialysis patients in previous studies have not been consistent. Shah et al[65] have noticed hypertriglyceridemia in 11% of patients on hemodialysis. Zolezzi et al have noticed raised total cholesterol in 20%, decreased HDL in 50% and raised triglycerides in 45% of their patients on hemodialysis. Ibels et al[8] have noticed decrease in triglyceride levels after dialysis. In this study, though the mean triglyceride level and TC/HDL ratio was increased compared to controls the levels were <150 mg/dl and < 6 mg/dl respectively. This may be due to poor appetite and dietary pattern low in calories and fat .

Lipid changes in post transplant patients – reported studies

The characteristic pattern noted in earlier studies were

(1) Increase in total cholesterol with increase in VLDL and LDL cholesterol

(2) Increase in Triglycerides.

(3) Decrease in HDL cholesterol

These changes are due to the improvement of diet, activation of LCAT, cumulative dose of steroids and other immunosuppressive agents like cyclosporine and concomitant use of antihypertensives in the transplant recipients.

Observation on lipid profile changes of post transplant patients showed the following results

The mean age of this group was 25.7 yrs and there was no significant difference in the lipid profile between males and females.

The total cholesterol levels were borderline high in 25% and elevated in 15% of the patients in this group.The mean total cholesterol in post transplant group was 192.2mg/dl and was significantly increased when compared to the controls which was 151.45mg/dl. The triglyceride levels were borderline high in 40% and elevated in 25%. The mean triglyceride level in the post transplant group was 158.4mg/dl and was significantly increased when compared to 113.95mg/dl in the controls.

The LDL levels were borderline high in 50% and elevated in 10% and HDL was decreased in 50% of the cases. The mean LDL cholesterol in the post transplant group was 121.37mg/dl and was significantly increased when compared to 79.86mg/dl in the controls. The mean HDL cholesterol in the post transplant group was 39.2mg/dl and was significantly decreased when compared to the control group which was 48.8mg/dl. The mean TC/HDL cholesterol ratio in the post transplant group was 4.21 and was significantly increased when compared to 3.15 in the controls

The final results revealed a (1) significant increase in serum triglycerides (2) significant increase in total cholesterol (3) significant increase in LDL cholesterol (4) significant decrease in HDL cholesterol (5) significant increase in total cholesterol/HDL ratio when compared to the control group. As

mentioned earlier these changes are due to use of steroids , cyclosporine, improvement in diet and activation of LCAT after transplantation. These changes are similar to western studies. Shah et al[65] have noticed hypercholesterolemia in 37.5% of transplant recipients. The mean cholesterol level was increased when compared to the controls but the elevation (192.2mg/dl) is not as high as expected which may be due to the poor socioeconomic status of the study group who mostly consume a low fat and a low calorie diet.

From this study it is inferred that dyslipidemias are common in chronic renal failure patients and especially more pronounced in transplant recipients. Since cardiovascular risk is excessive in patients with even minor renal dysfunction the same rationale of management should be applied as in the similar high risk population of diabetes. The appropriate management of dyslipidemia plays an important role in the overall care of the patient with chronic and ESRD and renal transplantation. Evaluation of dyslipidemias should occur at presentation with chronic renal disease, following a change in treatment modality and annually. Appropiate therapeutic life style change and drug therapy should be started. LDL level should be maintained below 100mg/dl, Triglycerides below 150 mg/dl and HDL should be above 50. Drug therapy should be used for LDL levels of 130 mg/dl and also for LDL levels of 100-129 mg/dl after 3 month of therapeutic life style change.

CONCLUSION

- There is no significant difference in the lipid profile between males and females in the different groups.

- On comparison with the control group

  - The mean total cholesterol is significantly increased in chronic renal failure patients after transplantation ($p<0.001$).

  - The mean triglyceride level is significantly increased in CRF patients on conservative management ($p=0.029$), on hemodialysis ($p=0.045$) and after transplantation ($p=0.004$).

  - The mean LDL cholesterol is significantly increased after transplantation ($p=0.001$).

  - The mean HDL cholesterol is significantly decreased in the conservative management group ($p=0.001$), the hemodialysis group ($p<0.001$) and in the post transplant group($p<0.001$).

  - The total cholesterol to HDL cholesterol ratio is significantly increased in CRF patients on conservative management ($p=0.002$), on hemodialysis ($p=0.0007$) and after transplantation ($p<0.001$).

- Due to increased prevalence of hyperlipidemia and its complications in chronic renal failure patients, early diagnosis of dyslipidemias is indicated and potential therapeutic approaches (therapeutic life style changes and pharmacotherapy) should be initiated to limit the long term consequences of cardiovascular disease in this population of patients, whose longevity is anticipated to increase with dialysis and transplantation.

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