A Dissertation on

EVALUATION OF LIPID PROFILE IN PATIENTS WITH NON-DIABETIC CHRONIC KIDNEY DISEASE STAGE 3,4 AND 5.

submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI

in fulfillment of the regulations
for the award of the degree of

M.D. (GENERAL MEDICINE)
BRANCH - I

KILPAUK MEDICAL COLLEGE CHENNAI.

MARCH 2009

B0NAFIDE CERTIFICATE

Certified that the dissertation titled **"EVALUATION OF LIPID PROFILE IN PATIENTS WITH NON-DIABETIC CHRONIC KIDNEY DISEASE STAGE 3,4 AND 5 "** is a bonafide work of the candidate **Dr.P.MOHANRAJ**, post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai – 10, done under my guidance and supervision, in partial fulfillment of regulations of **The Tamilnadu Dr. MGR Medical University** for the award of M.D. Degree Branch I, (General Medicine) during the academic period from May 2006 to March 2009.

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TO WHOMSOEVER IT MAY CONCERN

Dear Sir / Madam

Sub: Internal Medicine – MD PG's Dissertation Ethical Committee – Reg.

Ref: Requisition from H.O.D. Medicine.

This is in reference to the letter dated 2.1.2008 regarding Ethical committee meeting clearance with regard to the following topics

Sl.No	Name of the Post Graduate	Dissertation Topic
1	Dr. R.Ramprasad	A study on Prevalence and Risk Factors of Diabetic Nephropathy in Newly Detected Type 2 Diabetic Patients
2	Dr. V.Sakthivadivel	A study on Cardiac abnormalities in HIV infected individuals
3	Dr. K.S.Gopakumar	A study on Subclinical Hypothyroidism in females over 50 years of age
4	Dr. T.Karthikeyan	Inflammatory profile in Acute Myocardial Infarction

5	Dr. Maliyappa Vijay Kumar	A study on Prevalence of Microalbuminuria in HIV patients not on ART and Correlation with CD4 count
6	Dr. D.Radha	High sensitivity C - reactive protein as a determinant in the outcome of Acute ischemic stroke
7	Dr. Lakshmi Thampy M.S	A Study on the prevalence of increased LV mass & Proteinuria in newly diagnosed Hypertensive patients.
8	Dr. Manu Bhasker	A study on the effect of Intravenous Metoprolol along with Thrombolysis in Acute Myocardial infarction
9	Dr. P.Mohanraj	Evaluation of Lipid Profile in patients with non diabetic Chronic Kidney Disease Stage 3,4 and 5
10	Dr. P.Dhanalakshmi	A study On Metabolic Syndrome in Young Ischemic Stroke
11	Dr. V.Murugesan	A study on Electrocardiographic and Echocardiographic changes in Chronic Obstructive Airway Disease
12	Dr. M.Seetha	Effect of Right ventricular infarction on the immediate prognosis of Inferior wall Myocardial Infarction

We are glad to inform you that at the EC meeting held on 3.1.08 on the above topics were discussed and **Ethically approved**.

DEAN

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We confirm that no member of the study team is on the Ethics Committee and no member of the study team voted.

The trial will also follow the Ethics Guidelines for Bio-Medical Research On Human subjects issued by ICMR, New Delhi and will not involve any expense to the Government and will not be detrimental to the normal functioning of the Institution.

The study will also satisfy the revised order issued by the Government of Tamil Nadu, Health and Family Welfare Department G.O.MS.No:319, H & FW, Dept. dated 30.11.2001.

Acknowledgement

I am extremely grateful to the Dean Dr.M.Dhanapal,M.D.,D.M., Kilpauk medical college for granting me to permission to do this dissertation in Government Royapattah Hospital, Chennai .

I am very grateful to our Professor and Head of the department of medicine Dr.G.Rajendran, M.D., for his valuable suggestion in preparing this dissertation.

I am deeply indebted to my unit chief and teacher Prof. Dr.K.Rajendran, M.D., for his valuable guidance, perspectives, assortments of emerging views, compiled with patience and constructive criticisms throughout the gestation period has made this seemingly juvenile attempt a worthy informative and lucid contribution.

My humble gratitude in abundance to Professor of Nephrology Dr.J.H.BalaSingh, M.D., D.M., MNAMS, for being the role guiding force in the practical execution of this project and he graciously and gracefully accepted to my request.

I recall with great gratitude, the unit chiefs of department of medicine Prof.Dr.N.Raghu,M.D., Prof.Dr.N.Gunasekaran,M.D.,D.T.C.D., for having permitted me to work on their patients in their respective units.

I am extremely thankful to Prof.Dr.R.Nagendran, M.D., Head of the department of Biochemistry for the guidance and permission to utilize the research laboratory.

I am also thankful to my Assistant Professors in the department of medicine Dr.P.Paranthaman,M.D.,D.T.C.D., Dr.G.Ranjani,M.D., Dr.S.Kalaichelvi,M.D., for their constant encouragement, timely help and critical suggestions .

I also thank our patients without whom the study will not be possible.

I owe my thanks to the almighty for successful completion of this study.

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Aim of the study

1. To estimate various level of lipids in CRF patients.
2. To study whether any correlation exist between the severity of CRF and lipid alterations.
3. To examine which type of hyperlipoproteinemia predominates in these patients.
4. To examine whether the ratio between TC to HDL-C is altered in CRF patients.
5. To examine the association of hypertension in CRF patients.

INTRODUCTION

The national kidney foundation criteria for diagnosis of CKD are :

(i) Kidney damage for greater than or equal to 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate, manifest by either:

a. pathological abnormalities or
b. markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.

(ii) Glomerular filtration rate less than 60 mL/min/1.73 m^2 for greater than or equal to 3 months, with or without kidney damage [Ref. 1].

In accordance with the Kidney Disease Outcomes Quality Initiative (KDOQI) definition, a documented GRF of below 60mL/min/1.73 m^2 fulfils the definition of CKD without requiring any additional evidence of underlying kidney damage. This cutoff in GFR was selected because it represents over 50% reduction in kidney function as compared to the level for young healthy adults and it is supported by accumulating evidence

demonstrating the presence of complications as the glomerular filtration rate falls below 60 mL/min/1.73 m^2.

The commonest and most readily available marker of kidney damage resulting in glomerular dysfunction is the presence of proteinuria. Similarly, the presence of abnormal sediment on urine microscopy or the demonstration of multiple cysts on renal imaging in a patient with a family history of polycystic kidney disease would meet the requirement for objective kidney damage. Because the relationship of hypertension to kidney disease is complex and varied, hypertension by itself is not included in the above definition; instead the presence of absence of hypertension is noted separately in conjunction with the presence or absence and the severity of CKD.

Stage I represents subjects who do not have a clear filtration deficit and is defined as a normal or elevated kidney function (GRF>90ml/min/1.73m^2) in association with evidence of kidney damage , this latter is defined broadly but is most often represented by the presence of persistent albuminuria. Stage II is a mild reduction in kidney function (GRF 60-89 ml/min/1.73m^2) that occurs in association with kidney damage. CKD stages III and IV

correspond to moderately and severely decreased kidney function (GRF of 30-59 and 15-29 ml/min/1.73 m^2 respectively). This large a decrement in kidney function is classified as CKD regardless of the presence of additional evidence of kidney damage. Stage V represents kidney failure defined by either a GRF below 15 or the need for renal replacement therapy.

The most important parameter in the clinical evaluation of kidney function is the glomerular filtration rate (GFR), which is generally accepted as the best over all index of kidney function. The level of GRF correlates well (albeit not perfectly) with the likelihood of developing complications of kidney disease, such as anemia, hyperphosphatemia and uremic symptoms.

Since its introduction by Homer Smith, the gold standard for measurement of GRF has been clearance of the small carbohydrate moiety inulin (an 5200d uncharged polymer of fructose)-an ideal filtration marker because it is freely filtered in the glomeruli and is neither reabsorbed nor secreted by the tubules. Because clearance is defined as the volume of plasma cleared entirely of a substance in a unit of time, clearance of inulin equals GRF. Direct measure of GRF using inulin clearance is cumbersome, requiring intravenous infusion and timed urine collection. In research

studies, GRF has been measured by clearance of iothalamate (a small polyiodinated radiographic contrast molecule that can be radiolabeled), but that is also not clinically practical.

In daily clinical practice, serum creatinine concentration (SCr) has been the most commonly used parameter to evaluate kidney function. The small molecule creatinine (molecular weight 113 daltons) is endogeneously produced by muscle and excreted by the kidneys. Therefore, the reduction in GRF leads to an increase in SCr. Serum creatinine is easily and cheap to measure, and no urine collection is needed. Many laboratories report a normal reference range for SCr of around 0.7 to 1.4 mg/dL.

However, the national kidney foundation CKD guidelines explicitly recommend that clinicians “should not use serum creatinine as the sole means to assess the level of kidney function”. This departure from current clinical practice needs an explanation. One known problem is that renal creatinine clearance tends to over estimate GRF. More importantly, serum creatinine often does not reflect underlying GRF because SCr is a function not only of creatinine clearance (which reflects kidney function) but also creatinine production (which largely reflects muscle mass). Therefore, the

same SCr can represent very different underlying glomerular filtration rates in individuals because of muscle mass difference.

A clinically practical solution to this problem is to use SCr to estimate kidney function via equations that take into account variables such as age, sex, race, and body size (which are all important predictors of muscle mass and hence creatinine production).

A commonly used surrogate marker for actual creatinine clearance is the Cockcroft-Gault formula, which may be used to calculate an Estimated Creatinine Clearance, which in turn estimates GFR: It is named after the scientists who first published the formula, and it employs creatinine measurements and a patient's weight to predict the Creatinine clearance. The formula, as originally published, is:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

For creatinine in μmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women.

Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula

The most recently advocated formula for calculating the GFR is the one that was developed by the Modification of Diet in Renal Disease Study Group. The most commonly used formula is the "4-variable MDRD" which estimates GFR using four variables: serum creatinine, age, race, and gender. The original MDRD used six variables with the additional variables being the blood urea nitrogen and albumin levels. The equations have been validated in patients with chronic kidney disease; however both versions underestimate the GFR in healthy patients with GFRs over 60 mL/min. The equations have not been validated in acute renal failure.

For creatinine in mg/dL:

$$\mathrm{eGFR} = 186 \times \text{Serum Creatinine}^{-1.154} \times \mathrm{Age}^{-0.203} \times [1.21\ if\ Black] \times [0.742\ if\ Female]$$

When SCr is changing rapidly, such as during acute renal failure, it is wrong to estimate GRF using the Cockcroft-Gault or the MDRD equation. It may be possible under those circumstances to model the underlying kidney functions from the rate and pattern of change in SCr using complex mathematical models beyond the scope of usual clinical practice.

For patients with unusual body compositions or extremes of body sizes, SCr based equations will likely give invalid estimates of GRF because of alterations in the usual relationship between muscle mass and parameters such as age, sex, and weight. Examples include patients with hepatic cirrhosis, limb amputation, spinal cord injury or morbid obesity. For these patients, multiple 24-hr urine collections (to reduce inaccuracies in collection) may be the best way to evaluate GRF.

As GFR declines, the relative proportion of creatinine secretion versus filtration rises. Consequently, creatinine secretion has a greater effect on the serum creatinine concentration at lower levels of GFR. Polycystic kidney disease and tubulointerstitial disease seem to be associated with lower mean levels of creatinine secretion than other diseases [Ref 2]. Higher protein intake can cause increased creatinine secretion. Several medications, such as cimetidine, trimethoprim, and fenofibrate, can inhibit tubular secretion of creatinine. Some have advocated administration of cimetidine to block creatinine secretion during 24-hour urine collections for creatinine clearance, thereby allowing for a more accurate measurement of GFR, especially in patients with moderate to severe reductions in GFR.

Creatinine generation is directly proportional to muscle mass, which in turn varies according to age, sex, and race and is affected by conditions causing muscle wasting. Creatinine generation is also affected by dietary meat intake, because meat includes creatine, which can be converted to creatinine by cooking [Ref 3,4] . Increased meat intake can cause a long-term increase in serum creatinine because of an increase in the creatinine pool.

Extrarenal elimination of creatinine can occur in the gastrointestinal tract by bacterial degradation of creatinine contained in intestinal secretions. Extrarenal elimination is not detectable in normal individuals, but may account for up to 68% of daily creatinine generation in patients with severely reduced GFR[Ref 5,6] because of increased concentration of creatinine in gastrointestinal secretions and bacterial overgrowth of the upper gastrointestinal tract.

In principle, antibiotics could cause an increase in serum creatinine in patients with CKD because of eradication of bacterial overgrowth and decrease in extrarenal elimination of creatinine. This may be a relevant consideration in patients with CKD who develop superimposed acute renal failure.

Factors affecting glomerular filtration rate

- Kidney disease
- Pregnancy
- Reduced kidney perfusion
- Marked increase or deficit of extracellular fluid volume
- Nonsteroidal anti-inflammatory drug use
- Acute protein load and habitual protein intake
- Blood glucose control (in patients with diabetes)
- Level of arterial blood pressure and class of antihypertensive
- Agents used.

Clinical applications

Accurate estimation of GFR is critical to care of patients with CKD. The current staging system for CKD is built primarily on the level of GFR in that as GFR declines, the stage increases. Decreasing levels of GFR (or higher CKD stage) are associated with a higher prevalence of a wide range of symptoms and complications including hypertension, anemia, malnutrition, bone disease, and neuropathy. At each stage, accurate assessment of GFR is

required for evaluation and treatment. Currently, the most accurate method for estimation of GFR seems to be the MDRD Study equation.

Estimation of GFR from the MDRD Study equation is not appropriate for all patients. In these patients, a clearance measurement (either a 24-hour urine collection for creatinine clearance or an exogenous filtration) can be used.

A 24-hour urine collection may be required to estimate glomerular filtration rate in the following conditions

- Extremes of age and body size
- Severe malnutrition or obesity
- Disease of skeletal muscle
- Paraplegia or quadriplegia
- Vegetarian diet
- Rapidly changing kidney function
- Pregnancy
- Before dosing drugs with significant toxicity that are excreted by the kidneys

The uremic syndrome and the disease state associated with advanced renal impairment involve more than renal excretory failure. A host of metabolic and endocrine functions normally undertaken by the kidneys are also impaired, and this results in anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Furthermore, plasma levels of many hormones, including PTH, insulin, glucagon, sex hormones, and prolactin, change with renal failure as a result of urinary retention, decreased degradation, or abnormal regulation. Finally, progressive renal impairment is associated with worsening systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, while levels of so-called negative acute-phase reactants, such as albumin and ferritin, decline with progressive renal impairment. Thus, renal impairment is important in the malnutrition-inflammation-atherosclerosis/calcification syndrome, which contributes in turn to the acceleration of vascular disease and comorbidity associated with advanced renal disease.

Major Causes of Chronic Kidney Disease

Causes are Chronic tubulointerstitial nephropathies; Primary Glomerulopathies (Focal glomerulosclerosis, Idiopathic crescentic glomerulonephritis, IgA nephropathy, membranoproliferative

glomerulonephritis ,Membranous nephropathy); Glomerulopathies associated with systemic disease (Amyloidosis, Diabetes mellitus, Hemolytic-uremic syndrome, Postinfectious glomerulonephritis, SLE Wegener's granulomatosis); Hereditary nephropathies (Hereditary nephritis - Alport's syndrome, Medullary cystic disease, Nail-patella syndrome, Polycystic kidney disease); Hypertension (Malignant glomerulosclerosis, Nephroangiosclerosis); Obstructive uropathy (Benign prostatic hyperplasia ,Posterior urethral valves Retroperitoneal fibrosis, Ureteral obstruction by congenital, calculi, malignancies and Vesicoureteral reflux); Renal macrovascular disease (vasculopathy of renal arteries and veins) ; Renal artery stenosis caused by atherosclerosis or fibromuscular dysplasia.

The incidence of cardiovascular disease (CVD) is substantially higher in patients with chronic kidney disease (CKD) compared with the general population [Ref 7]. Studies have shown that hemodialysis patients with high cholesterol have lower mortality than those with low cholesterol. Dyslipidemias have also been linked to the rate of decline in kidney function, and it is possible that treatment of dyslipidemias may slow the rate of CKD progression [Ref 8]. The dyslipidemias associated with early stages of CKD generally worsen with advancing kidney failure and ultimately affect

most patients treated with maintenance dialysis and kidney transplantation.[Ref 9,10].

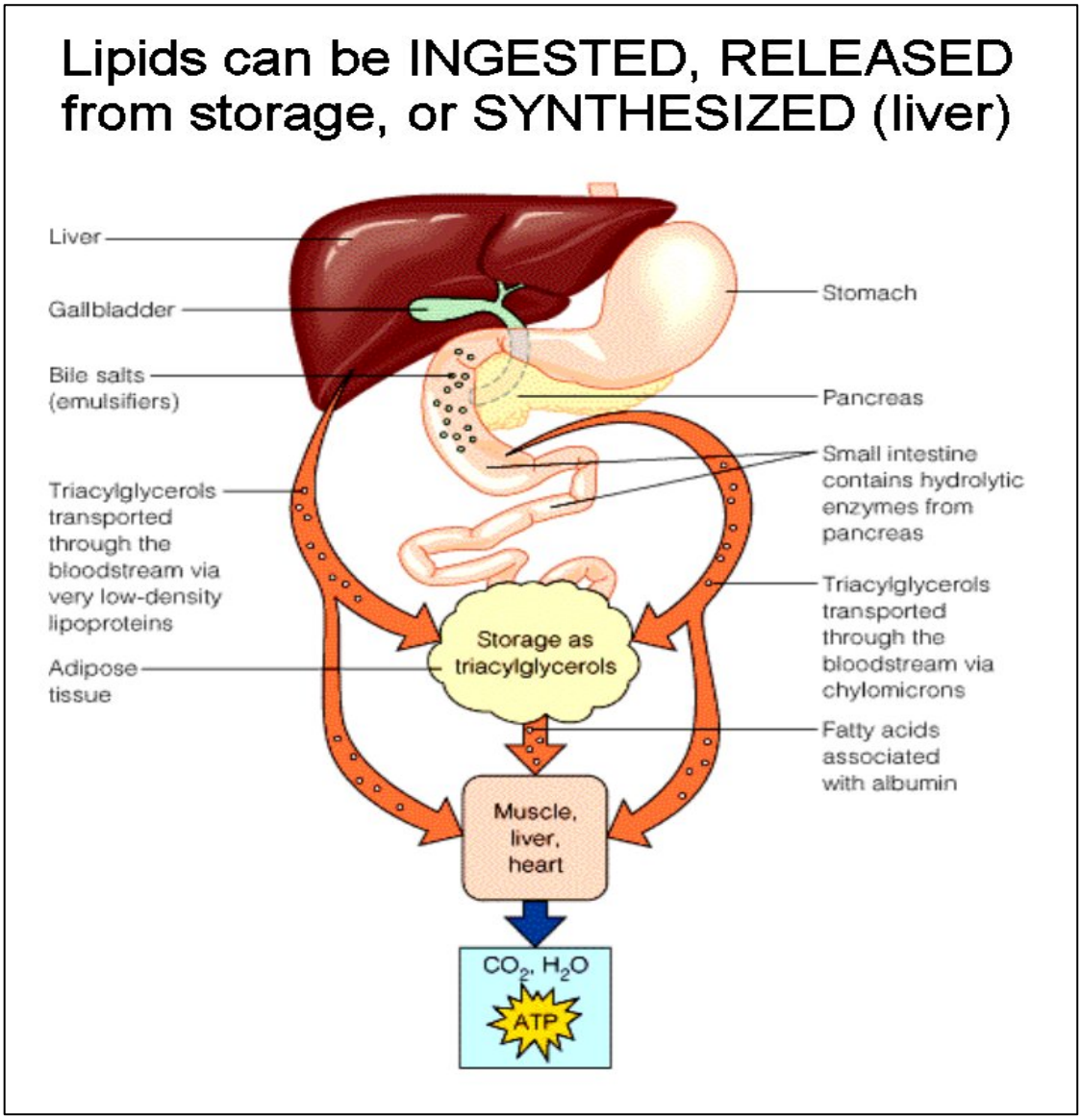
Frederickson Classification of Dyslipidemia

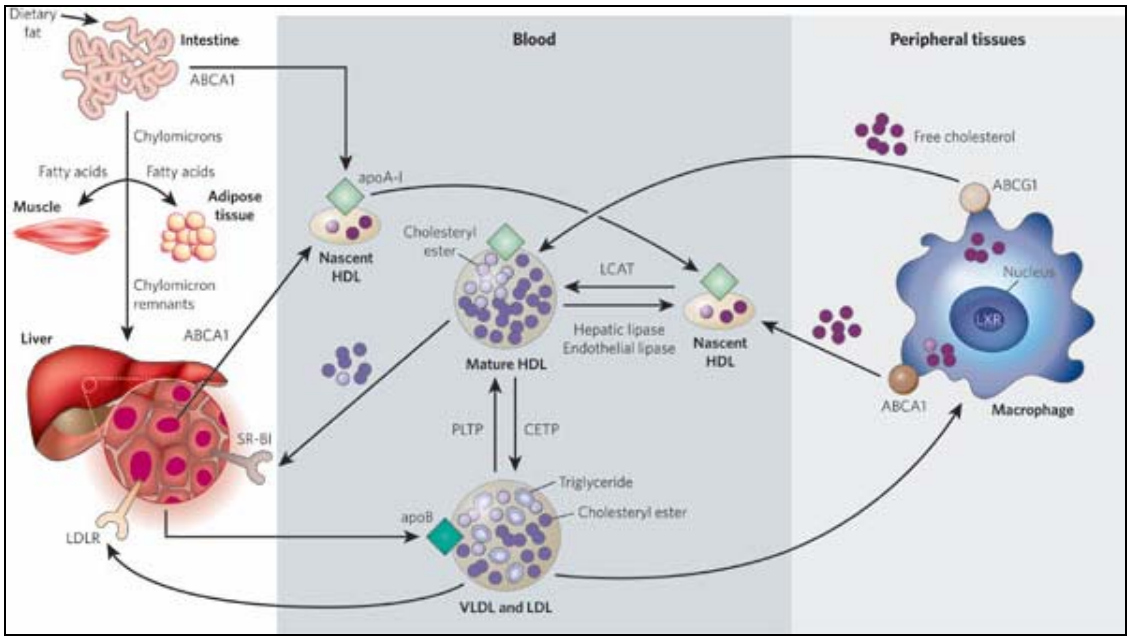
Hyperlipoproteinemia	Problems	Labs description	Treatment
Type I	Decreased lipoprotein lipase (LPL) or altered ApoC2	Elevated Chylomicrons	Diet Control
Type IIa	LDL receptor deficiency	Elevated LDL only	Bile Acid Sequestrants, Statins, Niacin
Type IIb	Decreased LDL receptor and Increased ApoB	Elevated LDL and VLDL and Triglycerides	Statins, Niacin, Fibrate
Type III	Defect in ApoE synthesis	Increased IDL	Drug of choice: Fibrate
Type IV	Increased VLDL production and Decreased elimination	Increased VLDL	Drug of choice: Fibrate, Niacin
Type V	Increased VLDL production and Decreased LPL	Increased VLDL and Chylomicrons	

CRF results in profound dysregulation of several key enzymes and receptors involved in the metabolism of lipoproteins, particularly those of HDL and triglyceride-rich lipoproteins. Downregulation of LCAT, apoA-1, and hepatic lipase together with upregulation of CETP are largely responsible for the reduction in HDL cholesterol and elevation of triglyceride in CRF.

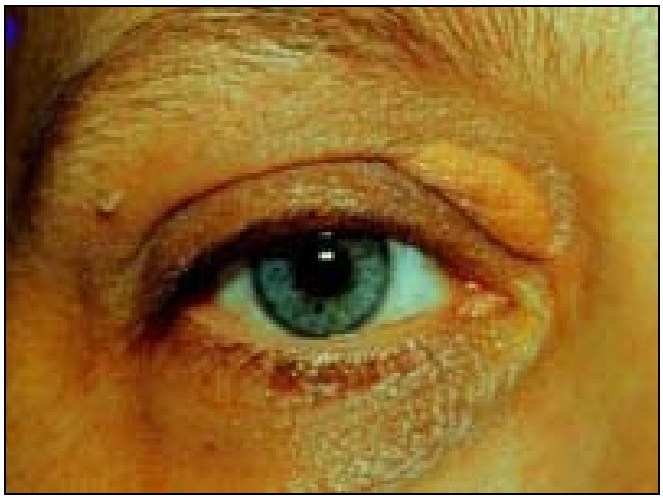
Downregulation of skeletal muscle and adipose tissue LPL, hepatic lipase, and the VLDL receptor and of hepatic LRP is collectively responsible for hypertriglyceridemia, impaired clearance, and elevated plasma levels of VLDL, IDL, and chylomicron remnants despite downregulation of hepatic triglyceride synthetic capacity (DGAT). Dysregulation of lipid metabolism can contribute to atherogenic diathesis and possibly to progression of renal disease and impaired energy metabolism in CRF.

Lipid Transport

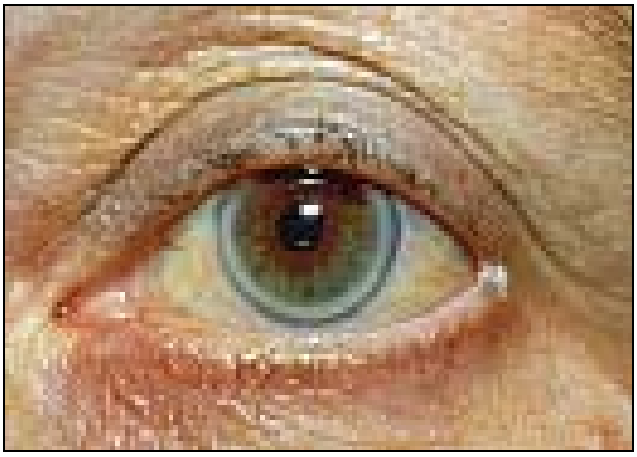



Dietary fat
Intestine
ABCA1
Chylomicrons
Fatty acids
Fatty acids
Muscle
Adipose tissue
Chylomicron remnants
Liver
ABCA1
SR-BI
LDLR
Blood
apoA-I
Nascent HDL
Cholesteryl ester
LCAT
Hepatic lipase
Endothelial lipase
Mature HDL
Nascent HDL
PLTP
CETP
Triglyceride
Cholesteryl ester
apoB
VLDL and LDL
Peripheral tissues
Free cholesterol
ABCG1
Nucleus
LXR
ABCA1
Macrophage

Xanthoma



Arcus senilis



Review of literature

CHRONIC RENAL FAILURE (CRF) is associated with premature atherosclerosis and increased incidence of cardiovascular morbidity and mortality.[Ref 11,12,13]. Several factors contribute to atherogenesis and cardiovascular disease in patients with CRF. Notable among the CRF-induced risk factors are lipid disorders, oxidative stress, inflammation, physical inactivity, anemia, hypertension, vascular calcification, endothelial dysfunction, and depressed nitric oxide availability [Ref 14,15,16,17].

CVD as the major cause of mortality in patients with mild to moderate CKD and end-stage renal disease (ESRD) [Ref 18,19]. Approximately 50% of patients with ESRD die from a cardiovascular event [Ref 20], which indicates a cardiovascular mortality that is 30 times higher in dialysis patients and 500 times higher in 25- to 34-year-old ESRD patients than in individuals from the general population of the same age and race.

In a retrospective cohort study only a tiny minority of patients (0.5–1%) with mild to moderate CKD developed ESRD over a 5-year follow-up, while as many as 19 and 24% of these patients with mild and moderate renal

insufficiency, respectively, died mostly of cardiovascular complications in the same period [Ref 21.] Dyslipidemia has been established as a well-known traditional risk factor for CVD in the general population and large-scale observational studies have shown that total and low-density lipoprotein (LDL)-cholesterol values are two of the most important independent predictors of cardiovascular morbidity and mortality [Ref 22] . Also, it is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia.

In the plasma, lipids are carried by water-soluble particles known as lipoproteins, which consist of a nonpolar lipid core (triglycerides, cholesterol esters) surrounded by an envelope composed of specific apolipoproteins (apo), phospholipids, and other polar lipids. The plasma lipoproteins are commonly classified as either high-density (HDL), low-density (LDL), intermediate-density (IDL), or very-low-density (VLDL) lipoproteins according to their ultracentrifugation characteristics. Chylomicrons and VLDL serve as vehicles to transport triglycerides and cholesterol from the sites of absorption (intestine) and endogenous production (liver) to the sites of consumption (myocytes, steroidogenic glands, etc.) or storage

(adipocyte). In contrast, HDL serves as a vehicle to transport surplus cholesterol from peripheral tissues to the liver for disposal.

The typical profile of patients with chronic kidney disease, that is, the constellation of moderate elevation of plasma triglyceride concentrations, combined with low plasma HDL-cholesterol, corresponds to the pattern of dyslipidemia type IV according to Frederickson et al. In CKD, total cholesterol is usually normal or even low. This may be the result of an additional microinflammatory state and/or malnutrition.

Although lipid abnormalities were originally considered as complications of ESRD, these changes can be present in early stages of CKD and may actively participate in the pathogenesis of serious complications such as atherosclerotic vascular disease. Although the nature of dyslipidemia can be significantly influenced by several intrinsic (nephrotic range proteinuria, concomitant diseases such as diabetes mellitus, hereditary disorders of lipid metabolism) or exogenous (epoietin administration, drugs such as steroids, calcineurin inhibitors, etc.) factors, the most common quantitative lipid abnormalities in predialysis CKD patients are hypertriglyceridemia, increased concentrations of triglyceride-

rich lipoprotein remnants, reduced high-density lipoprotein (HDL)-cholesterol levels as well as increased concentrations of lipoprotein(a) Lp(a).

Notably, total and LDL-cholesterol levels are usually within normal limits or slightly reduced in these individuals [Ref 23]. Hypertriglyceridemia represents an early feature of renal failure. Indeed, previous studies have shown that patients with impaired renal function exhibit increased concentrations of triglycerides even though serum creatinine levels are within normal limits [Ref 24,25]. In addition, individuals with renal insufficiency usually display abnormal increases in serum triglyceride levels after a fat meal (postprandial lipemia) [Ref 26].

Studies revealed that the accumulation of triglyceride-rich lipoproteins (very-low-density lipoprotein (VLDL), chylomicrons and their remnants) in individuals with predialysis CKD is mainly due to their decreased catabolism [Ref 27]. The downregulation of the expression of several genes [Ref 28,29,30], along with the changes in the composition of lipoprotein particles [Ref 31], and the direct inhibitory effect of various uremic ‘toxins’ on the enzymes involved in lipid metabolism [Ref 32], represent the most important pathophysiological mechanisms underlying the development of

hypertriglyceridemia in renal failure. Interestingly, it has been proposed that secondary hyperparathyroidism may also contribute to the impaired catabolism of triglyceride- rich lipoproteins [Ref 33,34], and that parathyroidectomy or the administration of the calcium channel blocker verapamil [Ref 35], may partially ameliorate the hypertriglyceridemia of CKD.

Nonnephrotic patients with stages 2 to 4 CKD generally have normal LDL levels, but triglycerides may be elevated and HDL may decrease the level of kidney function declines. This may be caused by reduced lipoprotein lipase activity. Among those are chronic exposures to high parathyroid hormone levels resulting in reductions in both hepatic triglycerides lipase and lipoprotein lipase [Ref 36] .Calcium accumulation in pancreatic islet cells with subsequent functional impairment of pancreas and glucose intolerance has also been postulated [Ref 37].Patient with CKD also have elevated Apo C-111 levels that may be associated with reduced lipoprotein lipase activity. It is well known that impaired insulin sensitivity represents an early feature of CKD. Thus, it could be hypothesized that the insulin resistance- driven overproduction of VLDL may significantly contribute to the development of hypertriglyceridemia in CKD patients.

Epidemiological studies have shown that HDL-cholesterol levels are inversely related to the future cardiovascular risk [Ref 38]. HDL particles possess multiple antiatherogenic activities including reverse cholesterol transport (transport of surplus cholesterol from the arterial wall to the liver for excretion) as well as antioxidative, anti-inflammatory and antithrombotic functions, which are attributed to HDL-associated apolipoproteins (mainly apolipoprotein AI) and enzymes (paraoxonase-1, platelet- activating factor acetylhydrolase and lecithin-cholesterol acyltransferase (LCAT)) [Ref 39].

Studies in patients or laboratory animals with predialysis renal failure consistently reveal decreased concentrations of HDL-cholesterol compared to individuals with normal renal function [Ref 40,41]. Several mechanisms, working in concert, may underlie this reduction in HDL-cholesterol levels, which is usually indicative of impaired reverse cholesterol transport. Thus, uremic patients usually exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL), diminished activity of LCAT (the enzyme responsible for the esterification of free cholesterol in HDL particles) [Ref 42]. As well as increased activity of cholesteryl ester transfer protein [Ref 43], that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL

cholesterol. In addition to their reduced efficiency as cholesterol acceptors, HDL particles from individuals with renal failure may also possess impaired antioxidative and anti-inflammatory function. This impairment can, at least in part, be attributed to the reduction in the activities of HDL-associated enzymes [Ref 44,45].

Plasma HDL concentration is consistently reduced, and maturation of cholesterol ester-poor HDL-3 to cholesterol ester-rich cardioprotective HDL-2 is impaired in CRF [Ref 46,47,48,49]. The recently proposed index of non-HDL-cholesterol, reflecting the sum of LDL and VLDL particles appears to be more sensitive and is a superior predictor of cardiovascular risk [Ref 50,51].Lp(a) represents an LDL-like particle distinguished from LDL by the presence of apolipoprotein(a) (apo(a)), which is attached to the apolipoprotein B-100 molecule through disulfide linkage [Ref 52] . Apo(a) is highly homologous to the plasma protease zymogen plasminogen and thus it has been suggested that Lp(a) may promote thrombogenesis by inhibiting fibrinolysis .The large concentration gradient of Lp(a) between the aorta and renal vein [Ref 53] as well as the identification of apo(a) fragments in urine [Ref 54] suggest that the kidney may actively participate in the degradation of Lp(a). Thus, it is not surprising that patients with primary kidney diseases (even

those with normal GFR values) usually exhibit markedly elevated concentrations of Lp (a) [Ref 55,56] as well as increased concentrations of LDL-unbound apo(a) [Ref 57] . IDL, an intermediate of VLDL catabolism, accumulates in the plasma of CKD patients [Ref 58,59,60]. The IDL concentration is a predictor of the severity or progression of atherosclerosis [Ref 61].

Chylomicrons, that is, large triglyceride-rich particles of intestinal origin, are only transiently present in plasma in the postprandial state under physiological conditions [Ref 62]. It has been postulated that prolonged postprandial persistence of chylomicrons in the circulation causes endothelial damage and promotes atherosclerosis .In CKD patients, the clearance of chylomicrons is severely impaired [Ref 63]. This abnormality may contribute to the hypertriglyceridemia in CKD.

In addition to the aforementioned quantitative changes in serum lipoprotein concentrations, patients with CKD display important qualitative alterations in lipid metabolism that cannot be easily assessed with conventional laboratory techniques .Thus, it has been shown that VLDLs from individuals with impaired renal function have increased cholesterol content, while their triglyceride content is usually reduced.

In contrast, chronic renal failure usually results in decreased cholesterol content of LDLs and HDLs, whereas the triglyceride content of these particles is relatively increased. Finally, although uremic patients usually have a normal or slightly reduced LDL-cholesterol concentration, they exhibit important disturbances in the density distribution of LDL subfractions that is characterized by a predominance of small, dense LDL particles [Ref 64,65]. These particles are more atherogenic than the large, buoyant ones and can substantially contribute to the pathogenesis of atherosclerotic vascular disease [Ref 66].

It should be noted that in many instances development and progression of renal insufficiency are accompanied by heavy proteinuria, leading to superimposition of nephrotic dyslipidemia [Ref 67], on CRF-induced lipid disorders. In these circumstances, plasma total cholesterol and LDL cholesterol concentrations are frequently elevated. However, with progression to ESRD and the consequent decline in proteinuria (reduced filtered protein), a lipid profile typical of CRF emerges. It is of note that losses of proteins through the peritoneum in ESRD patients treated with chronic peritoneal dialysis simulate nephrotic syndrome and lead to a lipid profile that frequently includes hypercholesterolemia and an elevated LDL

level. The effects of peritoneal losses of protein on lipid metabolism in peritoneal dialysis patients are compounded by peritoneal absorption of large quantities of glucose, which tends to accentuate the hypertriglyceridemia.

CONSEQUENCES OF DYSLIPIDEMIA

Progression of Renal Disease Hyperlipidemia can potentially accelerate progression of renal disease by several mechanisms. First, reabsorption of fatty acids, phospholipids, and cholesterol contained in the filtered proteins (albumin and lipoproteins) by tubular epithelial cells can stimulate tubulointerstitial inflammation, foam cell formation, and tissue injury [Ref 68,69]. Second, accumulation of lipoproteins in glomerular mesangium can promote matrix production and glomerulosclerosis [Ref 70,71,72]. In this context, native and oxidized lipoproteins, particularly LDL, stimulate production of matrix proteins by cultured mesangial cells and promote generation of proinflammatory cytokines, which can lead to recruitment and activation of circulating and resident macrophages [Ref 73,74,75].

In addition, impaired HDL-mediated reverse cholesterol transport can further contribute to tissue injury by limiting the unloading of the excess cellular cholesterol and phospholipid burden. In fact, low plasma HDL has

been identified as an independent risk factor for progression of renal disease [Ref 76,77.]Moreover, hereditary LCAT deficiency, which is associated with a marked reduction in HDL cholesterol and impaired HDL-mediated reverse cholesterol transport, results in progressive renal disease [Ref 78]. The Modification of Diet in Renal Disease (MDRD) study identified low plasma HDL cholesterol as an independent risk factor for progression of renal disease.

Cardiovascular Disease

The risk of cardiovascular morbidity and mortality is profoundly increased in patients with CKD. For instance, the majority of patients with CKD die of cardiovascular events before reaching ESRD. Moreover, cardiovascular mortality among dialysis-dependent ESRD patients is 10- to 30- fold greater than in the general population despite stratification for gender, age, race, and the presence of diabetes. Numerous factors contribute to atherogenic diathesis and the high risk of cardiovascular disease in CKD. These include oxidative stress, inflammation, hypertension, and altered metabolism of lipids, carbohydrates, nitric oxide, calcium, and phosphate, among others. While plasma cholesterol concentration is frequently elevated in patients with nephrotic proteinuria and mild to moderate renal

insufficiency, it is frequently normal or reduced and only occasionally elevated in those with ESRD. Accordingly, the high risk of cardiovascular disease in ESRD populations cannot be attributed to hypercholesterolemia. On the contrary, a reduction in plasma cholesterol (which denotes intense inflammation) predicts cardiovascular events [Ref 79,80,81], in contrast to the pattern in the general population.

Impact on Energy Metabolism

VLDL and chylomicrons are the principal vehicles for the delivery of fatty acids to the skeletal muscles and myocardium for energy production and to the adipose tissue for energy storage. Fatty acids and glucose are the principal sources of energy that fuel all mechanical, biochemical, and biophysical functions of the body. Thus impaired LPL-mediated lipolysis of VLDL and chylomicrons, as well as, diminished VLDL receptor-mediated uptake of VLDL by skeletal muscle and myocardium, can necessarily limit the availability of fatty acid fuel in these tissues.

An Example Of Reverse Epidemiology Following the seminal report of Degoulet et al. [Ref 82,] numerous investigators found a paradoxical inverse relationship between plasma cholesterol concentration and overall mortality,

as well as cardiovascular mortality [Ref 83,84]. Usually a U- or J-shaped relationship was noted between plasma cholesterol concentration and cardiovascular mortality i.e., a higher mortality at low as well as high plasma cholesterol concentrations .The most plausible explanation for this paradox is that this represents an example of reverse epidemiology i.e., a relationship, which is reversed by a confounding factor. The recent work of Liu et al , is important in this respect. They identified microinflammation as a confounding factor.

This finding is important, because in such circumstances serum cholesterol and LDL cholesterol concentrations may no longer be a valid guide to establish the indication for lipid-lowering therapy. In the general population as much as 75% of the excess risk of coronary heart disease could be explained by traditional Framingham risk factors [Ref 85]. However, use of traditional risk factors underestimates the CVD risk in patients with CKD [Ref 86], while the Framingham predictive instrument demonstrates poor overall accuracy in predicting cardiac events in patients with mild to moderate CKD [Ref 87]. Moreover, traditional CVD risk factors were found often to relate to outcome in ESRD dialysis patients in an opposite direction, a phenomenon termed ‘reverse epidemiology’.

Lipids in Hemodialysis and Peritoneal Dialysis

Dialysis is very effective for the amelioration of uremic symptoms and certain features of uremic toxicity. The initiation of renal replacement therapy as well as the choice of dialysis modality may also influence the phenotypic characteristics of uremic dyslipidemia in patients with ESRD. However, the lipid and apolipoprotein profile that characterizes predialytic renal failure remains essentially unchanged during long-term hemodialysis (HD) [Ref88]. Thus, HD patients usually display increased concentrations of intact or partially metabolized triglyceride-rich lipoproteins, reduced serum levels of HDL-cholesterol and elevated concentrations of Lp (a). Total and LDL-cholesterol values are within normal limits or reduced in this patient population, whereas the subfractionation of apolipoprotein B-containing lipoproteins usually reveals a predominance of small, dense LDL particles. The pathophysiological mechanisms that underlie the alterations in lipoprotein metabolism in HD patients are generally similar with those described in predialysis renal failure individuals.

Despite the neutral effect of dialysis on serum lipid profile, certain dialysis-related parameters may significantly affect lipoprotein metabolism and modify the features of dyslipidemia in HD patients. Thus, it has been shown that the use of high-flux polysulfone or cellulose triacetate membranes instead of low-flux membranes is accompanied by a significant reduction in serum triglyceride levels as well as by an increase in apolipoprotein AI and HDL-cholesterol levels. This improvement could, at least in part, be attributed to an increase in the apolipoprotein C-II/C-III ratio which increases the activity of lipoprotein lipase and facilitates the intravascular lipolysis of triglyceride rich-lipoproteins.

In addition, the type of dialysate may also significantly affect the serum levels of lipoproteins in HD patients. Indeed, it has been shown that the use of bicarbonate dialysate may result in higher HDL-cholesterol concentrations than the use of acetate dialysate. Another factor that can potentially affect lipoprotein metabolism in HD patients is the repeated use of heparin as anticoagulant. Heparin releases lipoprotein lipase from the endothelial surface and thus its chronic use may result in lipoprotein lipase depletion and defective catabolism of triglyceride-rich lipoproteins.

Finally, recent studies indicate that the use of the phosphate-binder sevelamer hydrochloride significantly reduces the concentrations of total cholesterol and apolipoprotein B in HD patients. Obviously, the cholesterol-lowering properties of this compound are irrelevant to phosphate reduction and can be mainly attributed to its bile acid sequestrating properties.

In contrast to HD patients whose serum lipoprotein concentrations resemble those of redialysis renal failure subjects, continuous ambulatory peritoneal dialysis (CAPD) patients usually exhibit a more atherogenic lipid profile that is characterized by higher total and LDL-cholesterol values, increased apolipoprotein B concentrations, and more pronounced hypertriglyceridemia. In addition, CAPD patients have increased concentrations of small, dense LDL, higher Lp (a) values and reduced HDL-cholesterol concentrations compared to healthy age- and sex-matched individuals.

The pathophysiological mechanisms that exacerbate dyslipidemia in CAPD individuals are not well characterized. However, a number of factors have been proposed to play contributory roles in this exacerbation. It is well known that CAPD patients lose substantial amount of proteins into the

peritoneal dialysate, resembling the protein losses observed in NS. This protein loss may, in turn, stimulate the hepatic production of albumin and cholesterol enriched lipoproteins thus leading to elevated concentrations of LDL-cholesterol and Lp (a). In addition, the absorption of glucose from the dialysis fluid and the resultant increase in insulin levels may enhance the hepatic synthesis and secretion of VLDL and possibly that of other lipoproteins such as Lp (a). Recent studies indicate that the reduction in glucose load with the use of less absorbed icodextrin- containing dialysis solution instead of glucose for the overnight dwell sufficiently reduces the serum levels of total and LDL-cholesterol as well as the concentrations of triglycerides and small, dense LDL particles.

It should be noted that even though substantial amounts of apolipoproteins and intact lipoproteins (especially HDL) are lost via the peritoneal cavity in CAPD patients, the pathophysiological significance of these losses as well as their impact on lipoprotein metabolism remain indeterminate. In a recent study we investigated the efficiency of the phosphate-binder sevelamer hydrochloride in the treatment of hyperphosphatemia and its influence on serum lipid parameters in patients on CAPD. The data from this prospective, randomized, cross-over study

indicate that, over a period of 8 weeks, the drug effectively lowered serum phosphorus and also had a significant beneficial effect on both total and LDL-cholesterol serum levels.

Drug Therapy of Dyslipidemia in CKD Patients

Interventional studies have shown that the pharmacological reduction of total and LDL-cholesterol values is followed by an impressive decrease in the risk of the development of ischemic events. Thus, based on the extremely high cardiovascular mortality that characterizes the individuals with CKD, the Work Group for Kidney Disease Outcomes Quality Initiative (K/DOQI) published the Clinical Practice Guidelines for Managing Dyslipidemias in CKD [Ref 89], and proposed the adoption of Adult Treatment Panel (ATP) III LDL-cholesterol targets [Ref 90], for individuals with stage 5 CKD. In other words, these guidelines suggested that in individuals with ESRD an LDL-cholesterol value lower that 100 mg/dl should be achieved.

However, the utilization of LDL cholesterol as a target for preventive therapy in patients with CKD has several important limitations. It is well known that LDL-cholesterol is commonly determined by the Friedewald calculation in specimens from fasting subjects and with triglyceride

concentrations of <400 mg/dl. However, the equation is considerably inaccurate even at triglyceride concentrations of 200–400 mg/dl [Ref 91]. Thus, since uremic dyslipidemia is mainly characterized by increased concentrations of triglycerides, the use of Friedewald equation for the determination of LDL cholesterol values in this patient population may result in important measurement errors. As a consequence, it has been proposed that a number of different equations that take into consideration the serum levels of apolipoprotein B may be more appropriate in individuals with impaired renal function.

An alternative approach to this problem is the calculation of non-HDL-cholesterol (total cholesterol – HDL cholesterol) values. The calculation of this parameter (which represents the sum of the concentrations of all apolipoprotein B-containing particles) overcomes the methodological limitations of LDLcholesterol determination, does not require fasting specimens [Ref 92] and, most importantly, in addition to LDL particles takes into account the concentrations of all apolipoprotein B-containing particles such as LDL, Lp(a), IDL and chylomicron remnants [Ref 93]. Several studies have shown that the concentrations of these particles (that are not captured by conventional LDL measurement) are elevated in patients with renal

failure and may independently contribute to the determination of future cardiovascular risk. The National Kidney Foundation guidelines suggest non-HDL-cholesterol values of < 130 mg/dl as a secondary target of therapy in individuals with triglyceride values of 1 200 mg/dl .

Treating high low-density lipoprotein cholesterol for CKD patients with LDL 100 to 129 mg/dL it is reasonable to attempt to lower LDL to less than 100 mg/dL with therapeutic lifestyle changes. If after 3 months this target has not been reached, a statin should be added. Patients with LDL greater than or equal to 130 mg/dL are unlikely to reach target with diet alone, so diet and a statin should generally be started simultaneously. Statins are safe in patients with CKD, but drug interactions (eg, with macrolide antibiotics, azole antifungal agents, dihydropyridine calcium channel blockers, and cyclosporine A) should be avoided or should prompt a reduction in the dose of the statin.

Acute and chronic liver disease should be ruled out before initiation of a statin, but it is not necessary to obtain routine liver enzymes to screen for hepatotoxicity thereafter. Patients should be told that if they develop unusual muscle soreness or pain, indicating possible statin-induced myopathy. It has

been suggested that a base line CPK be obtained to help interpret CPK levels when myopathy is suspected.

For patients with LDL persistently greater than or equal to 130 mg/dl despite diet and maximum statin therapy, consideration should be given to adding a second agent. For second agent, fibrates should be avoided. If triglycerides are not elevated then a bile acid sequestrant is an option. The new cholesterol absorption inhibitor ezetimibe may have fewer gastrointestinal adverse effects than bile acid sequestrant, and ezetimibe seems to be safe in patients with CKD. It is well known that statins are by far the most commonly prescribed hypolipidemic drugs in the general population, and numerous large, randomized, prospective studies have shown that their use is accompanied by an impressive reduction in the incidence of cardiovascular events [Ref 94].

On the other hand, data from studies conducted in individuals with CKD suggest that the effect of these drugs on cardiovascular morbidity and mortality in this patient population is significantly influenced by the severity of renal dysfunction. Thus, in several large, prospective, placebo-controlled trials of statins, post hoc analyses of subgroups with mild to moderate renal

failure revealed a significant reduction in cardiovascular morbidity and mortality [Ref 95,96,97,98]. The same results were also obtained by studying prespecified subgroups of individuals with impaired renal function in the HPS [Ref 99], and ASCOT-LLA [Ref 100], studies that utilized simvastatin and atorvastatin, respectively.

As a consequence, the use of statins as a first-line therapy for the prevention of ischemic events in dyslipidemic individuals with CKD (stages 1–3) seems to be a safe, reasonable and evidence-based approach. Nevertheless, similar findings were also reported in a recent small Scandinavian study that showed a significant decrease in cardiovascular end points after atorvastatin administration in patients with predialysis renal failure but no effect in individuals who were on maintenance HD [Ref 101].

Several mechanisms have been proposed for the explanation of the failure of statins to improve cardiovascular outcomes in individuals with advanced renal failure. Thus, it has been suggested that the development of atherosclerosis in this population may have a different athophysiological basis (arterial wall calcification, inflammation, etc.), whereas other investigators emphasized that lipoproteins other than LDL (such as Lp(a),

IDL, etc.) may play a significant role in the initiation and progression of coronary atherosclerosis [Ref 102].

Finally, it has been proposed that the beneficial effect of statins may be confounded by the presence of micro-inflammation and/or malnutrition in individuals with ESRD. Whatever the cause, and while awaiting the results of ongoing statin trials in this patient population, we believe that the decision for the administration of statins in HD patients should be individualized. It is well known that fibrates reduce the concentrations of triglycerides, increase the serum concentrations of HDL-cholesterol and induce a shift in the LDL subfraction distribution towards larger and more buoyant particles.

Thus, these drugs could represent an ideal option for the treatment of uremic dyslipidemia. However, it has been shown that the administration of fibrates (possibly with the exception of gemfibrozil) in individuals with impaired renal function is associated with an extremely high risk of muscular toxicity [Ref 103,104]. In addition, these drugs also significantly increase serum Creatinine values. Although it has been proposed that this increase does not represent a true deterioration in renal function but rather is due to increased metabolic production of creatinine.

In addition, the impact of fibrates on cardiovascular end points in individuals with impaired renal function has not been extensively studied.

Thus, although an observational study suggested that the use of fibrates in patients with renal failure does not reduce total mortality [Ref 105], a post hoc analysis of the secondary prevention VAHIT study revealed that the administration of gemfibrozil in individuals with moderate renal failure reduced the risk of the primary end point (coronary death or nonfatal myocardial infarction) by 27% [Ref 106].

In our opinion fibrates should be used only in the subpopulation of patients with CKD who exhibit extremely elevated triglycerides values (1 500 mg/dl). In these cases the risk of acute pancreatitis justifies the use of gemfibrozil as the fibrate of choice in individuals with impaired renal function, although previous studies have shown that its administration in CKD patients may, in some cases, be followed by muscle aches and a significant rise in serum creatine phosphokinase values.

A number of other hypolipidemic drugs that are increasingly used in the general population (such as niacin –3 polyunsaturated fatty acids and ezetimibe) may also play important roles in the management of uremic

dyslipidemia. However, although small studies have documented the efficiency and the tolerability of these substances in patients with chronic kidney disease, there is a lack of evidence concerning their impact on the cardiovascular risk in this patient population.

The patients with LDL greater than or equal to 100 mg/dl, the LDL should be the target of therapy. Patients with normal LDL but triglycerides greater than or equal to 200 mg/dl and non-HDL cholesterol greater than or equal to 130 mg/dl, however should be treated. The goal should be reduce the non-HDL cholesterol to less than 130 mg/dl.

P

MATERIALS AND METHODS

1. This study was conducted in 50 patients of CKD in stage 3,4 and 5. They are selected as inpatients of Government Royapettah Hospital during January 2008 to August 2008. This study also included 50 people as control group.

2. Study design: Case control study.

Inclusion Criteria

1. Patients with chronic kidney disease stage 3,4 and 5 on conservative management or dialysis irrespective of etiology except due to diabetes mellitus.
2. Patients with creatinine clearance less than 60ml/min were included.
3. Patients with bilaterally contracted kidneys on abdomen USG with poor cortico medullary differentiation were included.

Exclusion Criteria

Patients with obesity, diabetes mellitus, past history of coronary heart disease , patients with smoking and alcoholism , pregnancy, patients on B-blockers and OCPs were excluded.

50 age and sex matched normal healthy individuals were selected as control. A detailed history and clinical examination were performed in all patients. Height, weight, BP of all patients were recorded. Apart from routine investigations blood urea, creatinine, electrolytes, creatinine clearance by using Cockcroft-Gault equation were measured.

NKF KDOQI (National Kidney Foundation- Kidney Disease Outcomes Quality Initiative) staging system was used to classify patients.

Stage 1: GFR >90 ml/min/1.73m^2

Stage 2: GFR 60-89 ml/min/1.73m^2

Stage 3: GFR 30-59 ml/min/1.73m^2

Stage 4: GFR 15-29 ml/min/1.73m^2

Stage 5: GFR <15 ml/min/1.73m^2 (or dialysis).

Blood pressure:

Right upper arm blood pressure is taken in supine position by using sphygmomanometer under appropriate condition.

Renal function test:

Blood samples are collected for blood urea and serum creatinine and analyzed in the laboratory at GRH, Chennai.

USG abdomen:

Ultrasonogram of abdomen was done for all individuals in this study.

Lipid profile:

Blood samples were obtained on one occasion from antecubital venepuncture after an over night fast (12 hrs) from all patients.

Triglycerides were estimated by enzymatic colorimetric method.

TC was estimated using enzymatic method.

HDL was estimated by phosphotungstate method.

LDL cholesterol was calculated by Friedewald`s equation.

LDL = TC - Triglycerides/5 – HDL

The VLDL was estimated by dividing the plasma Triglycerides by 5. This formula is used only on patients with fasting Triglycerides level of less than 350 mg/dl.

According to National Cholesterol Treatment Program Adult Treatment Panel III guidelines, normal values are,

LDL cholesterol (with 2+ risk factors)	<130 mg/dl
HDL cholesterol	>40 mg/dl
Triglycerides	<150 mg/dl
Total cholesterol	<200 mg/dl

ECG:

A standard 12 lead resting electrocardiogram was taken for all individuals in this study.

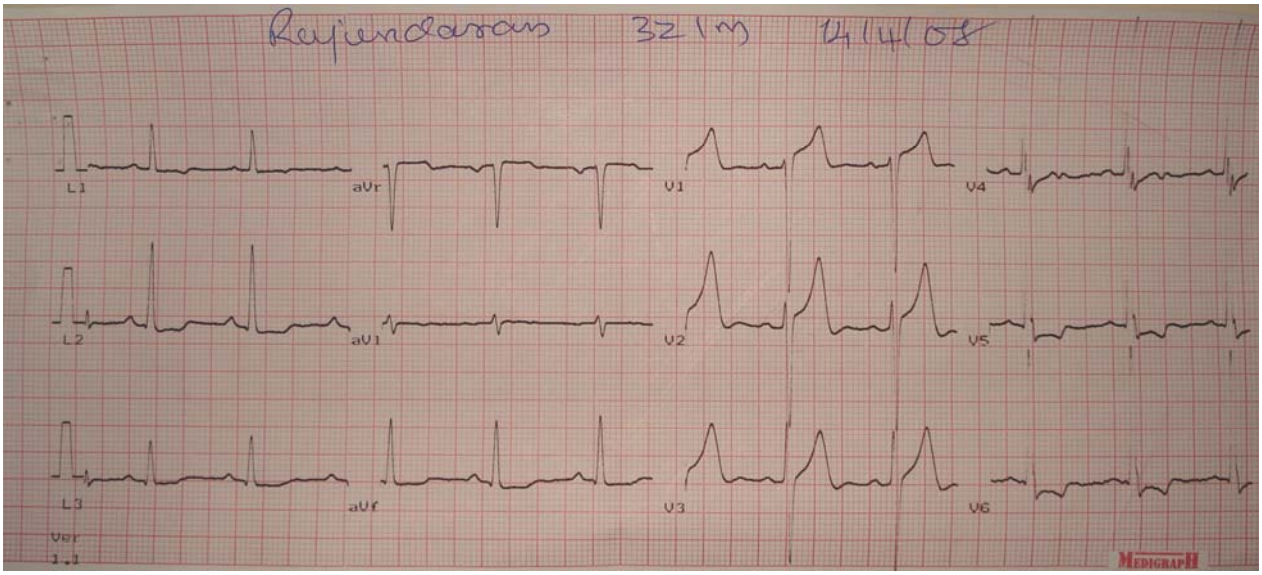
Romhilt-Estes point score system [Ref 107]:

Probable left ventricular hypertrophy is diagnosed if 4 points are present and definite left ventricular hypertrophy is diagnosed if 5 or more points are present.

Romhilt-Estes point score system

Criterion	Points
Any limb R wave or S wave >/=2.0 mV (20 mm) OR S in V1 or S in V2 >/= 3.0 mV (30 mm) OR R in V5 or R in V6 >/= 3.0 mV (30 mm)	3
ST-T wave changes typical of LVH Taking digitalis Not taking digitalis	 1 3
Left atrial abnormality P terminal force in V1 is 1 mm or more in depth with a duration >/= 40 ms (0.04 sec)	3
Left axis deviation >/= -30[a]	2
QRS duration >/= 90 ms	1
Intrinsicoid deflection in V5 or V6 >/= 50 ms (0.05 sec) *	1

ECG – Features of LVH



Results and observation

One hundred patients took part in this study. Out of hundred patients fifty were known case of CKD and the remaining fifty were control. Of the 50 CKD patients 18 were female and the remaining 32 were male. Their age varied from 28 to 52 yrs. All the 50 patients who took part in the study were found to be hypertensive at the beginning of the study. Their systolic BP varied from 130 to 180 mmHg and diastolic BP varied from 90 to 120 mmHg. Of the 50 patients 34 were known hypertensive on treatment, others were newly detected for the first time on admission. Five patients had previous history of dialysis.

Eight patients had arcus senilis and on fundus examination ten patients showed features of hypertensive retinopathy grade 3. Xanthoma was found in two patients. Blood urea levels varied from 47 mg/dl to 160 mg/dl. Creatinine levels varied from 3 mg/dl to 12 mg/dl. 32 patients had bilateral contracted kidneys on ultrasonogram. In 8 patients electro cardiogram showed features of LVH. In 14 patients electro cardiogram showed features of myocardial ischemia.

Total cholesterol was above 200 mg/dl in 13(26%) patients. Serum triglycerides were above the upper limit of normal (150 mg/dl) in 39 (78%) patients. HDL was less than 40 mg/dl in 45 (90%) patients. LDL cholesterol was above 130 mg/dl in 14(28%) patients and above 100 mg/dl in 42(84%) patients. Ratio between Total cholesterol and HDL cholesterol was above 6 in 20(40%) patients. Type 4 hyperlipidemia was present in 39 out of 50 patients.

Observations about triglycerides in this study;

For study group;

The lowest value of triglycerides in this study was 53 mg/dl. The highest value was 338 mg/dl. Mean triglycerides of the study group was 197.26 mg/dl. The mean deviation was 45.51 mg/dl. The standard deviation was 59.75 mg/dl. The standard error of mean was 8.45.

For control group;

The lowest value of triglycerides in this control group was 72mg/dl. The highest value was 212 mg/dl. Mean triglycerides of the control group was 127.78 mg/dl. The mean deviation was 20.54 mg/dl. The standard deviation was 27.53 mg/dl. The standard error of mean was 3.89.

Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. The standard error of difference between the two mean was 9.30. The actual difference of the mean between the two groups was 69.48, which is more than twice of standard error of difference between the two mean. The P value equals 0.0002. By conventional criteria, this difference is considered to be extremely statistically significant. So the difference in serum triglycerides values between the two groups is statistically significant.

Observations about HDL cholesterol in this study;

For study group;

The lowest value of HDL cholesterol in this study was 29 mg/dl. The highest value was 52 mg/dl. Mean HDL cholesterol of the study group was 34.18 mg/dl. The mean deviation was 3.46 mg/dl. The standard deviation was 4.62mg/dl. The standard error of mean was 0.65.

For control group;

The lowest value of HDL cholesterol in this control group was 38 mg/dl. The highest value was 78 mg/dl. Mean HDL cholesterol of the control group was 52.90 mg/dl. The mean deviation was 8.82 mg/dl. The standard deviation was 10.41 mg/dl. The standard error of mean was 1.47.

Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. The standard error of difference between the two mean was 1.61. The actual difference of the mean between the two groups was 18.72, which is more than twice of standard error of difference between the two mean. The P value is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant. So the difference in serum HDL cholesterol values between the two groups is statistically significant.

Observations about LDL cholesterol in this study;

For study group;

The lowest value of LDL cholesterol in this study was 70 mg/dl. The highest value was 209 mg/dl. Mean LDL cholesterol of the study group was 118.61mg/dl. The mean deviation was 14.72 mg/dl. The standard deviation was 21.27mg/dl. The standard error of mean was 3.01.

For control group;

The lowest value of LDL cholesterol in this control group was 49 mg/dl. The highest value was 154 mg/dl. Mean LDL cholesterol of the control group was 100.02 mg/dl. The mean deviation was 19.55 mg/dl. The standard deviation was 23.92 mg/dl. The standard error of mean was 3.38.

Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. The standard error of difference between the two mean was 4.53. The actual difference of the mean between the two groups was 18.59, which is more than twice of standard error of difference between the two mean. The P value equals 0.0005. By conventional criteria, this difference is considered to be extremely statistically significant. So the difference in serum LDL cholesterol values between the two groups is statistically significant.

Observations about total cholesterol in this study;

For study group;

The lowest value of total cholesterol in this study was 125 mg/dl. The highest value was 276 mg/dl. Mean total cholesterol of the study group was 192.24mg/dl. The mean deviation was 14.64 mg/dl. The standard deviation was 22.55mg/dl. The standard error of mean was 3.19.

For control group;

The lowest value of total cholesterol in this control group was 141 mg/dl. The highest value was 230 mg/dl. Mean total cholesterol of the control group was 178.48 mg/dl. The mean deviation was 16.66 mg/dl. The standard deviation was 20.34 mg/dl. The standard error of mean was 2.88.

Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. The standard error of difference between the two mean was 4.29. The actual difference of the mean between the two groups was 13.76, which is more than twice of standard error of difference between the two mean. The P value equals 0.0019. By conventional criteria, this difference is considered to be very statistically significant. So the difference in serum total cholesterol values between the two groups is statistically significant.

Ratio between total cholesterol and HDL cholesterol

The ratio between total cholesterol and HDL cholesterol is considered as a risk factor for coronary artery disease, when the value exceeds 6. In this study 20 out of 50 patients were found to have more than 6.

For study group;

The lowest value of ratio between total cholesterol and HDL cholesterol in this study was 3.37. The highest value was 7.88. Mean ratio between total cholesterol and HDL cholesterol of the study group was 5.7. The mean deviation was 0.8. The standard deviation was 1.0. The standard error of mean was 0.1.

For control group;

The lowest value of ratio between total cholesterol and HDL cholesterol in this control group was 2.3. The highest value was 5.4. Mean ratio between total cholesterol and HDL cholesterol of the control group was 3.5. The mean deviation was 0.7. The standard deviation was 0.9. The standard error of mean was 0.1.

Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. The standard error of difference between the two mean was 0.19. The actual difference of the mean between the two groups was 2.2, which is more than twice of standard error of difference between the two mean. The P value is less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant. So the difference in ratio between total cholesterol and HDL cholesterol between the two groups is statistically significant.

All the 20 patients with ratio of TC to HDL-C of more than 6 were having Creatinine clearance of less than 29ml/min i.e, stage 4 and 5 CKD.In Peritoneal Dialysis patients, both total cholesterol and LDL cholesterol are within normal limits whereas HDL cholesterol is decreased. It was found that the serum concentration of increased triglycerides, decreased HDL cholesterol ,increased LDL cholesterol ,increased total cholesterol were statistically significant in CKD patients stage 3,4 and 5.

P

Discussion

The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide and are associated with poor outcomes. CVD as the major cause of mortality in patients with mild to moderate CKD and end- stage renal disease (ESRD). Approximately 50% of patients with ESRD die from a cardiovascular event, which indicates a cardiovascular mortality that is 30 times higher in dialysis patients and 500 times higher in 25- to 34-year-old ESRD patients than in individuals from the general population of the same age and race. Premature CVD extends from mild to moderate stages of CKD.

Vaziri ND, Moradi H et al study states that the most common quantitative lipid abnormalities in predialysis CKD patients are hypertriglyceridemia, increased concentrations of triglyceride-rich lipoprotein remnants, reduced high-density lipoprotein (HDL)-cholesterol levels as well as increased concentrations of lipoprotein(a) (Lp(a))[Ref 108]. Notably, total and LDL-cholesterol levels are usually within normal limits or slightly reduced in these individuals.

Liu Y, Coresh J, Eustace JA, et al reported in their study that the typical profile of patients with chronic kidney disease, that is, the constellation of

moderate elevation of plasma triglyceride concentrations, combined with low plasma HDL-cholesterol, corresponds to the pattern of dyslipidemia type IV according to Frederickson et al. In CKD, total cholesterol is usually normal or even low. This may be the result of an additional microinflammatory state and/or malnutrition [Ref 109].

In our study, lipid profile shows increased plasma triglyceride concentrations, combined with low plasma HDL-cholesterol as similar with that of Vaziri ND, Moradi H et al and Liu Y, Coresh J, Eustace JA, et al study but, total cholesterol and, LDL-cholesterol were increased.

The most common type of dyslipidemia observed in Liu Y, Coresh J, Eustace JA, et al study was type IV according to Frederickson et al.[Ref 110] Similar reports were observed by Bagdade JD, Yee E, Wilson D, and Shafrir E et al [Ref 111]. Also in our study the most common type of dyslipidemia is type IV according to Frederickson.

Plasma triglyceride concentration is frequently elevated in patients and experimental animals with CRF. However, plasma cholesterol concentration is usually normal, even reduced, and only occasionally elevated in patients with

end-stage renal disease (ESRD). Elevation of plasma triglycerides in ESRD patients is accompanied by increased plasma concentration and impaired clearance of VLDL. This is associated with the accumulation of atherogenic VLDL remnants, commonly known as IDL. Similarly, clearance of chylomicrons is impaired and plasma concentration of chylomicron remnants is elevated in CRF patients. In contrast, plasma concentration of LDL is usually normal and only occasionally elevated in ESRD patients. Plasma HDL concentration is consistently reduced [Ref 112].

In addition to the quantitative abnormalities cited above, the composition of plasma lipoproteins is altered in CRF [Ref 113]. For instance, the cholesterol content of VLDL is relatively increased and its triglyceride content is relatively reduced in CRF. In contrast, CRF results in a relative reduction in cholesterol and relative increase in the triglyceride content of LDL. Similarly, cholesterol ester and free cholesterol content of HDL are consistently reduced, whereas its triglyceride content is elevated, in CRF. The above compositional abnormalities are present in nearly all patients with mild to severe renal insufficiency (even those with normal plasma total cholesterol and triglyceride levels) and point to redistribution of cholesterol from HDL to VLDL and ID and defective removal of triglycerides from LDL and HDL particles.

The most common lipid abnormality in our study is decreased HDL in 74% of patients. Similar observation has been reported by Burrell et al. HDL – cholesterol was found to have a positive correlation with creatinine clearance by grutz macher et al. LCAT plays an important role in HDL-mediated cholesterol uptake from the extrahepatic tissues. LCAT deficiency can potentially account for diminished plasma HDL cholesterol and impaired HDL maturation in CRF.

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 Ref 114.

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.

Hypertriglyceridemia is a common feature of CRF [Ref 115] and causes include increased synthesis and/or diminished clearance from the circulation. Because renal insufficiency causes insulin resistance, which can, in turn, promote hepatic VLDL production, it has been suggested that increased production may be responsible, in part, for CRF-associated elevations in plasma VLDL and triglycerides.

The relationship between total cholesterol and atherosclerotic CAD is curvilinear according to the Multiple Risk Factor Intervention Trial (MRFIT) .If a risk ratio of 1.0 is arbitrarily assigned at a total cholesterol level of 200 mg/dl, the risk ratio increased to 2 at 250 mg/dl and 4 at 300 mg/dl. The Cholesterol Lowering Atherosclerotic Study (CLAS) demonstrated the benefit of cholesterol lowering even in patient with normal or moderately increased cholesterol level.

Although desirable blood Cholesterol value may be below 200 mg/dl or even much lower at 150 mg/dl, it needs reemphasizing that the cholesterol level is only part of the patient's absolute global risk.

LDL-cholesterol values above 130 mg/dl despite diet warrant drug therapy in those at medium risk, while in those at highest risk with CHD or equivalents, the goal is less than 100 mg/dl or less than 70 mg/dl in some cases. The calculation of non-HDL-cholesterol (total cholesterol – HDL cholesterol) values represents the sum of the concentrations of all apolipoprotein B-containing particles, overcomes the methodological limitations of LDL cholesterol determination, does not require fasting specimens and, most importantly, in addition to LDL particles takes into account the concentrations of all apolipoprotein B-containing particles such as VLDL, Lp(a), IDL and chylomicron remnants .

Several studies have shown that the concentrations of these particles (that are not captured by conventional LDL measurement) are elevated in patients with renal failure and may independently contribute to the determination of future cardiovascular risk [Ref 116,117]. The National Kidney Foundation guidelines suggest non-HDL-cholesterol values of 130 mg/dl as a secondary target of therapy in individuals with triglyceride values of 1 200 mg/dl . Usually a U- or J-shaped relationship was noted between plasma cholesterol concentration and cardiovascular mortality i.e., a higher mortality at low as well as high plasma cholesterol concentrations .The most plausible explanation for this paradox is

that this represents an example of reverse epidemiology [Ref 118,119,] i.e., a relationship, which is reversed by a confounding factor. The recent work of Liu et al. [Ref 120], is important in this respect. They identified microinflammation as a confounding factor.

Patients with CKD are at high risk for developing CVD. Most CKD patients have a 10 year risk of coronary heart disease events greater than or equal to 20%, placing them in the hightest risk category according to the national cholesterol education program adult treatment panel 3 guidelines.[Ref 121]. Meta analysis of 13 small prospective studies revealed a significant reduction in the rate of decline in the glomerular filtration rate (GFR) and marginal reductions in proteinuria and progression toward ESRD with lipid-lowering therapy primarily with various statins [Ref 122] .

Similarly, the Heart Protection Study showed a significantly lower rate of rise in serum creatinine concentration in the statin-treated group compared with the placebotreated group [Ref 123]. Also, in a large study of patients with coronary heart disease and dyslipidemia, statin administration for 3 yr resulted in a significant improvement in creatinine clearance compared with a placebo group.

However, among patients with a baseline GFR below 40 ml/min, statin administration was associated with a significantly lower rate of decline in estimated GFR. The beneficial effects of statins have been attributed to both the lipid-lowering and lipid-independent anti-inflammatory (via interference with isoprenylation processes) action of these drugs.

Dyslipidemia represents an integral component of CKD. Disturbances in lipoprotein metabolism (mainly accumulation of intact or partially metabolized apolipoprotein B-containing particles as well as reduced concentrations of HDL-cholesterol) are evident even at the early stages of CKD and usually follow a downhill course that parallels the deterioration in renal function. Since several intrinsic (genetic, primary kidney disease) or exogenous (drugs, method of renal replacement) factors can influence the phenotypic expression of these alterations, the precise knowledge of the pathophysiological mechanisms that underlie their development is of paramount importance.

Recently published studies indicate that dyslipidemia in these patients may actively participate in the pathogenesis of CVD as well as in the deterioration of renal function. Thus, we believe that the current evidence dictates the use of statins in patients with mild to moderate CKD. On the other

hand, in subjects with ESRD the decision for the institution of lipid-lowering therapy should be individualized.

Thus, in individuals with established CVD as well as in those who run a high risk for acute pancreatitis due to severe hypertriglyceridemia, the administration of hypolipidemic drugs (statins and gemfibrozil respectively) is a safe and reasonable approach.

Conclusion

1. Most common lipid abnormality in this study is statistically significant reduction of HDL-Cholesterol level in patients with Chronic Kidney Disease stage 3,4 and 5 .
2. There is a statistically significant increase in serum triglycerides level in patients with CKD stage 3,4 and 5.
3. There is a statistically significant increase in serum LDL-Cholesterol and Total Cholesterol level in patients with CKD stage 3,4 and 5 .
4. There is a negative correlation between serum HDL-Cholesterol and severity of renal failure.
5. There is a positive correlation between the ratio of Total Cholesterol to HDL-Cholesterol and severity of CKD.
6. In Peritoneal Dialysis patients, both Total Cholesterol and LDL-Cholesterol are within normal limits whereas HDL- Cholesterol is decreased.
7. Systemic hypertension is statistically associated with CKD.

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Proforma

A Study on Dyslipidemia in CKD

Name of the patient :

Age / Sex :

IP/OP No :

Address :

Height (mts) : Weight (kgs) : BMI :

Diagnosis :

Chief Complaints :

Past History of

1. DM : Yes/No
2. Coronary heart disease : Yes/No
3. Hypertension : Yes/No
4. Thyroid Disease : Yes/No
5. Drug intake (Steriods, Anti thyroid drugs, Estrogen/OCP, B-blockers) : Yes/No
6. PD : Yes/No
7. HD : Yes/No

Personal History of

1. Smoking :
2. Alcoholism :

General Examination

PR (per min) :

BP (mm Hg) :

Xanthomas/Xanthelesma :

Arcus senilis :

Fundus changes :

Systemic Examination

CVS :

RS :

Abdomen :

CNS :

Investigations

Blood sugar(mg/dL) :

Urea (mg/dL) :

Creatinine (mg/dL) :

Sodium(mEql/L) :

Potassium (mEql/L) :

Creatinine clearance (ml/min) :

Lipid profile(mg/dL)

TC :

TGL :

HDL –C :

LDL- C :

Ratio of TC to HDL-C :

USG abdomen :

ECG :

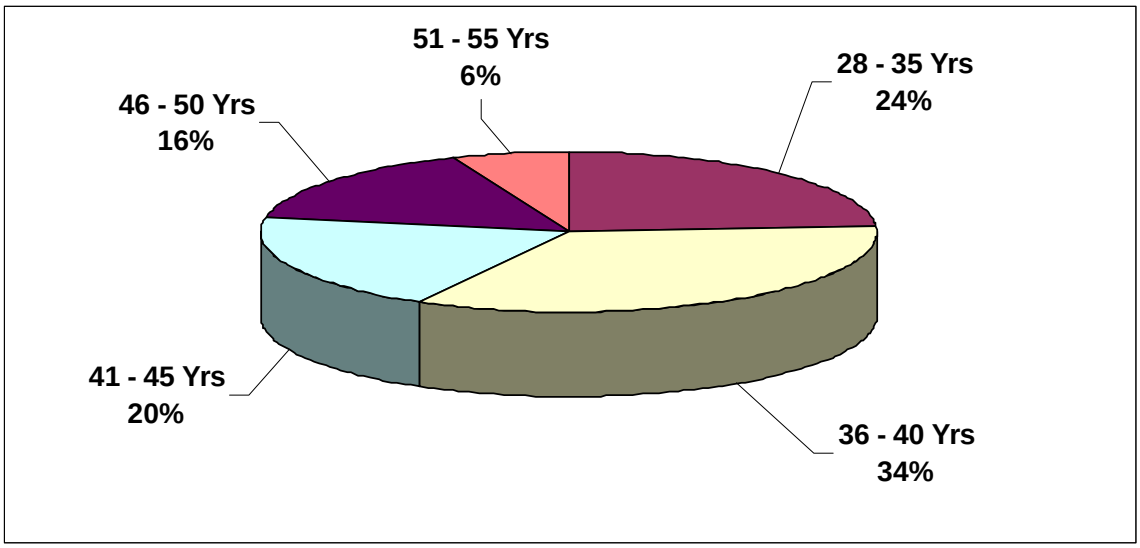
Table 1. Age Distribution in this Study

Age (Yrs)	No of Patients	Percentage
< 28	0	0
28 - 35	12	24
36 - 40	17	34
41 - 45	10	20
46 - 50	8	16
51 - 55	3	6

Table 2. Sex Distribution in this Study

Sex	No of Patients	Percentage
Male	32	64
Female	18	36

Age Distribution in this Study



Sex Distribution in this Study

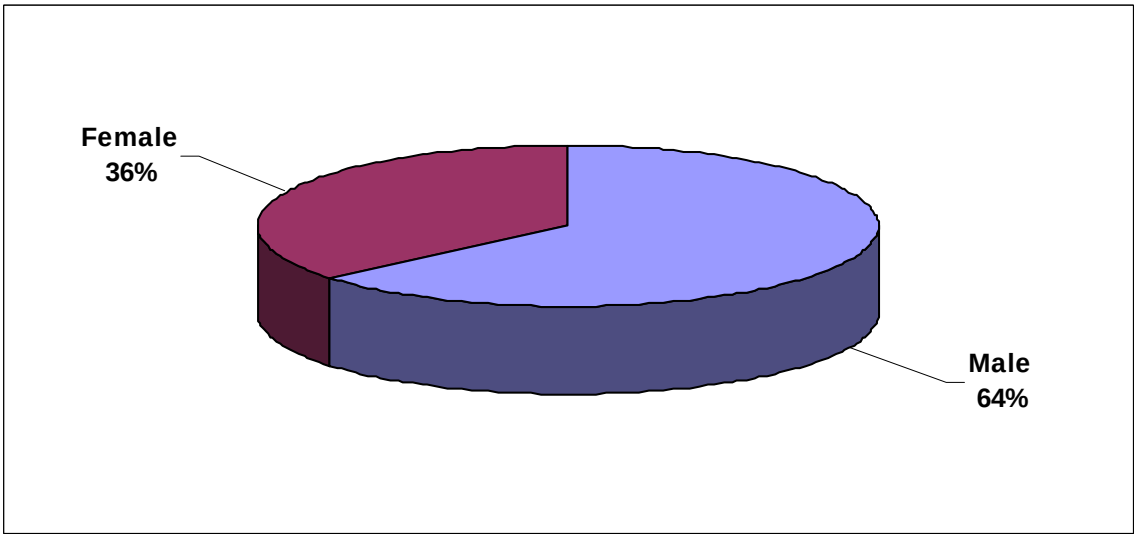


Table 3. Classification of Systemic Hypertension JNC-VII

BP Classification	SBP mm Hg	DBP mm Hg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥160	or ≥100

When systolic and diastolic pressure falls into different categories, the higher category should be selected to classify the individuals BP.

Isolated Systemic Hypertension is defined as systolic BP of greater than 140 mmHg and a diastolic BP of less than 90 mmHg.

Table 4. Systemic Hypertension in the Study

BP Classification	Number of Patients	Percentage
Stage 1 hypertension	26	52
Stage 2 hypertension	24	48

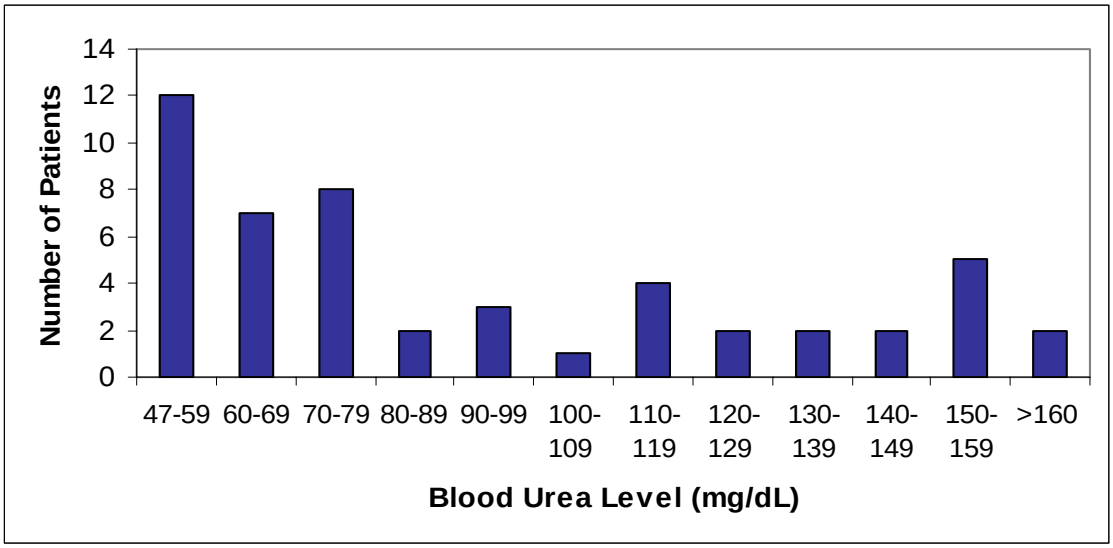
Table 5. Blood Urea – An Analysis in this Study

Blood Urea (mg/dL)	No. of Patients	Percentage
47-59	12	24
60-69	7	14
70-79	8	16
80-89	2	4
90-99	3	6
100-109	1	2
110-119	4	8
120-129	2	4
130-139	2	4
140-149	2	4
150-159	5	10
>160	2	4

Table 6. Serum Creatinine – An Analysis in this Study

Serum Creatinine (mg/dL)	No. of Patients	Percentage
3-5.9	16	32
6-8.9	20	40
9-11.9	14	28

Blood Urea – An Analysis in this Study



Serum Creatinine – An Analysis in this Study

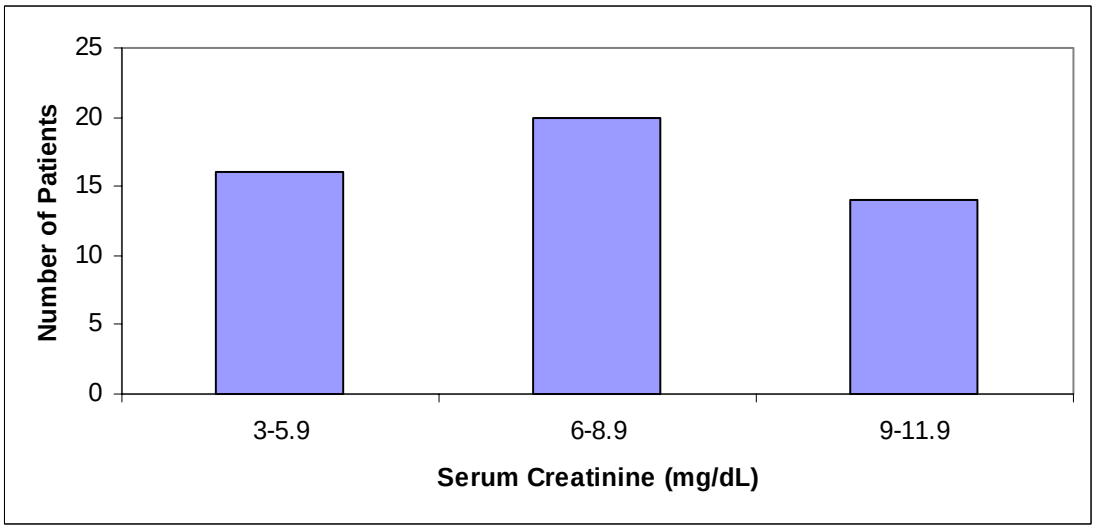


Table 7. Statistical Analysis – Study Group

	TC	TGL	HDL-C	LDL-C	Ratio
Mean	192.24	197.26	34.18	118.61	5.7
Mean Deviation	14.64	45.51	3.46	14.72	0.8
Std Deviation	22.55	59.75	4.62	21.27	1.0
Std Error of Mean	3.19	8.45	0.65	3.01	0.1
Std Error of Difference Between Two Mean	4.29	9.30	1.61	4.53	0.2

Table 8. Statistical Analysis – Control Group

	TC	TGL	HDL-C	LDL-C	Ratio
Mean	178.48	127.78	52.9	100.02	3.5
Mean Deviation	16.66	20.54	8.82	19.55	0.7
Std Deviation	20.34	27.53	10.41	23.92	0.9
Std Error of Mean	2.88	3.89	1.47	3.38	0.1

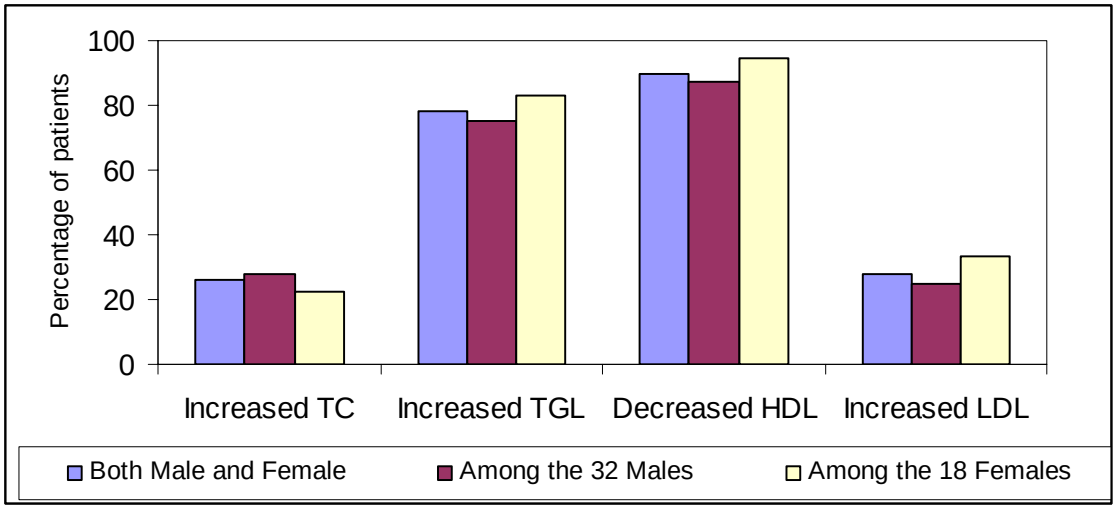
Table 9. Lipid Abnormality in Study Group

Lipid Disorder	Both Male and Female in % (No of Patients)	Among the 32 Males in % (No of Patients)	Among the 18 Females in % (No of Patients)
Increased TC	26 (13)	28.1(9)	22.2(4)
Increased TGL	78(39)	75 (24)	83.3(15)
Decreased HDL	90 (45)	87.5 (28)	94.4 (17)
Increased LDL	28(14)	25(8)	33.3(6)

Table 10. Lipid Abnormality in Control Group

Lipid Disorder	No. of Patients	Percentage
Increased TC	7	14
Increased TGL	3	6
Decreased HDL	3	6
Increased LDL	4	8

Lipid Abnormality in Study Group



Lipid Abnormality in Control Group

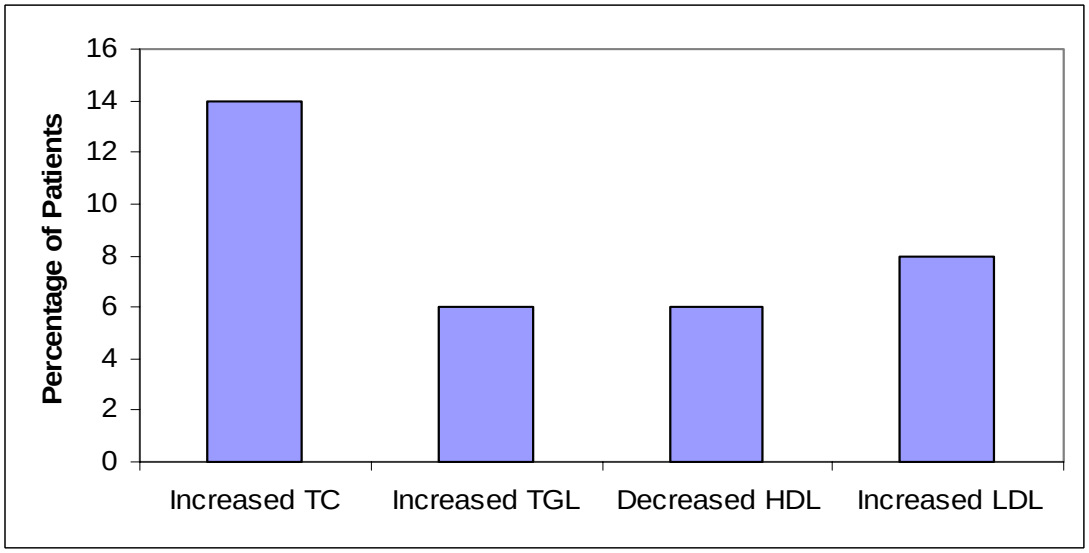


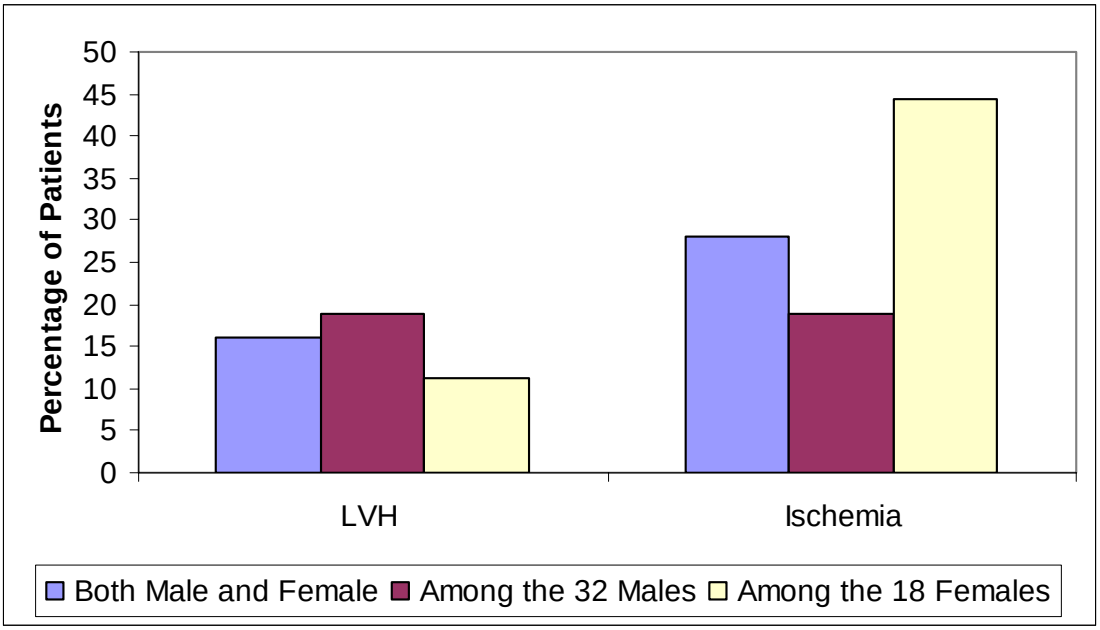
Table 11. ECG Changes in CKD Patients

Type of ECG changes	Both Male and Female in % (No of Patients)	Among the 32 Males in % (No of Patients)	Among the 18 Females in % (No of Patients)
LVH	16 (8)	18.8 (6)	11.1 (2)
Ischemia	28 (14)	18.8 (6)	44.4 (8)

Table 12. Comparative Analysis of Previous Reports with Present Study

Study	TC	TGL	HDL-C	LDL-C
Liu Y, Coresh J, Eustace JA, et al.	Normal or even low	Increased	Decreased	Normal
Vaziri ND et al.	Normal or even low	Increased	Decreased	Normal or slightly reduced
Present study	Increased	Increased	Decreased	Increased

ECG Changes in CKD Patients



Lipid Profile – Control Group

S.No	TC	TGL	HDL-C	LDL-C	Ratio
1	202	212	40	120	5.1
2	192	140	46	118	4.2
3	205	132	41	138	5.0
4	193	128	45	122	4.3
5	191	144	42	120	4.5
6	205	140	38	139	5.4
7	204	140	54	122	3.8
8	178	118	56	98	3.2
9	183	144	59	95	3.1
10	170	132	43	101	4.0
11	199	124	76	98	2.6
12	183	146	39	115	4.7
13	188	132	47	115	4.0
14	230	140	48	154	4.8
15	146	122	50	72	2.9
16	152	134	41	84	3.7
17	171	128	45	100	3.8
18	164	122	53	87	3.1
19	179	140	78	73	2.3
20	159	104	69	69	2.3
21	160	112	70	68	2.3
22	209	114	39	147	5.4
23	194	102	45	129	4.3
24	177	98	48	109	3.7
25	171	192	67	66	2.6

S.No	TC	TGL	HDL-C	LDL-C	Ratio
26	170	138	66	76	2.6
27	159	92	60	81	2.7
28	142	198	53	49	2.7
29	160	108	58	80	2.8
30	214	148	60	124	3.6
31	154	134	58	69	2.7
32	192	100	58	114	3.3
33	141	126	46	70	3.1
34	182	148	42	110	4.3
35	168	131	49	93	3.4
36	197	98	40	137	4.9
37	160	92	44	98	3.6
38	177	94	53	105	3.3
39	199	140	58	113	3.4
40	178	150	52	96	3.4
41	180	144	59	92	3.1
42	170	72	60	96	2.8
43	195	84	62	116	3.1
44	173	86	64	92	2.7
45	184	142	68	88	2.7
46	200	98	60	120	3.3
47	150	104	64	65	2.3
48	153	142	46	79	3.3
49	154	142	45	81	3.4
50	167	138	41	98	4.1