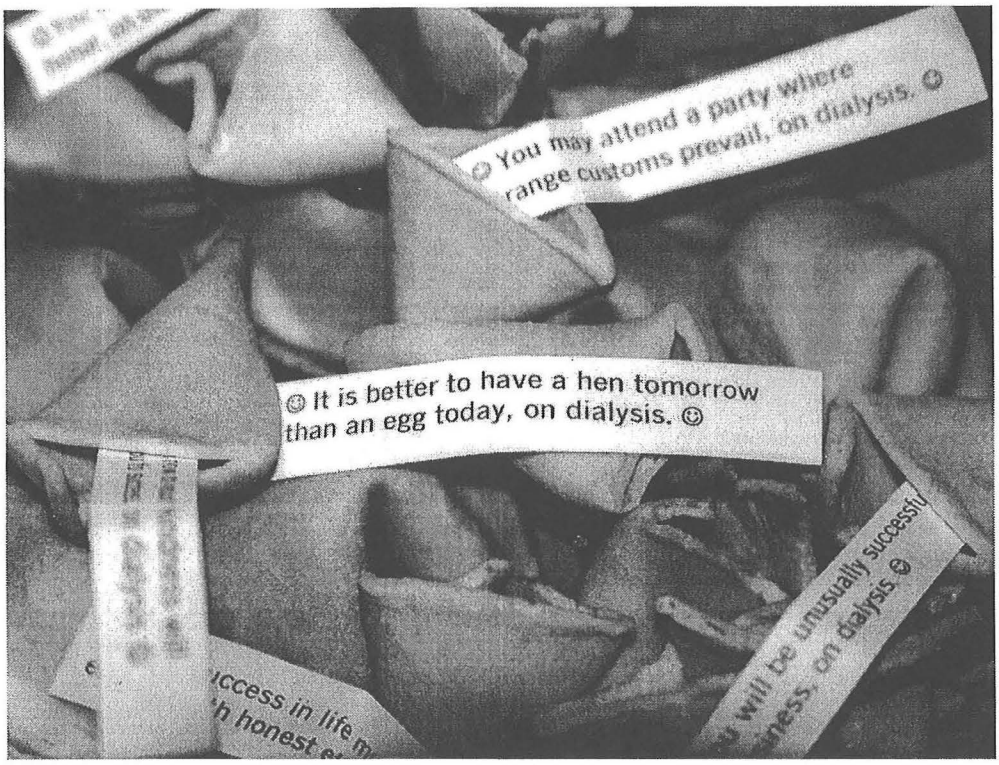
# Dyslipidemia and Renal Disease: Coincidence, Complicity, or Fate?

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This is to acknowledge that John Middleton, M.D., has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Middleton will not be discussing "off-label" uses in his presentation.

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**Dyslipidemia, Morbidity and Mortality in Renal Disease.** The span and quality of lives for patients with renal disease are restricted by complications from cardiovascular disease. Patients with nephrotic syndrome, progressive chronic renal failure, and end-stage renal disease (ESRD) are at increased risk of heart disease due to abnormal lipid metabolism. Over the last decade our management of patients with permanently impaired renal function has resulted in better medications, enhanced dialysis techniques, and refined immunosuppression protocols for renal transplantation. However, cardiovascular disease accounts for nearly half of the deaths in patients maintained on regular dialysis treatments, and strokes cause an additional 6% of deaths (118). Recent advances in preventing allograft rejection and treating infectious complications are almost completely masked by cardiovascular complications in transplant patients (56). In addition to dyslipidemia, a variety of factors likely increase cardiovascular risk in patients with renal disease. This discussion will address how abnormal lipoprotein metabolism contributes to the morbidity and mortality of patients with renal disease.

**Rearranging the "chicken-or-egg?" question.** The relationships among renal disease, cardiovascular disease, and dyslipidemia are discontinuous and possibly bi-directional. On the one hand, some patients with renal disease suffer increased cardiovascular morbidity and mortality due to traditional risk factors. In nephrotic syndrome, for instance, patients are at risk for cardiac events due to co-morbid conditions and elevated circulating LDL levels, similar to the general population (45). The situation is different for patients maintained on dialysis, where the "traditional" risk estimates of total and LDL cholesterol may be within acceptable range, but the patients experience numerous cardiovascular events (36,123). To further complicate these relationships, there is a two-way relationship between kidney function and lipid metabolism. We will explore conditions where abnormal lipids and disturbed metabolism create a primary insult to the kidney, and we will review the data that suggest that circulating lipids are toxic for progressive renal diseases.

RISK FACTORS FOR VASCULAR DISEASE IN PATIENTS WITH RENAL DYSFUNCTION

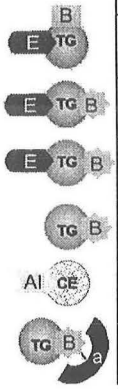
- TRADITIONAL FACTORS:
  - HYPERLIPIDEMIA
  - HYPERTENSION
  - DIABETES MELLITUS
  - SMOKING
  - SEDENTARY LIFESTYLE
- DYSLIPIDEMIA
- ELEVATED PTH LEVELS
- DECREASED 1,25 VITAMIN D
- ARTERIAL CALCIFICATION
- HYPERURICEMIA
- ABNORMAL GLUCOSE METABOLISM
- INFLAMMATION
- PROTHROMBOTIC FACTORS

**Normal Metabolism of Lipids and Transfer of Plasma Lipoproteins.** Cholesterol and triglyceride arise from exogenous or endogenous sources and are continuously shuttled from sites of absorption or formation to regions of utilization or storage. This process requires coupling of water-insoluble lipids with specific apolipoproteins to form lipoproteins

particles that are soluble (10,61). Major lipoprotein classes can be classified according to size and density, as shown in Figure 1. In general terms, plasma concentrations of these lipoproteins are controlled by governors of synthesis, interconversion among particle types, and catabolism. Each step involves: 1) The apolipoproteins (apo) A-I, A-II, A-IV, B, C-I, C-II, C-III, D, E and apo (a); 2) The converting proteins lipoprotein lipase (LPL), hepatic lipase (HL), lecithin-cholesterol acyl transferase (LCAT), and cholesterol ester transfer protein; 3) The lipoprotein receptors for LDL, the LDL-related protein, and scavenger receptors. Different forms of renal disease can affect metabolism at any of these loci.

A fraction of cholesterol is derived from diet. Non-esterified ester, along with triacylglycerol and apo E, is incorporated into chylomicron particles (108,126). By interacting with the hepatic LDL receptor and LDL-related protein, chylomicrons are removed from circulation. VLDL is formed after addition of apo B in the liver, and VLDL carries triglycerides with cholesterol synthesized *de novo* in the liver or from chylomicrons. Other apolipoproteins (e.g., apo C and apo E) are added after the VLDL has entered the plasma (108,126). Lipoprotein lipase (LPL) is the peripheral enzyme that binds VLDL, releases fatty acids, and allows triglyceride uptake in tissues. The catabolism of VLDL requires LPL and availability of apo C-II (58).

**Figure 1**: Lipoprotein Classification




| | Density (g/ml) | Unique apo-lipoproteins | Other apo-lipoproteins |
|---|---|---|---|
| Chylomicrons | <.94 | B48b | A-I, A-IV, C-I, C-II, C-III; E |
| VLDL | .94-1.006 | B100 | C-I, C-II, C-III; E |
| IDL | 1.006-1.019 | B100 | C-I, C-II, C-III; E |
| LDL | 1.019-1.063 | B100 | |
| HDL | 1.063-1.21 | A-I and A-II | C-I, C-II, C-III; D; E |
| Lp(a) | | a and B | |

Most of the cholesterol in the body derives from the process of "reverse" cholesterol transport. Every cell is capable of synthesizing cholesterol from acetyl CoA and incorporating it into the cell membrane. The membrane non-esterified cholesterol can be dispersed into the surrounding fluid to return to the liver. Cholesterol associates with apo A-I to form the HDL particle, and the cholesterol becomes esterified within the HDL particle by action of LCAT (47,58,108). Cholesterol ester is transferred to apo B-containing particles, VLDL and LDL, a process that requires cholesterol ester transfer protein (47). A triglyceride-rich particle remains, HDL-2. Hepatic lipase promotes cholesterol ester uptake by liver and forms the relatively triglyceride-poor HDL-3. In the normal state, then, by combined actions of cholesterol intake and reverse transport, HDL and LDL particles are the primary means of circulating cholesterol to the liver (83,108,126).

**Lipoprotein (a) (Lp(a)).** The Lp(a) particle has a unique mode of regulation, particularly in patients with renal disease, and it is an important contributor to atherogenic risk. Lp(a) is composed of LDL covalently bound to apo (a) via a disulfide bond through apoB-100. The Lp(a) particle is structurally distinct because of the nature of apo (a), one of the most polymorphic human proteins known (48). Apo (a) is highly glycolsylated and varies in size

from 300-800 kDa, and it exhibits a structural homology to plasminogen (48,75). Repeat sequences (called Kringles) KI-KIII that are present in plasminogen are absent in apo (a). Instead, KV is present in one copy, and KIV is expressed in a highly variable number of copies (48,75). A better understanding of the means of genetic control of apo (a), and especially the KIV repeats is critical. There is an inverse correlation with the apo (a) isoform size (determined by the number of KIV repeats) and the serum concentration of Lp(a) (94), and genetic control of the apo (a) isoform accounts for 40-70% of the inter-individual variability (48,94).

For patients with renal disease, the genetic and acquired conditions that control plasma Lp(a) may be particularly important. In the general population, most surveys suggest that Lp(a) is an independent risk factor for coronary artery disease (24,46,71,73,75,104,107). The plasma concentration of Lp(a) varies over 1000-fold among different patients (72,75). Patients who are normolipemic but have serum Lp(a) >30 mg/dl, a level present in 20% Caucasians and 50-60% Blacks, carry a nearly 2-fold higher risk of having a myocardial infarction (12,15,40,70,71). If both LDL and Lp(a) are elevated, the relative risk approaches 5 for myocardial infarction (71,72). It remains unclear if Lp(a) serves a specific metabolic function or if it is merely an evolutionary by-product. Regardless, the overwhelming message from current observations is that high Lp(a) levels confer increased cardiovascular risk.

**Estimated lipoprotein abnormalities in target populations**

| | Cholesterol >240 | LDL-C >130 | HDL-C <35 | TC >200 | Lp(a) >30 |
|---|---|---|---|---|---|
| General US pop'n (%) | 20 | 40 | 15 | 15 | 15 |
| NS (%) | 90 | 85 | 50 | 60 | 60 |
| CRF (%) | 30 | 10 | 35 | 40 | 45 |
| ESRD:HD (%) | 20 | 30 | 50 | 45 | 30 |
| ESRD:PD (%) | 25 | 45 | 20 | 50 | 50 |
| ESRD:Tx (%) | 60 | 60 | 15 | 35 | 25 |

## NEPHROTIC SYNDROME AND DYSLIPIDEMIA

Hyperlipidemia either in adults or children is a hallmark of nephrotic syndrome (99). Changes in serum lipids are characterized by increased cholesterol levels, although hypertriglyceridemia may be present as well (30,99). Nephrotic patients lose intermediate-sized proteins, predominantly albumin, in the urine. The low serum albumin that results lowers plasma oncotic pressure. Paradoxically, the abundance of high molecular weight proteins such as lipoproteins are increased in the serum (99). In nephrotic syndrome,

variable increases in VLDL, LDL, Lp(a), and IDL particles occur, with near-normal total HDL, compared to normal subjects (33,58,91,99,104,125).

**What triggers a change in lipid profiles in patients who excrete high amounts of protein in the urine?** The stimulus for these changes in nephrotic syndrome is unclear. One postulate states that proteinuria reduces serum oncotic pressure, and this leads to an increase in hepatic synthesis of proteins. In fact, low oncotic pressure and hyperlipidemia in humans are partially reversed by dextran infusions (59). However, dyslipidemia in nephrotic rats is not fully reproduced in animals that are devoid of serum albumin (26). An alternative theory suggests that a substance that is excreted in the urine in nephrotic syndrome ( a "liporegulator") is excreted in the urine in nephrotic syndrome, and that this creates abnormal lipid catabolism or increased synthesis. In one series of observations heparan sulfate, an activator for LPL, was decreased in the plasma in patients with nephrotic syndrome (59). Infusion of small amounts of heparan sulfate normalized the rate of chylomicron disappearance in nephrotic animals, a profile that is usually prolonged in nephrotic syndrome (59). The liver is an important site of sensing the diminished plasma oncotic pressure in nephrotics, but the kidney is probably responsible for losing a substance that maintains normal lipid metabolism (99).

**Abnormal lipid metabolism in nephrotic syndrome.** Most observations suggest that the abnormal lipid profile in nephrotic syndrome results from aberrant removal of serum lipids or components from serum. In the case of VLDL, nephrosis diminishes the abundance of mRNA for LPL (58). Even more dramatic, the endothelial-bound pool of LPL can be reduced as much as 90% compared to normal amounts (60). The abundance of ApoC-II, a circulating factor that is required for full LPL activity, is diminished in nephrotic patients compared to the excess serum concentration of VLDL(58,125). These changes in LPL quantity, activation, and location diminish VLDL clearance in nephrotic syndrome.

**Factors that Lead to Dyslipidemia in Nephrotic Syndrome**

- Diminished apo C-II/VLDL ratio
- Decreased VLDL receptor expression
- Lower HL amount
- Diminished LPL activity
- Loss of LPL binding to endothelial surface
- Increased VLDL apo B-100 levels due to diminished catabolism
- Higher LDL apo B as a consequence of enhanced synthesis
- Acquired hepatic LDL receptor deficiency

In addition to increases in plasma VLDL, nephrotic patients also tend to exhibit abnormal plasma HDL. In nephrotic patients, LCAT activity is diminished because hypoalbuminemia limits access of the enzyme to lecithin, and a secondary decrease in HDL2 results (58,83). HDL metabolism is further altered in nephrotic syndrome by a marked down-regulation of an HDL receptor (83). Therefore, the efficiency of HDL as the primary vehicle for reverse cholesterol transport is limited in nephrosis (Figure 2).

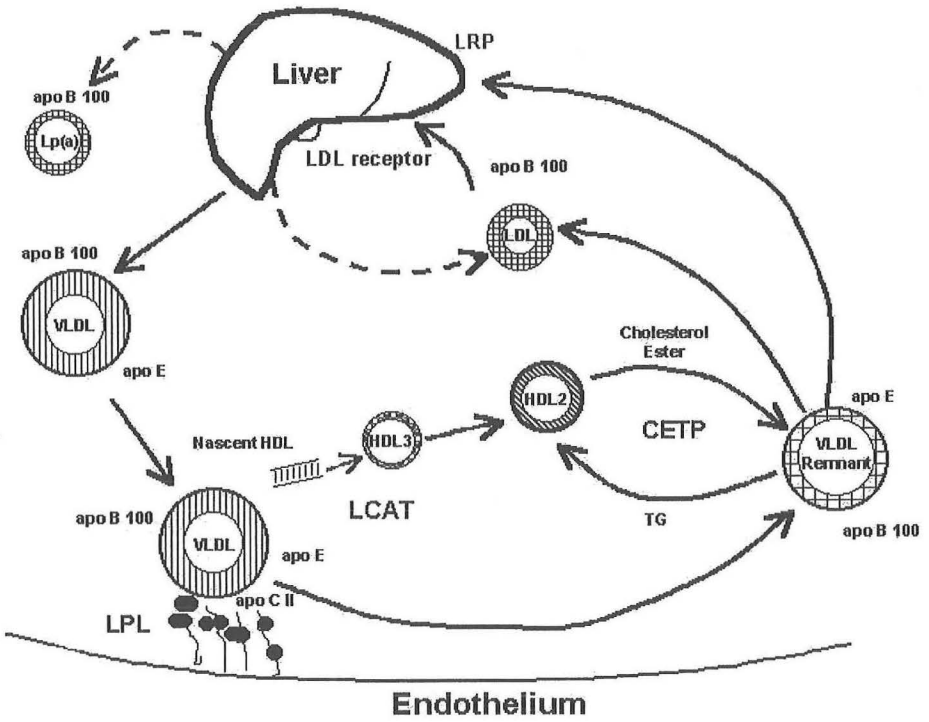



**Figure 2:** Relevant sites for dyslipidemia in nephrotic syndrome (58).

Several mechanisms may explain augmented synthesis of lipoproteins in nephrosis. In 1979, Marsh and Sparks proposed an "overproduction" hypothesis: synthesis of a large group of proteins (including albumin) is increased in the liver, and this change includes a coordinated increased synthesis of apo B and, ultimately, apo B-containing lipoproteins (87). Davis and co-workers suggested that low serum albumin increases apo B synthesis by hepatocytes in a less direct manner, by increasing the available free fatty acids (28). In normal patients, LDL arises from VLDL, but in patients with nephrotic syndrome some of the LDL apo B is derived from liver synthesis rather than VLDL (33,58). To directly address these possible mechanisms, a metabolic study of a small group of patients with nephrotic syndrome showed that absolute synthetic rate of apo B-100 did not correlate with albumin production (30). In addition, Vega and coworkers here at UT Southwestern demonstrated that LDL apo B kinetics differed in nephrotic patients, depending if they had hypercholesterolemia alone or combined with hypertriglyceridemia (121). These observations suggest that nephrotic patients, in addition to hepatic synthesis, may form LDL through an alternate pathway. Therefore, increased VLDL in nephrotic patients probably results from a decreased catabolism, while increased LDL likely results from enhanced synthesis (30).

Plasma concentrations of lipoprotein (a) (Lp(a)) are also commonly elevated in patients with nephrotic syndrome. In cross-sectional studies, Lp(a) correlates with urinary albumin excretion (18,42). In a small study of non-diabetic glomerular diseases with nephrotic syndrome and hypertension, mean Lp(a) levels were more than 4-fold elevated compared

to normal controls, but levels decreased 40% with combined ACE inhibitor and NSAID therapy (39). The elevation in Lp(a) in nephrotic syndrome is most likely due to enhanced synthesis alone, independent of the apo (a) isoform (42,104). Much information about the metabolism of Lp(a) is lacking, but given its unique metabolism and homology with plasminogen, it could be an important mediator of the clinical complications of nephrotic syndrome.

**Does nephrotic dyslipidemia predispose to atheromatous disease?** A major hazard of nephrotic syndrome is the development of a hypercoagulable state. This risk arises from altered endothelial cell function, increased platelet reactivity, loss of coagulation inhibitors in the urine, and increased procoagulant factors (99). Even though adult patients are more likely to have complications from venous rather than arterial thrombosis, an increase in coronary events occurs in patients with nephrotic syndrome. Even after controlling for age, gender, hypertension, and smoking, the relative risk for myocardial infarction was 5.5 and for coronary death was 2.8 in one retrospective study of nephrotic patients (84). It is unclear if this risk is due to the hypercoagulable state or to nephrotic dyslipidemia.

**Factors that Lead to Dyslipidemia in Patients with Pre-ESRD Renal Failure**

- Diminished LDL plasma clearance
  - Lower LDL-R abundance
  - Poor LDL-R binding
  - Abnormal conformation of LDL apo B or LDL-R
- Decreased LPL activity
- Decreased HL activity
- Accumulation of CETP inhibitor
- Modified LDL composition
- ? Decreased Lp(a) clearance

## DYSLIPIDEMIA IN PATIENTS WITH DIMINISHED GFR

Even in the absence of nephrotic syndrome, serum lipids have abnormal composition in patients with diminished renal function. Lipid abnormalities begin to be recognized in patients when the GFR falls below 40-50ml/min (9). The most common biochemical abnormality is hypertriglyceridemia (7,8,37,49,54,61,62). The profile usually shows minimally elevated LDL, decreased HDL, and dramatically increased VLDL (8,9,58). Most patients with renal failure have markedly reduced reverse cholesterol transport. There is reduced cholesterol transport from the HDL particle to LDL and VLDL components (84). Apolipoprotein profiles show increased plasma concentration of apo C-III as the earliest detectable change as the GFR diminishes (7). Compared to normal subjects, patients with mild degrees of renal insufficiency have decreased apo A-I and apo A-II, normal levels of apo B and apo C-I, and elevated concentrations of apoC-II, C-III and apoE (8). Compared with other patients with hypertriglyceridemia (e.g., type 2 diabetes mellitus or type IV hyperlipoproteinemia), patients with chronic renal failure have

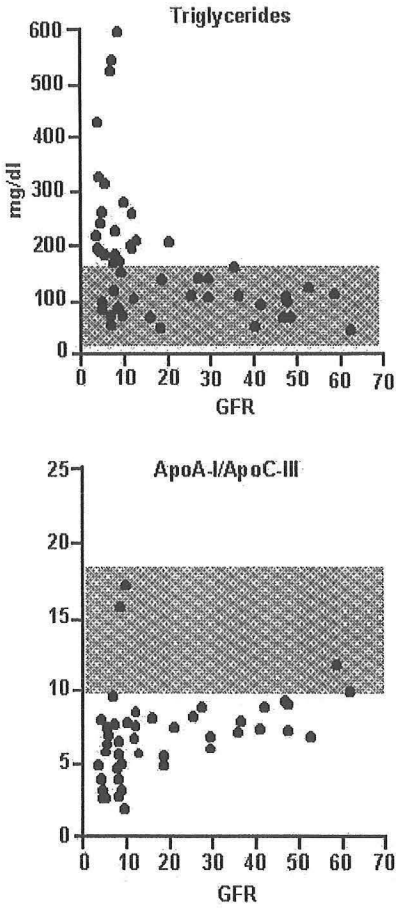



**Figure 3:** Changes in plasma triglyceride and apolipoproteins in chronic renal failure (10).

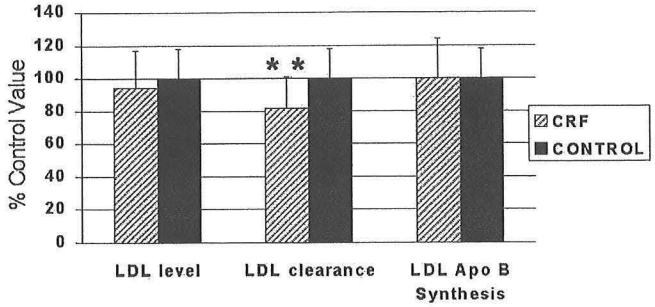



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**Figure 4:** Diminished LDL clearance in patients with pre-ESRD renal failure.

especially low apo A-I, Apo A-II, apo B, apo C-I and apo E (8). As the GFR falls, triglyceride-rich particles are formed that incorporate apo C-III (8) (Figure 3).

Several "defects" are present in uremia that impair lipoprotein metabolism (8,75). As GFR decreases, LCAT activity falls (75). In metabolic studies in humans with renal failure, the synthetic rate of LDL apo B is similar to normal patients, but the clearance of radiolabeled LDL is significantly delayed (49) (Figure 4). The possible contributors to poor LDL clearance include: 1. Attenuated affinity of the LDL particle for its receptor (83,122). Changes in LDL components, such as carbamylation, oxidation, or glycosylation, could result in altered conformation of apo B and a decreased affinity for the LDL receptor (49,84). 2. The LDL receptor becomes abnormal in uremia. The uremic environment could cause the LDL receptor to undergo post-translational modification (49). 3. The abundance of the LDL receptor may be decreased in chronic renal failure, decreasing clearance of the LDL particle. At least at the mRNA level, this has been demonstrated for peripheral tissues in patients with renal failure (103).

**Patients with pre-ESRD renal failure and Lp(a).** Lipoprotein a (Lp(a)) has a strong negative correlation to GFR. Liver failure, androgens, estrogens, thyroid hormone, and nicotinic acid all decrease hepatic synthesis and thus decrease plasma Lp(a) levels (48,75). In contrast, it has been described for more than ten years that elevated Lp(a) plasma concentrations are present in patients with renal failure (6,24,42,66,68,75,81,92,93,97). When GFR falls, elevated plasma levels of Lp(a) may result from lower clearance. With normal renal function, Lp(a) concentration is 9% lower in renal veins compared to aorta, suggesting that intact Lp(a) is taken up by the kidney (74). Even though intact Lp(a) is not detectable in urine, proteolytic fragments are excreted

(48,74,94). Alternatively, the kidney could play an indirect role to control Lp(a) concentration. Patients with chronic renal failure could have a circulating secondary signal that controls Lp(a) synthesis or clearance (75). Though the precise mechanism is unknown, kidney failure is one of the most common acquired states that affects plasma levels of Lp(a).

Surprisingly few studies have directly examined the relationship between GFR and Lp(a). Lp(a) is increased in patients with moderate renal insufficiency, suggesting that changes in clearance occur early in the disease (17). In Figure 5 a significant correlation was observed in over 400 subjects with normal or minimally depressed creatinine clearances (114). In other cross-sectional studies, no difference was found in the frequency of low molecular weight apo(a) isoforms between patients with normal and early impaired renal function, suggesting that renal failure alone is responsible for elevation of serum Lp(a) levels in patients with moderately decreased GFR (102). The data support that patients with abnormal renal function could be at an especially high risk to develop complications of elevated plasma Lp(a).

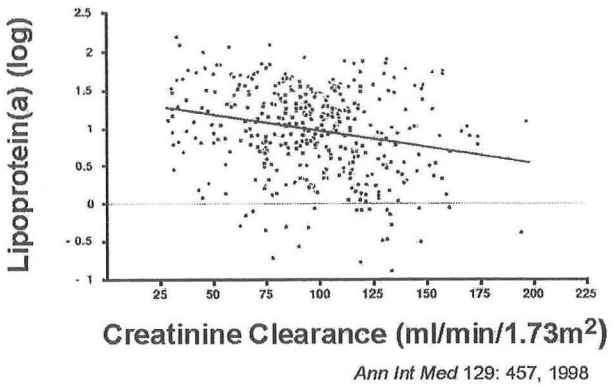



**Figure 5:** Relationship between GFR and Lp(a) in cross-section of patients with moderate renal failure.

Compared to other demographic groups, plasma concentrations of Lp(a) are 2-3-fold higher in African Americans (12,15,40). Since Lp(a) is implicated in the progression of coronary artery disease and glomerular sclerosis, it may explain the disproportionate morbidity and mortality associated with hypertension in African Americans. For example, only 12% of the U.S. population is black, but blacks comprise more than 30% of the ESRD population in this country (118). Furthermore, more than 36% of patients with hypertension as a cause of ESRD are African American (2,19). It is not clear what accounts for the apparent increased renal and cardiovascular morbidity in the African American population, it is not accounted for solely by the higher prevalence of hypertension nor by socioeconomic factors.

**Does abnormal lipid metabolism in pre-ESRD renal failure increase risk for coronary artery disease?** Cardiac complications in chronic renal failure can have myriad manifestations. The prevalence of left ventricular hypertrophy (LVH) is probably higher in patients with CRF than the general population. Nearly a third of patients with GFR 25-49ml/min and nearly a half of those <25ml/min have evidence of LVH (81). Children with diminished GFR are more likely to have increased LV mass compared to normals (52). The prevalence of coronary artery disease in the general population is 5-12% (80). In pre-ESRD renal failure, the prevalence of coronary disease is probably significantly higher. In one follow-up study in France, 147 otherwise healthy, pre-ESRD patients were followed

for 10 years, and parameters that pertained to atherogenesis were examined (54). The incidence of myocardial infarction was 2-3-fold higher in patients with renal insufficiency than in the general population in France, and the independent risk factors (determined by multivariate analysis) were smoking, systolic blood pressure, HDL cholesterol, and fibrinogen (54). Total cholesterol, triglyceride, apo A and apo B, Lp(a) were not predictive of events. In a series of patients with more severe renal insufficiency managed without dialysis in Sweden, nearly 45% had evidence of arterial occlusive disease (8). These data suggest that atheromatous complications are more common in patients with decreased GFR, even before the start of renal replacement therapy.

**Is abnormal lipid metabolism in pre-ESRD renal failure toxic to the kidneys?** Several relationships are possible to explain the concurrence of dyslipidemia and renal failure: 1. They occur simultaneously but are not causally related; 2. The loss of kidney function initiates the abnormal lipid metabolism; 3. Both abnormalities share an initiating factor; or 4. Abnormal lipid metabolism promotes renal failure.

**Can lipids be toxic to normal kidneys?** Several extreme maneuvers in laboratory animals and a few human conditions demonstrate that impaired lipid metabolism can be a primary renal insult (reviewed in 44). Severe abnormalities of circulating lipids are present in the disorder of insulin resistance and lipodystrophy (89). The kidney disease that commonly occurs in this disorder is membranoproliferative glomerulonephritis (89). In LCAT deficiency, patients who are homozygous (-/-) for LCAT have been described to have, in addition to severe abnormalities in LDL metabolism, a primary glomerular disease (41). Kidney biopsies show evidence of enlarged lipid-laden glomeruli and ultimately, advancing glomerulosclerosis. Interestingly, serum from these patients are also completely deficient in Lp(a) and apo(a), suggesting that action of LCAT on LDL is required for Lp(a) synthesis (32).

Lipoprotein glomerulopathy (LPG) is an unusual and rare disease recently described in Japan, characterized by capillary occlusion with intraglomerular lipoprotein thrombi and high plasma concentrations of apo E (55,67,98,109) (Figure 6). In the glomerulus, electron microscopy shows that lipoprotein thrombi consist of lipid granules of various sizes (90). In a few cases described, the glomerular lesion is associated with inherited apo E variants, including apo E2 (Arg145Pro) Sendai (110) and apo E2 (Arg25Cys) Kyoto (55,90,98). LDL receptor-binding activities of the variants may affect the receptor-binding ability of apo E (90). Different from other types of hyperlipoprotein abnormalities, the

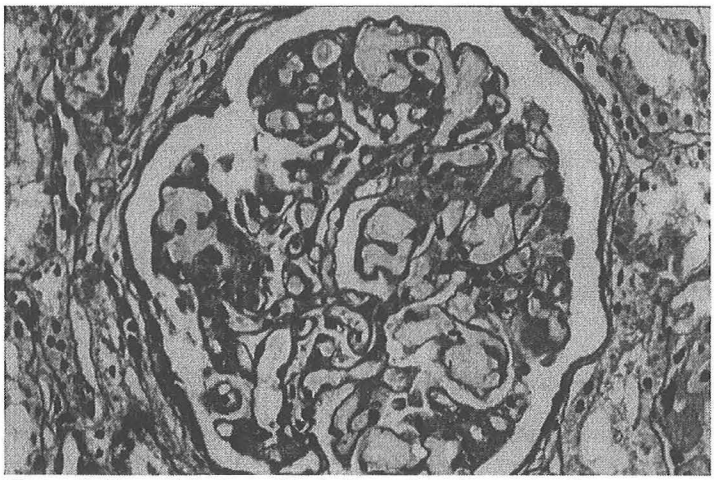


**Figure 6:** Lipoprotein deposition in lipoprotein glomerulopathy

lesions in LPG appear to be limited to the kidney, since hypertension, liver disease, and other end-organ abnormalities are lacking (110). LPG and LCAT deficiency are exceedingly uncommon, and the majority of patients with primary hyperlipidemia do not have evidence of glomerular damage (125). However, a better understanding of the pathogenic genetic and environmental factors in these uncommon examples of dyslipidemia may help with better treatment of more common renal diseases.

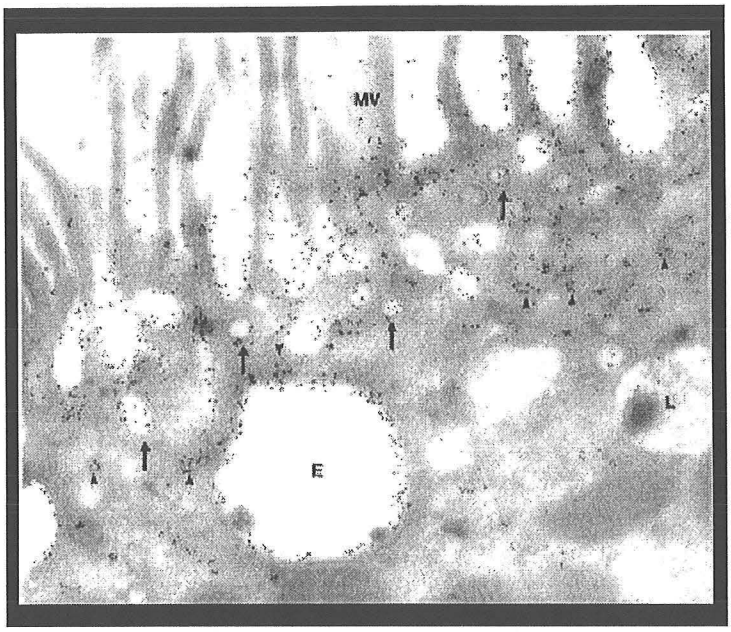
**Do lipid disorders enhance progression of underlying renal disease?** Nearly all chronic renal diseases, regardless of the initial insult, worsen over time. This inescapable fate suggests common pathophysiologic mechanisms. Observers have remarked on the similarity between atheromatous disease and kidney failure for hundreds of years. The Anatomist Richard Bright coined the term "lardacious kidney" to describe the post-mortem appearance of patients afflicted with progressive chronic renal failure (17). Virchow lectured on "Bright's disease" in more contemporary literature (late 1800's), and he noted the striking similarities between renal tissue in patients who died from uremia and of arteries compromised by the process of atherosclerosis (55). Interest continues in the role that dyslipidemia plays in progressive renal disease (18,43,69,78).

**How could lipids promote renal disease?** Experimental and clinical observations support that lipoproteins and their components can promote renal injury in either glomerular or interstitial areas. In the glomerulus, LDL and VLDL lipoproteins can bind directly to glycosaminoglycans of the basement membrane and allow plasma macromolecules to gain access to the extracapillary space (43,44,51,77,85). In the glomerulus, these macromolecules and lipoproteins can aggregate, undergo phagocytosis, and become oxidized by monocytes or macrophages (85,101). Lipoprotein binding to the glomerulus can also affect the electrostatic barrier of the basement membrane, inducing proteinuria and causing secondary tubulointerstitial injury (44).

Dietary and pharmacologic interventions in experimental glomerular injury also suggest that lipids favor progression of disease. In animal forms of glomerular injury created by ablation, a high cholesterol diet exacerbates renal function (10,34,62,78). Conversely, increasing dietary linoleic acid or by treating with clofibrate limits progression of established glomerular disease in rodents (62). In an obese rat that is prone to develop glomerulosclerosis, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor restricts development of the renal lesions (57). However, similar to humans, not all experimental animals with hyperlipidemia experience advancement of renal damage (10).

Lipoproteins may also enhance progression of interstitial disease. New observations have recently evolved from a surprising source, an experimental model of immune complex glomerulonephritis called passive Heymann nephritis. Heymann nephritis is induced by injecting foreign antibodies into rats. Originally, the induction was performed with antibodies raised against crude glomerular homogenate (63). Recently the relevant endogenous antigen in Heymann nephritis was discovered to be the membrane glycoprotein called megalin (63). Megalin is a large protein (~600kD) that is expressed in

glomerular podocytes and proximal tubules, and it binds circulating autoantibodies that create subepithelial immune deposits (63). In the proximal tubule, ultrastructural examination confirms localization to the brush border of the first and second segments (21). Megalin is also is localized to distinct coated pits and endosomes, consistent with an endocytic apparatus (21) (Figure 7). When megalin was cloned, it became clear that it shared many structural traits of the LDL receptor (21). In addition to binding a variety of compounds such as aminoglycosides, albumin, and Vitamin D binding protein, megalin also binds and internalizes apo E and apo B (21,60). The endocytic process marshaled by megalin appears to be distinct from the LDL receptor *in vivo*, since a naturally-occurring mutant of apo B-100 that does not bind to the LDL receptor internalizes in the proximal tubule by adjoining with megalin (20,60). Once megalin has facilitated endocytosis, the lipids can undergo peroxidation, stimulate macrophages to secrete IL-1, IL-8, TNF, and IL-6, and mediate progressive interstitial fibrosis (60,63,77,101,122). Characterization of the Heymann nephritis antigen actually identified a novel entry mechanism for apolipoproteins in renal tubules.




*J Amer Soc Neph* 10: 2224, 1999

**Figure 7:** Localization of megalin to proximal tubule epithelium, near bases of microvilli (MV), in vesicles (arrows), and forming endosomes (E).

Clinical observations also suggest that lipid metabolism is important for progression of glomerular sclerosis in humans. On kidney biopsy of glomerulonephritis, 10% of patients have detectable lipid deposition (usually apo B-containing lipoproteins) in the glomerulus (79). Immunoreactive Lp(a) has also been detected in glomeruli of patients with glomerulonephritis (75). In an observational study of adult non-diabetic patients with chronic renal diseases (mean GFR~40ml/min), total cholesterol, LDL-cholesterol, and apo B were all significantly associated with a more rapid decline in renal function (113). However, not all studies support this relationship. In a follow-up of a cohort of 138 patients with CRF, the only detected risk factors for progression of renal disease were proteinuria, baseline creatinine clearance, chronic interstitial nephritis and hypertensive nephrosclerosis (88). The degree of dyslipidemia, as measured by conventional sampling and testing, was not a risk factor for the development of ESRD. Very few intervention trials

have been performed to date, and better prospective trials are needed to establish the role lipids may play in progressive nephropathies.

In summary, patients with decreased GFR display altered plasma concentration and composition of lipids. The changes can be summarized as modest increases in apo B-containing lipoproteins of very low and low densities and decreased levels of apo A-containing lipoproteins of high density. There is a strong inverse relationship between GFR and plasma concentration of the atherogenic lipoprotein Lp(a). These changes may increase the predilection for cardiovascular disease in patients with mild to moderate degrees of renal failure, and they could promote the progression of chronic renal failure to ESRD.

## DYSLIPIDEMIA IN END-STAGE RENAL DISEASE (ESRD)

Why would lipoprotein abnormalities become different when patients develop ESRD? In addition to advancing uremia, several other factors should be considered once a patient requires renal replacement therapy. The majority of patients who enter dialysis programs have experienced months of protein depletion, as estimated either by dietary history or urea kinetics (22,36). In any form of dialysis, and perhaps in opportunistic illnesses, inflammatory mediators related to infections will alter lipid metabolism (13,29). The procedure of hemodialysis includes heparin treatment, that may deplete tissue stores of LPL (7), and immune activation that follows blood contact with "bio-incompatible" dialyzer membranes (100,123). Peritoneal dialysis, as it is currently performed, exposes patients to high concentrations of glucose via the dialysate solutions. With the underlying insulin resistance in most dialysis patients, this predisposes to hypertriglyceridemia. In addition, some patients lose as much as 20g albumin each day from the peritoneal surfaces during dialysis, and this can create protein malnutrition and evoke increased hepatic lipoprotein synthesis (31,64). Even otherwise successful transplantation may not obviate unfavorable lipid profiles, particularly under the influence of immunosuppressive medications (5,65). Therefore, lipid metabolism and the resulting profiles can be expected to evolve as patients migrate from chronic renal failure to ESRD. The disturbances can be characterized as changes in abundance, dynamics, and of composition of circulating lipid moieties.

**Quantitative changes in serum lipids in ESRD.** The quantitative changes in serum lipids in patients with ESRD differ slightly from those patients with smaller decrements in GFR. Compared to chronic renal failure, a patient with ESRD is more likely to have low HDL but less likely to display elevated triglycerides, total cholesterol, or LDL cholesterol (106,113,115)

**Altered dynamics of lipid metabolism.** Most patients with ESRD have profound reductions in reverse cholesterol transport. Patients with only minimal residual native GFR have decreased cholesterol transport from the HDL particle to LDL and VLDL components (84). Similar to the pre-ESRD patients, part of the defect results from a decrease in LCAT activity (75). In ESRD, since very little cholesterol is transferred to VLDL and LDL,

additional influences may be inhibiting transport such as endogenous inhibition of the cholesterol ester transfer protein (3). In one study, the endogenous low activity of cholesterol ester transfer protein in a group of patients with ESRD was found to be augmented by the hemodialysis procedure (3). This can cause a transient shift from triglyceride-rich toward triglyceride-depleted LDL, and a possible increased atherogenic risk.

**Unique Influences on Lipid Metabolism in Renal Replacement Therapy**

- General:
  - -Malnutrition of uremia
  - -Diet
- Hemodialysis-related:
  - -Exposure to heparin
  - -Cytokine release with blood-membrane contact
  - -Membrane biocompatibility
  - -Infection risk
- Peritoneal dialysis-related:
  - -Increased glucose uptake
  - -Infection
  - -Albumin losses
- Transplant-related:
  - -Steroid exposure
  - -Cyclosporine
  - -Tacrolimus
  - -Sirolimus

**Modified composition of circulating lipid particles.** The composition of lipoproteins undergo dramatic changes in ESRD patients. First, patients with ESRD are more likely to have LDL in the circulation that is in an oxidized form (13,35). Oxidation of LDL is a crucial step in the pathogenesis of atherosclerosis, and oxidative stress could contribute to the accelerated atherosclerosis in dialysis patients (46,95). Oxidation of LDL is required for macrophage uptake and cellular accumulation of cholesterol (126). Since antioxidants normally circulate in plasma, LDL oxidation presumably occurs in the arterial intima, or another site sequestered from the plasma (126). The microenvironment provided by the matrix of the artery wall probably plays an important role in oxidative modification of LDL (46). Oxidized LDL is cleared more readily from the circulation, and presumably incorporated in peripheral tissues, and patients with ESRD than in normals due to increased expression of a scavenger protein (46,95). Oxidized LDL induces endothelial cells to produce monocyte chemoattractant protein-1 (MCP-1) and monocyte colony stimulating factor (M-CSF), leading to enhanced monocyte tethering, activation, and attachment (13).

Second, patients with ESRD (even non-diabetics) have higher concentrations of advanced glycosylation end products (AGEs) (105). In ESRD, AGEs accumulate from oxidative and carbonyl stress of uremia (105). When LDL particles become AGEs, the plasma half-life is prolonged and the LDL has increased capability to enter the endothelial cell (46,84). From that point, LDL-AGE can accelerate atherosclerosis through cross-linking of proteins, modification of matrix components, improved platelet aggregation, and impaired vascular relaxation (105).

Third, ESRD is one of the conditions that is associated with small, dense LDL particles in the circulation that are rich in triglycerides (31, 115). Several epidemiologic studies suggest an increased cardiovascular risk is associated with triglyceride-rich dense

subclasses of LDL (23,40,116). It is controversial if the "atherogenic phenotype" of dense LDL particles is independently predictive of cardiovascular events in the general population (12,23). Whereas only 2.5-7% of the general population has increased plasma concentrations of the small triglyceride-rich LDL, 40-48% of patients on peritoneal dialysis and 23-28% of those on hemodialysis have the trait (31,96). These abnormalities in the LDL composition can persist after renal transplantation (106). Altered LDL particle size forms an important component of the metabolic abnormalities that contribute to the increased cardiovascular risk found in ESRD (96).

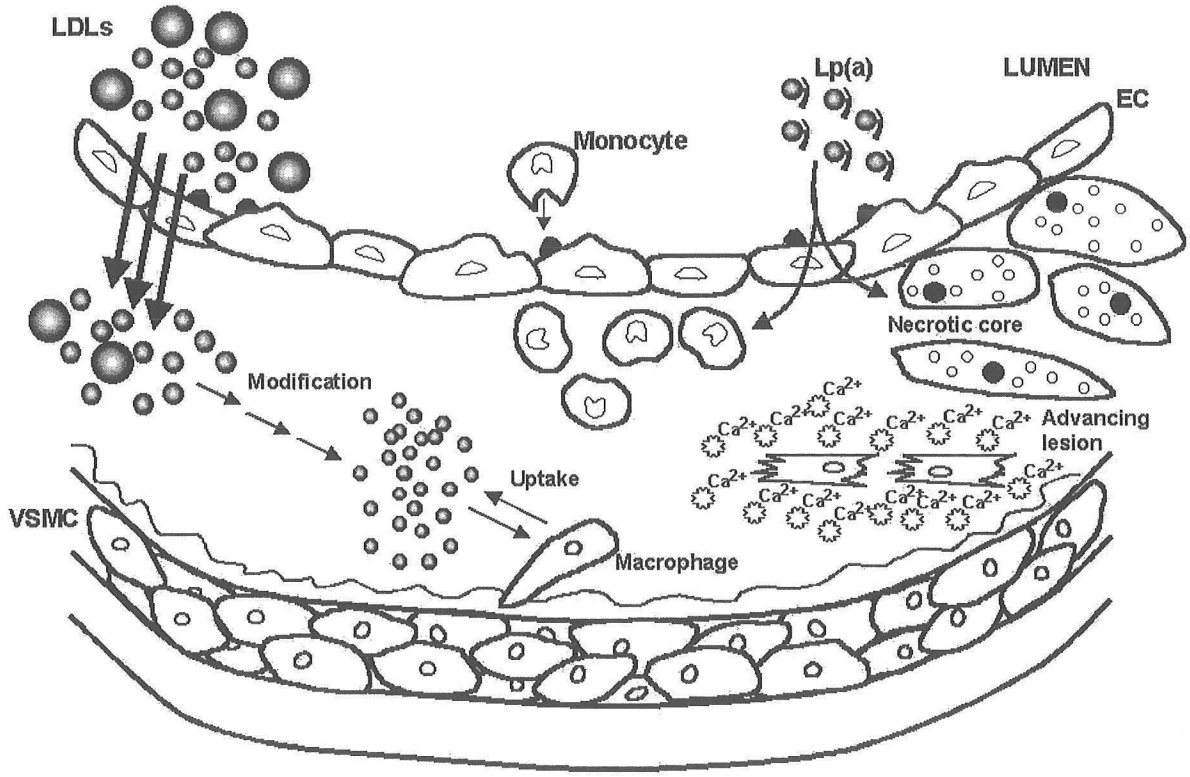



**Figure 8:** Proposed pathogenesis of plaque development in ESRD

**Lp(a) in ESRD.** In studies that included sufficient numbers of patients and appropriate controls, Lp(a) levels range from 80-400% higher in peritoneal dialysis patients and 27-77% higher in hemodialysis patients than in patients with normal renal function (75, 94). Plasma concentrations of Lp(a) in hemodialysis patients are particularly dependent on the apo (a) phenotype, since more dramatically elevated levels occur when more than 22 KIV repeats are present (73). In fact, this high molecular weight apo (a) phenotype may be more predictive of cardiovascular risk than the plasma Lp(a) concentration in patients with ESRD (24, 70, 73). A depiction of the advancement of atherogenesis in ESRD is shown

in Figure 8, with possible contributions by Lp(a), triglyceride-rich and modified LDL, endothelial adhesion molecules, tissue calcification, and inflammation.

**Patients managed with peritoneal dialysis.** In 1996, approximately 14% of the nearly 210,000 US patients maintained on dialysis received a form of peritoneal dialysis (118). Compared to patients on hemodialysis, patients on peritoneal dialysis display substantially higher total LDL levels, but with similar VLDL, HDL, and triglyceride levels (11,27,31). The VLDL in patients on peritoneal dialysis tends have higher cholesterol content than patient on hemodialysis, but the small, dense triglyceride-rich form of LDL was also more likely (31). These differences support that either enhanced glucose reabsorption or albumin losses in patients on peritoneal dialysis create the metabolic disturbance.

**Patients with ESRD managed with transplantation.** The hyperlipidemia associated with renal transplantation has become a major obstacle to improving patient outcomes. Possible influences include diet and shared genetic predispositions, but immunosuppressive medications have a major effect on lipid metabolism. Abnormalities that are typically seen include elevations in total and VLDL cholesterol and increases in triglycerides and VLDL (65). In a series of 500 renal allograft recipients taking cyclosporine, there was a 37% incidence of cholesterol levels over 300mg/dl (119). Triglyceride elevations may be especially striking with high doses of steroids and with newer immunosuppressive medications such as sirolimus (16). In contrast to patients on dialysis or with pre-ESRD renal failure, the HDL levels are often elevated post-transplant (65,119).

Despite the improved outcomes with immunosuppressive protocols and treatments for infectious complications, the cardiovascular mortality of renal transplantation has not improved over the last several years (5). More than half of the deaths in renal transplant recipients who had functioning allografts were due to cardiovascular disease (65). Furthermore, the lesion of chronic allograft nephropathy shares histologic features with atherosclerosis (56). Patients with loss of GFR that is attributed to chronic allograft dysfunction tend to have more dramatic elevations in total and LDL cholesterol (56,65). Thus, the consequences of hyperlipidemia in the post-transplant patient may be even more exaggerated than those with native kidney dysfunction.

**Coronary artery disease in ESRD.** The observations above suggest that patients with ESRD have traditional and non-traditional risks for developing coronary artery disease. It is not clear if these known risk factors are sufficient to explain the tremendous burden of coronary artery disease seen in dialysis patients. Approximately 44% of mortality on dialysis is due to cardiovascular disease, and 22% of the cardiac deaths occur due to myocardial infarction (118). The burden of heart disease is not unique to the US, since the death rate due to myocardial infarction and ischemia in the United Kingdom and Italy is 15-19-fold higher in dialysis patients than in the general populations of those countries (35,36). With increasing numbers of elderly patients enrolling in dialysis programs, it is difficult to determine dialysis itself accelerates atherosclerosis. In an 18-year follow-up study of patients initiating dialysis, more than half of myocardial infarctions occurred within

the first two years of entering the program (46a) (Figure 9). This suggests either that dialysis itself is an extreme "stress test," or that the procedure promotes coronary artery occlusion.

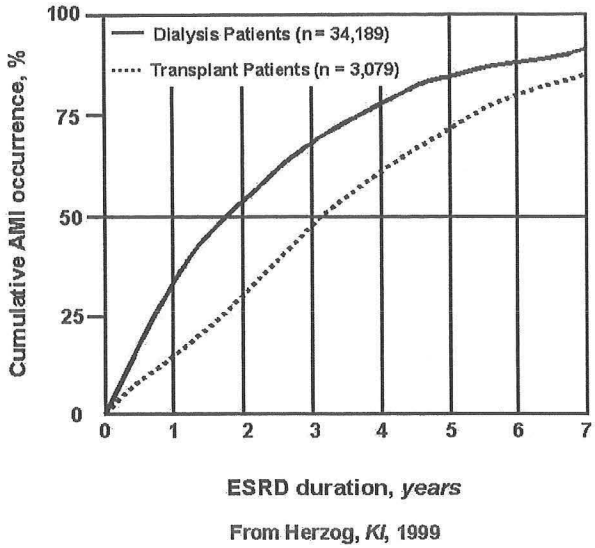



**Figure 9:** Cumulative occurrence of acute myorcardial infarction in ESRD patients

## THERAPY

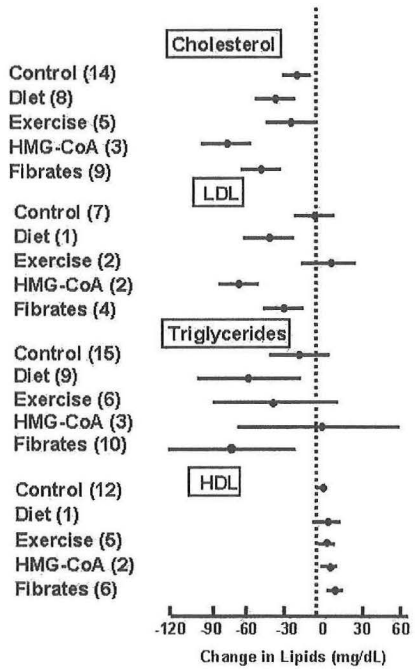
**Paying heed to "the gap" in patients with renal disease.** The population of patients with ESRD in the US adds new patients at an alarming rate, more than 80,000 patients each year (118). The bulk of these patients have their lives sustained with dialysis, but 28% of the US ESRD population have functioning allografts (118). While concerns about lipid management are well-known to Nephrologists, general practitioners should consider two facts: First, over three million people in the US have serum creatinine levels over 1.7 mg/dl, and nearly a million people have creatinine levels over 2.0 mg/dl (53). Although serum creatinine is not a perfect estimate of GFR, this suggests a tremendous burden of patients with renal disease. Second, most patients with renal disease are probably unaware of their illness. In household interviews of civilian, non-institutionalized people in the US, the prevalence of patients with self-reported "kidney trouble" in White and Black elderly subjects was 2.1% and 2.4% respectively (1). These rates are 2-7-fold lower than the prevalence of elevated serum creatinines in the same demographic groups and indicate a gap in recognition of renal disease that is staggering (53). Therefore, most patients with renal dysfunction and attendant complications are probably being followed by general practitioners.

The gap in awareness of renal disease may be particularly important for African Americans, a demographic group with a high prevalence of cardiovascular and renal diseases. We are a center for The African American Study of Kidney Disease and Hypertension (AASK Study), a multicenter prospective randomized double-blinded controlled trial to determine the effects of blood pressure control and the use of specific antihypertensive medications on the progression of hypertensive nephrosclerosis. The prospective protocol will be completed the end of 2001. We used data from screening for the AASK trial to examine baseline characteristics. In 1,418 non-diabetic patients, LDL and cholesterol correlated with extent of proteinuria, and HDL was positively correlated to GFR (102). Moreover, 54% of the screened patients with at least two risk factors for cardiovascular disease had LDL levels above 130mg/dl, the recommended threshold for treatment (102). A staggering 90% of these patients had not been prescribed lipid-lowering drug therapy. These observations suggest that inadequate management may contribute

to progression of renal disease and severity of cardiovascular complications in African Americans.

**Interventions to limit progression of disease.** Pharmacologic interventions that decrease plasma concentrations of total and LDL-cholesterol in chronic diseases such as diabetic nephropathy and idiopathic membranous nephropathy have been in small groups of patients, and thus far demonstrate a modest benefit of lipid-lowering therapy (76,117). A recent preliminary report of a meta-analysis of similar trials concluded that efforts to lower LDL cholesterol were beneficial in restricting progression of disease (38). Large prospective trials of lipid-lowering therapy should be initiated that use renal function as the primary endpoint.

**Interventions for traditional cardiovascular risks.** Some forms of dyslipidemia seen in patients with renal disease are clearly associated with increased cardiovascular risk and perhaps with progression of disease. Non-pharmacologic therapy in the form of a soy-based diet can significantly decrease total cholesterol, LDL, and apo B but not change triglyceride levels in patients with nephrotic syndrome (25). The atherogenic phenotype of ESRD is characterized by circulation of small, dense triglyceride-rich LDL particles. The size and composition of these particles can be altered by adjusting oral intake to reduce serum triglyceride levels. To medically treat the traditional cardiovascular risks in patients with decreased GFR, fibric acid derivatives would seem to be the first choice because they can increase VLDL metabolism and normalize HDL plasma concentrations (124). Gemfibrozil does not substantially accumulate in renal failure and has a better safety profile than clofibrate (111). Nicotinic acid preparations are also an option in ESRD patients with elevated triglyceride levels, but the adverse symptoms limit compliance (125). HMG-CoA reductase inhibitors are well-tolerated in patients with nephrotic syndrome and decreased GFR, but they may not be clearly indicated in ESRD patients without elevations in LDL (124,125). Even if large prospective controlled trials have not yet been performed in patients with renal disease, treatment of the traditional forms of dyslipidemia seems sensible (99). Effects of these treatments in hemodialysis patients are summarized in Figure 10.




From *AJKD* 32 (supp 3): S142, 1998

**Figure 10:** Summary of effects of intervention in hemodialysis patients

**Interventions for non-traditional cardiovascular risks.** The uremic state favors oxidation of lipoproteins, and this may be successfully modified using powerful antioxidants such as probucol or with dietary changes like "Mediterranean" diets and supplemental beta

carotene and vitamin E (46,126). In a recent study by Dr. Jialal's group here in Dallas, alpha-tocopherol supplementation (800 I.U. per day for 12 weeks) in dialysis patients decreased the susceptibility of LDL to *in vitro* oxidation, and the benefits appeared to be greater in patients on peritoneal dialysis (50). Vitamin E supplementation may provide protection against coronary disease in patients with chronic renal failure.

In patients with hyperhomocysteinemia, folate, vitamin B12, and vitamin B6 can decrease homocysteine levels (46). In patients with renal insufficiency, doses higher than the 0.65mg folate per day are probably required for the same effect on plasma homocysteine level as in patients without renal failure (14,70). Even though a relation is present between elevated homocysteine levels and vascular disease in some observational and epidemiologic studies, no large prospective trials have yet been completed that demonstrate a clinical benefit of homocysteine-lowering therapy (46,112).

**SUMMARY OF RECOMMENDATIONS:**

- EARLY RECOGNITION OF RENAL DISEASE
- LIMIT CONFOUNDING OR SUPERIMPOSED PROBLEMS
  - -AGGRESSIVELY TREAT BP
  - -LIMIT SECONDARY HYPERPARATHYROIDISM
  - -CONTROL SERUM CALCIUM AND PHOSPHORUS
  - -DIAGNOSE AND TREAT ANEMIA
  - -OPTIMIZE CONTROL OF DIABETES
  - -? TREAT ELEVATED HOMOCYSTEINE
- CONTROL PROTEINURIA
- TREAT DYSLIPIDEMIA
  - -DIET
  - -FIBRATES
  - -NICOTINIC ACID
  - -STATINS
  - -ANTIOXIDANTS

The elevated Lp(a) that occurs in renal diseases may be more difficult to manage. Several studies suggest that if proteinuria can be reduced in nephrotic syndrome, the plasma levels of Lp(a) will return toward normal (39). When ESRD patients receive a successful renal allograft, Lp(a) plasma levels rapidly decline (5). However, if a patient with ESRD has minimal residual GFR and is not a candidate for renal transplant, the options to treat elevated Lp(a) are limited. A diet that is rich in fish oil may reduce Lp(a) regardless of apo(a) isoform (86). Statins typically do not affect elevated Lp(a) levels, but one report suggested that in patients with elevated Lp(a) due to persistent nephrotic syndrome, HMG CoA reductase inhibition reduced plasma concentrations by nearly a third (18,104). Otherwise, nicotinic acid (3-4g/d) and estrogen-replacement therapy in post-menopausal women are the most prominent drug interventions that have been demonstrated to significantly lower plasma Lp(a) concentrations (4).

## SUMMARY

The challenge for all of us - Primary Care physicians and Nephrologists - is to extend the life expectancy of patients with renal disease. This will require us to look beyond our traditional means of diagnosing renal failure, limiting progression of renal failure, optimizing delivery of dialysis, and improving allograft survival. The fortunes of our patients are

increasingly dependent on managing risks, both cardiovascular and renal. We should aggressively treat the risks associated with dyslipidemia in our patients with renal disease.

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