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The role of lipid abnormalities in renal and vascular injury

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Once a critical number of nephrons are injured by disease, it appears that the adaptive changes that occur may be critical in the subsequent progressive loss of the remaining nephrons and ultimately, renal function. A variety of risk factors have been identified that appear to be associated with progression of renal disease. Two such risk factors, hypertension and hyperlipidemia, have been extensively studied and experimental data suggest that these factors interact contributing to the development of glomerular injury. The mechanism whereby hyperlipidemia participates in glomerular injury is unknown. Morphologically, expansion of the glomerular mesangium with various matrix proteins, segmental deposition of apolipoproteins and an increased number of glomerular macrophages and foam cells have all been described. The role of each of these factors in progressive nephron destruction has not been clarified. Altered platelet function and other lipid-derived inflammatory mediators may also participate in glomerular damage. Biochemically, an increased cortical content of cholesterol esters and reduced content of polyunsaturated fatty acids are typical renal tissue lipid changes in lipid-induced glomerular injury. These tissue lipid alterations are reminiscent of vascular compositional changes seen early in the development of atherosclerosis. Importantly, therapies directed at reducing circulating lipids have ameliorated glomerular and interstitial injury suggesting that hyperlipidemia is an important modulator of renal damage that may contribute to the progression of renal disease. The role that alterations in lipid metabolism play in human renal disease is only currently being investigated.

Hyperlipidemia is a frequent clinical accompaniment of various renal diseases. Over one hundred years ago, Virchow pointed out an association between kidney disease and lipid deposition that he termed «fatty metamorphoses»[1]. Then, as now, it was unclear whether lipid deposits were a cause or merely a reflection of secondary events within the kidney. Munk in 1916 described lipid deposits in kidneys of patients with nephrotic syndrome[2]. He speculated that the renal disease could be a result of these systemic abnormalities and thus, he coined the term lipoid nephrosis, the nomenclature that persisted for nearly fifty years to describe what is now usually referred to as nil lesion or minimal change nephropathy. In 1922, Farr, while evaluating patients with the nephrotic syndrome, speculated that severe hyperlipidemia caused glomerular capillary endothelial injury that eventually contributed to the development of glomerulosclerosis[3]. Kimmelstiel and Wilson in their original description of diabetic nephropathy found prominent deposits of neutral lipids in afferent arterioles, in Bowman's capsule, and in renal tubules[4]. They also reported that there wore segmental lipid deposits within glomerular tufts, although the classic nodular lesion that bears their name stained only faintly with Sudan black. Similar observations were subsequently reported by Wilens, which led him to speculate that diabetic nephropathy might be a result of hypertension and hyperlipidemia[5]. More recently, a number of investigators have begun to reevaluate the potential role of hyperlipidemia in renal disease[6-9]. Clinically, it has been recognized in the past decade that abnormalities of glomerular permselec-

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tivity, as reflected merely by an increase in albuminuria, are frequently associated with the development of cardiovascular disease in patients with essential hypertension as well as in patients with type I and type II diabetes[10, 11]. Whether this is only reflective of diffuse vascular injury or whether the albuminuria is a marker for those patients developing lipid abnormalities or both, is only currently being investigated[12, 13].

Lipoprotein abnormalities and renal disease

The presence of abnormalities in circulating lipoproteins makes the notion that lipid alterations could cause or contribute to progressive renal injury plausible. Patients with the nephrotic syndrome[14-16] or diabetes[12, 13], and even patients with moderate or marked decreases in renal function frequently have alterations in circulating lipoproteins[14]. For example, in patients with glomerular filtration rates < 60 ml/min, very low density lipoproteins (VLDL) are frequently elevated and high density lipoproteins (HDL) are decreased. These lipoprotein abnormalities may be the result of decreased lipoprotein lipase activity as well as decreased lecithin cholesterol acyltransferase (LCAT) enzyme activity and could possibly contribute to vascular and renal injury. Patients with a nephrotic syndrome have hyperlipidemia that is directly proportional to the magnitude of urine albumin excretion and inversely to the degree of hypoalbuminemia[14-16]. The hyperlipidemia is probably a consequence of both increased production and decreased metabolism of VLDL and intermediate density lipoproteins (IDL). Atherogenic low density lipoproteins (LDL) may also be increased, possibly as a result of increased VLDL and IDL precursors and/or direct hepatic overproduction. Levels of total HDL are usually unaltered in patients with the nephrotic syndrome, although levels of the putatively antiatherogenic HDL_2 may be reduced. Recently, it has been demonstrated that an increased lipoprotein(a) (Lp(a)) occurs in patients with proteinuria and reduced renal function[17]. Lipoprotein(a) has recently been shown to be an independent risk factor in the development of atherosclerosis in patients with hypercholesterolemia[18]. Importantly, Lp(a) has recently been shown to be elevated in dialysis patients and could contribute to the high incidence of atherosclerosis in these patients[19]. A three-fold greater mortality rate was reported in hemodialysis patients with elevated Lp(a).

While it is recognized that these abnormalities in lipoproteins are associated with an increased risk of atherosclerotic vascular injury, whether they, in an analogous manner, contribute to renal disease has only recently been proposed[6-9]. Attention has been directed to the development of lipid abnormalities in patients with both type I and type II diabetes that occur early in the clinical course of nephropathy[10, 11]. Data have suggested that increments in LDL and decreases in HDL_2 occur in patients with type I and type II diabetes at the onset of microalbuminuria[10, 11]. These clinical observations provide a potential explanation for the dramatically increased incidence of atherosclerosis seen in patients with diabetic nephropathy. In addition, changes in lipoprotein composition, such as decreased density, increased size and triglyceride enrichment and decreased apolipoprotein content and glycosylation of lipoproteins have been reported in diabetic patients. Finally, studies have suggested that Lp(a) is increased in patients with stage III and IV diabetic nephropathy providing an additional putative risk factor for the development of vascular injury in these patients[20, 21].

Do primary lipid abnormalities cause renal disease?

The incidence of renal disease in patients with most common forms of primary hyperlipidemia, although unknown, is presumably low. Indeed one recent study has suggested that there is not an increased incidence of microalbuminuria in patients with primary lipid abnormalities[22]. On the other hand, autopsy studies have suggested that there is an important relationship between the development of global glomerulosclerosis and atherosclerosis suggesting a potentially important relationship between factors leading to atherosclerosis and those leading to glomerulosclerosis[23]. As discussed in the subsequent sections, these clinical observations are consistent with the experimental studies in which lipid abnormalities are predominantly seen to be modulators of progressive renal disease rather than primary initiators of renal disease. Nonetheless, there are a number of unique abnormalities of lipid metabolism that are associated with the development of renal disease. Patients with deficiency of LCAT are unable to normally esterify cholesterol and develop abnormally large lipid-laden high density lipoproteins. A hereditary form of LCAT deficiency has been reported to cause glomerular lipid deposition and progressive renal insufficiency[24]. In some patients with liver disease, lipoprotein compositional abnormalities have also been reported to cause progressive glomerular destruction[25]. Recently, a number of case reports have detailed an unusual form of the nephrotic syndrome associated with mesangial expansion, mesangial proliferation, and focal glomerulosclerosis (FGS) with increased circulating levels of apolipoprotein (apo) E and glomerular deposits of lipoproteins[26]. Collectively, these syndromes, although uncommon, indicate that lipoprotein abnormalities, particularly those characterized by unusually large and abnormally composed lipoproteins, can sometimes cause glomerular injury. On the other hand, the apparently uncommon occurrence of overt primary renal disease in patients with common hyperlipidemias suggests that lipids may only cause renal injury, when additional predisposing factors such as hypertension or immune-mediated glomerular damage are present. In this regard, Lee and colleagues have recently suggested that apo B can be identified in glomeruli of patients with proteinuria of various etiologies[27].

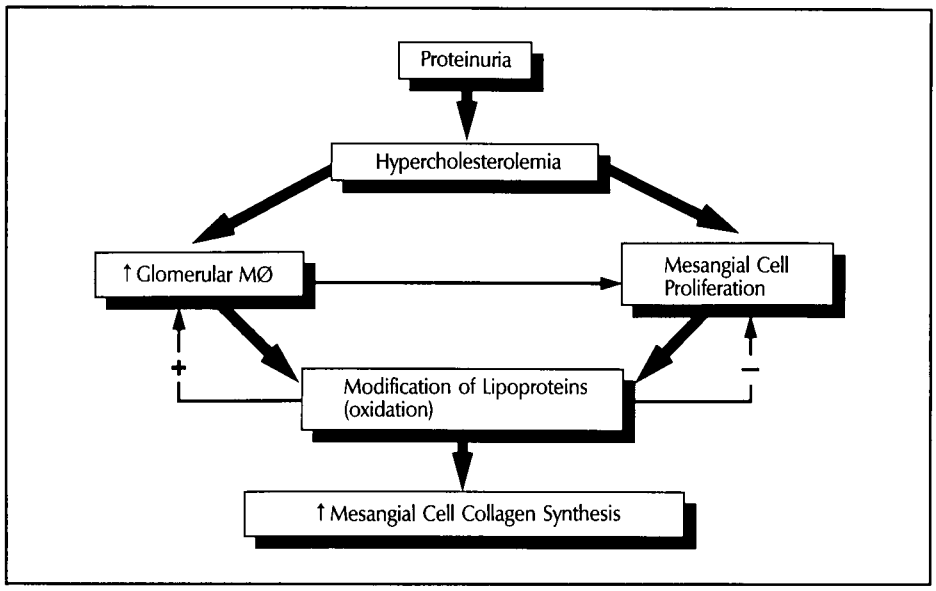

Fig. 1.—Mechanisms of lipid-induced renal injury. Proteinuria is an important factor that contributes to secondary hypercholesterolemia. Increased cholesterol has been shown to be associated with an increased influx of glomerular macrophages and ultimately formation of foam cells. In addition, low density lipoprotein cholesterol has been shown to induce mesangial cell proliferation, which in turn may oxidize this lipid, rendering it cytotoxic as well as being a potent chemoattractant for macrophages. Finally, hypercholesterolemia appears to influence directly and indirectly mesangial matrix protein synthesis resulting in mesangial expansion.

Recently, in patients with type I diabetic nephropathy, Mulec and colleagues suggested that the rate of decline in renal function in diabetic patients was significantly correlated with total serum cholesterol levels. In patients with a total serum cholesterol of > 7 mmol/L, the rate of decline in GFR was 8.4 ± 5.3 ml/min/yr[28]. For those with a total serum cholesterol of < 7 mmol/L, the rate of decline of renal function was significantly lower at 2.3 ml/min/yr[28]. The level of albuminuria was not significantly different between the groups and mean arterial pressure was only 3 mmHg higher in the high cholesterol group. In addition, metabolic control, as indicated by similar hemoglobin AIC levels, was comparable in both groups[28]. This study suggests that hypercholesterolemia could contribute to the rate of progression of renal disease in patients with diabetic nephropathy, particularly when other risk factors such as hypertension and metabolic control have been appropriately addressed. In addition, recent studies in patients with focal and segmental glomerulosclerosis have suggested that hyperlipidemia may be an important factor in progressive loss of glomerular function[29]. A further suggestion that lipids participate in glomerular injury was provided by an uncontrolled study in patients with a nephrotic syndrome. In this brief report, after 48 weeks of therapy, LDL cholesterol was reduced by over 50 %, and this was associated with partial remission of the nephrotic syndrome, with a decrease in albuminuria from 5.8 to 2.3 gm/24 hr[30]. This decrease in proteinuria was associated with improvement in plasma protein levels while serum creatinine levels remained normal. The results of this preliminary study suggested that reduction in circulating cholesterol levels over time may be associated with improvement in the filtration barrier injury leading to proteinuria. Additional studies are needed in order to evaluate the effectiveness of antilipemic therapeutic interventions on the progression of renal disease in man.

The role of lipids in experimental renal disease

The mechanisms involved in progressive renal injury have been extensively investigated during the past decade and a number of physiologic and metabolic changes that occur in the course of progressive renal disease may contribute to nephron destruction. Based on pharmacological and dietary intervention studies, it has been postulated that hemodynamic factors, particularly glomerular hypertension, are important in the pathogenesis of progressive renal injury[31]. Additionally, experimental studies have demonstrated that genetic, immune, and metabolic factors, specifically abnormal lipid metabolism, may modulate glomerular damage[32]. Support for the notion that lipids are involved in renal injury can be derived from a number of experimental investigations. First, high cholesterol diets are associated with a mild degree of albuminuria and modest glomerular injury in different animal species[33,34]. Importantly, this form of lipid-induced glomerular injury is relatively modest. However, when diet-induced hypercholesterolemia is combined with hypertension or other forms of glomerular injury, a synergistic effect on glomerular injury is seen[35]. Second, pharmacologic agents including cholestyramine, 3-hydroxy 3-methyl coenzyme A (HMG-CoA) reductase inhibitors, probucol and fibrate derivatives have reduced circulating lipids and ameliorated glomerular injury in different experimental models of renal disease associated with hyperlipidemia[36-41]. Third, intake of large amounts of dietary polyunsaturated fatty acids of the omega-3 and omega-6 class has also decreased cir-

culating lipids and reduced glomerular injury in a variety of models of renal disease[9]. Finally, fat free diets such as those induced by essential fatty acid deficient diets have also been associated with amelioration of structural injury. In this latter dietary maneuver, an important role for glomerular macrophages has recently been postulated as a key factor in explaining some aspects of the mechanisms of progressive renal disease[42, 43]. Indeed, the frequent finding of foam cells in the setting of renal diseases in which lipids may play an important role lends credence to the potential importance of the macrophage in modulating some aspects of progressive renal disease.

Dietary-induced hypercholesterolemia

It is well-established that feeding a high cholesterol diet to different animal species leads to FGS[8]. The extent of glomerular injury is correlated with circulating cholesterol levels. Histologically, glomerular hypercellularity and expansion of the mesangial matrix were demonstrated as early morphologic changes in animals fed a high cholesterol diet[33]. In rats, glomerular enlargement, mesangial expansion, and hypercellularity were evident even after only 1 month of increased circulating cholesterol[33, 34, 44]. These changes in the glomerular mesangium preceded the appearance of FGS and were not associated with a significant increase in albuminuria. Immunocytochemical studies have recently demonstrated that the glomerular hypercellularity was, in part, a result of an increase in ED1 positive macrophages[44]. Importantly, the increased fractional mesangial area seen in dietary induced hypercholesterolemia was a result of an increase in matrix components including type IV collagen, fibronectin and laminin[44]. A high cholesterol diet has also been associated, over time, with changes in the lipid composition of the renal cortex. Specifically, an increased content of cholesterol esters and a significant reduction in cortical arachidonic acid and increased linoleic acid content were found in the cortical phospholipid fraction, suggesting an inhibitory effect of elevated cholesterol levels on desaturation and elongation of the essential fatty acid[34]. These changes in cholesterol esters and fatty acids were also found to significantly correlate with the presence of glomerular injury[34]. Thus, increased dietary-cholesterol induced cellular, morphologic and biochemical changes in kidneys similar to changes in large vessels induced by hypercholesterolemia associated with the development of atherosclerosis[45]. The precise role that these glomerular changes play in the development of FGS remains to be defined. The degree of glomerular injury induced by diet-induced hypercholesterolemia in otherwise normal kidneys was relatively modest. However, the presence of hypertension, preexisting glomerular disease, or a reduction in the number of functioning nephrons all significantly increased the extent and severity of glomerular damage[35].

Although hypercholesterolemia was associated with glomerular injury, the mechanism whereby this occurred is unknown. Recent advances in our understanding of the metabolism of lipoproteins have suggested that modifications in the structure of lipoproteins may affect the potential for vascular injury[46]. In this regard, probucol, an antilipemic agent with antioxidant activity, has been shown to modify diet-induced hypercholesterolemic glomerular injury independent of changes in circulating cholesterol levels[47]. These data suggested the possibility that the local glomerular deposition of lipoproteins and their oxidation may be important in lipid-induced glomerular injury. In support of this concept, mesangial cells have been shown to express receptors for LDL[48-50]. In addition, LDL cholesterol induced a biphasic effect on mesangial cell proliferation. At lower concentrations LDL stimulated proliferation, whereas at higher concentrations of LDL (> 1000 μg/ml) inhibition of mesangial cell growth was observed and cytotoxicity was demonstrated. The inhibition of mesangial cell growth at the higher LDL concentrations was associated with a tenfold increase in LDL malonaldehyde, a measure of lipid peroxidation[50]. Since mesangial cells are known to generate reactive oxygen molecules[51], the influence of scavengers of toxic oxygen molecules was evaluated. Both superoxide dismutase and butylated hydroxytoluene, scavengers of reactive oxygen molecules, decreased formation of malonaldehyde and abrogated the cytotoxic effects of oxidized LDL[50]. Thus, mesangial cellderived reactive oxygen molecules may be important in altering lipids and rendering them cytotoxic. Recently, it has been suggested that oxidation of arachidonic acid products through lipoxygenase pathway may be an importanthe mechanism whereby the oxidation of LDL may occur[52]. The possibility that mesangial cells can oxidize LDL is of interest. Oxidized LDL has been recently demonstrated to be present in atherosclerotic lesions[53]. In addition, oxidized LDL has been reported to be increased in the circulation of diabetic patients[53]. Oxidized LDL is chemoattractant for macrophages and is also endocytosed by macrophages and mesangial cells at a more rapid rate than normal LDL through a scavenger receptor mechanism[53]. This ultimately leads to increased formation of cholesterol esters in foam cells. The biochemical demonstration of increased cholesterol esters and the appearance of macrophages and foam cells in glomeruli of cholesterol fed rats lends credence to the notion the oxidized LDL could participate in the glomerular injury seen in models of lipid induced renal disease.

Pharmacological treatment of hyperlipidemia and the pathogenesis of glomerulosclerosis

The importance of systemic and glomerular hypertension in modulating progressive renal injury has been studied. In the remnant kidney model, for example, removal of 80-90 % of renal mass was associated with hypertension, proteinuria, uremia and death[31]. In addition abnor-

mal circulating lipids were found soon after ablative surgery and secondary hypercholesterolemia developed as albuminuria worsened. We have shown that therapy with clofibrate or lovastatin effectively prevented the secondary hypercholesterolemia in the remnant kidney model, and this was associated with a reduction in proteinuria and decreased glomerular damage[39]. The effect of these agents appeared independent of effects on systemic or glomerular pressures. Similar results have been recently reported with probucol[41].

The Dahl salt-sensitive model is a model of systemic hypertension in which albuminuria and progressive glomerular damage are present[54]. Interestingly, hyperlipidemia was evident before many of the structural and functional changes developed in these rats. Therapy with lovastatin has been demonstrated to prevent the progressive increase in cholesterol levels and dramatically reduce albuminuria and FGS[40]. Thus, in two experimental models of systemic and glomerular hypertension associated with hypercholesterolemia, therapy with lipid lowering agents reduced the degree of proteinuria and the extent of glomerular injury. In addition, these studies also supported the notion that an interaction between hyperlipidemia and hypertension occurs at a glomerular level. Finally, in studies of the nephrotic syndrome induced by aminonucleoside of puromycin, a reduction in circulating lipids by cholestyramine or lovastatin has been shown to decrease glomerular injury and preserve renal function[37, 38].

In the obese Zucker rat, hyperlipidemia and microalbuminuria are present at 10-12 weeks of age[55, 56]. Hypercholesterolemia became more pronounced as albuminuria increased. Mesangial matrix expansion and an increase in mesangial cellularity accompanied the development of albuminuria. At 6 months of age, FGS was evident and subsequently progressed. Mild systemic hypertension and reduced renal function became manifest as glomerular and tubular interstitial injury evolved. Immunohistochemical studies to define the changes in mesangial matrix in obese Zucker rats before the development of FGS have demonstrated that, at 24-28 weeks of age, obese rats have increased mesangial fibronectin, laminin and type IV collagen compared to lean Zucker rats. Thus, these studies indicated that morphologic changes in the mesangial matrix by light microscopy were associated with an increased presence of specific matrix proteins. In addition, we have demonstrated increased apo B deposits in glomerulosclerotic areas and segmental areas of mesangial expansion. Since apo B is the principal apolipoprotein of VLDL in rats, this observation may have important implications with respect to lipid-mesangial cell interactions. Characterization of the increased glomerular cellularity by immunocytochemical techniques has demonstrated that in the obese rat glomeruli a thereefold increase in the number of Ia+ cells was present in the mesangial region. These glomerular cellular changes were similar to those reported by us in dietary-induced hypercholesterolemic rats. Micropuncture studies in obese and lean Zucker rats demonstrated normal glomerular function at 10-12 weeks of age, when only mild glomerular matrix expansion and minimal albuminuria (< 5 mg/24 hr) were present[56]. We have recently studied older obese Zucker rats at 22-26 weeks of age[57]. At this time, albuminuria was increased (> 50 mg/24 hr), glomerular mesangial expansion was marked but FGS was minimal. In these studies, a single nephron filtration rate was maintained by an increased P_{GC}[57]. The mechanism responsible for the development of glomerular hypertension in older obese Zucker rats is unknown. Alterations in glomerular production of vasoactive substances or changes in blood rheology could have participated in the development of these hemodynamics. In addition, systemic blood pressure is slightly higher in obese Zucker rats at this age and this also may have contributed to the increment in glomerular pressure. Thus, in this experimental model, glomerular hypertension developed late in the course of glomerular injury and may play a role in further amplifying renal injury. Since hyperlipidemia was an early change in obese Zucker rats and preceded not only FGS but also hemodynamic changes, we hypothesized that hyperlipidemia contributed to glomerular injury. To test this hypothesis, we reduced circulating lipids with clofibrate or lovastatin[36]. These therapies decreased serum lipids, reduced albuminuria, and prevented FGS. In addition, with each of these therapies, a decrease in mesangial cellularity and matrix expansion was observed. Micropuncture assessments performed after four weeks of antilipemic therapy falled to demonstrate alterations in glomerular hemodynamic function that could explain these beneficial effects.

Recent experiments utilizing lovastatin in obese Zucker rats with established nephropathy have suggested that this therapy reduced the extent and severity of glomerular injury[58]. Indeed, reduction in the severity of structural injury to the glomeruli was associated with a lower systemic blood pressure and a slight reduction in urine protein excretion. Although lipid levels were reduced in these studies, they were not normalized and glomerular macrophage number was not significantly altered by this therapy. Thus, in models of experimental disease in which hypercholesterolemia is a primary abnormality (the obese Zucker rat), or in models in which abnormalities of lipids occur as a consequence of renal disease, pharmacologic modifications of circulating lipids resulted in amelioration of glomerular injury and preservation of renal function. These experimental data provide a mandate for further evaluation of the role of hyperlipidemia in patients with renal disease, not only as an important modulator of atherosclerosis but also for its role in the progressive nature of renal disease.

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