Apolipoprotein E (ApoE) is a major constituent of plasma lipoproteins with many biological actions of great significance. Beyond the known influence of ApoE polymorphisms on serum lipid profile, the pathogenesis of atherosclerosis, and the development of neurodegenerative disorders, ApoE also has a major role in the pathogenesis and progression of a variety of renal diseases, as well as in the atherosclerotic complications associated with them. Briefly, the polymorphisms of ApoE are major determinants of plasma lipid levels in uremic patients. They may affect the risk for cardiovascular disease in this population, predispose to the development of diabetic nephropathy, influence the severity of certain glomerulopathies, and regulate mesangial and glomerular functions locally in the kidney microenvironment. Finally, certain mutations of the ApoE gene are associated with a recently described nephropathy, termed lipoprotein glomerulopathy.


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INDEX WORDS: Apolipoprotein E (ApoE); renal disease; renal failure; hemodialysis (HD); continuous ambulatory peritoneal dialysis (CAPD); kidney; transplantation.

Apolipoprotein E (ApoE), a 34,200-kd protein consisting of 299 amino acids, has a major role in the metabolism of lipids and lipoproteins. It is found in chylomicrons, chylomicron remnants, very low-density lipoproteins (VLDLs), VLDL remnants, and a subfraction of the high-density lipoproteins (HDLs), serving as a ligand for their receptor-mediated catabolism through the low-density lipoprotein (LDL) receptor (ApoB100/E) and ApoE receptor.

The ApoE gene, located on chromosome 19q13.2, has 3 common alleles, e2, e3, and e4, coding for the 3 main isoforms of the ApoE protein: E2 (Arg158→Cys), E3 (parent isoform), and E4 (Arg112→Cys). Therefore, there are 6 common ApoE polymorphisms: ApoE3/3, ApoE4/4, ApoE2/2, ApoE2/3, ApoE4/2, and ApoE4/3. Studies involving Caucasians have shown that e3 is the most frequent allele (~77%), whereas the e4 allele has a relative frequency of approximately 14% and the e2 allele is found in approximately 8% of the population. ApoE isoforms differ in their receptor-binding ability; E4 has the maximum binding capacity, whereas E2 is defective in its ability to bind to ApoE receptors.

The different functional properties of the ApoE isoforms result in a characteristic pattern of differences in plasma lipid and apolipoprotein levels, with lower plasma total cholesterol (T-Chol) and LDL cholesterol (LDL-C) levels in ApoE2 carriers than ApoE3/3 subjects and higher levels in ApoE4 carriers. The ApoE4-induced increase in T-Chol and LDL-C levels is caused by an increase in intestinal absorption of dietary cholesterol and downregulation of LDL receptors on the surface of hepatic cells resulting from increased delivery of cholesterol to these cells, owing to the enhanced interaction of ApoE4-containing remnants and ApoE receptors. No other single genomic polymorphism has been identified with such a large contribution (up to 17%) in the general interindividual variability in plasma cholesterol concentrations. Furthermore, ApoE stimulates VLDL triglyceride production and inhibits ApoC-II–dependent lipolysis in an isoform-independent manner; 20% to 40% of the intervariability of triglyceride levels is determined by plasma ApoE levels. Furthermore, ApoE-enriched HDL may have a significant role in reverse-cholesterol transport in humans. Finally, ApoE polymorphism determines the hypolipidemic effects of diet, exercise, and drugs, such as statins, fibrates, cholestryamine, hormone replacement therapy, and tamoxifen.

The ApoE polymorphism also is implicated in the pathogenesis of type III hyperlipidemia (familial dysbeta-lipoproteinemia), which is characterized by combined and often severe mixed hyperlipidemia caused by the accumulation of B-VLDL (remnant) particles in plasma, leading to accelerated atherosclerosis. Patients with this
disorder are homozygous for the ApoE2 allele (ApoE2/2). However, only 1% of these patients develop type III hyperlipidemia; additional factors (eg, diabetes mellitus [DM], obesity, and hypothyroidism) clearly are required for its clinical expression.10

ApoE also has a key role in the atherosclerotic process: the ApoE4 allele commonly is associated with an increased prevalence of coronary heart disease,11 as well as of ischemic cerebrovascular disease, independently of plasma lipid levels,12 whereas ApoE-deficient (−/−) mice are more prone to the rapid development of atherosclerotic lesions.13 ApoE not only influences plasma lipoprotein levels, but also facilitates cellular cholesterol efflux from foam cells, regulates the inflammatory process, and possesses antioxidant activity locally in the intima wall of vessels.13

Finally, ApoE has a critical role in neurobiology. The E4 allele is the major susceptible gene related to the occurrence and early age of onset of Alzheimer’s disease. One of the major functions of ApoE in the central nervous system is to mediate neuronal repair, remodeling, and protection, with ApoE4 being less effective than the E3 and E2 alleles.6

Conversely, atherosclerotic vascular disease is the leading cause of death in patients with end-stage renal disease (ESRD); approximately 60% of deaths within this group occur because of complications of atherosclerotic cardiovascular disease.14,15 Abnormal lipoprotein metabolism has an important role in the acceleration of atherosclerosis in these patients. Dyslipidemia in patients with renal disease is characterized by increased levels of plasma T-Cho and LDL-C,16 as well as triglycerides, in patients with nephrotic syndrome or renal transplant recipients and by hypertriglycerideremia and decreased levels of HDL cholesterol (HDL-C) in patients with ESRD.17-20 Increased lipoprotein(a) (Lp[a]) level is an additional characteristic of dyslipidemia in renal diseases and may contribute to the accelerated atherosclerosis observed in these patients,21-24 whereas the ApoE polymorphism has been shown to influence Lp(a) levels in nonuremic subjects.25 Finally, novel markers of inflammation and cardiovascular risk, such as C-reactive protein and the platelet activating factor acetylhydrolase, also have been studied in this population.26,27

| Table 1. Possible Roles of ApoE and Its Polymorphisms in Renal Diseases |
|------------------|-----------------------------------------------|
| 1. Regulation of plasma lipid levels in patients with ESRD |
| 2. Modulation of the risk for atherosclerosis in patients with ESRD and renal transplant recipients |
| 3. Predisposition to ESRD and influence on the development, progression, and response to treatment of certain glomerulopathies |
| 4. Effect on the development and progression of DN in patients with type 1 and type 2 DM |
| 5. Pathogenesis of LPG |
| 6. Effect on bone-fracture risk in HD patients |
| 7. Influence on the development of dialysis-related amyloidosis |
| 8. Modulation of risk for acute renal failure in postbypass surgical patients |
| 9. Autocrine modulator of glomerular and mesangial function and proliferation |

Lipoprotein abnormalities predispose to the development of global glomerulosclerosis in a way analogous to that of atherosclerosis deteriorating renal function in patients with renal disease.28 In this context, we briefly review the effects of ApoE and its polymorphisms on lipoprotein metabolism, the development of atherosclerosis, and the progression of renal failure in uremic patients (Table 1).

PREVALENCE OF ApoE ALLELES IN NONDIABETIC RENAL DISEASE

In most studies, there is no difference concerning the frequencies of ApoE alleles and genotypes between patients undergoing maintenance hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) and control subjects in different ethnic populations.29-32 Conversely, a higher frequency of ApoE2 and a lower frequency of ApoE4 found in a large cohort of Japanese patients with ESRD may suggest that ApoE2 carries a possible genetic predisposition to ESRD, at least in this population.33 Furthermore, a 4.8-times overexpression of ApoE4 was found in a small number of adult nephrotic Caucasian patients compared with healthy control subjects.34

In another study of Swedish renal transplant recipients, a significantly increased frequency of the ApoE3/4 genotype (38.3% versus 16% in the control group; \(P < 0.001\)) and the e4 allele (44% versus 30%; \(P < 0.01\)) led the investigators to speculate that ApoE3/4 genotype may be a spe-
cific risk factor for the progression of renal failure requiring renal transplantation. Although no difference in prevalence of ApoE genotypes was found in pediatric or adult patients with immunoglobulin A nephropathy, an increased frequency of the $e4$ allele was found in children with nephrotic glomerular diseases (20.7% versus 10.8% in controls). In the same study, children with focal segmental glomerulosclerosis had greater frequencies of both the ApoE4/3 genotype and $e4$ allele.

EFFECT OF ApoE POLYMORPHISM ON SERUM LIPOPROTEIN LEVELS IN PATIENTS WITH RENAL DISEASE

Results of most studies examining the influence of ApoE polymorphism on serum lipid levels in uremic patients are in agreement with those of the general population; ApoE4 is accompanied by increased cholesterol levels (Table 2). Specifically, in a study involving 269 patients on HD therapy, serum T-Chol and LDL-C levels were greater in those with the Apo4/3 phenotype compared with those with the ApoE3/3 and ApoE3/2 phenotypes, whereas there was no significant link between ApoE phenotype and serum levels of triglycerides, HDL-C, or Lp(a). In another study of 245 patients on HD therapy, those with the ApoE2/2, ApoE4/4, and ApoE4/3 phenotypes had greater mean plasma cholesterol and triglyceride concentrations than those with the ApoE3/3 or ApoE3/2 phenotype. In the same study, ApoB levels increased in the order of E2/2 less than E3/2 less than E3/3 less than E4/3 less than E4/4, whereas ApoE levels decreased in the same order.

Dyslipoproteinemia in HD patients results predominately from the accumulation of triglyceride-rich remnants or intermediate-density lipoproteins, thus resembling the previously described type III hyperlipidemia. This may explain why homozygous ApoE2/2 patients had the greatest T-Chol and triglyceride levels in the previously mentioned study. Furthermore, individuals with ApoE2/2 and nephrotic-range proteinuria may express the full-blown type III hyperlipidemia or even chylomicronemia because of decreased clearance of triglyceride-rich particles mediated by the loss of lipolytic enzymes and the low interaction of lipoproteins with specific receptors. Type III hyperlipidemia also has been described in pediatric patients with renal failure and ApoE2/2 homozygosity. ApoE2/2-induced severe type III hyperlipoproteinemia is related closely to the development of a specific glomerulopathy, characterized by proteinuria and marked accumulation of foam cells in glomeruli (glomerular lipidosis). Lipid-lowering therapy, as well as plasmapheresis, may be effective in the treatment of this glomerulopathy. Furthermore, ApoE2 homozygosity and type III hyperlipoproteinemia may be associated with a lipoprotein glomerulopathy (LPG)—like disease. In this case, extensive lipoprotein depositions in glo-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>29</td>
<td>269 HD patients</td>
<td>ApoE4/3 is associated with higher serum T-Chol and LDL-C levels than 3/3 or 3/2; no difference in triglyceride, HDL-C, and Lp(a) levels</td>
</tr>
<tr>
<td>30</td>
<td>245 HD patients</td>
<td>ApoE2/2, 3/4, and 4/4 are associated with higher T-Chol and triglyceride levels than 3/3 and 3/2</td>
</tr>
<tr>
<td>32</td>
<td>493 HD patients</td>
<td>ApoE3/4 is associated with higher LDL-C and lower HDL-C levels compared with E3/2</td>
</tr>
<tr>
<td>46</td>
<td>23 CAPD patients</td>
<td>ApoE4/3 is associated with increased T-Chol and LDL-C levels compared with ApoE2/2 and E3/2</td>
</tr>
<tr>
<td>31</td>
<td>51 CAPD patients</td>
<td>ApoE4/3 and 4/4 are associated with higher LDL-C levels compared with E3/3</td>
</tr>
<tr>
<td>47</td>
<td>54 CAPD patients</td>
<td>ApoE3/2 is associated with higher T-Chol and triglyceride and lower ApoB and Lp(a) levels compared with E3/3 and E3/4</td>
</tr>
<tr>
<td>39-45</td>
<td>Case reports of homozygous E2/2 patients with proteinuria or renal failure</td>
<td>Development of type III hyperlipoproteinemia</td>
</tr>
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</table>
meruli as lipoprotein thrombi were present, but electron microscopy studies failed to show the formation of striae resembling fingerprints, which is the typical histological feature of LPG (discussed later). In another study involving 493 Japanese patients on HD therapy, those with the ApoE3/4 genotype had significantly greater LDL-C and ApoB levels, significantly lower HDL-C levels, and a higher atherogenic index compared with those with ApoE3/2. ApoE levels were significantly lower in patients with ApoE3/4 than those with ApoE3/3 or ApoE3/2 in the same study. The ApoE4 allele was associated with increased T-Chol levels in 23 patients on CAPD therapy, whereas in another study of 54 Korean patients on CAPD therapy, the ApoE3/2 genotype was accompanied by higher T-Chol and triglyceride levels and lower ApoB and Lp(a) levels. Finally, in a study of 51 patients on CAPD therapy, E4 carriers had greater LDL-C levels.

ApoE POLYMORPHISM AND RISK FOR ATHEROSCLEROSIS IN PATIENTS WITH RENAL FAILURE

Although the E4 allele generally has been associated with a more atherogenic profile in patients with ESRD, there is much controversy in the literature concerning the relation between ApoE polymorphism and the development of atherosclerosis in this population. In a study of 269 HD patients, no significant association between ApoE genotype and carotid artery intima-media thickness was found. Furthermore, in a cross-sectional study of 493 HD patients, ApoE phenotype was not an independent risk factor for atherosclerotic vascular disease. Conversely, increased frequency of the E4 allele was found among a small number of CAPD patients with established cardiovascular disease in a cross-sectional study. Moreover, in a cohort of 66 HD patients, a significantly greater prevalence of the E4 allele was found in patients with increased intima-media thickness (>0.75 mm; 21.2% versus 3.0% in patients with intima-media thickness <0.75 mm; P = 0.0004). Additionally, in the only prospective study, which involved 157 Chinese uremic patients (119 patients, HD; 38 patients, CAPD), the cumulative occurrence of ischemic cerebrovascular disease during a 2-year follow-up period was 36.8% in e4 carriers compared with 5.6% in non-e4 carriers (P < 0.05 in stepwise regression analysis).

Finally, the ApoE4 allele was found to be a genetic marker for coronary artery disease and global atherosclerosis (odds ratios, 10.2 and 6.4, respectively) in male renal transplant recipients in a cross-sectional study of 110 Spanish patients.

ApoE POLYMORPHISM AND DIABETIC NEPHROPATHY

Diabetic nephropathy (DN) is a major contributor to the high mortality of patients with DM, whereas DN is the most commonly recognized cause of ESRD in developed countries. Although several acquired risk factors have been identified for the development of DN (such as abnormal lipoprotein metabolism, hypertension, and hyperglycemia), a genetic susceptibility is thought to contribute to the pathogenesis of this complication. In this context, the influence of the ApoE polymorphism on the development of DN in patients with either type 1 or type 2 DM has been examined extensively (Table 3).

Studies of patients with type 1 DM have shown either that the E2 allele is a risk factor for DN or no association between ApoE polymorphism and DN exists. More specifically, in a large study involving patients with long-lasting type 1 DM (223 patients with DN, 196 control subjects without DN), the risk for DN was 3.1 times greater in carriers of the E2 allele than noncarriers. In the same study, heterozygous parents for the E2 allele preferentially transmitted E2 to offspring with DN, whereas other polymorphisms flanking the ApoE region were not associated with nephropathy. To explain this association, the investigators proposed that either the dyslipidemia caused by the E2 allele may promote the development of DN or accumulation of ApoE2 protein in the mesangial area may change the properties of mesangial matrix or influence cell functions. Furthermore, another study found that the presence of the E2 allele was associated with increased risk for DN in Caucasian subjects with type 1 DM (odds ratio, 4.3). In a study examining 162 German patients with type 1 DM, multiple linear regression analysis showed the E2 allele was a negative predictor of creatinine clearance and a positive predictor of urinary albumin excretion. Finally,
in an analysis of results of the Pittsburgh Epidemiology of Diabetes Complication Study, non-ApoE3/3 genotype was associated with increased prevalence of overt DN (odds ratio, 7.2).57 Conversely, no contribution of the ApoE polymorphism to genetic susceptibility to DN in individuals with type 1 DM was found in a small case-control study58 in either a large study involving 494 patients with type 1 DM with different stages of DN (Genetic de la Nephropathie Diabetique Study),59 a study of 198 patients with type 1 DM, 60 or a large cohort of 617 subjects of the European Diabetes Study. 61 Reasons for these conflicting results are poorly understood, but may be related to different diagnostic criteria for DN, ethnic factors, dietary differences among the populations studied, variable degrees of linkage disequilibrium if the E2 allele is only a marker of susceptibility, interactions with other genetic or environmental factors among the different populations, or sampling errors (eg, people with the E2 allele live longer than those without this allele).62

Similar discrepancies are noticed with regard to the association of ApoE polymorphism and the development of DN in patients with type 2 DM. In a study involving 158 Japanese patients with long-term type 2 DM, the E2 allele was associated strongly with DN (odds ratio, 10.1), whereas the E4 allele was found to be protective (odds ratio, 0.129) in logistical regression analysis.63 In the same study, levels of plasma triglycerides and remnants were significantly higher in ApoE2 patients and significantly lower in ApoE4 patients than in those with ApoE3/3, whereas ApoE2 triglyceride-rich lipoproteins stimulated the accumulation of cholesteryl esters by human mesangial cells significantly more compared with ApoE3/3 or ApoE4 triglyceride-rich lipoproteins.63 Moreover, the frequency of ApoE2 allele was significantly greater in Taiwanese patients with type 2 DM with DN than those without DN regardless of serum lipid levels.64 In a previous study of Japanese patients with type 2 DM, frequency of the E2 allele was greater in patients with DN and renal failure than those with preserved renal function.65 Finally, similar results were obtained in Korean patients with type 2 DM; the ApoE2 allele was significantly more frequent in the macroalbuminuria group (odds ratio, 3.46) compared with the normoalbuminuria group.66

Conversely, the prevalence of DN was 2-fold greater in E2 noncarriers in a study of 134 Caucasian patients with type 2 DM.67 There also are conflicting results regarding the impact of allele E4 on the development of DN. In a study of 178 Japanese patients with type 2 DM, the E4 allele was associated with reduced relative risk for progression of DN. E4 allele incidence was lower in patients with renal failure than those with preserved renal function, whereas progres-

### Table 3. ApoE Polymorphisms and DN

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Results</th>
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<tbody>
<tr>
<td>Type 1 DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>223 Caucasian patients</td>
<td>E2 allele predisposes to DN (OR, 3.1)</td>
</tr>
<tr>
<td>55</td>
<td>252 Caucasian patients</td>
<td>E2 allele predisposes to DN (OR, 4.3)</td>
</tr>
<tr>
<td>56</td>
<td>162 German patients</td>
<td>E2 allele is a negative predictor of creatinine clearance and positive predictor of albuminuria</td>
</tr>
<tr>
<td>57</td>
<td>56 Caucasian patients</td>
<td>Non-ApoE3/3 genotype predisposes to overt DN (OR, 7.2)</td>
</tr>
<tr>
<td>58-61</td>
<td>Total of &gt;1,000 Caucasian patients</td>
<td>No association between ApoE genotype and DN</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>158 Japanese patients</td>
<td>E2 allele is strongly associated with DN (OR, 10.1); E4 allele protects from DN (OR, 0.129)</td>
</tr>
<tr>
<td>64</td>
<td>214 Taiwanese patients</td>
<td>E2 allele predisposes to DN</td>
</tr>
<tr>
<td>65</td>
<td>146 Japanese patients</td>
<td>E2 allele is found more frequently in patients with DN and renal failure</td>
</tr>
<tr>
<td>66</td>
<td>167 Korean patients</td>
<td>E2 allele is associated with macroalbuminuria (OR, 3.46)</td>
</tr>
<tr>
<td>67</td>
<td>134 Finnish patients</td>
<td>Non-E2 alleles are associated with increased risk for DN (OR, 2.0)</td>
</tr>
<tr>
<td>68</td>
<td>178 Japanese patients</td>
<td>E4 allele reduces risk for DN progression</td>
</tr>
<tr>
<td>69</td>
<td>84 Caucasian patients</td>
<td>E4 allele speeds up rate of glomerular filtration rate decline in patients with progressive DN</td>
</tr>
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</table>

Abbreviation: OR, odds ratio.
sion to dialysis therapy (renal survival time) was delayed in ApoE4 carriers compared with non-E4 carriers despite greater T-Cho and LDL-C levels in ApoE4 carriers. Possible explanations for the previously mentioned protective role of the E4 allele include: (1) enhanced clearance of VLDLs and their remnants, the accumulation of which predominates in overt proteinuric states; (2) differential modulation of the bioactivity of growth factors caused by the different capacity of the ApoE isoproteins in binding to the extracellular glycosaminoglycans in the kidney; or (3) the speculation that E4 may not be the truly protective gene, but may be in a linkage disequilibrium with an unknown renal protective allele. However, in a 9-year follow-up study of 84 Caucasian patients with type 2 DM, the ApoE4 allele may speed up the rate of decline in glomerular filtration rate in patients with progressive diabetic renal disease.

LIPOPROTEIN GLOMERULOPATHY

Renal lipidoses are seen in some systemic disorders caused by inherited abnormalities of lipid metabolism (Fabry’s disease, fish eye disease, and von Gierke’s disease) and type III hyperlipoproteinemia, as discussed, as well as secondary to nephrotic syndrome. However, LPG is a unique and rare disorder recently described in the literature. Approximately 25 cases have been reported to date: 23 cases of Asian origin and only 2 cases of Caucasian origin. The unique histological features of this disorder include the presence of lipoprotein thrombi into the markedly dilated capillary lumina of the affected glomeruli. Foam cells, vascular changes, or interstitial lesions are not commonly seen, but segmental sclerosis and periglomerular fibrosis can be found in advanced stages of the disease. Sudan staining shows lipid droplets in the capillary lumina, whereas electron microscopy shows granules and vacuoles, which form striae resembling fingerprints.

Patients with LPG are from 4 to 69 years of age, and the male:female ratio is approximately 2:1. They usually present with nephrotic-range proteinuria without systemic manifestations, whereas half these patients show renal failure 1 to 27 years after disease onset. LPG shows a characteristic plasma lipoprotein profile; in most cases, levels of intermediate-density lipoproteins are increased, resembling type III hyperlipoproteinemia, whereas ApoE levels always are elevated by at least 2-fold.

Genetic studies showed that LPG is associated with the presence of rare mutant forms of ApoE, such as ApoE2 Sendai (Arg145→Pro), ApoE Kyoto (Arg25→Cys), ApoE Tokyo (deletion of Leu, Arg, Lys at codons 141 to 143), ApoE1 (Gln 156-Gly 173→0), and ApoE Maebashi. Additionally, as noted, ApoE2/2 could induce an LPG-like disease. Furthermore, virus-mediated transduction of ApoE2 Sendai in ApoE-deficient hypercholesterolemic mice resulted in partial correction of the hypercholesterolemia and a marked, but temporal, increase in plasma triglyceride levels. Histological examination of the ApoE2 Sendai–infected mice showed renal features identical to those seen in LPG, confirming that ApoE2 Sendai is an etiologic factor in some cases of LPG. Therefore, although ApoE2 Sendai is still one strong inducer of LPG, other reports now suggest that type III hyperlipoproteinemia caused by any ApoE mutation may cause LPG.

ApoE2 Sendai has shown diminished LDL receptor binding capacity, but almost normal heparin binding, whereas ApoE Kyoto has shown increased binding capacity to endothelial cells. Abnormal structure of these ApoE isoforms may cause aggregated deposits to form in the glomerulus or may interact with matrix proteins or cell-surface proteins in the glomerulus, leading to retention and accumulation of lipoproteins. Finally, various therapeutic trials have been proposed for this disorder (lipid-lowering agents, LDL apheresis) without success. Renal transplantation was performed in 3 patients, but all attempts failed because of recurrence of LPG. Most recently, intensive lipid-lowering therapy in a 36-year-old man with LPG resulted in complete remission of proteinuria and pathological features.

ApoE AND OTHER ASPECTS OF RENAL DISEASE

Other Nephropathies

Although ApoE2 was not more frequent in 104 Japanese patients with immunoglobulin A nephropathy compared with healthy individuals, ApoE2 was associated with the severity of histological damage in these patients.
A study of 107 children with primary idiopathic nephrotic syndrome, the ApoE2 allele and ApoE2/3 genotype were significantly more common in patients with steroid-resistant nephrotic syndrome compared with those with steroid-sensitive nephrotic syndrome and the control group \( (P < 0.05) \). ApoE genotype did not seem to influence the risk for vascular rejection in renal transplant recipients in a previously mentioned study. Finally, in another study of a Japanese population, 86 patients with glomerulonephritis with proteinuria had a greater frequency of the ApoE2 allele, whereas a greater prevalence of nephrotic syndrome was found in proteinuric patients with glomerulonephritis with ApoE2.

**Bone Fracture Risk in HD Patients**

In a study of 219 HD patients, ApoE4/4 and ApoE4/3 genotypes were significantly more frequent in patients with a history of bone fractures than the ApoE2/3 and 2/2 genotypes (44% versus 16%; \( P < 0.005; \) odds ratio, 3.7). HD patients with genotypes E3/4 and E4/4 tend to have much lower than average serum vitamin K concentrations, which has been associated with increased risk for bone fractures.

**Dialysis-Related Amyloidosis**

Dialysis-related amyloidosis is a serious complication of long-term dialysis treatment, whereas the presence of ApoE in amyloid deposits has been shown. ApoE2 represented a protective factor that delayed the onset of amyloidosis in 1 study.

**Acute Renal Impairment**

The only study that examined the influence of ApoE polymorphism on acute renal failure is a prospective observational study of 564 coronary bypass surgical patients. This study found an association between ApoE polymorphism and postoperative peak creatinine concentrations in these patients: ApoE4 allele was associated with a less marked postoperative increase in serum creatinine levels after cardiac surgery in patients with normal preoperative renal function compared with the E3 or E2 allele. Findings of this study may reflect isoform-specific differences in the evolution of occult renal impairment relating to known interactions of ApoE with inflammation and tissue repair responses.

**Role of ApoE in the Kidney Microenvironment**

The role of ApoE in the kidney is unclear. Kidney biopsies of ApoE-deficient mice indicate increased mesangial cell proliferation and matrix formation, key features of the pathogenesis of renal diseases independently of the presence of hyperlipidemia. ApoE (especially the E3 isoform) inhibits mesangial cell proliferation and mesangial cell apoptosis induced by oxidized LDL in experimental models. In the same studies, ApoE induced the mesangial matrix heparin sulfate proteoglycan (HSPG), whereas loss of HSPG in the basement membrane and mesangial matrix is associated with disruption of the filtration barrier. In addition to these effects of ApoE on mesangial cell proliferation, vascular endothelial cells also are implicated. First, ApoE-deficient mice have reduced renal blood flow compared with wild-type mice. Furthermore, ApoE-null mice, when fed a hypercholesterolemic diet, show activation of glomerular capillary endothelial cells, recruitment and adhesion of blood monocytes, and, finally, transformation of these macrophages into foam cells in the mesangial area.

ApoE is synthesized in human kidney, particularly kidney cortex, and is a moderately abundant product of the kidneys, with correspondence to the specific isoforms of plasma ApoE. A more marked decrease in plasma ApoE levels in anephric patients compared with those on dialysis therapy shows that ApoE production from the renal parenchyma contributes to the serum pool of ApoE. Conversely, there is evidence that the kidney may have a role in the removal of free forms of lipoprotein particles, such as free ApoE. Finally, immunocytochemical staining of renal biopsy specimens of glomerular diseases shows the deposition of ApoE (as well as of ApoB) in the mesangial area and glomerular cells. This deposition is mainly receptor mediated and may be associated with mesangial expansion, glomerular sclerosis, and proteinuria.

**CONCLUSION**

ApoE and its polymorphisms have a major role in the pathogenesis of renal disease. They influence the serum lipid profile of patients with
ESRD and, consequently, the risk for atherosclerotic vascular disease. They are associated with the development and progression of DN, as well as other glomerulopathies, with the e2 allele as a predisposing factor in most studies. Additionally, novel mutations of ApoE are the etiologic factors of LPG. Finally, ApoE acts as an autocrine regulator of mesangial and glomerular function. Additional clinical and molecular studies are needed to elucidate the spectrum of ApoE involvement in the pathogenesis of renal diseases and determine whether ApoE genotyping of these patients in clinical practice will be of value for their better management.

REFERENCES

42. Amatruz JM, Margolis S, Hutchins GM: Type 3 hyperlipoproteinemia with mesangial foam cells in renal glomeruli. Arch Pathol 96:51-54, 1976
65. Eto M, Horita K, Morikawa A, et al: Increased frequency of apolipoprotein e2 allele in non-insulin depen-
99. Alsayed N, Reboucet R: Abnormal concentrations of CII, CIII, and E apolipoproteins among apolipoprotein B-


