Pharmacologic Treatment of Hyperlipidemia Reduces Glomerular Injury in Rat 5/6 Nephrectomy Model of Chronic Renal Failure

Bertram L. Kasiske, Michael P. O’Donnell, William J. Garvis, and William F. Keane

The role of lipid abnormalities in the pathogenesis of focal glomerulosclerosis was investigated in the rat remnant kidney model of chronic renal failure. Rats subjected to right nephrectomy and two-thirds segmental infarction of the left kidney (5/6 nephrectomy) were treated for 10 weeks with the lipid-lowering agent clofibric acid. Both serum cholesterol and urine albumin excretion were significantly reduced by clofibric acid. At 10 weeks, the percent of glomeruli with focal glomerulosclerosis was 5 ± 2% in clofibric acid–treated and 24 ± 5% in untreated 5/6 nephrectomy rats (p<0.01). Inulin clearance was greater in clofibric acid–treated than in untreated 5/6 nephrectomy rats (0.28 ± 0.02 versus 0.22 ± 0.02 ml/min 100 g body wt, p<0.05). Body weight, kidney weight, and systemic blood pressure were not significantly altered by clofibric acid. Micropuncture studies, performed in separate groups of clofibric acid–treated and untreated 5/6 nephrectomy rats, demonstrated elevated single nephron glomerular filtration rates and glomerular capillary pressures 4 weeks after surgery. However, clofibric acid did not significantly alter single nephron glomerular filtration rates (95 ± 2.1 nl/min in treated versus 97.0 ± 6.2 nl/min in untreated, p>0.05) or glomerular capillary pressures (56.6 ± 1.5 mm Hg in treated versus 57.8 ± 0.8 mm Hg in untreated, p>0.05) in 5/6 nephrectomy rats. In a separate set of experiments, 5/6 nephrectomy rats were treated with the specific cholesterol synthesis inhibitor, mevinolin. Mevinolin improved serum lipid levels and reduced albuminuria in 5/6 nephrectomy rats without causing significant alterations in blood pressure. Focal glomerulosclerosis was also reduced by mevinolin (11 ± 2% versus 30 ± 3%, p<0.01). These results suggest that lipid abnormalities may be important in the pathogenesis of focal glomerulosclerosis in the rat 5/6 nephrectomy model of chronic renal failure. (Circulation Research 1988;62:367-374)

Focal glomerulosclerosis occurs in a variety of immune and nonimmune renal diseases.1 Its pathogenesis is unclear. The rat remnant kidney model, in which the amount of functional renal mass is reduced surgically, has been used to study factors important in the development and progression of focal glomerulosclerosis. Glomerular injury in this model may be analogous to that occurring in residual intact nephrons in patients with chronic progressive renal disease. Recently, it has been suggested that compensatory increases in glomerular capillary pressures and flows that occur in remaining nephrons after reduction of renal mass may cause or contribute to progressive glomerular damage.2 3 In addition, other mechanisms, such as abnormal mesangial processing of phlogogenic macromolecules and alterations in coagulation, may participate in the pathogenesis of focal glomerulosclerosis.4 5 Recent experimental results have indicated that abnormalities in lipid metabolism, which invariably accompany renal disease of diverse etiologies, may contribute to progressive glomerular injury.6 8 10

The present study was designed to investigate the role of hypercholesterolemia and hypertriglyceridemia in the pathogenesis of focal glomerulosclerosis in the rat 5/6 nephrectomy model of chronic renal failure. Rats with a 5/6 reduction in renal mass were treated with the lipid-lowering agent clofibric acid [2-(p-chlorophenoxy)-2-methylpropionic acid]. The effects of this agent on systemic blood pressure, urine albumin excretion, and whole kidney and superficial nephron function as well as renal histology were examined. It was found that clofibric acid preserved renal structure and function in 5/6 nephrectomy rats without altering systemic or glomerular capillary hypertension.

In a separate study, 5/6 nephrectomy rats were treated with mevinolin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor that blocks cholesterol synthesis. Mevinolin caused reductions in serum lipid levels, albuminuria, and focal glomerulosclerosis. These results suggest that lipid abnormalities, which accompany a reduction in renal mass, may be important in the pathogenesis of glomerular injury.

Materials and Methods

Experimental Design

Male Sprague-Dawley rats weighing 220–245 g were obtained from Charles River Breeding Laboratories, Wilmington, Massachusetts. In the first set of

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Table of Abbreviations

- BW, body weight
- C_t, inulin clearance
- LKW, left kidney weight
- MAP, mean arterial pressure
- P_a, free-flow tubular pressure
- P_s, stop-flow tubular pressure
- P_e, efferent pressure
- P_o, glomerular capillary hydraulic pressure
- P_g, glomerular ultrafiltration coefficient
- ΔP, mean transcapillary hydraulic pressure difference
- K_g, glomerular ultrafiltration coefficient
- SNPF, superficial nephron plasma flow
- SNGFR, superficial nephron glomerular filtration rate
- SNPF, superficial nephron plasma flow

Experiments, group 1 (n = 10) consisted of rats subjected to 5/6 nephrectomy (see below). Group 2 (n = 11) rats were subjected to 5/6 nephrectomy and were treated with clofibric acid (Sigma Chemical, St. Louis, Missouri). Clofibric acid dissolved in propylene glycol (50-125 mg/ml) was injected subcutaneously. Rats in group 2 received 50 mg clofibric acid/kg body wt daily for 3 weeks, followed by 125 mg/kg body wt daily for the remainder of the study period. These doses of clofibric acid were chosen to parallel anticipated changes in renal elimination of the drug. Six normal, two-kidney rats served as a third untreated control group (group 3) for this first set of experiments.

In the second set of experiments, micropuncture was performed in six additional untreated (group 4) and six clofibric acid–treated (group 5) 5/6 nephrectomy rats. Micropuncture studies were carried out 4 weeks after surgery in both groups. Micropuncture studies were also carried out in eight two-kidney controls matched for body weight (group 6).

In the third set of experiments, an additional group of 13 5/6 nephrectomy rats (group 7) were injected with vehicle and compared with 15 5/6 nephrectomy rats (group 8) treated with mevinolin (Merck Sharp & Dohme, West Point, Pennsylvania). Using propylene glycol as the vehicle, 4 mg mevinolin/kg body wt was injected subcutaneously each day. To examine the possibility that differences in food intake could account for some of the observed effects of mevinolin, one half of the rats in groups 7 and 8 were pair fed. An additional group of eight ad libitum–fed, two-kidney, untreated rats were also used as controls (group 9).

In all of these investigations, renal ablation (5/6 nephrectomy) was carried out using the same technique. The surgical procedure included isolation of the left renal artery branches and ligation of the inferior and superior branches, leaving only the posterior branch intact. The right kidney was removed simultaneously.

All rats were fed standard laboratory chow (Ralston Purina, St. Louis, Missouri) and were allowed free access to water. Pair-fed mevinolin–treated and untreated rats from groups 7 and 8 were housed individually. All other rats were housed two per cage and were fed ad libitum.

Except in the rats subjected to micropuncture (groups 4, 5, and 6), blood pressure, urine albumin excretion, and serum chemistries were obtained both early (4–6 weeks) and late (7–10 weeks) after 5/6 nephrectomy (see below). Tail blood for serum chemistries was obtained from rats fasted for 18 hours and subjected to light ether anesthesia. At 10 weeks, C_t determinations were made on all group 1 and group 2 rats (see below). Left kidney weight and renal tissue for histologic studies were obtained at 10 weeks (see below).

Renal Function Studies
Rats were anesthetized with sodium pentobarbital, 50 mg/kg body wt i.p. A tracheostomy was performed. The femoral artery and vein were cannulated with PE-50 tubing for continuous monitoring of mean arterial pressure, blood sampling, and intravenous infusions. The bladder was cannulated, and a maintenance infusion of lactated Ringer’s solution was begun at the rate of 0.3 ml/100 g body wt/hr. The rate of infusion was adjusted to maintain a constant hematocrit. Tritiated inulin (New England Nuclear, Boston, Massachusetts) was given as a bolus intravenous injection, 1.0 μCi/100 g body wt, followed by continuous infusion of 0.6 μCi/100 g body wt. Thirty minutes after the inulin bolus, two 30-minute urine collections with midpoint blood samples were obtained to determine C_t. The mean of the two C_t determinations was taken as the C_t for that rat. Results are expressed as milliliters per minute and milliliters per minute per 100 grams body weight.

Blood Pressure and Urine Albumin Determination
Rats were trained to rest quietly in warmed restraining devices daily for at least three days before blood pressures were measured. Morning blood pressure measurements were obtained in awake, quiet, restrained rats using a tail-cuff system (model MK IV, Narco Biosystems, Houston, Texas). At least three separate determinations were made to obtain a mean systolic blood pressure measurement for each rat.

To determine albumin excretion rates, 24-hour urine excretions were collected from rats individually housed in metabolic cages. During urine collection, rats were deprived of food to avoid contamination of the urine but were allowed free access to water. Urine albumin concentration was measured with a laser nephelometer (Hyland, Deerfield, Illinois) using a monospecific antibody to rat serum albumin (Cappel Laboratories, West Chester, Pennsylvania).

Serum Chemistries
Triglycerides, cholesterol, and creatinine were measured in serum using an autoanalyzer (model Astra 8, Beckman, Brea, California). All results are expressed as milligrams per deciliters.

Histology
Tissue for light microscopy was fixed in Zenker’s solution and stained with periodic acid–Schiff. All tissue was evaluated without prior knowledge of the
group to which the rat belonged. A semiquantitative scoring system was used to assess the amount of mesangial matrix expansion as previously described. In each tissue specimen, a minimum of 50 glomeruli were examined. For each glomerulus, the amount of mesangial matrix expansion was graded from 0 to 4+ according to the percent of the glomerular tuft involved. A mesangial expansion score was obtained for each tissue specimen by multiplying the degree of mesangial expansion (0-4+) by the percent of glomeruli with the same degree of injury. The amount of mesangial expansion for the specimen was then obtained by the addition of these scores. In addition, the percent of glomeruli with focal glomerulosclerosis was determined for each tissue specimen by dividing the number of glomeruli with any focal glomerulosclerosis by the total number of nephrons in the specimen.

The extent of tubular dilation, tubular epithelial cell flattening, and interstitial fibrosis was qualitatively assessed. A score of 0-4+ was assigned to reflect the severity of these tubulointerstitial changes for each specimen.

**Single Nephron Function Studies**

Rats were not fasted prior to micropuncture. Studies were carried out in euvoletic animals using techniques previously described. Briefly, rats were anesthetized with sodium pentobarbital (50 mg/kg body wt) and placed on a heated table to maintain body temperature between 36.5° and 37.5° C. A tracheostomy was performed, the left femoral vein was cannulated with a PE-50 catheter (o.d. 5-8 μm) filled with 2.0 M NaCl. P_α was estimated by the stop-flow technique with measurements of P_α in first surface convolutions distal to Bowman’s space. During these measurements, an arterial blood sample was obtained for total protein determination and calculation of P_α using the Landis-Pappenheimer equation. Blood samples were taken from efferent vascular welling points and were analyzed, together with an arterial sample, for total protein content using the micro-Lowry technique. Measurements of glomerular pressures (P_α, P_γ), arterial and efferent arteriolar protein concentrations, and SNGFR were all performed on each rat. In all cases, filtration pressure equilibrium was not attained, and unique values for K, were calculated as previously described.

**Statistical Analysis**

Results are expressed as mean ± SEM. The statistical significance of differences between groups was assessed using analysis of variance with the Bonferroni method for comparing multiple groups. Nonparametric data were analyzed using the Kruskal-Wallis method. Differences were considered significant for p<0.05.

**Results**

**General Characteristics of Experimental Groups**

After surgery, all rats gained weight. Although two-kidney control rats weighed more than 5/6 nephrectomy rats, clofibric acid–treated rats weighed the same as untreated 5/6 nephrectomy rats at all times throughout the study (Table 1). Mevinolin-treated 5/6 nephrectomy rats had a modest (8.5%), but statistically significant, reduction in body weight (Table 2). This reduction in body weight could not be attributed to altered food intake because the difference in body weight between mevinolin-treated and untreated 5/6 nephrectomy rats was comparable in pair-fed (379 ± 12 g versus 409 ± 12 g) and ad libitum–fed rats (393 ± 12 versus 439 ± 11 g). Kidney weight was not significantly altered by either clofibric acid or mevinolin (Tables 1 and 2).

**Blood Pressure**

Tail-cuff blood pressures were elevated in all 5/6 nephrectomy rats compared with two-kidney controls (Tables 1 and 2). Neither clofibric acid nor mevinolin had any statistically significant effects on blood pressure (Tables 1 and 2).

**Triglycerides and Cholesterol**

Fasting serum triglyceride levels tended to be elevated in 5/6 nephrectomy rats compared with controls (Tables 1 and 2). Only mevinolin caused a substantial reduction in triglyceride levels (Table 2). Both clofibric acid and mevinolin caused significant reductions in the
Table 1. Effects of Clofibrac Acid on 5/6 Nephrectomy Rats

<table>
<thead>
<tr>
<th></th>
<th>Group 1 5/6 nephrectomy (n=10)</th>
<th>Group 2 5/6 nephrectomy clofibric acid (n=11)</th>
<th>Group 3 two-kidney controls (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>401 ± 15*</td>
<td>416 ± 16*</td>
<td>484 ± 20†</td>
</tr>
<tr>
<td>Left kidney weight (g)</td>
<td>2.03 ± 0.08*</td>
<td>1.88 ± 0.12*</td>
<td>1.47 ± 0.06†</td>
</tr>
<tr>
<td>Blood pressure, early</td>
<td>197 ± 10*</td>
<td>183 ± 7*</td>
<td>142 ± 2†</td>
</tr>
<tr>
<td>Triglycerides, early</td>
<td>71 ± 6*</td>
<td>77 ± 6*</td>
<td>52 ± 12*</td>
</tr>
<tr>
<td>Cholesterol, early</td>
<td>76 ± 4*</td>
<td>45 ± 3†</td>
<td>40 ± 2†</td>
</tr>
<tr>
<td>Cholesterol, late</td>
<td>94 ± 7*</td>
<td>53 ± 6†</td>
<td>43 ± 3†</td>
</tr>
<tr>
<td>Albuminuria, early</td>
<td>28.0 ± 7*</td>
<td>3.3 ± 0.8†</td>
<td>0.8 ± 0.2†</td>
</tr>
<tr>
<td>Albuminuria, late</td>
<td>62.5 ± 10*</td>
<td>11.0 ± 4.0†</td>
<td>0.6 ± 0.1†</td>
</tr>
</tbody>
</table>

*Mean ± SEM; shared superscripts indicate p>0.05.

Table 2. Effects of Mevinolin on 5/6 Nephrectomy Rats

<table>
<thead>
<tr>
<th></th>
<th>Group 7 5/6 nephrectomy (n=13)</th>
<th>Group 8 5/6 nephrectomy mevinolin (n=15)</th>
<th>Group 9 two-kidney controls (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>422 ± 8*</td>
<td>386 ± 9†</td>
<td>487 ± 16‡</td>
</tr>
<tr>
<td>Left kidney weight</td>
<td>1.80 ± 0.1*</td>
<td>1.72 ± 0.05*</td>
<td>1.51 ± 0.2†</td>
</tr>
<tr>
<td>Blood pressure, early</td>
<td>185 ± 5*</td>
<td>169 ± 7‡</td>
<td>114 ± 6‡</td>
</tr>
<tr>
<td>Triglycerides, early</td>
<td>130 ± 9*</td>
<td>97 ± 7†</td>
<td>85 ± 11†</td>
</tr>
<tr>
<td>Cholesterol, early</td>
<td>132 ± 6*</td>
<td>89 ± 5†</td>
<td>66 ± 10†</td>
</tr>
<tr>
<td>Cholesterol, late</td>
<td>138 ± 8*</td>
<td>92 ± 8‡</td>
<td>56 ± 11‡</td>
</tr>
<tr>
<td>Albuminuria, early</td>
<td>37.9 ± 8.1*</td>
<td>13.8 ± 3†</td>
<td>0.5 ± 0.3‡</td>
</tr>
<tr>
<td>Albuminuria, late</td>
<td>83.8 ± 8.6*</td>
<td>43.6 ± 7†</td>
<td>0.8 ± 0.6‡</td>
</tr>
</tbody>
</table>

*Mean ± SEM; shared superscripts indicate p>0.05.
Table 3. Renal Function In Untreated and Clofibric Acid-Treated 5/6 Nephrectomy Rats

<table>
<thead>
<tr>
<th>Group 1: 5/6 nephrectomy (n=10)</th>
<th>Serum creatinine at 5 weeks (mg/dl)</th>
<th>Serum creatinine at 10 weeks (mg/dl)</th>
<th>Inulin clearance at 10 weeks (ml/min)</th>
<th>Inulin clearance per 100 grams body weight (ml/min/100 g body wt)</th>
<th>Mean arterial pressure (anesthesia) (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.11 ± 0.03*</td>
<td>1.09 ± 0.13*</td>
<td>0.90 ± 0.09*</td>
<td>0.22 ± 0.02*</td>
<td>157 ± 11*</td>
</tr>
<tr>
<td>Group 2: 5/6 nephrectomy + clofibric acid (n=11)</td>
<td>0.99 ± 0.05*</td>
<td>0.76 ± 0.04†</td>
<td>1.20 ± 0.11*</td>
<td>0.28 ± 0.02†</td>
<td>151 ± 12*</td>
</tr>
<tr>
<td>Group 3: two-kidney controls (n=6)</td>
<td>0.55 ± 0.07†</td>
<td>0.53 ± 0.04‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SEM; shared superscripts indicate p > 0.05.

served between untreated (group 4) and clofibric acid-treated (group 5) rats subjected to micropuncture 4 weeks after 5/6 nephrectomy (Table 4). Serum cholesterol was reduced by 20% in group 5 compared with group 4 rats (75.7 ± 6.8 versus 94.5 ± 6.5 mg/dl, p = 0.07). Compared with control (0.5 ± 0.1 mg/24 hr), urine albumin excretion was only modestly elevated in group 4 (7.6 ± 3.2 mg/24 hr) and group 5 (6.8 ± 1.4 mg/24 hr) rats. Focal glomerulosclerosis was minimal at this age. In both groups, less than 5% of glomeruli exhibited focal glomerulosclerosis. Thus, 3 weeks after surgery, there was minimal glomerular injury in both 5/6 nephrectomy micropuncture groups. Compared with normal rats (group 6), both group 4 and group 5 rats demonstrated marked increases in SNGFR and SNPF (Table 4). Moreover, P_{oc} and ΔP were significantly increased in group 4 and group 5 5/6 nephrectomy rats (Table 4). These functional alterations in the Sprague-Dawley remnant kidney were similar to those documented in the Munich-Wistar rat.2,3 However, the increased Kf that characterized the Sprague-Dawley remnant kidney was not observed in the Munich-Wistar rat.2,3 This difference in Kf response to renal ablation could be due to differences in these two strains of rats. Nevertheless, clofibric acid did not alter SNGFR, SNPF, or intraglomerular hydraulic pressures in this remnant kidney model (Table 4).

Discussion

Clofibric acid is the pharmacologically active form of the lipid-lowering agent clofibrate.18 Clofibrlic acid inhibits hepatic release of lipoproteins, interferes with albumin binding of free fatty acids, inhibits cholesterol biosynthesis, improves fatty acid metabolism, and enhances lipoprotein lipase activity.13 In the present study, clofibrlic acid substantially reduced the marked glomerular, tubulointerstitial, and vascular injury that

![Image of figure 1](http://circres.ahajournals.org/)

**Figure 1.** Percent of glomeruli with focal glomerulosclerosis in groups 1, 2, 7, and 8. p<0.01 group 1 versus 2 and group 7 versus 8.
glomerulosclerosis. Prostaglandin production may be altered by reductions in glomerular capillary pressures. Whether the protective effects of clofibric acid seen in the present study were related to alterations in prostaglandin synthesis in unknown.

To further investigate the possibility that the reduction in glomerular injury associated with clofibric acid treatment was specifically related to improved lipid metabolism, a separate set of experiments was carried out using a structurally unrelated lipid-lowering agent. Mevinolin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis. In the present studies, mevinolin was shown to lower serum cholesterol and increase low-density lipoprotein receptors.

Recent studies in the 5/6 nephrectomy model have shown that dietary and pharmacologic maneuvers that lower glomerular capillary pressure retard the development of focal glomerulosclerosis. Indeed, normalization of glomerular capillary pressure with the angiotensin-converting enzyme inhibitor enalapril reduced glomerular size and diminished renal injury in this model. In the present study, glomerular area was reduced, but glomerular capillary pressures were unaltered by clofibric acid in 5/6 nephrectomy rats. Thus, it is unlikely that the beneficial effects of clofibric acid result from alterations in capillary pressures.

Similarly, experimental maneuvers that alter prostaglandin metabolism appear to preserve renal structure and function in the 5/6 nephrectomy model. The specific thromboxane synthesis inhibitor, OKY 1581, increased glomerular filtration rate and ameliorated glomerular injury. Also, a linoleic acid–enriched diet augmented renal production of vasodilatory prostaglandins, ameliorated proteinuria, and reduced focal glomerulosclerosis. Prostaglandin production may be affected by alterations in cholesterol and triglyceride metabolism. Whether the protective effects of clofibric acid seen in the present study were related to alterations in prostaglandin synthesis in unknown.
there were important changes in triglyceride metabolism that were not detected by measuring fasting triglyceride levels.

Clofibrate acid and mevinolin may have reduced renal injury by decreasing the amount of lipid deposition in remnant nephrons. Altered cholesterol and/or triglyceride metabolism have been shown to influence the development and progression of focal glomerulosclerosis in a number of animal models. Dietary cholesterol supplementation, for example, exacerbated injury by decreasing the amount of lipid deposition in triglyceride levels. Clotilde acid analogue, reduced focal glomerulosclerosis in puromycin aminonucleoside-treated rats fed a lipogenic diet. The results of these and other studies suggest a potential role for lipids in the pathogenesis of focal glomerulosclerosis.

Results of experiments using the remnant kidney model suggest that several factors may be important in the pathogenesis of glomerular injury in chronic renal failure. These mechanisms are not necessarily mutually exclusive. It is possible that increased glomerular capillary pressure, coagulation factors, and lipid abnormalities interact synergistically in the pathogenesis of focal glomerulosclerosis. Indeed, a similar relation between these factors has been shown to be important in the development of atherosclerosis. The glomerulus has many structural features that resemble arteries commonly involved in atherosclerosis. Mesangial cells, for example, are structurally similar to arterial smooth muscle cells important in the pathogenesis of atherosclerosis. Lipid-laden macrophages are frequently found in both early atherosclerosis lesions and focal glomerulosclerosis. Thus, factors important in the pathogenesis of focal glomerulosclerosis may be similar to those that influence the development of atherosclerosis. The results of the present study suggest lipid abnormalities, together with increased glomerular capillary pressure and coagulation factors, may be important in the pathogenesis of focal glomerulosclerosis.

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**KEY WORDS** • clofibrate • clofibric acid • mevinolin • focal glomerulosclerosis • remnant kidney • hyperlipidemia
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