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 clofibrac acid. Both serum cholesterol and urine albumin excretion were significantly reduced by clofibrac acid. At 10 weeks, the percent of glomeruli with focal glomerulosclerosis was 5 ± 2% in clofibrac acid–treated and 24 ± 5% in untreated 5/6 nephrectomy rats (p<0.01). Inulin clearance was greater in clofibrac 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 clofibrac acid. Micropuncture studies, performed in separate groups of clofibrac acid–treated and untreated 5/6 nephrectomy rats, demonstrated elevated single nephron glomerular filtration rates and glomerular capillary pressures 4 weeks after surgery. However, clofibrac 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. 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. In addition, other mechanisms, such as abnormal mesangial processing of phosphoglycogen macromolecules and alterations in coagulation, may participate in the pathogenesis of focal glomerulosclerosis. Recent experimental results have indicated that abnormalities in lipid metabolism, which invariably accompany renal disease of diverse etiologies, may contribute to progressive glomerular injury.

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 clofibrac 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 clofibrac 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-methylglutarylcoenzyme 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
Table of Abbreviations

- BW, body weight
- C<sub>in</sub>, inulin clearance
- LKW, left kidney weight
- MAP, mean arterial pressure
- P<sub>r</sub>, free-flow tubular pressure
- P<sub>e</sub>, efferent pressure
- P<sub>fr</sub>, stop-flow tubular pressure
- Pt, free-flow tubular pressure
- MAP, mean arterial pressure
- Cta, inulin clearance
- BW, body weight

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 clofibrate acid (Sigma Chemical, St. Louis, Missouri). Clofibrate acid dissolved in propylene glycol (50–125 mg/ml) was injected subcutaneously. Rats in group 2 received 50 mg clofibrate 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 clofibrate 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 clofibrate 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<sub>in</sub> 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 /uCi/100 g body wt, followed by continuous infusion of 0.6 /uCi/100 g body wt. Thirty minutes after the inulin bolus, two 30-minute urine collections with midpoint blood samples were obtained to determine C<sub>in</sub>. The mean of the two C<sub>in</sub> determinations was taken as the C<sub>in</sub> 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 cages 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 euolemic rats 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 (PE-50), and a solution of lactated Ringer’s containing 25 μCi [3H]inulin/ml (New England Nuclear) was infused at a rate of 0.5 ml/100 g body wt/hr. The femoral artery was cannulated with PE-50 tubing, and MAP was monitored with a digital display pressure transducer (model 91, Western Laboratories, Morrison, Colorado). A PE-50 catheter was placed in the bladder. The remnant kidney was exposed by a subcostal incision, dissected free of perirenal tissue, immobilized in a plastic holder, and continuously bathed with mineral oil at 37° C.

After a 45-minute stabilization period, urine was collected under mineral oil in preweighed tubes for a period of 20–30 minutes. During this interval, three timed (2–3-minute) proximal tubular fluid collections were obtained from superficial nephrons using sharpened glass pipettes (tip diameter 8–10 μm) filled with Sudan black-colored mineral oil. These collections were made just proximal to an oil column of several tubular diameters in length. Arterial blood samples were also collected during this period. Urine volumes were determined gravimetrically. Samples of urine, plasma, and tubular fluid were added to 10-ml scintillation cocktail (SCINT-A, Packard, Downers Grove, Illinois), and radioactivity of the samples was measured in a liquid scintillation spectrometer (model LS230, Beckman Instruments, Fullerton, California).

P<sub>T</sub> was measured under free-flow conditions in one group of tubules and after blockage of the tubular lumen (P<sub>T</sub>) with Sudan black-colored mineral oil in a different group of tubules. P<sub>T</sub> was determined in randomly selected efferent vascular welling points, or “star” vessels. All pressure measurements were performed with a servo-nulling micropressure system (W-P Instruments, New Haven, Connecticut) and micropipettes (o.d. 5–8 μm) filled with 2.0 M NaCl. P<sub>aw</sub> was estimated by the stop-flow technique with measurements of P<sub>aw</sub> 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<sub>a</sub> 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<sub>rf</sub>, P<sub>f</sub>), 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<sub>f</sub> were calculated as previously described.

Statistical Analysis

Results are expressed as mean±SEM. The statistical significance of differences between group means 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 ± 6 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 Clofibrate Add on 5/6 Nephrectomy Rats

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5/6 nephrectomy</td>
<td>clofibrate acid</td>
<td>two-kidney controls</td>
</tr>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 11)</td>
<td>(n = 6)</td>
</tr>
<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 (mm Hg)</td>
<td>197 ± 10*</td>
<td>183 ± 7*</td>
<td>142 ± 2†</td>
</tr>
<tr>
<td>Triglycerides, early (mg/dl)</td>
<td>71 ± 6*</td>
<td>77 ± 6*</td>
<td>52 ± 12*</td>
</tr>
<tr>
<td>Cholesterol, early (mg/dl)</td>
<td>76 ± 4*</td>
<td>45 ± 3†</td>
<td>40 ± 2†</td>
</tr>
<tr>
<td>Cholesterol, late (mg/dl)</td>
<td>94 ± 7*</td>
<td>53 ± 6†</td>
<td>43 ± 3†</td>
</tr>
<tr>
<td>Albuminuria, early (mg/24 hr)</td>
<td>28.0 ± 7*</td>
<td>3.3 ± 0.8†</td>
<td>0.8 ± 0.2†</td>
</tr>
<tr>
<td>Albuminuria, late (mg/24 hr)</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.

hypercholesterolemia associated with 5/6 nephrectomy (Tables 1 and 2).

Urine Albumin Excretion

Both clofibrate acid and mevinolin caused significant reductions in urine albumin excretion (Tables 1 and 2). The reduced albuminuria was evident both early and late in the experimental periods.

Renal Function

Five weeks after surgery, mean serum creatinine in group 1 and group 2 5/6 nephrectomy rats was approximately twice that of normal group 3 rats (Table 3). Creatinine levels were similar in untreated group 1 and clofibrate acid–treated group 2 rats at 5 weeks (Table 3). By 10 weeks, however, serum creatinine had decreased in the treated rats. As a result, at 10 weeks serum creatinine was significantly less in clofibrate acid–treated rats (group 2) compared with untreated (group 1) 5/6 nephrectomy rats (Table 3).

Results of C_t measurements paralleled changes in serum creatinine. Ten weeks after 5/6 nephrectomy, C_t of clofibrate acid–treated group 2 rats was greater than that of untreated group 1 rats (Table 3), but this difference was of borderline significance (p = 0.056). When C_w was normalized for body weight, however, C_w/100 g body wt in the clofibrate acid–treated rats was significantly greater than that of untreated 5/6 nephrectomy rats (Table 3).

Histology

Clofibrate acid caused a fourfold reduction in the percent of glomeruli with sclerosis (Figure 1). Similarly, the extent of mesangial matrix expansion was markedly reduced by treatment with clofibrate acid. The mesangial matrix score in group 1 untreated 5/6 nephrectomy rats was 175 ± 14 compared with 89 ± 11 in group 2 clofibrate acid–treated rats (p<0.05) and 32 ± 3 in group 3 two-kidney controls (p<0.05 versus groups 1 and 2). Tubulointerstitial injury paralleled the degree of glomerular damage. Mean tubulointerstitial injury scores were 2.6 ± 0.3 and 0.7 ± 0.2 for groups 1 and 2, respectively (p<0.05). No tubulointerstitial damage was seen in group 3 two-kidney controls.

Mevinolin caused a reduction in glomerular injury comparable to that seen in clofibrate acid–treated 5/6 nephrectomy rats. Focal glomerulosclerosis, for example, was reduced by more than 50% in mevinolin-treated 5/6 nephrectomy rats (Figure 1). Similar reductions in mesangial matrix and tubulointerstitial injury were seen in mevinolin-treated rats.

Superficial Nephron Function

No statistically significant differences in body weight, kidney weight, or blood pressure were ob-

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

<table>
<thead>
<tr>
<th></th>
<th>Group 7</th>
<th>Group 8</th>
<th>Group 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5/6 nephrectomy</td>
<td>5/6 nephrectomy</td>
<td>two-kidney controls</td>
</tr>
<tr>
<td></td>
<td>(n = 13)</td>
<td>mevinolin</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>422 ± 8*</td>
<td>386 ± 9†</td>
<td>487 ± 16†</td>
</tr>
<tr>
<td>Left kidney weight (g)</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 (mm Hg)</td>
<td>185 ± 5*</td>
<td>169 ± 7*</td>
<td>114 ± 6†</td>
</tr>
<tr>
<td>Triglycerides, early (mg/dl)</td>
<td>130 ± 9*</td>
<td>97 ± 7†</td>
<td>85 ± 11†</td>
</tr>
<tr>
<td>Cholesterol, early (mg/dl)</td>
<td>132 ± 6*</td>
<td>89 ± 5†</td>
<td>66 ± 10†</td>
</tr>
<tr>
<td>Cholesterol, late (mg/dl)</td>
<td>138 ± 8*</td>
<td>92 ± 8†</td>
<td>56 ± 11†</td>
</tr>
<tr>
<td>Albuminuria, early (mg/24 hr)</td>
<td>37.9 ± 8.1*</td>
<td>13.8 ± 3†</td>
<td>0.5 ± 0.3†</td>
</tr>
<tr>
<td>Albuminuria, late (mg/24 hr)</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</th>
<th>Condition</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>1</td>
<td>5/6 nephrectomy (n = 10)</td>
<td>1.11 ± 0.03*</td>
<td>0.90 ± 0.09*</td>
<td>1.09 ± 0.13*</td>
<td>0.22 ± 0.02*</td>
<td>157 ± 11*</td>
</tr>
<tr>
<td>2</td>
<td>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>3</td>
<td>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.

Discussion

Clofibric acid is the pharmacologically active form of the lipid-lowering agent clofibrate. Clofibric 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. In the present study, clofibric acid substantially reduced the marked glomerular, tubulointerstitial, and vascular injury that
characterizes the rat 5/6 nephrectomy model of chronic renal failure. Renal function was also significantly preserved by clofibric acid.

The mechanism by which clofibric acid exerted its beneficial effects cannot be determined from the results of this investigation. Marked reductions in dietary protein intake have been shown to reduce glomerular injury in 5/6 nephrectomy rats. Since body weight was not affected by clofibric acid, it is unlikely that the reduction in glomerular injury seen in the clofibric acid study resulted from marked reductions in food intake. Platelet inhibition with acetylsalicyclic acid and dipyridamole has been shown to reduce blood pressure and ameliorate glomerular injury in the rat remnant kidney model. It is possible that clofibric acid directly or indirectly altered platelet function and that platelet inhibition reduced the amount of glomerular injury. Although clofibric acid has been reported to alter platelet function in vitro, the significance of these findings is controversial.

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Vol 62, No 2, February 1988

Table 4. Single Nephron Function in Untreated and Clofibric Acid–Treated Rats 4 Weeks After 5/6 Nephrectomy

<table>
<thead>
<tr>
<th>Group</th>
<th>BW (g)</th>
<th>LKW (g)</th>
<th>MAP (mm Hg)</th>
<th>SNGFR (nl/min)</th>
<th>SNPF (nl/min)</th>
<th>SNFF</th>
<th>Cₐ (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 4, untreated 5/6 nephrectomy rats (n = 6); Group 5, clofibric acid–treated 5/6 nephrectomy rats (n = 6); Group 6, two-kidney controls (n = 8); BW, body weight; LKW, left kidney weight; MAP, mean arterial pressure during micropuncture; SNGFR, single nephron glomerular filtration rate; SNPF, single nephron plasma flow; SNFF, single nephron filtration fraction; Cₐ, arterial plasma protein concentration; ΔPc, glomerular capillary hydraulic pressure; ΔPf, mean transcapillary hydraulic pressure difference; Kf, glomerular ultrafiltration coefficient.</td>
<td></td>
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</tr>
<tr>
<td>Group 4</td>
<td>325 ± 17</td>
<td>1.38 ± 0.14</td>
<td>138 ± 5</td>
<td>97.0 ± 6.2*</td>
<td>305 ± 17*</td>
<td>0.32 ± 0.02</td>
<td>5.3 ± 0.1</td>
</tr>
<tr>
<td>Group 5</td>
<td>337 ± 20</td>
<td>1.42 ± 0.13</td>
<td>152 ± 6*</td>
<td>95.3 ± 2.1*</td>
<td>291 ± 16*</td>
<td>0.33 ± 0.02</td>
<td>5.0 ± 0.1</td>
</tr>
<tr>
<td>Group 6</td>
<td>351 ± 9</td>
<td>1.15 ± 0.03</td>
<td>124 ± 4</td>
<td>35.5 ± 1.9</td>
<td>111 ± 11</td>
<td>0.33 ± 0.02</td>
<td>5.2 ± 0.1</td>
</tr>
</tbody>
</table>

* p < 0.05 versus group 6.

From the results of the present studies, it is also difficult to determine the relative importance of altered cholesterol and triglyceride metabolism in the pathogenesis of glomerular injury. Serum lipids were uniformly higher in the 5/6 nephrectomy and two-kidney control rats in the mevinolin experiments compared with corresponding groups of rats in the clofibric acid experiments (Tables 1 and 2). Nevertheless, cholesterol was increased by 100% in untreated 5/6 nephrectomy rats compared with 11 ± 2% in the mevinolin-treated rats. However, the substantial variability in the amount of glomerulosclerosis within each group and the fact that the two sets of experiments were not carried out at the same time make it difficult to conclude that the protective effect of clofibric acid was greater than that of mevinolin.

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there were important changes in triglyceride metabolism that were not detected by measuring fasting triglyceride levels.

Clofibric 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 sclerosis in a number of animal models. Dietary injury by decreasing the amount of lipid deposition in triglyceride levels.

Although the mechanism of injury is unknown, increased levels of cholesterol in renal tissue have been measured, and glomerular lipid deposits have been observed.924

Investigations using the puromycin aminonucleoside rat model of the nephrotic syndrome have also suggested a potential role for lipids in the pathogenesis of focal glomerulosclerosis. Rats given multiple injections of puromycin aminonucleoside developed proteinuria, focal glomerulosclerosis, and a significant deposition of lipids in the mesangial.27'28 Halofenate, a clofibric acid analogue, reduced focal glomerulosclerosis in puromycin aminonucleoside-treated rats fed a lipogenic diet.27 The results of these and other studies are consistent with the hypothesis that alterations in lipid metabolism may have an important role in the development and progression of renal injury in animal models 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.30 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.30 Lipid-laden macrophages are frequently found in both early atherosclerosis lesions and focal glomerulosclerosis.3132 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.

Acknowledgments

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