Fosinopril ameliorates exogenous cholesterol-induced incipient glomerular lesions in obese Zucker rats. Effects on eicosanoid secretion

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Abstract

Background. To date, the role of dietary cholesterol as a risk factor for some diabetic nephropathy, such as mesangial expansion and glomerular lesions, is unknown. Controversy also exists regarding the effects of prostaglandin-induced changes in glomerular haemodynamics on the appearance of glomerulosclerosis.

Methods. We have used obese Zucker rats (OZRs) as a model of early nephropathy to evaluate the effect of hypercholesterolaemic diet on glomerular prosta glandin secretion and on the development of glomerular lesions. Due to the role of angiotensin II (Ang II) in glomerular haemodynamics, we have also evaluated its effects on glomerular eicosanoid secretion. Furthermore, as it has been suggested recently by clinical studies that angiotensin-converting enzyme inhibitors (ACEIs) reduce serum lipids associated with proteinuria, we have also evaluated the effect of the ACEI, fosinopril, both in vivo and in vitro, using 24 h glomeruli cultures.

Results. Results showed that a cholesterol-rich diet significantly increased serum cholesterol, proteinuria and glomerular eicosanoid secretion, and caused macrophage-ED1 cell deposits in the glomerular mesangium. Segmentary lesions only appeared in those rats with the highest percentage of glomerular xanthomatous (macrophage-ED1) cells. Ang II, per se, caused a marked rise in glomerular prosaglandin E2 and thromboxane B2. The inhibition of Ang II synthesis with fosinopril reduced all the parameters listed above, whereas Ang II (10−6 M) increased the secretion of TxB2 and tended to increase PGE2 secretion in glomerular culture.

Conclusions. In conclusion, exogenous cholesterol per se may contribute to nephropathy by increasing eicosanoid secretion, serum lipid profile, urinary protein excretion and the development of glomerular lesions. Fosinopril reduced all these parameters probably by its effects on Ang II.

Key words: angiotensin-converting enzyme inhibitors; angiotensin II; eicosanoid secretion; incipient glomerular lesion; macrophage-ED1 cells; nephropathy; xanthomatous cells

Introduction

Lipid abnormalities are one of the non-immunological factors that contribute to the progression of glomerulosclerosis as well as to kidney disease associated with essential hypertension, diabetes mellitus and hyperlipidaemia [1]. In fact, high cholesterol diets are usually used to exacerbate the renal damage in experimental animal models [2]. However, the exact way in which lipids cause glomerulosclerosis or contribute to diabetic and hypertensive nephropathy remains unclear [3,4].

In the obese Zucker rat (OZR) model of type II diabetes [5], glomerulosclerosis develops spontaneously with ageing, probably in relation to lipid abnormalities because the treatment of these rats with lipid-lowering agents, such as lovastatin or clofibric acid, not only reduces serum lipid levels, but decreases albuminuria and improves glomerulosclerosis [6]. However, these beneficial effects could be due to mechanisms other than the hypolipidaemic action itself. Different studies have shown that hypolipi daemic drugs decrease glomerular sclerosis without inducing any changes in glomerular haemodynamics [6,7]. Thus, in spite of the fact that the renal damage seen with high cholesterol intake is associated with an increase in systemic blood pressure and intraglomerular hydrostatic pressure [8], some authors have suggested that the haemodynamic changes do not play a significant pathogenic role. However, increased glomerular capillary pressure, hyperfiltration and hyperperfusion have been shown to occur in animals with reduced kidney mass, diabetes mellitus and amino nucleoside nephrosis, and these alterations have been incriminated in the genesis of glomerular sclerotic lesions [9]. Haemodynamic alterations have been claimed to play a role in the pathogenesis of diabetes, and prostaglandins, in turn, have profound...
effects on glomerular haemodynamics. Furthermore, abnormalities of prostaglandin metabolism have been described in various tissues from diabetics [10], and seem to be involved in the pathogenesis of its vascular complications [11].

For these reasons, the present study focused firstly on the role of exogenous cholesterol in the initiation and exacerbation of spontaneous glomerular lesions, using young OZR, in which genotype-related nephropathy was not yet evident, as a model of incipient renal damage. We also sought to ascertain the glomerular eicosanoid secretion during this early nephropathy state. In contrast to most of the studies that have evaluated the effects of dietary-induced hypercholesterolaemia, which have involved long-term experiments, our aim was to characterize the early glomerular changes that occur in diet-induced hypercholesterolaemia in OZR by assessing whether or not glomerular eicosanoid secretion influences renal damage. Furthermore, we have used OZR to evaluate if genotype could exacerbate the hypercholesterolaemic diet-induced nephropathy. To date, there are only two studies that have evaluated the early glomerular changes produced by hyperlipidaemia. One of these studies used a model of diet-induced hypercholesterolaemia, in which the first glomerular change was mesangial expansion with foam cell deposits [12]. The second study used rats with streptozotocin-induced diabetes at a stage when glomerulosclerosis was not yet established and mesangial expansion was also the main future found [13]. In a recent interesting study, Lavaud et al. showed the importance of a mononuclear/macrophage influx at a very early stage which can stimulate mesangial cell proliferation and synthesis of several cytokines and vasoactives substances, which latterly could produce glomerulosclerosis lesions, and they focused on the significance of inflammation [14].

On the other hand, taking into account the role of Ang II in the regulation of glomerular haemodynamics [15] and hypertrophy [16], as well as its contribution to the pathogenesis of glomerulosclerosis [17], we have also evaluated the effect both of this peptide and of an angiotensin-converting enzyme inhibitor (ACEI; fosinopril) upon glomerular eicosanoid secretion.

In fact, fosinopril recently has been associated with an improvement of lipid abnormalities associated with proteinuria (patients treated with ACEIs showed a decrease in serum cholesterol that could partially be explained by a reduction in proteinuria) [18–20].

Materials and methods

Experimental design

Eight-week-old OZRs (IFFA CREDO, Lyon, France) were randomized in three different groups according to the diet and treatment given: rats were fed standard rodent chow (ZN), standard chow supplemented with 4.5% cholesterol and 1% cholic acid (hypercholesterolaemic diet, ZC) (UAR, Lyon, France) or a hypercholesterolaemic diet plus fosinopril (25 mg/kg/day) (ZF) (kindly given by Bristol-Miers Squibb, Madrid, Spain) administered in the drinking water as is the usual procedure of other investigators. Lean Zucker rats (LZRs) fed standard (LN) and hypercholesterolaemic diet (LC) were used as controls. There were eight rats in each of the experimental groups, and all of them were allowed free access to food and water. The animals were killed after 8 weeks of treatment.

Laboratory measurements

Body weight and dietary intake were monitored weekly whereas blood pressure and proteinuria were measured every month. Blood pressure was measured by the tail-cuff method. For urine collection, rats were housed individually in metabolic cages for 24 h with free access to water. Proteinuria was measured by the sulfosalicylic acid method.

After 8 weeks of treatment, rats were anaesthetized with an intraperitoneal injection of a mixture of atropine (1 mg), diazepam (5 mg) and ketolar (20 mg), one dose per 400 g of body weight. Then, the kidneys were removed and kept in cold Hank’s balanced salt solution (HBSS) plus 2% fetal bovine serum (FBS) for glomerular isolation. A kidney slice from each rat was obtained for histological analysis using the haematoxylin–eosin stain. One hundred glomeruli were studied to assess the presence and severity of focal lesions (FSGL). The method was based on that previously described by Kasiske et al. [6]. The number of foam cells in each glomerulus was counted, with a minimum of 50 glomeruli surveyed per kidney section. The ED1 monoclonal antibody (1/30, Biogenesis, New Fields, UK) was used to identify the foam xanthomatous cells found in the glomerular mesangium as macrophages.

Glomeruli culture and prostaglandin secretion

Glomeruli were isolated as previously described [21]. Briefly, kidneys were decapsulated and renal cortices dissected on ice to maintain cell viability. Glomerular isolation was obtained by enzymatic digestion of renal cortices with collagenase P (1.5 mg/ml) under continuos gentle shaking in a 37 °C water bath for 5 min. Afterwards, the glomerular suspension was passed successively through 100, 75, and 75 μm pore size sieves. Glomeruli were collected from the upper surface of the 75 μm sieve, and the Bowman’s capsule was removed by passing the glomerular suspension through a needle. Glomerular purity was checked by light microscopy and always exceeded 90%.

To evaluate the effect of cholesterol and Ang II on eicosanoid secretion, glomeruli were plated in a 24-well culture flask, at 500 glomeruli/well, and incubated in 1 ml of RPMI 1640 plus 20% FBS for 24 h at 37 °C in an atmosphere of 5% CO₂. One half of these cultures were stimulated with Ang II (10−6 M). After the incubation period, the supernatant was removed and centrifuged at 12,000 r.p.m. for 6 min at 4 °C and then kept at −70 °C until processed for eicosanoid analysis. Eicosanoids [prostaglandin E2 (PGE2) and thromboxane B2 (TXB2)] were measured using specific enzyme immunoassay kits (Cayman Chemical, Ann Arbor, MI) at 1/10 dilution. Results were expressed as pg/ml and also corrected by glomerular protein concentration (pg/μg protein).
To measure glomerular protein concentration, 0.5 ml of 1 M NaOH was added into each well and incubated at 37 °C for 1 h. The solution obtained was diluted 1/2 with PO₄H₃/phosphate buffer (1/10), and the protein concentration was measured with the Biorad reagent (Biorad, Madrid, Spain).

**Statistical analysis**

Results were expressed as means ± SEM. Comparisons of means among groups was performed using the one-way ANOVA followed by the post-hoc Scheffé test. Non-parametric tests were used for glomerular cultures. Simple and multiple correlation was also performed. \( P < 0.05 \) was considered statistically significant in every case.

**Results**

**Animal parameters**

The effects of cholesterol and fosinopril on body weight, kidney and liver weights are detailed in Table 1. During the experiment, all rats gained weight, but the increment was lower in those fed the hypercholesterolaemic diet (Figure 1), who also had a lower food intake (Table 1). In the OZR, however, intake was higher than in their lean counterparts (Table 1). Hypercholesterolaemic diet had no effect on the ratio of kidney to body weight, indicating that it did not induce renal hypertrophy. However, hypercholesterolaemic diet increased the ratio of liver to body weight (Table 1). There also were no differences in systolic blood pressure in relation to hypercholesterolaemic diet, as well as between lean and obese Zucker rats (LN, LC and ZN: 141 ± 3; ZC and ZF: 146 ± 32).

**Biochemical parameters**

As summarized in Table 2, neither the hypercholesterolaemic diet nor fosinopril administration caused changes in serum creatinine, albumin, proteins and glucose. However, the cholesterol-enriched diet induced a significant increase in serum cholesterol, which was higher in OZR as compared with their lean counterparts (Table 3). In addition, a marginally significant increase in serum triglycerides (\( P = 0.053 \)) with the hypercholesterolaemic diet was also observed in OZR (Table 3). Likewise, proteinuria only increased in OZR fed the hypercholesterolaemic diet (Table 4). Fosinopril administration significantly reduced both serum cholesterol and proteinuria in OZR as compared with the ZC group (Tables 3 and 4).

**Histological analysis**

Histologically, the appearance of early glomerular injury was only observed in those groups of rats fed the hypercholesterolaemic diet (Figure 2). The main feature was the presence of xanthomatous (macrophage-ED1) cells in the glomerular mesangium, which was more marked in OZR fed the cholesterol-enriched diet.

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**Table 1. Effects of cholesterol on body, kidney and liver weight, and on food intake**

<table>
<thead>
<tr>
<th></th>
<th>LN</th>
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<th>ZN</th>
<th>ZC</th>
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<tbody>
<tr>
<td>Body weight (g)</td>
<td>335 ± 10</td>
<td>267 ± 14*</td>
<td>478 ± 17b, c, e</td>
<td>395 ± 11</td>
<td>339 ± 10</td>
</tr>
<tr>
<td>Food intake (g/24 h)</td>
<td>20.5 ± 0.8</td>
<td>11 ± 0.3*</td>
<td>27.3 ± 0.9b, c, f</td>
<td>13.8 ± 0.8</td>
<td>12.1 ± 0.4</td>
</tr>
<tr>
<td>Kidney weight/BW (%)</td>
<td>0.4 ± 0.0</td>
<td>0.4 ± 0.0</td>
<td>0.3 ± 0.0f</td>
<td>0.3 ± 0.0f,b</td>
<td>0.4 ± 0.0</td>
</tr>
<tr>
<td>Liver weight/BW (%)</td>
<td>2.6 ± 0.2</td>
<td>9.1 ± 0.2*</td>
<td>3.4 ± 0.3b</td>
<td>8.7 ± 0.2b</td>
<td>7.3 ± 0.2</td>
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ANOVA, \( P \) between groups <0.05: bLN vs LC; cZN vs ZC; dZN vs ZF; eZC vs ZF; fZN vs LN; gZN vs LC; hZC vs LC; iZC vs LN.

L, lean Zucker rats; Z, obese Zucker rats; N, normal diet; C, cholesterol-enriched diet; F, fosinopril treatment.
Table 2. Serum creatinine (CR), albumin (ALB), proteins (PROT) and glucose (GL)

<table>
<thead>
<tr>
<th></th>
<th>LN</th>
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<th>ZN</th>
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<tbody>
<tr>
<td>CR (mg/dl)</td>
<td>0.64±0.06</td>
<td>0.77±0.23</td>
<td>0.81±0.19</td>
<td>0.99±0.19</td>
<td>0.96±0.14</td>
</tr>
<tr>
<td>ALB (g/l)</td>
<td>32±3.3</td>
<td>30±1.1</td>
<td>42±2.9</td>
<td>36±1.2</td>
<td>36±4.3</td>
</tr>
<tr>
<td>PROT (g/l)</td>
<td>54±9</td>
<td>61±2.1</td>
<td>60±8</td>
<td>71±3.4</td>
<td>78±10.9</td>
</tr>
<tr>
<td>GL (mg/dl)</td>
<td>136±16</td>
<td>83±13</td>
<td>168±19*</td>
<td>102±10</td>
<td>108±26</td>
</tr>
</tbody>
</table>

ANOVA, P between groups <0.05: *ZN vs LC.
L, lean Zucker rats; Z, obese Zucker rats; N, normal diet; C, cholesterol-enriched diet; F, fosinopril treatment.

Table 3. Effects of hypercholesterolaemic diet on serum lipids

<table>
<thead>
<tr>
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<th>LN</th>
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<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>88±10</td>
<td>906±174*</td>
<td>221±16</td>
<td>1723±143&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
<td>1018±109</td>
</tr>
<tr>
<td>Tryglicerides (mg/dl)</td>
<td>70±9</td>
<td>352±100</td>
<td>367±60</td>
<td>667±124*</td>
<td>513±94</td>
</tr>
</tbody>
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ANOVA, P between groups <0.05: *LC vs LN; <sup>b</sup>ZC vs ZN; <sup>c</sup>ZC vs ZF; <sup>d</sup>ZC vs LC. *P=0.053, ZC vs ZN.
L, lean Zucker rats; Z, obese Zucker rats; N, normal diet; C, cholesterol-enriched diet; F, fosinopril treatment.

Table 4. Effects of hypercholesterolaemic diet on proteinuria

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<th>ZF</th>
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<tbody>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>1.92±0.74</td>
<td>1.86±0.54</td>
<td>2.46±0.61</td>
<td>44.72±5.01*</td>
<td>3.21±0.62</td>
</tr>
</tbody>
</table>

ANOVA, P between groups <0.05: *ZN vs ZF, LN, LC.
L, lean Zucker rats; Z, obese Zucker rats; N, normal diet; C, cholesterol-enriched diet; F, fosinopril treatment.

Macrophage-ED1 cells (%)

Fig. 2. The percentage of glomeruli with xanthomatous (macrophage-ED1) cells increased in those rats fed a hypercholesterolaemic diet. The 'a' and 'b' indicate that the effect of diet was significant. ANOVA, P<0.05: *LC vs LN; <sup>b</sup>ZC vs ZN, ZF and LC.

enriched diet, as compared with their lean counterparts. The positive stain for ED1 identified these foam cells as monocytes/macrophages. Segmentary lesions occurred only in three rats of the ZC group, in which we also observed a single focus of tubulo-interstitial injury. In contrast, no lesions were found in the LC group. The percentage of glomeruli with xanthomatous (macrophage-ED1) cells significantly correlated (P<0.01) with serum cholesterol (r=0.81), tryglicerides (r=0.62) and proteinuria (r=0.78).
Eicosanoid secretion

The hypercholesterolaemic diet significantly increased PGE$_2$ secretion in glomerular culture, and fosinopril almost abolished this effect ($P=0.06$) (Figure 3). TxB$_2$ also showed a trend towards an increase in those groups fed a cholesterol-enriched diet ($P=0.012$) (Figure 3). PGE$_2$ significantly correlated ($P=0.01$) with the percentage of glomeruli with macrophage-ED1 cells ($r=0.6$), the serum cholesterol ($r=0.5$) and proteinuria ($r=0.43$). TxB$_2$ marginally correlated with macrophage-ED1 cell deposits ($P=0.07$, $r=0.33$) and proteinuria ($P=0.08$, $r=0.31$).

When Ang II was added to the culture medium, TxB$_2$ significantly increased $[5845\pm448\text{ vs } 6391\pm571\text{ (pg/ml)}, P<0.01]$ and PGE$_2$ also showed a marked tendency to rise $[1819\pm249\text{ vs } 2195\pm303\text{ (pg/ml)}, P=0.06]$. Furthermore, Ang II increased the glomerular protein concentration (µg/ml) $[814\pm18\text{ vs } 904\pm16, P<0.01]$.

Discussion

The OZR is considered to be one of the better models that mimic the features of human diabetic nephropathy [5]. It has been suggested that lipid abnormalities contribute to the development of glomerulosclerosis in this animal model [5]. However, the relationship between serum cholesterol and diabetic nephropathy is still controversial [3,4]. There are some studies in humans that could not find differences in glomerular filtration rate, urinary albumin excretion, blood pressure, duration of diabetes or metabolic control between hypercholesterolaemic patients and those with normal serum cholesterol [4]. In contrast, other studies both in animals [8] and humans [3,22] suggest that cholesterol could be a mediator of renal injury in diabetes. As the aim of this study was to establish the net effect of exogenous cholesterol in the development of early-stage nephropathy, we performed a short-term experiment using young Zucker rats. Furthermore, in the light of the recently described relationship [18] between the hypolipidaemic effect of fosinopril and a decrease in proteinuria, we have also evaluated the in vivo renal effects of this drug.

Differences in histological and biochemical parameters between obese and lean Zucker rats were only minor. Indeed, we found no differences in blood pressure or in the degree of kidney hypertrophy as assessed by the kidney weight/body weight ratio. Similar results were obtained by Guijarro et al. [12] on a different animal model. On the other hand, exogenous cholesterol, per se, induced changes in body weight, proteinuria and serum lipid profile. As has been widely documented [8,12], body weight decreased both in obese and lean Zucker rats, probably because of the reduction in food intake (see Table 1).

Even though lipid abnormalities present in OZRs mainly involve triglycerides [5], the rise in cholesterol levels was the most marked in our study. Although fatty liver is a characteristic feature of adult OZRs [5], no differences were observed between lean and obese Zucker rats. In fact, the increase in liver weight was caused by the cholesterol-enriched diet, as has already been reported [23].

In our experiments, proteinuria did not develop when OZRs ate standard chow. In the present study, this only developed when these animals were on a cholesterol-enriched diet, suggesting that both serum abnormalities [5] and exogenous cholesterol supply are necessary for its development. It has been suggested
that in hyperlipidaemic conditions, changes in very low density lipoprotein composition would be able to damage the filtration barrier, allowing the passage of macromolecules to the glomerular mesangium [23].

This hyperlipidaemic environment might also explain the presence of xanthomatous (macrophage-ED1) cells in the mesangial region, the histological hallmark of those rats fed the hypercholesterolaemic diet, as occurs in vascular atherosclerosis injury. These cells have also been found in guinea pigs fed a diet containing 2% cholesterol [24] as well as in experimental models of nephrosis [25]. We identified them as monocytes/macrophages, confirming the finding of Hattori et al. [26] in ExHC rats. In a recent paper, Lavaud et al. showed an increase of glomerular macrophage density in 1-month-old obese rats and observed a close relationship with hyperlipidaemia. They suggested that these active macrophages can stimulate mesangial cell proliferation and synthesis of cytokines involved in the pathogenesis of glomerulosclerosis.

Although it is well known that macrophages play an important role in the pathogenesis of immune glomerular lesions [27], we prefer to measure xanthomatous/macrophage cells because the glomerulosclerosis-related hyperlipidaemia could be a similar process to that which occurs in atherosclerosis vascular lesions and could be implicated more in glomerular injury than in macrophages without lipid deposits. In addition, macrophages are a characteristic feature of adult OZR kidneys [28]. It is thus conceivable that they could participate in the development of diabetic nephropathy. The exact mechanism responsible for the mesangial monocyte/macrophage infiltration is at present not well understood, but our results favor the idea that lipid abnormalities of the OZR itself [8,24] and the effect of the exogenous cholesterol supply [29] may play a synergistic role. Furthermore, the accumulation of macrophage-ED1 cells preceded the appearance of segmentary glomerular lesions. Only in the three OZRs with the highest percentage of mesangial xanthomatous (macrophage-ED1) cell deposits were glomerular lesions evident, and tubulointerstitial foci were observed in only one of them. This sequence of events agrees with other experimental studies [12] that suggested that macrophages may mediate the initiation of the sclerotic process, thus participating in the development of nephropathy.

Hypercholesterolaemic diet could also facilitate the development of nephropathy by modifying the glomerular eicosanoid secretion. Indeed, macrophages are one of the major producers of eicosanoids, and a cholesterol-enriched diet may modify macrophage function by altering prostaglandin production [30]. In fact, our results showed a significant increase in PGE\(_2\) secretion and a marked tendency to increase TxB\(_2\) in those rats fed a hypercholesterolaemic diet, whereas OZRs, on their own, had no effect on eicosanoid secretion. Similar increases in PGE\(_2\) have been observed during the early phases of type I diabetes mellitus in relation to the hyperfiltration state of incipient diabetic nephropathy [31], in several experimental models of type I diabetes mellitus [32], as well as in ischaemic acute renal failure [33]. In contrast, when diabetic nephropathy is well established, with proteinuria and glomerular damage, TxB\(_2\) secretion predominates [34]. It is well known that Ang II is largely involved in the regulation of glomerular haemodynamics. In agreement with other authors [35], our results show that this effect could also be mediated by increased glomerular eicosanoid secretion.

Although there was no differences in arterial blood pressure, fosinopril treatment significantly reduced serum cholesterol, proteinuria and the accumulation of macrophage-ED1 cells. Clinical and experimental studies have already shown that besides their antihypertensive effects, treatment with ACEIs could slow the progression of different nephropathies whether associated [36] or not [37] with glomerular hypertension. These drugs also reduced the appearance of proteinuria and glomerulosclerosis both in models of endogenous hyperlipidaemia, such as the OZR [38] and the Imai rat [39], and in experimentally induced nephropathy [40]. Our study has shown that these beneficial effects also occur when exogenous cholesterol is administered.

As fosinopril inhibits the synthesis of angiotensin-converting enzyme, it seems quite obvious that Ang II inhibition could account for some of the beneficial effects of this drug [41]. However, it has to be taken into account that ACEIs are involved in the recovery of the glomerular permeability barrier [40], thus reducing proteinuria, and that their hypolipidaemic effect could contribute directly to the reduction of foam cells. Recently, Keilani et al. [18] have reported an improvement in the lipid profile in conjunction with a decrease in protein excretion in patients with proteinuric renal disease.

Although it has been suggested that ACEIs may stimulate PGE\(_2\) synthesis as a mechanism to attenuate the effect of Ang II [42], in our study fosinopril tended to reduce the secretion of both PGE\(_2\) and TxB\(_2\) in 24 h glomeruli cultures, probably by inhibiting Ang II synthesis. These results suggest that the reduction in glomerular capillary hydraulic pressure observed in rats with streptozotocin-induced diabetes when they were treated with ACEIs [43] could be related to a reduced eicosanoid secretion.

In summary, the present study suggests that exogenous cholesterol, per se, contributes to the development of glomerular lesions that characterize nephropathy in OZRs, mainly by increasing serum lipid concentration, xanthomatous macrophage cell deposits in the mesangial region, proteinuria and TxB\(_2\) and PGE\(_2\) glomerular secretion. In turn, the presence of the macrophage-ED1 cells in the glomerular mesangium precedes the appearance of glomerular segmentary lesions.

Furthermore, Ang II mediates an increase in glomerular eicosanoid secretion, and its reduction by an ACEI (fosinopril) slows the nephropathy development reducing glomerular eicosanoid secretion, proteinuria and serum lipids.

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2233