Effect of 3 Years of Antihypertensive Therapy on Renal Structure in Type 1 Diabetic Patients With Albuminuria

The European Study for the Prevention of Renal Disease in Type 1 Diabetes (ESPRIT)

The European Study for the Prevention of Renal Disease in Type 1 Diabetes (ESPRIT) Study Group

In the treatment of diabetic nephropathy, ACE inhibitor therapy reduces albumin excretion and slows the rate of decline in glomerular filtration rate (GFR). Our study was designed to investigate whether these effects lay in amelioration of the underlying glomerular structural abnormalities. A total of 54 type 1 diabetic patients with albuminuria and blood pressure (BP) <150/90 mmHg were randomized to receive 10 mg enalapril once daily, 10 mg nifedipine retard twice daily, or placebo in a multicenter double-blind study of 3 years’ duration. Renal biopsy was performed at baseline and follow-up, and tissue was analyzed by standard morphometric methods. BP, GFR, albumin excretion rate (AER), and HbA1c were measured every 6 months. Enalapril lowered AER after 6 months by 26% (P < 0.05); however, this reduction was not sustained at 3 years. There was no significant effect of nifedipine or placebo on AER. GFR decreased by a similar average rate of 4.1 ml · min⁻¹ · year⁻¹ (95% CI 2.6–5.6) in all three groups. BP and HbA1c were unchanged throughout the study in all groups. At baseline, nearly all biopsies showed classic appearances of diabetic glomerulopathy. There was no detectable effect of enalapril compared with either nifedipine or placebo on renal structure over 3 years. However, we found that patients with increased AER have established glomerulopathy and a progressive average decline in GFR of 4.1 ml · min⁻¹ · year⁻¹ in the absence of overt hypertension, and baseline AER appeared predictive of subsequent mesangial volume fraction (r² = 0.20, P = 0.0018). In this small cohort of nonhypertensive patients studied for 3 years, disease evolution appears unaffected by treatment with either enalapril or nifedipine. Diabetes 50:843–850, 2001

Diabetic nephropathy is responsible for over 40% of all patients requiring renal replacement therapy in the U.S. (1) and is the second most common cause of renal failure in Europe (2), carrying with it considerable excess cardiovascular mortality (3). The clinical manifestations of diabetic nephropathy, namely albuminuria, hypertension, and a progressive decline in the glomerular filtration rate, are underpinned by distinct structural changes in the glomerular tuft, which include thickening of the peripheral glomerular basement membrane and expansion of the mesangium together with an increase in the number of occluded glomeruli (4,5). Aggressive control of arterial hypertension slows the rate of decline in glomerular filtration rate in patients with type 1 diabetes and proteinuria (6,7). Treatment with ACE inhibitor (ACEI) therapy in type 1 diabetic patients with advanced nephropathy reduces the risk of doubling serum creatinine, or the combined end point of entering end-stage renal failure or dying, by ~50% over a mean follow-up period of 3 years (8). These effects are thought to be due to an ACEI-specific renoprotective action, which appears, at least in part, to be independent of blood pressure (BP) control. ACEIs also reduce the risk of progression from microalbuminuria to overt nephropathy in type 1 diabetic patients, an effect that is also partly independent of BP reduction (9).

It is unclear, however, whether ACEIs achieve these results by a direct effect on renal structure—changes that are critical to the progression of disease and eventual organ failure. This pilot study was therefore designed to compare and contrast the effects of the ACEI enalapril with nifedipine retard and placebo on glomerular and interstitial ultrastructure in type 1 diabetic patients with an elevated albumin excretion rate (AER) but without hypertension.

RESEARCH DESIGN AND METHODS

Patients. The detailed protocol of this study has been previously published (10). Briefly, to be eligible, patients had to meet the following criteria: be between 18 and 65 years of age; have type 1 diabetes, defined as diagnosis before the age of 40 years and C-peptide negative (fasting level <20 pmol/l); have an AER between 30 and 1,500 μg/min; have a glomerular filtration rate (GFR) >70 ml/min by local measurement of 51Cr-EDTA clearance; and have a serum creatinine level <130 μmol/l and sitting BP ≤150/90 mmHg on no antihypertensive treatment. Patients with normal BP (<150/90 mmHg, as
defined at the outset of the study in 1980) were chosen to eliminate the powerful confounding effect of hypertension and BP lowering and to allow the prospective study of a true placebo-treated group. Patients also had to agree to a renal biopsy at entry and the end of the study and demonstrate tablet compliance of at least 85% during the baseline period. Strict exclusion criteria included uncontrolled diabetes (HbA1c level >6 SDs above the local normal range), current antihypertensive or nonsteroidal analgesic therapy, hyperkalemia, other renal or urinary tract disease, liver disease, recent cerebrovascular or cardiac disease, pregnancy, and any contraindication to renal biopsy.

Patients were recruited from four diabetic and two renal centers in the U.K. and Italy. A total of 54 patients were enrolled into the study and randomly allocated to either enalapril once daily, 10 mg nifedipine retard twice daily, or placebo, all with matching dummy tablets, in a double-blind prospective trial.

**Procedures.** Patients were seen in a metabolic ward after an overnight fast. Arterial systolic and diastolic BPs (Korotkoff phases I and V) were measured to the nearest 2 mmHg in the nondominant arm using a random zero sphygmomanometer (Hawksley, Lancing, East Sussex, U.K.) and the patient had been sitting quietly for 5 min. The average value was calculated from three readings, at least 1 min apart. Recordings were made at three separate visits in the 2 months before renal biopsy, at baseline, and at 6-month intervals thereafter. Blinded treatment could be doubled and extra antihypertensive agents (thiazides, methylolap and hydralazine) added according to a predetermined schedule if any of the systolic or diastolic BPs were >160 and 100 mmHg, respectively, or increased by 30% from baseline values. Urine albumin concentration was measured by immunoturbidimetry at a central laboratory at Guy's Hospital. GFR was calculated as the median of three timed overnight urine collections (11).

**Electron microscopy**. Morphometric measurements were made on a single glomerular profile from five glomeruli per biopsy—a sampling protocol that has been shown in our laboratory to be more efficient than and as precise as multiple-level sampling (15). The mean value per patient was calculated from the five individual estimates.

Mesangial volume fraction (Vv mes) was estimated from the montages using standard stereological methods. Briefly, fine points falling on mesangium were counted and expressed as a fraction of the number of coarse points falling on the glomerulus, using a test grid of coarse to fine points in a ratio of 1:4. The boundary of the glomerulus was defined by the minimal string polygon. Matrix volume fraction (Vv mat) was estimated from the high-power micrographs. Points on mesangial matrix were counted, excluding cellular elements, and expressed as a fraction of the glomerulus (18).

Relative surface density of the peripheral glomerular basement membrane (the filtration surface) was estimated from the montages by counting intersections between test lines and the capillary loops (18). Filtration surface per glomerulus was calculated as the product of the surface density measurement and the glomerular volume. Glomerular basement membrane thickness (GBMT) was estimated from high-power micrographs by the orthogonal intercept method of Jensen et al. (19).

RENAL STRUCTURE AND ANTIHYPERTENSIVE THERAPY
addition, we explored whether baseline AER and GFR were associated with changes in the main structural outcome measures. The analysis was carried out using SAS version 6.12 software (SAS, Cary, NC) for personal computers. Sample size calculations were based on data available at the time the study was planned in 1989. Differences between treatment groups in the change from baseline of 3.8 ml · min⁻¹ · year⁻¹ in GFR, 88 nm in GBMT, 0.04 in Vv mes, and 0.26 $3 \times 10^6$ mm³ in MGV were estimated to be detectable with a sample size of 20 patients per treatment group with 80% power at the 0.05 two-tailed significance level.

**RESULTS**

**Baseline**

**Demographic and clinical characteristics.** Baseline clinical and biochemical characteristics of the diabetic patients in each treatment group are shown in Table 1. Patients were well matched for age, duration of diabetes, and arterial BP. The average age was 38 years (range 20–64), and average duration of diabetes was 20 years (2–43). Of the patients, 63% were male. There were 23 patients from the U.K. and 31 from Italy. AER, GFR, HbA1c, and serum creatinine levels were similar in the three groups. Two patients had an isolated BP recording outwith the entry criteria at randomization, but the average BP beforehand was 121/90 mmHg. Similarly, four patients had an AER at baseline marginally outside the inclusion range. Glycemic control was poor in some patients, in keeping with previously reported cohorts (8).

The in-house reference group of 14 normal subjects had a mean age of 37 years (range 20–60), and 43% of subjects were male. No other clinical data were available for these subjects.

Four patients had a baseline GFR >135 ml/min and could therefore be classified as hyperfiltering (20).

Four patients discontinued the study: one patient was uncooperative, one declined the final biopsy, one developed nephrotic syndrome, and one developed anorexia, depression, and abdominal pain. Six patients had insufficient biopsy material available for analysis: four at baseline and two further at follow-up. A total of 42 patients (n = 15 for enalapril, n = 11 for nifedipine, and n = 16 for placebo) had both measurements of renal function and structure at baseline and follow-up. There were no significant differences in the baseline characteristics of these patients compared with the original cohort.

**Structural measurements**

Glomerular ultrastructure was highly abnormal in almost all of the 50 patients with analyzable tissue at baseline with lesions typical of diabetic glomerulopathy. In particular, the glomerular basement membrane was markedly thickened, and Vv mes and Vv mat significantly increased compared with values obtained in our laboratory from 14 normal kidney donors (Table 2). Patients with clinical nephropathy (AER $>200$ mg/min) had increased GBMT, Vv mes, and Vv mat compared with those with microalbuminuria.

**TABLE 1**

Clinical characteristics of the 54 patients at entry into the study

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Nifedipine</th>
<th>Placebo</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>11:7</td>
<td>10:8</td>
<td>13:5</td>
<td>34:20</td>
</tr>
<tr>
<td>Age at entry to study (years)</td>
<td>37 (24–64)</td>
<td>39 (24–56)</td>
<td>38 (20–60)</td>
<td>38 (20–64)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>21 (7–37)</td>
<td>18 (2–32)</td>
<td>24 (9–43)</td>
<td>20 (2–43)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121 (91–149)</td>
<td>127 (103–153)</td>
<td>124 (95–147)</td>
<td>124 (91–153)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 (61–93)</td>
<td>73 (62–85)</td>
<td>78 (69–88)</td>
<td>76 (61–93)</td>
</tr>
<tr>
<td>Retinopathy (present:absent)</td>
<td>9.7†</td>
<td>13.5</td>
<td></td>
<td>14:4</td>
</tr>
<tr>
<td>GFR (ml·min⁻¹·1.73 m⁻²)</td>
<td>106 (71–162)</td>
<td>100 (62–143)</td>
<td>102 (62–135)</td>
<td>103 (62–162)</td>
</tr>
<tr>
<td>Overnight AER (µg/min)⁎</td>
<td>161 (29–1,599)</td>
<td>180 (26–1,499)</td>
<td>104 (30–1,486)</td>
<td>146 (26–1,599)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>78 (48–111)</td>
<td>79 (50–129)</td>
<td>84 (56–115)</td>
<td>80 (48–129)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 (5.3–13.0)</td>
<td>8.6 (5.3–12.1)</td>
<td>8.6 (4.9–13.2)</td>
<td>8.5 (4.9–13.2)</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>22</td>
</tr>
</tbody>
</table>

Data are means (range) or geometric means⁎ (range) unless otherwise indicated. HbA1c data are normalized to a normal reference range of 3.7–6.0%. †Retinopathy data unavailable on two patients.

**TABLE 2**

Renal structure in the 50 patients with analyzable tissue at baseline

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Nifedipine</th>
<th>Placebo</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glomerular volume ($×10^6$ µm³)</td>
<td>4.1 (1.8–5.8)</td>
<td>4.4 (1.8–7.1)</td>
<td>3.5 (2.0–5.4)</td>
<td>4.0 (1.8–7.1)</td>
</tr>
<tr>
<td>Vv mes</td>
<td>0.32 (0.18–0.52)</td>
<td>0.36 (0.17–0.52)</td>
<td>0.28 (0.19–0.42)</td>
<td>0.32 (0.17–0.52)</td>
</tr>
<tr>
<td>Vv mat</td>
<td>0.20 (0.10–0.30)</td>
<td>0.23 (0.09–0.37)</td>
<td>0.18 (0.10–0.29)</td>
<td>0.20 (0.10–0.37)</td>
</tr>
<tr>
<td>GBMT (nm)</td>
<td>600 (292–875)</td>
<td>586 (389–800)</td>
<td>550 (295–832)</td>
<td>578 (292–875)</td>
</tr>
<tr>
<td>Filtration surface per glomerulus (mm²)</td>
<td>0.34 (0.15–0.63)</td>
<td>0.33 (0.16–0.41)</td>
<td>0.35 (0.20–0.72)</td>
<td>0.34 (0.09–0.72)</td>
</tr>
<tr>
<td>Vv interstitium</td>
<td>0.19 (0.12–0.27)</td>
<td>0.20 (0.14–0.27)</td>
<td>0.20 (0.11–0.29)</td>
<td>0.20 (0.11–0.29)</td>
</tr>
<tr>
<td>Percent occluded glomeruli</td>
<td>13.7 (0–38.3)</td>
<td>11.5 (0–50.0)</td>
<td>13.0 (0–43.5)</td>
<td>12.7 (0–50.0)</td>
</tr>
</tbody>
</table>

Data are means (range).
HbA1c values did not change over the course of the study or between treatment groups over the study duration, though there were no significant differences either within enalapril-treated group after 6 months of treatment, although there was a significant antiproteinuric effect at 6 months in the enalapril-treated patients. GFR declined significantly throughout the study in all groups at an average rate of 4.1 ml min⁻¹ year⁻¹ (95% CI 2.6–5.6) (Fig. 1C). GFR declined significantly over the study duration both in patients with microalbuminuria and in those with clinical nephropathy (mean ± SD, −3.12 ± 5.35 and −6.97 ± 6.88 ml min⁻¹ year⁻¹; P < 0.05), but the rates of decline were different between groups (P = 0.02).

Fractional clearance of albumin decreased by 38% in the enalapril-treated group after 6 months of treatment, although there were no significant differences either within or between treatment groups over the study duration. HbA1c values did not change over the course of the study and were not different between treatment groups.

There were no significant changes in the structural parameters from baseline to follow-up in individual treatment groups (Table 3). In particular, Vv mes (Fig. 2A) and Vv mat (Fig. 2B) remained stable in the enalapril-treated group throughout the study, despite the initial fall in AER. The slight increases in Vv mes seen in the nifedipine- and placebo-treated groups were not statistically significant. Although GFR declined, filtration surface per glomerulus increased slightly in the enalapril-treated patients (Table 3). There were no significant changes in GBMT (Fig. 2C), Vv interstitial, or the percentage of occluded glomeruli in any treatment group.

Despite a significant reduction in AER after 6 months of enalapril treatment, there was no significant difference between baseline and 3-year values in any treatment group. Furthermore, no differences between treatments were detected in any of the major efficacy endpoints of the study. It was therefore considered valid to pool patient data to explore possible associations between baseline AER and subsequent progression. There was no significant relationship between baseline AER and the changes in glomerular and tubulointerstitial structure. However, there was a significant association between baseline AER...
and final Vv mes, such that 20% of the variation in follow-up Vv mes could be explained by AER ($P = 0.0018$). Final GFR was also associated with baseline AER, but this only accounted for 7% of the observed variation ($P = 0.065$).

The analysis including the baseline value as a covariate indicated a significant effect for the covariate for Vv mes and percentage of occluded glomeruli. In both cases, the nature of the covariate relationship was such that a lower baseline value led to a greater degree of deterioration during the study period.

**DISCUSSION**

Our pilot study was designed to investigate the potential effect of ACEIs on the evolution of renal structural abnor-

![Table 3](image)

**TABLE 3**

Changes in structural efficacy measurements from baseline to 3 years of follow-up in the 42 patients with tissue available for analysis.

<table>
<thead>
<tr>
<th></th>
<th>Enalapril (n = 15)</th>
<th>Nifedipine (n = 11)</th>
<th>Placebo (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean glomerular volume</strong> (×10⁶ μm³)</td>
<td>4.0 (1.8–5.8) 0.417 ± 0.247</td>
<td>4.5 (2.8–7.1) –0.015 ± 0.278</td>
<td>3.6 (2.2–5.4) 0.698 ± 0.231</td>
</tr>
<tr>
<td>Vv mes</td>
<td>0.33 (0.18–0.52) 0.024 ± 0.021</td>
<td>0.37 (0.25–0.52) 0.044 ± 0.024</td>
<td>0.28 (0.19–0.42) 0.048 ± 0.020</td>
</tr>
<tr>
<td>Vv mat</td>
<td>0.20 (0.10–0.30) –0.006 ± 0.011</td>
<td>0.223 (0.16–0.37) 0.014 ± 0.013</td>
<td>0.18 (0.1–0.29) 0.004 ± 0.011</td>
</tr>
<tr>
<td>GBMT (nm)</td>
<td>595 (292–875) 5.3 ± 21.3</td>
<td>574 (453–759) 40.5 ± 24.7</td>
<td>547 (295–832) –5.2 ± 20.5</td>
</tr>
<tr>
<td>Filtration surface per glomerulus (mm²)</td>
<td>0.32 (0.15–0.63) 0.128 ± 0.034</td>
<td>0.33 (0.16–0.41) 0.031 ± 0.039</td>
<td>0.36 (0.24–0.72) 0.053 ± 0.032</td>
</tr>
<tr>
<td>Volume fraction interstitium/cortex</td>
<td>0.19 (0.12–0.27) 0.026 ± 0.015</td>
<td>0.2 (0.14–0.27) 0.007 ± 0.018</td>
<td>0.21 (0.11–0.229) 0.009 ± 0.015</td>
</tr>
<tr>
<td>Percent occluded glomeruli</td>
<td>14.3 (0–38.3) 2.24 ± 5.42</td>
<td>13.0 (0–50.0) 7.83 ± 6.29</td>
<td>13.8 (0–43.5) 4.71 ± 5.23</td>
</tr>
</tbody>
</table>

Data are means (range) or means ± SEM.

**FIG. 2.** Vv mes (A), Vv mat (B), and GBMT (C) in individual patients at baseline and after 3 years of follow-up in type 1 diabetic patients with albuminuria treated with enalapril, nifedipine, and placebo.

ESPRIT STUDY GROUP

DIABETES, VOL. 50, APRIL 2001 847
nalities in diabetic nephropathy. We selected type 1 diabetic patients who had developed albuminuria but whose BP was in the normal range. This protocol was an attempt to eliminate the powerful confounding effects of hypertension and its reduction by assessing the effect of ACE inhibition on glomerular structure independent of BP changes above the normal range. This design also permitted prospective comparison with a true placebo group at outset.

Our cross-sectional baseline data clearly demonstrate that advanced glomerular structural abnormalities are present in type 1 diabetic patients with albuminuria in the absence of overt hypertension. These lesions are typical of those reported in hypertensive proteinuric patients, and similar relationships between renal function and glomerular structure were found. AER was associated with Vv mes, Vv mat, and GBM thickness (21,22). GFR was inversely related to age, as occurs in the normal population after the fourth decade (23), and was also lower in patients with >10% of occluded glomeruli per biopsy. However, the estimate of occluded glomeruli from needle biopsies is subject to considerable error, mostly because of the nonrandom clustering and a small average sample size of 25 glomeruli per specimen. Despite this fact, our cohort was thought to be a valid group in which to test our hypothesis. GFR declined at an average rate of 4.1 ml · min⁻¹ · year⁻¹ irrespective of treatment group, which is similar to that reported in hypertensive diabetic patients with proteinuria after good control of BP has been achieved (24). This result suggests that in this selected group of patients, factors other than elevated BP are responsible for disease progression.

Reduction in GFR may be more rapid and a consequence of metabolic changes in patients with glomerular hyperfiltration (20). This is, however, an unlikely explanation in our patients, because metabolic control was similar and stable in the three groups, and only four subjects had a supranormal GFR at baseline. Albuminuria, particularly in the nephrotic range, has been shown to be a determinant of disease progression in chronic nephropathies including diabetes, and reduction of albuminuria during treatment with ACEIs has been associated with an attenuated rate of decline in GFR (25–27). This relationship was not detected in our diabetic patients probably because baseline albuminuria was much lower in our study, follow-up was shorter, and BP was normal—all factors that may contribute to mask the association. We did, however, find a significant relationship between baseline albuminuria and Vv mes at follow-up. Mesangial expansion is the lesion that most closely relates to loss of GFR in diabetic nephropathy (28), and it may be that in the absence of hypertension, albuminuria itself is the dominant factor for progressive renal damage in diabetes, an observation corroborated by Jacobsen et al. (29) in a series of normotensive type 1 diabetic patients with nephropathy in whom the rate of GFR decline was substantially lower at 1 ml · min⁻¹ · year⁻¹. Two-thirds of our patients had microalbuminuria at baseline, and previous studies have implied that GFR remains stable until albuminuria reaches the clinical range of >300 mg/day (30). Our subjects with microalbuminuria, however, exhibited a significant decline in GFR, suggesting that even low levels of albuminuria may be detrimental to renal function.

The majority of our patients had a mean BP <100 mmHg (equivalent to 135/80 mmHg) at follow-up. These values, may still be too high to prevent continuing end-organ damage. Clinical studies suggest that a target mean BP of 92 mmHg is desirable to slow progression of proteinuric renal diseases including diabetic nephropathy (31). It is possible that a combination of lowest achievable systemic BP together with significant reductions in albuminuria may afford the best renal protection in diabetes.

In our series with good preservation of renal function and absence of systemic hypertension, significant glomerular lesions were seen at baseline as reported by others (32). Our longitudinal results showed no effect of either active treatment on glomerular structure over 3 years. Moreover, there were no significant changes in glomerulopathy in the placebo-treated group during the study. There are several possible reasons for these findings. First, this group of patients without hypertension may have a significantly slower progression of structural lesions, as suggested by a number of experimental animal data (33). Second, reversal or arrest of the lesions may not be detectable within the 3-year duration of our study. Recently reported observations in patients undergoing pancreas transplantation have shown no change in glomerulopathy after 5 years of normoglycemia but have shown significant resolution at 10 years (34). Thus, the lesions may take as long to resolve as they do to develop. Third, although the estimated variability in our structural end points at baseline were very close to that observed, thus validating our initial power calculations, the achieved number of evaluative patients per group was less than the target, and structural changes in the placebo group over 3 years were less than anticipated. These factors might have contributed to our failure to detect a difference between groups. Finally, the severity of glomerulopathy at baseline may have affected the rate of further structural damage. Evidence that became available after our study was underway suggests that the rate of change of GBMT and Vv mes is slower when the lesions are more advanced at outset—findings confirmed regarding Vv mes and the percentage of occluded glomeruli in our patients. In a small cohort of type 1 diabetic patients with a long disease duration, there was no change in GBMT over a 5-year period, and Vv mes only increased slowly at an approximate rate of 0.012 per year (35). In contrast, in young type 1 diabetic patients with microalbuminuria, GBMT increased by 140 nm over 30 months, and mesangial expansion occurred twice as fast at ~0.024 per year (36).

The continued loss of GFR in our patients may thus be the result of a combination of structural and hemodynamic changes. This notwithstanding, an effect of marginal changes in structure on GFR cannot be completely excluded. The relationship between functional and structural parameters is relatively imprecise with, for example, a reported two- to threefold range of filtration surface per glomerulus corresponding to a given GFR within the range of 80–120 ml/min (37). This imprecision may explain why the observed increase in filtration surface in the enalapril group did not translate into an amelioration in the rate of change of GFR. In addition, GFR was measured seven
times in each patient during our 3-year study, thus allowing a more precise estimate of the rate of change compared with the baseline and follow-up comparison available for renal structure.

We used a dose of enalapril lower than the maximum conventionally used dose to treat hypertension. However, 10 mg once daily produces significant ACE inhibition after 24 h (38) and a sustained reduction in systolic BP of ~7 mmHg in hypertensive patients (39) and was thought unlikely to cause hypotensive symptoms in our cohort of normotensive patients. An average daily dose of enalapril of 11 mg/day has been shown to reduce AER by 60% compared with metoprolol over a mean follow-up of 2 years in type 1 diabetic patients with nephropathy (40). The initial reduction in AER at 6 months in the enalapril-treated patients in our study was not observed in the other two groups and was of a magnitude similar to that seen in previously published studies, implying that effective ACE inhibition was achieved (9).

There have been at least four other studies of the effects of antihypertensive therapy on glomerular structure in diabetic patients (41-44). Only one of these was conducted exclusively in type 1 diabetic subjects (43). These workers studied 13 patients with microalbuminuria, treated with either enalapril (20 mg daily, dose frequency unspecified) or metoprolol, and found no significant change in glomerular structure over a mean follow-up of 38 months. The authors then contrasted these results with those from historical control subjects, who underwent repeat renal biopsy within 3 years and who demonstrated significant increases in GBMT and in an estimate of mesangial expansion. They concluded that antihypertensive therapy stabilizes glomerular structure at this early stage in the development of nephropathy. Their control group, however, had on average a higher HbA1c, higher BP, and higher AER at follow-up than the actively treated groups. The main findings of no detectable change in glomerular structure in the antihypertensive-treated patients are compatible with our own results, even though the treated patients in that study had considerably less severe lesions at baseline. The number of patients studied by these workers was fewer than that in our study. A power calculation was reported, suggesting that a sample size of six patients would be adequate to detect a 25% increase in unspecified structural parameters with a power of 80% at a 0.05 significance level, but reported Vv mes did not change significantly in either the antihypertensive treatment or the historical control groups during the study (43). Therefore, we feel it is premature to conclude from these data that antihypertensive therapy halts progression of the key renal structural changes in diabetes over a 3-year period. Our findings are in accordance with this view.

Two studies were performed in type 2 diabetic patients (41) or a mixture of types of diabetic patients (42) with and without hypertension at baseline and rely mostly on light microscopic analysis. Both showed a stabilization in Vv interstitium in the ACEI-treated groups, and one also showed stabilization in GBMT in the small number of treated patients in whom there was tissue available for electron microscopic analysis (42). We found no significant effect of treatment with enalapril or nifedipine retard on Vv interstitium, and it is possible that changes in this part of the kidney are more responsive to ACEIs in type 2 hypertensive diabetic patients.

In conclusion, this first prospective placebo-controlled intervention study comparing the effects of different antihypertensive treatments on glomerular and interstitial ultrastructure in type 1 diabetic patients with albuminuria did not show any detectable impact of enalapril compared with either nifedipine or placebo on renal structure over 3 years. We have shown that patients with increased AER have established glomerulopathy and a progressive decline in GFR in the absence of overt hypertension. In this context, baseline AER appeared predictive of subsequent mesangial volume fraction. We acknowledge the limitations of the size and duration of our study and have become aware of the slow changes in glomerular structure in normotensive patients. Therefore, our results call for further structural studies in larger numbers of patients with a narrower range of albuminuria and GFR, with less severe glomerular structural changes, and perhaps with higher doses of antihypertensive agents over longer periods of time.

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APPENDIX

Contributors

The members of the European Study for the Prevention of Renal Disease in Type 1 Diabetes (ESPRIT) Study Group are listed below. The study idea was conceived by Professor G.C. Viberti. Renal biopsies were analyzed in the Biomedical Electron Microscopy Unit, University of Newcastle upon Tyne, by Dr. L.A. Baines, Dr. J.M. Macleod, and Mrs. K.E. White. Albumin assays were performed by Miss A. Collins. GFRs were determined by Dr. F. Gaspari. Statistical analysis was performed by Mrs. H. Tate. The article was written by Dr. L.A. Baines, Dr. R.W. Bilous, Mrs. H. Tate, Professor G. Remuzzi, and Professor G.C. Viberti.

ESPRIT Study Group members

U.K.

Guy’s Hospital, London: Dr. K. Earle, Dr. D.J. Barnes, Dr. S.H. Thomas, Dr. I. Abbs, Miss A. Collins, and Professor G.C. Viberti; University of Newcastle upon Tyne and Middlesbrough General Hospital: Dr. L.A. Baines, Dr. J.M. MacLeod, Mrs. K.E. White, Dr. S.M. Marshall, and Dr. R.W. Bilous; Royal Victoria Infirmary, Newcastle upon Tyne: Dr. M.K. Ward; South Cleveland Hospital, Middlesbrough: Dr. J.R. Cove-Smith and Dr. A.D. Paterson; Northern General Hospital, Sheffield: Professor A.M. El Nahas; Merck, Sharp and Dohme, Herts: Mrs. H. Tate, Dr. A. Hersh, Dr. R. Tomiak, and Dr. P. Robinson.
REFERENCES