Proteinuria in atherosclerotic renovascular disease

A.D. MAKANJUOLA, M. SURESH, P. LABOI, P. A. KALRA and J.E. SCOBLE

From the Department of Nephrology and Transplantation, Guy’s Hospital, London, and
1Department of Nephrology, Hope Hospital, Salford, UK

Summary

Proteinuria is well described in atherosclerotic renovascular disease (ARVD), but the prevalence is unknown, and the pathogenesis may vary between patients. Substantial proteinuria (>2 g/day) however, would be regarded by many as atypical of ARVD. We studied 94 patients (52 male) with ARVD, median age 67 years (range 49–87). Digital subtraction angiography was performed on all patients. Protein was assayed in 24-h urine samples and GFR derived using the Cockroft-Gault formula. Fortyt-nine patients (52%) had proteinuria <0.5 g/24 h. Proteinuria increased with worsening renal function. Biopsies from seven non-diabetic patients with substantial proteinuria showed: minimal changes (1); glomerular sclerosis with marked ischaemic changes (3); focal glomerulosclerosis (2); and athero-emboli (1). Proteinuria, rather than being indicative of other pathology, is often a marker of severity of parenchymal disorder in atherosclerotic nephropathy, which itself is the major determinant of renal dysfunction in patients with ARVD.

Introduction

In 1988, Jacobson defined the reversible renal impairment due to renal artery narrowing as ischaemic nephropathy.1 It is now recognized that the renal disease associated with atherosclerotic renal artery stenosis is more complex than just a direct response to ischaemia,2 and the processes may include focal segmental glomerulosclerosis (FSGS)3 and athero-embolic disease.3, 4 In many forms of renal disease, proteinuria is a predictor of progressive renal dysfunction.5 Although there are individual case reports or series, there has been no investigation into the frequency of proteinuria in atherosclerotic renovascular disease (ARVD). We investigated the prevalence and magnitude of proteinuria in patients with ARVD.

Methods

Patients from two renal centres with angiographically-confirmed ARVD were investigated to determine their renal function and degree of proteinuria. Protein was quantified from 24-h urine samples collected prior to or 4–8 weeks following angiography. The majority of patients had been referred for investigation of renal dysfunction rather than solely for investigation of hypertension. There was often a suspicion of renovascular disease at the time of referral.

To ensure uniformity between the two centres during data analysis, GFR was calculated using the Cockroft-Gault formula:6

\[
GFR \text{ (ml/min) } = K \left(1.2 \times (140 - \text{age in years}) \times \text{weight in kg/plasma creatinine in } \mu\text{mol/l}\right)
\]

Arterial anatomy was determined by digital subtraction angiography. Radiological findings were reported either as ‘normal’, ‘stenosis’ or ‘occlusion’. Stenoses were graded as mild (<25%), moderate (25–50%), or severe (>50%). Patients with proven ARVD were scored between 0 and 2, according to a ‘patency index’ as follows: 0, occlusion in one vessel; 1, normal vessel; with intermediate values derived as 1 minus the degree of stenosis. A patient

Address correspondence to Dr A.D. Makanjuola, Department of Nephrology and Transplantation, Guy’s Hospital, London SE1 9RT

© Association of Physicians 1999
with 50% stenosis on one side and occlusion on the other would therefore score 0.5 (0.5 + 0), and a patient with bilateral 50% stenosis would score 1 (0.5 + 0.5).

Data were also obtained for age at presentation, sex, and the presence or absence of diabetes and hypertension.

Correlation of GFR and proteinuria

Patients were arbitrarily stratified into four groups according to their GFR (ml/min): <10 (n = 9); 10–25 (n = 36); 25–50 (n = 33); and >50 (n = 16). Mean proteinuria as well as the standard error of the mean (SEM) was calculated for each group (Figure 1). Statistical analysis was done using ANOVA, comparing all four groups of patients.

**Correlation of proteinuria and patency index**

Mean proteinuria was plotted against patency index in the scatter diagram shown in Figure 2. There was no correlation between the parameters (r = 0.05).

![Figure 1. Relationship between mean proteinuria and GFR. Number of patients per group is shown in the vertical bars. p < 0.0325 with ANOVA, comparing all the groups of patients.](image)

![Figure 2. Relationship between mean proteinuria and patency index in patients with ARVD. Correlation coefficient r = 0.05.](image)

**Results**

Patient characteristics are shown in Table 1. Ninety-four patients were available for study, 52 males and 42 females (M:F = 1.2:1), of whom 87 (92.6%) were on treatment for hypertension. Some were on angiotensin-converting-enzyme inhibitors (ACEIs) prior to diagnosis, but these were usually discontinued on suspicion or confirmation of the diagnosis of ARVD. The mean age of the patients was 66 years (range 49–87).

There were 20 diabetic patients, all of whom were type II diabetics. Five had substantial proteinuria (mean 1.37 g) and all underwent renal biopsy. Features in keeping with diabetic nephropathy were present in four, and these patients were excluded from data analysis. In the fifth patient, the biopsy showed athero-emboli, but no evidence of diabetic nephropathy. The other 15 diabetics had lesser degrees of proteinuria (mean 0.58 g) and lacked clinical features such as retinopathy or peripheral neuropathy, which argued against diabetic nephropathy being comorbidly present with ARVD, but as renal biopsies were not performed on these patients, it is impossible to be certain.

The proteinuria increased significantly (p < 0.0325) in magnitude as GFR declined in these patients. We were concerned that the diabetic patients included in the study might skew these results. Subgroup analysis however, showed that there was an even distribution between groups, as seven of the 15 diabetics included had GFRs <25 ml/min. Similarly, there was no difference in prevalence of treated hypertension between the groups.

Biopsies were performed on seven non-diabetic patients who had substantial proteinuria; especially where there was a suspicion that there might be coincident intrinsic glomerular pathology unrelated to renovascular disease. Minimal changes were detected in one patient with unilateral renal artery stenosis who had a biopsy performed on the contralateral kidney. FSGS was found in three patients (the immunofluorescence pattern suggested that this was secondary, rather than idiopathic FSGS).

**Table 1** Characteristics of patients in relation to renal function

<table>
<thead>
<tr>
<th>Glomerular filtrate rate</th>
<th>&lt;10</th>
<th>10–25</th>
<th>26–50</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>69.8</td>
<td>67.7</td>
<td>66.6</td>
<td>65.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55.6</td>
<td>48.6</td>
<td>59.4</td>
<td>62.5</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>11</td>
<td>22.9</td>
<td>21.9</td>
<td>25</td>
</tr>
<tr>
<td>Mean patency index</td>
<td>0.91</td>
<td>0.96</td>
<td>0.93</td>
<td>0.86</td>
</tr>
</tbody>
</table>
Proteinuria has been recognized as an important predictor of renal dysfunction in the best-studied progressive renal disease, diabetic nephropathy. In some studies, the magnification of the risk of progression of renal disease by proteinuria is as great in non-diabetic patients as it is in those with diabetes. Other investigators have observed the importance of proteinuria as a predictor of mortality in the general population. Could this be due to occult atherosclerotic nephropathy in these patients?

The mechanism of proteinuria in these patients is complex. The case that Chen et al. reported, of removal of a kidney with renal artery occlusion curing nephrotic range proteinuria, lends support for a central role for hyper-reninaemia. In their patient, proteinuria fell gradually rather than instantaneously after the nephrectomy, suggesting that the proteinuria did not originate solely from the kidney with the occluded renal artery. In atero-embolic disease, the regular occurrence of proteinuria suggests a more direct response, perhaps due to cholesterol crystal embolization, which is occasionally associated with an acute-phase response. That FSGS can develop in a kidney with renal artery stenosis provokes interesting mechanistic hypotheses, which however, are difficult to prove. Although we only obtained biopsy material in a minority of our patients with ARVD, a spectrum of parenchymal disorders were observed. As the renal histological changes can be focal, we suggest that pathogenetic mechanisms can vary, and that several distinct changes may co-exist in the individual patient. We therefore feel the term ‘atherosclerotic nephropathy’ is a more appropriate term to describe the spectrum of renal disease associated with ARVD.

ACEIs are useful agents for attenuating proteinuria, but we have been reluctant to initiate the liberal use of these agents in our patients pre- or post-angioplasty. This is because of the progressive nature of the renal artery narrowing and the risk of restenosis following intervention. However, it is interesting that in Mikhail et al., three of the patients with progressive renal dysfunction after angioplasty actually had 24-h urine protein values well above the normal range. Single kidney GFR estimations on these patients showed that progressive renal dysfunction occurred independently of restenosis. Significant proteinuria not uncommonly accompanies such functional deterioration, and as such, there may yet be a rationale for ACEIs or angiotensin II receptor antagonists in the long-term treatment of subgroups of patients with ARVD. The challenge for the nephrologist will be to identify such subgroups.

### References


### Table 2

<table>
<thead>
<tr>
<th>Biopsy findings</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>4</td>
</tr>
<tr>
<td>FSGS</td>
<td>3</td>
</tr>
<tr>
<td>Glomerulocicerosis with marked ischaemic change</td>
<td>2</td>
</tr>
<tr>
<td>Minimal changes</td>
<td>1</td>
</tr>
<tr>
<td>Athero-embolic disease</td>
<td>1</td>
</tr>
</tbody>
</table>

FSGS, focal segmental glomerulosclerosis.

glomerulosclerosis with marked ischaemic changes in two patients, and atero-embolic disease with cholesterol clefs in one diabetic patient in the absence of overt diabetic changes (Table 2).


