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Original Article

Clinicopathological correlation in biopsy-proven atherosclerotic nephropathy: implications for renal functional outcome in atherosclerotic renovascular disease

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Abstract

Background. Atherosclerotic renovascular disease (ARVD) is commonly associated with renal failure. It is now recognized that intrarenal damage, (ischaemic or atherosclerotic nephropathy) is a major contributor to the renal impairment in these patients. In this study the impact of histological changes upon renal functional outcome was investigated in patients with atherosclerotic nephropathy.

Methods. The Hope Hospital renal biopsy database (1985–1998) was interrogated for patients with histology compatible with atherosclerotic nephropathy. Case-note review enabled the assessment of several clinical parameters and outcomes, including change in creatinine clearance per year (ΔCrCl (ml/min/year)), blood pressure control, dialysis need, and death. Renal parenchymal damage was analysed by morphometric analysis (of interstitial fibrosis and glomerulosclerosis) and a semi-quantitative chronic damage score (score 0–3 (normal–severe) for each of glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriolar hyalinosis; maximum = 12). Patients were stratified into two groups who had either deteriorating (group 1) or stable (group 2) renal function during follow-up.

Results. Twenty-five patients (age 64.7 ± 10.5, range 43–83 years; 17 male, eight female) were identified. Sixteen patients had undergone angiography; two had significant (> 50%) renal artery stenosis. Mean follow-up was 25.6 ± 14.8 (range 5–50) months. Group 1 patients had ΔCrCl −7.4 ± 6.8 ml/min/year, $n = 14$ and group 2 patients had ΔCrCl 4.8 ± 7.0 ml/min/year, $n = 11$. Four patients in group 1 developed end-stage renal disease and five patients died (three in group 1 and two in group 2). At study entry, group 1 patients had worse renal function (CrCl 27.6 ± 17.6 *vs* 36.0 ± 33.9, NS), greater proteinuria (1.2 *vs* 0.5 g/24 h, NS), and higher systolic blood pressure (167.1 ± 30.8 mmHg *vs* 150.6 ± 37.8, NS) compared with group 2 patients. Group 1 patients showed more glomerulosclerosis (51.6 *vs* 24.9%, $P < 0.01$), greater proportional interstitial volume (44.9 *vs* 33.9%, $P < 0.02$), and higher overall chronic damage score ($P < 0.05$) than those in group 2. There was a significant correlation between renal functional outcome and chronic damage score, glomerulosclerosis and proportional interstitial volume for the entire patient cohort.

Conclusion. In patients with atherosclerotic nephropathy the severity of histopathological damage is an important determinant and predictor of renal functional outcome.

Keywords: atherosclerotic nephropathy; atherosclerotic renovascular disease; chronic damage score; glomerulosclerosis; interstitial fibrosis

Introduction

Atherosclerotic renovascular disease (ARVD) is a common cause of chronic renal failure (CRF) and many patients with end-stage renal disease (ESRD) also have ARVD [1]. Although with an ageing population the prevalence of this condition is increasing, the pathogenesis of CRF and the risk of progression to ESRD in patients with ARVD are not well established [2].

Evidence now suggests that in the majority of patients with ARVD, the cause of CRF is unlikely to be due simply to the ischaemic effect of a proximal renal artery stenosis (RAS). Revascularization of a significantly stenosed renal artery, whether this be with angioplasty with or without stenting, or by surgery, is accompanied by an unpredictable renal functional outcome, with only a minority of patients exhibiting

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improved renal function, but a similar proportion manifesting progressive functional deterioration [3]. Furthermore, a recent study has found no correlation between renal artery patency and glomerular filtration rate (GFR) in ARVD patients [4].

It is likely, therefore, that parenchymal injury, with or without small-vessel disease, is the main determinant of renal dysfunction in most patients with ARVD. Such renal parenchymal injury has been termed 'ischaemic nephropathy' [5] and histological changes include a constellation of interstitial fibrosis, tubular atrophy, glomerulosclerosis (including focal segmental glomerulosclerosis), periglomerular fibrosis, and a variety of arteriolar abnormalities. With the recognition that ischaemia is not always responsible for the CRF in patients with ARVD, 'atherosclerotic nephropathy' has also recently been used to describe this intra-renal damage [6]. Many of these histological features are non-specific and are encapsulated by the term arteriolonephrosclerosis [7], which can result from a variety of insults to the kidney, including hypertension and ischaemia. Such changes in the unaffected (non-RAS) kidney in ARVD are likely to be important in the pathogenesis of CRF, and this is borne out by isotopic techniques that estimate individual kidney function [8].

The clinical significance of the various renal histological abnormalities in patients with ARVD is unknown. Investigation is difficult largely because renal biopsies are not regularly or systematically obtained in these patients. In this study we investigated the impact of histological changes upon renal functional outcome in a group of patients whose renal biopsy appearances were compatible with ischaemic or atherosclerotic nephropathy, irrespective of whether or not significant ARVD had been demonstrated at angiography.

Subjects and methods

Patient population

The Hope Hospital renal pathology database (1985–1998) was interrogated for patients with renal biopsy findings compatible with atherosclerotic nephropathy. These changes included angionephrosclerosis with interstitial fibrosis, with or without ischaemic collapse of glomerular capillaries, and atheroembolic disease. All renal biopsies had been performed for investigation of unexplained proteinuria or renal impairment. Patients with renal biopsies that showed mild–moderate vascular changes alone, in keeping only with hypertensive damage, and those with evidence of another primary renal disease, such as diabetic nephropathy, were excluded from the study. The case notes of the appropriate patients were retrieved and data extracted from them.

Clinical data collection and end-points

Data collection was retrospective and included timed 24-h urine collections with corresponding serum samples used to measure creatinine clearance and proteinuria. Baseline characteristics were noted at the time of renal biopsy and renal functional outcome was assessed by change in creatinine clearance per year (ΔCrCl (ml/min/year)) over the follow-up period. Where renal angiograms had been performed the presence of aortic atheroma, as shown by the presence of aortic plaques (graded as mild, moderate, or severe) and significant RAS (>50% stenosis) were noted by two independent clinicians blinded to the clinical information. Blood pressure at the beginning and the end of the follow-up period was recorded. Clinical endpoints were death, commencement of dialysis, or the last clinic visit data of those surviving patients with chronic renal failure.

Histological analysis

Histopathological findings in the renal biopsies were analysed by three independent pathologists who were blinded to the clinical information. Two separate techniques were used to quantitatively assess the severity of histological injury.

Morphometric analysis. The proportional interstitial volume was determined using a Chalkley graticule (Graticules Ltd, Tonbridge, UK). The entire renal cortex was analysed for each biopsy, excluding fields that contained large arteries. As no biopsy showed oedema, interstitial volume was a measure of the extent of interstitial fibrosis. The number of globally sclerosed glomeruli in each biopsy was counted and expressed as a percentage of the total.

Semi-quantitative analysis. The extent of glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriolar hyalinosis was assessed semi-quantitatively and scored variously 0–3 (Table 1). The total score for each biopsy was also calculated ('chronic damage score', maximum = 12). The chronic damage score was a modified version of the Banff classification of renal allograft pathology [9]. The median score for each histological parameter was derived from the assessments of all three pathologists for each patient. Where assessments were clearly discordant, the slides were reviewed and a consensus score identified.

Definition of renal functional stability or deterioration

In order to establish whether renal functional outcome was related to the extent of histological injury, patients were stratified into two groups based upon ΔCrCl over the

Table 1. Semi-quantitative histological scoring of renal biopsies

Histological score	0	1	2	3
Glomerulosclerosis (% of glomeruli showing at least moderate mesangial expansion)	0	<25	25–50	>50
Interstitial fibrosis (% of cortical area showing fibrosis)	0	<25	25–50	>50
Tubular atrophy (% of cortical tubules showing atrophy)	0	<25	25–50	>50
Arteriolar hyalinosis (% of arterioles showing at least moderate hyaline thickening)	0	<25	25–50	>50

Modified from Solez *et al.* [9].

follow up period. Those patients whose ΔCrCl fell by >1 ml/min/year (group 1) were considered to have deteriorating renal function. This cut-off point for ΔCrCl was selected because a loss of GFR of up to 1ml/min/year may be considered physiological in patients aged over 40 years. Patients included in group 2 were those with stable renal function.

Statistical analysis

Statistical methods were employed to establish whether there were significant differences in the demographic, clinical and histopathological findings between those patients with deteriorating and those with stable renal function. Data sets following a normal distribution (age, renal function, blood pressure, and interstitial volume measurements) were described in terms of their mean and standard deviation (SD). Data that did not follow a normal distribution (semi-quantitative histological scores) and proteinuria were described in terms of the median value and interquartile range (IQR). One-way ANOVA tests were used to test significance between continuous data sets. Unpaired non-normal data was analysed using the Mann–Whitney U test. Pearson's correlation coefficient was used to test whether any significant association existed between renal functional outcome and histological injury in the entire patient population. A statistical difference was considered significant at a level of $P<0.05$.

Results

Clinical features

Twenty-five patients (age 64.7 ± 10.5, range 43–83, years; 17 male, eight female) were identified as having biopsies consistent with atherosclerotic nephropathy. Angiography had been performed in 16 patients and this revealed aortic atheroma in all cases. Of these, two had mild atheroma, 12 had moderate atheroma, of whom two had significant RAS, (one patient had unilateral right RAS, the other RAS in a solitary kidney), and two had severe atheroma but no evidence of RAS. In all 25 patients the left kidney had been biopsied. The mean follow up period was 25.6 ± 14.8 months (range 5–50). During this time, 14 patients had a declining renal function (ΔCrCl -7.4 ± 6.8 ml/min/year, group 1) and 11 patients stable renal function (ΔCrCl 4.8 ± 7.0 ml/min/year, group 2). The follow-up periods were similar for the two groups (28.4 ± 15.5 *vs* 22.1 ± 13.9 months), but four patients in the group with declining renal function developed ESRD and required dialysis. The number of deaths was similar in the two groups (3 and 2 respectively), and causes of death were malignancy or respiratory failure (two of each in both groups) and myocardial infarction in the other patient.

The clinical characteristics of the two groups at the time of study entry are summarized in Table 2. Age was similar, but group 1 patients who subsequently had progressive renal functional deterioration had worse renal function (CrCl 27.6 ± 17.6 *vs* 36.0 ± 33.9), greater proteinuria (1.2 *vs* 0.5 g/24 h) and higher systolic blood pressure (167.1 ± 30.8 mmHg *vs* 150.6 ± 37.8) compared with group 2 patients. However, none of these differences was statistically significant.

Histopathological features

Using morphometric analysis, patients in group 1 showed a significantly higher percentage of globally sclerosed glomeruli (51.6 ± 25.1 *vs* 24.9 ± 20.0; $P<0.01$) and a greater proportional interstitial volume (44.9 ± 8.7 *vs* $33.9\pm9.5\%$; $P<0.02$) compared with those in group 2.

Significant differences between the groups were found for the overall score ($P<0.05$) and for glomerulosclerosis ($P<0.05$) when scored semi-quantitatively. There were no significant differences between the groups in scores for tubular atrophy, interstitial fibrosis, and arteriolar thickening.

Cholesterol emboli were seen in two biopsies, one in each group. Ischaemic collapse of glomerular capillaries was seen in the biopsies of five patients, of which three had worsening renal function. Chronic inflammatory cell infiltration within the interstitium was seen in five of the biopsies in group 1 patients, in one case this infiltrate involved more than 25 per cent of the interstitium.

Table 2. Clinical findings of patients with atherosclerotic nephropathy. Group 1 patients had deteriorating renal function and group 2 patients had stable renal function

	Group 1 $n=14$ (mean ± SD)	Group 2 $n=11$ (mean ± SD)
Age (years)	64.2 ± 12.1	65.5 ± 8.6
CrCl at study entry (ml/min/year)	27.6 ± 17.6	36.0 ± 33.9
Systolic BP at study entry (mmHg)	167.1 ± 30.8	150.6 ± 37.8
Diastolic BP at study entry (mmHg)	87.5 ± 14.6	88.0 ± 25.3
Systolic BP at study end (mmHg)	143.9 ± 25.6	136.3 ± 10.1
Diastolic BP at study end (mmHg)	79.3 ± 10.0	81.1 ± 6.6
	(median (IQR))	(median (IQR))
Proteinuria (g/24 h)	1.2 (0.4–2.2)	0.5 (0.2–1.2)

All findings were non-significant.

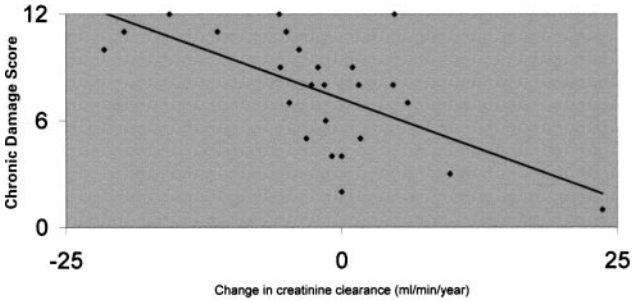

Fig. 1. Correlation of renal functional outcome and chronic damage score (maximum = 12) ($r = -0.639$; $P < 0.002$).

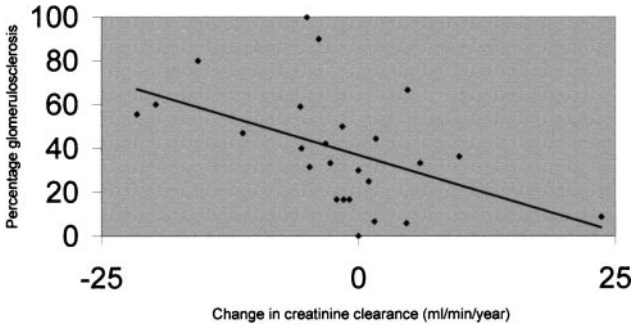

Fig. 2. Correlation of renal functional outcome and percentage of glomerulosclerosis by morphometric analysis ($r = -0.486$; $P < 0.02$).

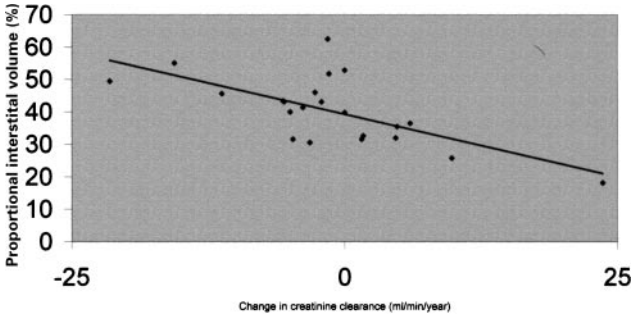

Fig. 3. Correlation of renal functional outcome and proportion of interstitial volume by morphometric analysis ($r = -0.509$; $P < 0.002$).

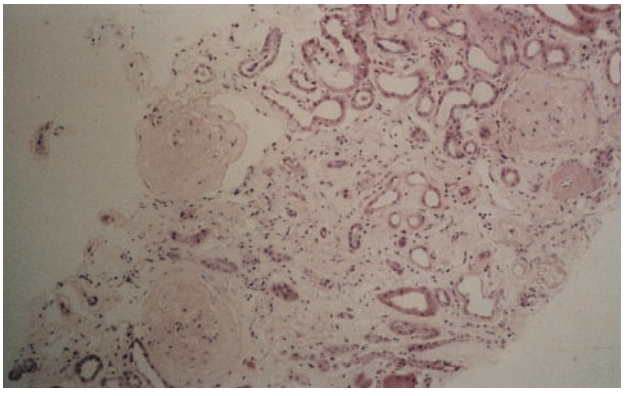

Fig. 4. Atherosclerotic nephropathy. Widespread tubular loss and interstitial fibrosis with glomerulosclerosis (H&E $\times 10$).

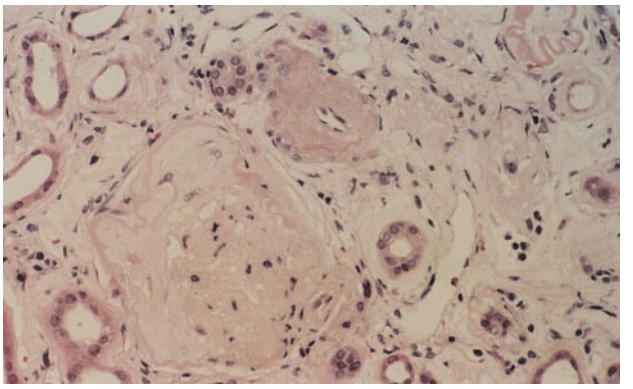

Fig. 5. Atherosclerotic nephropathy. Glomerulosclerosis, periglomerular fibrosis and arteriolar hyalinosis (H&E $\times 25$).

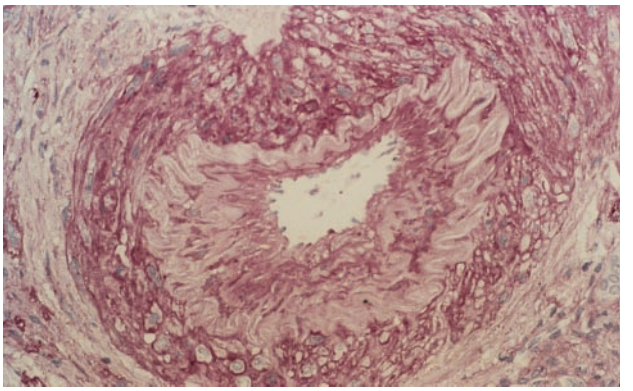

Fig. 6. Atherosclerotic nephropathy. Severe vascular changes: intimal hyperplasia, reduplication of the internal elastic lamina, medial hypertrophy, and perivascular fibrosis (H&E $\times 40$).

Correlation studies performed in all 25 patients showed statistically significant correlations between renal functional outcome (ΔCrCl) and the overall chronic damage score (Figure 1), percentage glomerulosclerosis (Figure 2), and also proportional interstitial volume (Figure 3).

In those 16 patients who had undergone angiography, there was an equal distribution of aortic atheroma severity in the two groups. Examples of the typical histopathological changes investigated within this study are shown in Figures 4–6.

Discussion

The pathogenesis of chronic renal failure in ARVD is not fully understood. The haemodynamic effect of a significant proximal RAS can undoubtedly lead to a decrease in renal perfusion, intra-renal ischaemia, and progressive renal dysfunction in a proportion of patients. However, these are probably that minority of patients whose renal function improves after angioplasty [10,11], stenting [12,13], or surgical revascularization [14]. In the majority of patients with ARVD, renal function remains stable, or deteriorates, after revascularization [3] and residual renal artery

patency appears to be unrelated to renal function [4], the notable exceptions being those patients with renal-artery occlusion (RAO) affecting either or both kidneys [15]. This suggests that renal parenchymal injury may be a more important factor in determining the renal functional outcome in patients with ARVD than was previously recognized.

Apart from the variable functional outcomes after revascularization procedures, further insight into the importance of parenchymal injury has been provided by isotopic studies that reliably estimate individual kidney function [8]. Thus, single-kidney GFR is often similarly decreased in both the contralateral 'normal' kidney and the kidney with a significant RAS within the same patient. The fact that proteinuria rises significantly with decreasing renal function in ARVD patients [16] lends further support, as here proteinuria is likely to be a marker of severity of parenchymal damage.

The renal histological abnormalities in ARVD patients have been described previously [5], but reports have usually focused on those kidneys with significant RAS or RAO. There is now overwhelming evidence that damage often also occurs within the contralateral kidney that is unaffected by RAS. The importance of these histological changes in determining the outcome in ARVD has rarely been investigated, as renal biopsies are not systematically performed in patients with ARVD. When biopsy does take place, it is usually from the affected kidney in order to assess the severity of intra-renal damage during consideration of the value of revascularization [17]. Histological changes compatible with 'atherosclerotic nephropathy' are non-specific and are recognized in patients who do not have significant RAS. For example, arteriosclerosis and arteriolosclerosis have been found in the absence of, or anticipating the onset of, hypertension, in young African black patients and in some animal models, leading to the hypothesis that some vascular nephropathies stem from a genetic defect [7]. We would anticipate, therefore, that in patients with atheroma, changes of atherosclerotic nephropathy are likely to occur in kidneys both affected and unaffected by significant RAS. Hence, in this study, in order to assess the impact of the severity of such histological changes upon renal functional outcome, the main selection criterion was a renal biopsy diagnosis consistent with atherosclerotic nephropathy rather than angiographically proven ARVD. Indeed, in the 16 patients who did undergo angiography, all had evidence of aortic atheroma, two had peripheral vascular disease, and only two patients had significant RAS.

After separating the patients with atherosclerotic nephropathy into two groups, based upon renal functional outcome, we identified differences in certain clinical parameters between the groups. Those patients whose renal function deteriorated over the follow-up period had worse initial renal function, and greater systolic blood pressure and proteinuria at study entry than the patients with subsequent stable renal function. Although not statistically significant, these differences in clinical parameters are similar to those that have been shown to affect progression of renal dysfunction in other chronic renal diseases [18]. Renal histological analysis, using two different quantitative techniques, revealed significant overall differences between the two outcome groups. Patients in the declining renal function group had a higher proportion of both interstitial volume (and hence, interstitial fibrosis) and of glomerulosclerosis. Although the overall semi-quantitative chronic damage score can perhaps be considered artefactually derived, this was again significantly higher in group 1 patients. Further, when the entire patient group was considered as a whole, there were significant correlations between renal functional progression and the above histological parameters.

This study shows that in patients who have renal biopsies consistent with atherosclerotic nephropathy, the severity of histopathological damage will predict the probable renal functional prognosis. This correlation between biopsy findings and renal functional outcome, by inference to the association of atherosclerotic nephropathy with ARVD, lends further support to renal parenchymal damage being an important determinant of renal functional outcome in patients with ARVD. However, we feel that it is now important to clarify whether, within the same patient with ARVD, the range of renal histological changes observed in a kidney affected by RAS can be differentiated from those within a kidney supplied by a patent renal artery. Future clinical studies will also need to focus on the impact of any such differential changes upon renal functional prognosis. With an ageing population, in whom ARVD is an increasingly recognized cause of ESRD, appreciation of this clinicopathological correlation is highly important and it may guide clinical management. For example, if a patient with significant RAS were to have adverse histology in the contralateral kidney, then the clinician may be more inclined to consider revascularization of the RAS in order to prevent the development of ESRD.

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