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Renal histology in polycystic kidney disease with incipient and advanced renal failure

MARTIN ZEIER, PETER FEHRENBACH, STEFFEN GEBERTH, KLAUS MÖHRING, RÜDIGER WALDHERR, and EBERHARD RITZ

Departments of Internal Medicine, Urology and Pathology, University of Heidelberg, Heidelberg, Germany

Renal histology in polycystic kidney disease with incipient and advanced renal failure. Renal specimens were obtained at surgery or postmortem from patients with autosomal dominant polycystic kidney disease (ADPKD). Patients had either serum creatinine (S_{Cr}) below 350 μmol/liter ($N = 12$) or terminal renal failure ($N = 50$). Specimens were examined by two independent observers using a carefully validated score system. Mean glomerular diameters were similar in ADPKD patients with early renal failure (176 ± 38 μm) and in victims of traffic accidents (177 ± 23 μm), while they were significantly greater in diabetics with comparable renal function (205 ± 16 μm). Glomerular diameters in ADPKD patients with terminal renal failure (191 ± 45 μm) and with early renal failure were not significantly different. On average, 29% of glomeruli (17 to 62) were globally sclerosed in early renal failure, and 49% (19 to 93) in terminal renal failure. The proportion of glomeruli with segmental sclerosis was less than 4% in both groups. Marked vascular sclerosis, interstitial fibrosis, and tubular atrophy were present in early renal failure, and even more so in terminal renal failure. Interstitial infiltrates were scarce and consisted mainly of CD4 positive lymphocytes and CD68 positive macrophages. Immunestaining with monoclonal renin antibodies showed an increased juxtaglomerular index and expression of renin by arterioles adjacent to cysts, as well as by cyst wall epithelia. The data show more severe vascular and interstitial, but not glomerular, changes in ADPKD with advanced as compared to early renal failure.

In autosomal dominant polycystic kidney disease (ADPKD), renal cysts are demonstrable early, that is, at 12 weeks of gestation [1, 2], but terminal renal failure does usually not supervene before the fourth to sixth decades of life [3]. Several mechanisms have been suggested to explain progression of renal failure. Franz and Reubi proposed a mathematical model according to which renal failure resulted from compression of renal parenchyma by expanding cysts [4], a hypothesis that had been advanced before by Dalgaard [5] and Lund [6]. The alternative concept of maladaptive functional changes of residual nephrons has been proposed as a mechanism underlying progression in several renal diseases [7, 8] including ADPKD. Although focal-segmental glomerular sclerosis is a predictor of adverse renal outcome in patients with glomerular and non-glomerular disease [9, 10], implying an important role of glomerular lesions, the importance of vascular lesions [11] and interstitial fibrosis [12] for progression has also been documented. The relative roles of glomerular, vascular or interstitial changes in the progression of renal failure of ADPKD have not been explored to date. In the present study we compared the histology of kidneys of patients with ADPKD in early or late renal failure. We reasoned that such comparison may indirectly provide clues concerning the mechanisms of progression in this disease.

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Methods

Patients

We examined the kidneys of 62 ADPKD patients. Twelve patients had normal renal function or were in early renal failure (7 males, 5 females; median S_{Cr} 190 μmol/liter; 83 to 350); some clinical information is given in Table 1. Furthermore, we examined 50 patients with terminal renal failure (21 males, 29 females). Twelve patients with terminal renal failure ($S_{Cr} > 800$ μmol/liter) had not yet entered a renal replacement program at the time of nephrectomy, seven patients had been on dialysis for less than and 31 patients for more than one year. Kidney specimens were obtained surgically prior to dialysis or at postmortem. They were embedded in paraffin and stained with HE or PAS, respectively. The control groups were: (1) 13 patients (6 male, 7 female) with type II diabetes, overt proteinuria and early renal failure (median S_{Cr} 115 μmol/liter (64 to 250); median proteinuria 1.09 g/24 hours (0.5 to 4.6), and (2) in 15 subjects coming to postmortem after traffic accidents (median age 33 years, 19 to 58; 9 males, 6 females), renal disease was excluded by renal histology.

Analysis of tissue specimens. The following analyses were carried out:

(1) To measure glomerular diameters (in μm, using the longer of two perpendicular diameters of the glomerular capsule) at least 100 glomeruli per patient were randomly selected from the sections and measured.
(2) The proportions of glomeruli exhibiting segmental sclerosis (as a putative marker of glomerular overperfusion) or global sclerosis (as a putative marker of glomerular ischemia) were recorded.
(3) The severity of vascular sclerosis of preglomerular vessels (Fig. 1), of interstitial fibrosis (Fig. 2), tubular atrophy (Fig. 2), and of interstitial infiltrates was evaluated using a score system from zero to three.

Table 1. Clinical information

N	S_{Cr} μmol/liter	Blood pressure mm Hg	Indication for nephrectomy
1	350	170/100	Infection
2	250	160/100	Bleeding
3	216	170/110	Infection
4	190	140/90	Infection
5	160	160/95	Stone/infection
6	220	220/130	Infection
7	233	Hypertension no figures available	Stone/infection
8	90	Hypertension no figures available	Bleeding
9	100	160/100	Infection
10	83	150/100	Subarachnoidal Hemorrhage (autopsy)
11	190	180/90	Infection
12	116	150/90	Stone/infection

In more than 90% of the specimens the same score was found by one examiner on repeated occassions. Disagreement from day to day did not exceed a score value of one. Two independent observers differed maximally by a score value of one in 15% of the specimens.

In addition, immunohistological studies were performed on seven freshly removed ADPKD kidneys. Monovalent CD68 (KP1) antibody (marker for macrophages) and CD4/CD8 antibodies (marker for lymphocytes) were used to characterize mononuclear cells in interstitial infiltrates. A polyvalent antibody against Tamm-Horsfall protein was used to assess the interstitium for the presence of Tamm-Horsfall protein.

We further respectively examined liver and pancreas specimens of six and seven ADPKD patients to assess the degree of vascular lesions (score 0 to 3) and fibrosis (portal fields).

The juxtaglomerular apparatus was evaluated by immunocytochemistry (PAP-technique) using a monoclonal renin antibody [13, 14] in nephrectomy specimens of six ADPKD patients with terminal renal failure prior to dialysis. All patients were hypertensive and none had ACE inhibitors. As controls we examined six renal specimens obtained during tumor nephrectomy.

Statistical analyses

Data are given as mean and SD (or median and range). Data were analyzed by Wilcoxon test for random samples, by the rank projection test after Behen and Neuhaus [15] and by the procedure for multiple endpoint analysis [16] as appropriate.

Results

Glomerular diameters

Mean glomerular diameters of patients with ADPKD in early renal failure ($S_{Cr} < 350$ μmol/liter) and of age matched victims of traffic accidents were not significantly different (Table 2). In contrast, glomerular diameters were significantly higher in diabetic patients with similar renal function. There was no significant difference of glomerular diameter in ADPKD patients in early versus terminal renal failure, although glomeruli tended ($P < 0.08$) to be larger in the latter group.

The variability of glomerular diameters within patients was larger in ADPKD patients with terminal (44 μm; 25 to 136) rather than early renal failure (33 μm; 22 to 53).

Glomerular pathology (segmental and global sclerosis)

The average number of glomeruli examined was 108 in 12 ADPKD patients with early and 104 in 50 patients with terminal renal failure (Fig. 3). Glomeruli with cyst-formation were not evaluated. The average proportion of normal glomeruli in ADPKD patients with early renal failure was 67% (37 to 97) and was significantly less ($P < 0.05$) in all 50 patients with terminal renal failure (47%; 14 to 83), and specifically in the 12 patients without dialysis (49%; 17 to 81). Twenty-nine percent of glomeruli (17 to 62) in patients with early renal failure had global glomerular sclerosis versus 49% (19 to 93) in all 50 patients with terminal renal failure ($P < 0.05$), and 47% (19 to 66) in the 12 patients without dialysis. The proportion of glomeruli with segmental sclerosis was 4% in both groups (NS).

Sclerosis of preglomerular vessels

Vascular sclerosis (Fig. 4) was a prominent feature even in early renal failure (mean score 2.25; range 1 to 3). Higher scores were found in terminal renal failure (mean score 2.62; range 1 to 3; $P < 0.03$) both without and with dialysis. Vascular sclerosis was isotropically distributed with no evidence of local clustering. The median juxtaglomerular index, expressed as the number of immunoreactive JGAs/total number of glomerular sections was 23.8 (13.8 to 41 to 6), whereas it was below 10 in all six control kidneys (tumor nephrectomy). In individual JGAs the number of renin positive cells were markedly increased. Renin positive cells were occasionally noted in the walls of stretched arterioles (Fig. 5) surrounding large cysts. Furthermore, immunoreactive renin was observed in the apical portion of epithelial cells of normal proximal tubules and of "proximal cysts" as well as in some collecting ducts.

In the 38 dialyzed patients who had come to postmortem the left ventricular weight/body weight ratio was above normal (that is, above 0.004) in all. Similar LV/body wt ratios were noted in the 15 patients with a score of two (0.00716; range 0.0052 to 0.0123) and in 23 patients with a score of three, respectively (0.0069; 0.0045 to 0.0127).

Interstitial fibrosis

Marked interstitial fibrosis, that is, dense collagen bands with scarce fibroblasts, was found even in patients with normal renal function or early renal failure (mean score 1.8; range 1 to 3; Fig. 6). It was even more prominent in all 50 patients with terminal renal failure (mean score 2.6; 1 to 3; $P < 0.0002$) and specifically in the 12 patients without dialysis (mean score 2.5; 2 to 3). Fibrosis was more pronounced in areas adjacent to renal cysts. No interstitial deposits of Tamm-Horsfall protein were found by immunohistology.

Tubular atrophy

Marked tubular atrophy of noncystic nephrons was noted in patients with early renal failure (mean score 1.8 range 1 to 3) and in all 50 patients with terminal renal failure (2.5; range 1 to 3; $P < 0.01$), and specifically in the 12 patients without dialysis (2.5; 2 to 3).

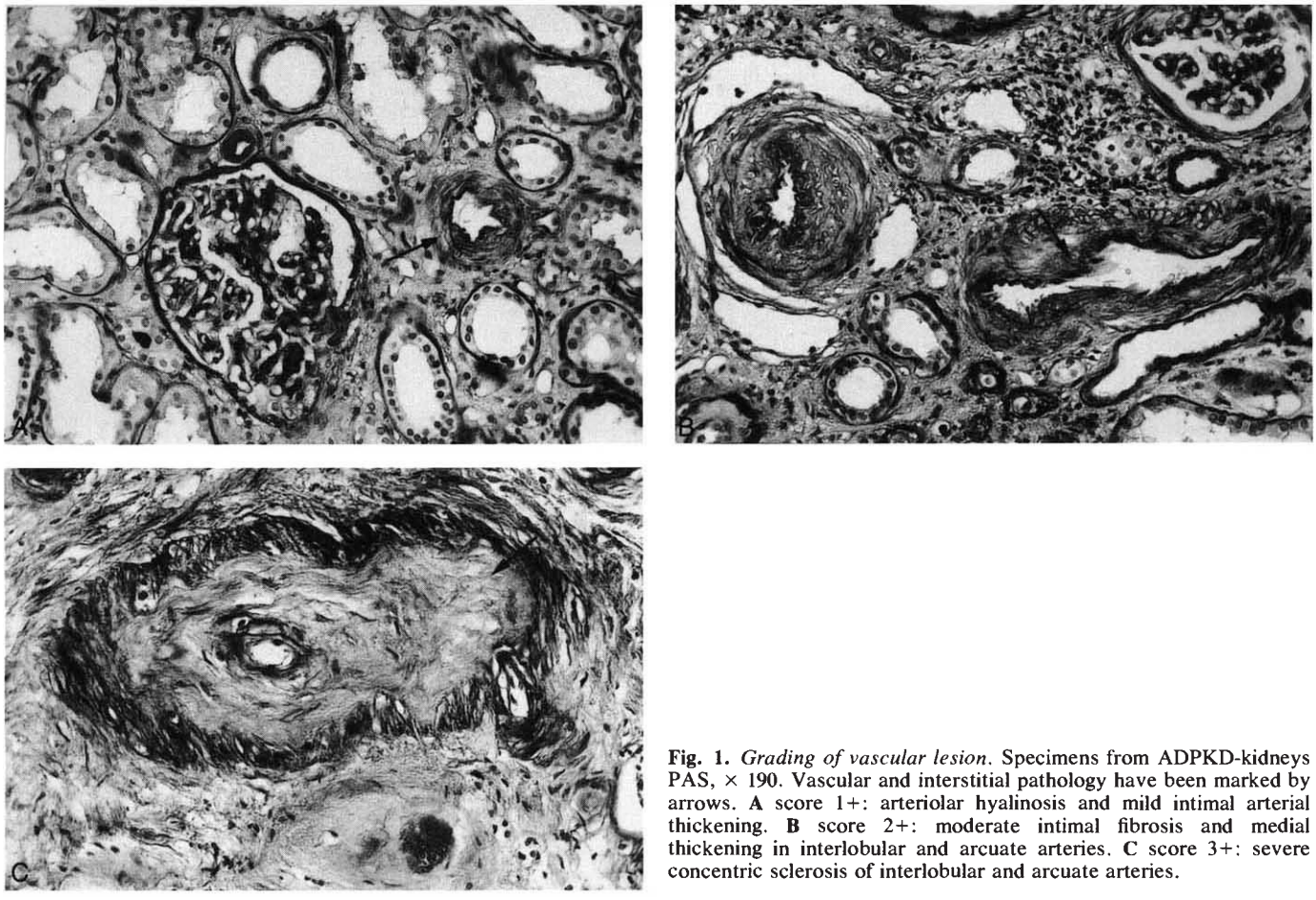

Fig. 1. *Grading of vascular lesion.* Specimens from ADPKD-kidneys PAS, × 190. Vascular and interstitial pathology have been marked by arrows. **A** score 1+: arteriolar hyalinosis and mild intimal arterial thickening. **B** score 2+: moderate intimal fibrosis and medial thickening in interlobular and arcuate arteries. **C** score 3+: severe concentric sclerosis of interlobular and arcuate arteries.

Interstitial infiltrates in ADPKD patients

Interstitial infiltrates were scarce in early (mean score 1.4; range 0 to 3) and terminal renal failure (1.4; range 1 to 3). Subtyping of white blood cells in the interstitial infiltrates of nonfixed specimens ($N = 7$) revealed a predominance of CD4 over CD8 positive lymphocytes, and CD68 positive macrophages.

Histological findings in liver and pancreas of ADPKD patients

Liver specimens were evaluated in six patients, three of whom had liver cysts. Only modest vascular sclerosis (mean score 1.3; range 1 to 2) and modest periportal fibrosis was found (mean score 1.2; range 1 to 2).

In seven pancreas specimens, the mean score for vascular sclerosis was 1.3 (range 1 to 2) and for interstitial fibrosis 1.2 (range 1 to 2). The patients were not diabetic as assessed from autopsy and clinical records.

Discussion

This is a retrospective histological study on renal specimens of patients with ADPKD obtained at nephrectomy or autopsy. The results document advanced sclerosis of preglomerular vessels, interstitial fibrosis and tubular atrophy even in patients with normal renal function or early renal failure. These lesions were even more pronounced in patients with terminal renal failure. Mean glomerular diameters were unchanged, although greater variability of glomerular size was noted than in control patients. Although the dialysis procedure in itself may cause alteration of renal morphology, dialysis is unlikely to explain more severe vascular and interstitial lesions in our patients with terminal renal failure, since the intensity of these changes was similar in patients with terminal renal failure who had not yet been dialyzed. A proportion of glomeruli exhibited global sclerosis, a putative marker of glomerular ischemia [17], but segmental glomerular sclerosis, a putative histological marker of glomerular hyperperfusion [18], was remarkable by its absence. In parallel, glomerular size tended to be normal at least in ADPKD with early renal failure. Segmental glomerular sclerosis, although it is certainly not specific for hyperperfusion [19, 20], is typical of hyperperfusion injury, as demonstrated by Bohle et al in diabetic glomerulosclerosis [19], and progressive renal failure of other etiologies [21].

Advanced vascular sclerosis and interstitial fibrosis were mainly restricted to the kidneys, although minor pathology was also noted in liver and pancreas which were examined as control tissues.

The above findings are of some interest with respect to the

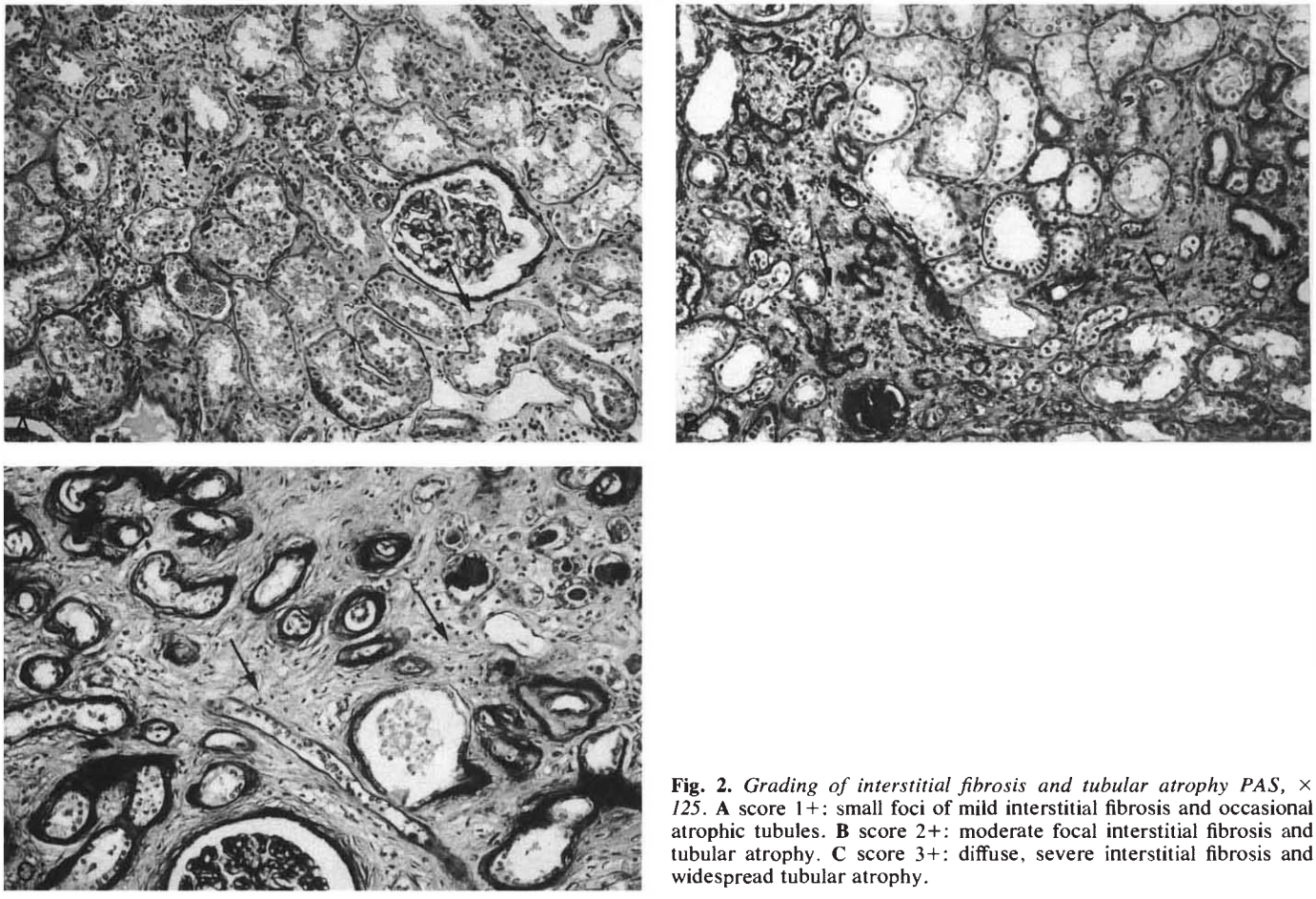

Fig. 2. *Grading of interstitial fibrosis and tubular atrophy PAS, × 125.* **A** score 1+: small foci of mild interstitial fibrosis and occasional atrophic tubules. **B** score 2+: moderate focal interstitial fibrosis and tubular atrophy. **C** score 3+: diffuse, severe interstitial fibrosis and widespread tubular atrophy.

Table 2. Comparison of glomerular diameters (μm)

	ADPKD (N = 12)	Diabetes (N = 13)	Controls (N = 15)
Normal renal function or early renal failure	176 ± 38[a] (118 to 243) (N = 45)	205 ± 16[b,c] (176 to 228)	177 ± 23 (144 to 221)
Terminal renal failure	191 ± 45[d] (140 to 261)	—	—

[a] Med. S_{Cr} 190 μmol/liter (range 83 to 350)
[b] Med. S_{Cr} 155 μmol/liter (range 64 to 250)
[c] Diabetes vs. ADPKD (early renal failure) $P < 0.03$
[d] ADPKD early vs. terminal renal failure NS

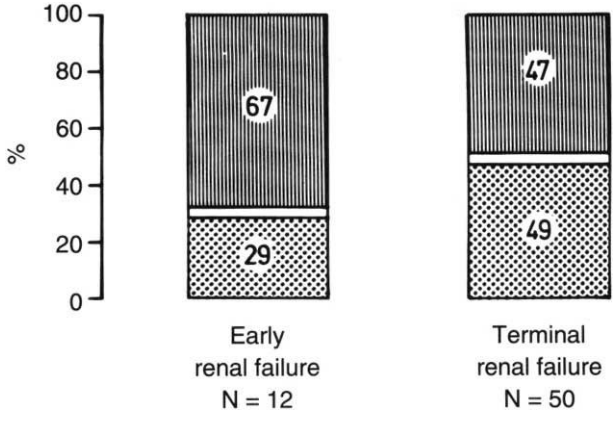

Fig. 3. *Glomerular pathology in patients with ADPKD in early and terminal renal failure.* Symbols are percent glomeruli with: segmental sclerosis (□); (▥) normal glomeruli; or global sclerosis (▩).

potential mechanisms causing progression of renal failure in ADPKD. Potential possibilities to consider are:

(1) Glomerular hyperperfusion of residual nephrons.
(2) Compression atrophy of renal parenchyma from expansion of cysts within the relatively non-compliant renal capsule [4].
(3) Hypertensive injury to the renal vasculature.
(4) Vascular sclerosis and interstitial fibrosis as late (blood pressure independent) consequences of the abnormal gene product.
(5) A combination of these.

Glomerular hyperperfusion has been recognized as an important mechanism of progression in several forms of renal disease [9, 10, 22, 23]. Based on measurement of endogeneous creatinine clearance it has been postulated that glomerular hyperfiltration is present at least in a subgroup of patients with ADPKD [8]. Therefore, it is of note that segmental glomerular sclerosis or glomerular enlargement were uncommon even in terminal

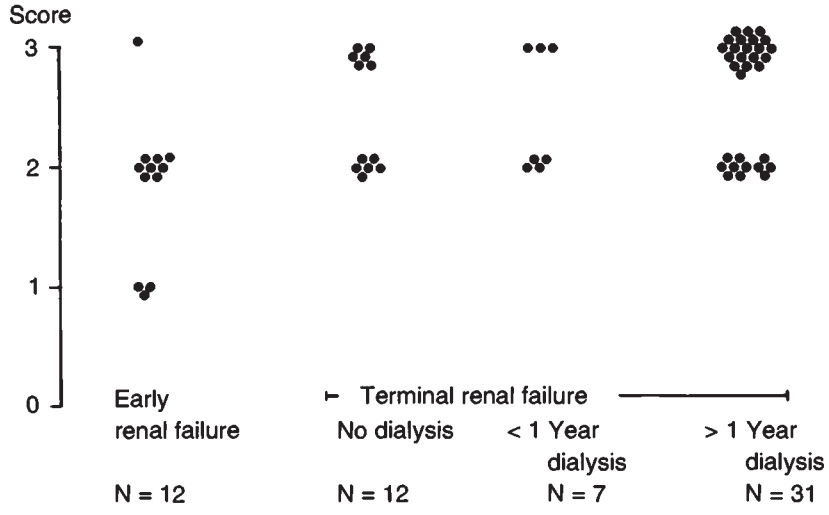

Fig. 4. *Vascular sclerosis in patients with ADPKD in early and terminal renal failure.*

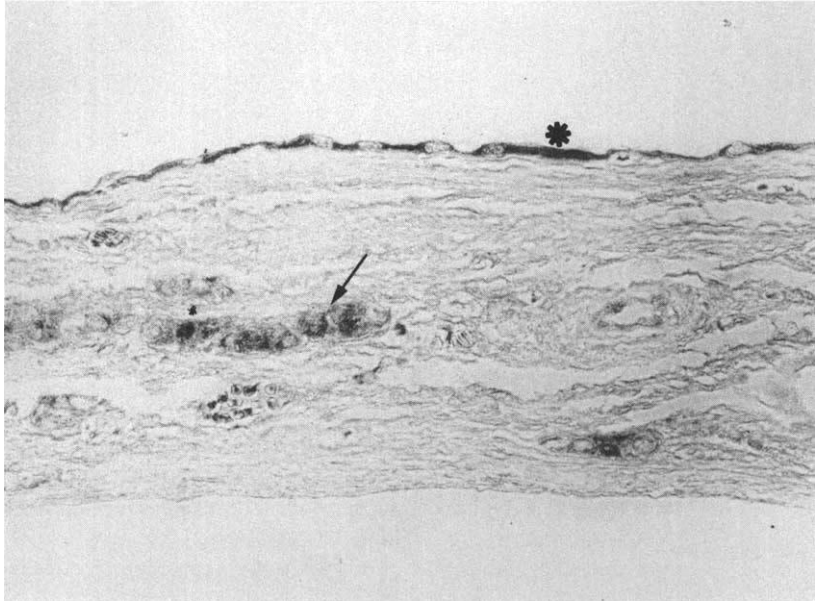

Fig. 5. *Stretched arteriolar vessel ( ) with renin-positive cells localized between two cysts.* Note the positive reaction of the cyst epithelium ( ). PAP-method, × 380.

renal failure. Errors of histological techniques are unlikely, since in a limited number of patients additional techniques, such as silver stain of glomeruli and PAS stain, did not substantially increase the proportion of glomeruli with segmental glomerular sclerosis. It is quite obvious that segmental glomerular sclerosis, if severe, may finally end up as global glomerular sclerosis, so that global glomerular sclerosis is not specific for ischemia. Our conclusion that at least the major cause of global glomerular sclerosis in ADPKD was ischemia is supported, however, by the virtual absence of segmental glomerular sclerosis. If the above sequence from segmental to glomerular sclerosis had taken place, one would have expected a higher prevalence of segmental sclerosis, the putative precursor lesion.

Our procedure was sensitive enough to detect glomerular hypertrophy known to exist in patients with diabetes [24]. Although the average glomerular diameter was unchanged in ADPKD the variability of glomerular diameters was greater than in normals. We cannot exclude that this due to incipient formation of glomerular microcysts. A clinical argument against a glomerular mechanism of progression is also the lack of major proteinuria in patients with ADPKD.

It is of note that even in patients with terminal renal failure, no less than 47% of glomeruli were normal by light microscopy. It is unlikely that this is due to sampling problems. A surprisingly high number of normal glomeruli was also found in dialysis patients suffering from other types of renal diseases [25].

The most striking finding of our study was severe sclerosis of the preglomerular vessels, both afferent arterioles and interlobular arteries. This lesion was present even in patients with normal renal function or early renal failure. It is of note that in two patients of this group vascular lesions were present despite normotensive blood pressure values (at least at the time of nephrectomy). Although no formal comparison was made, it is

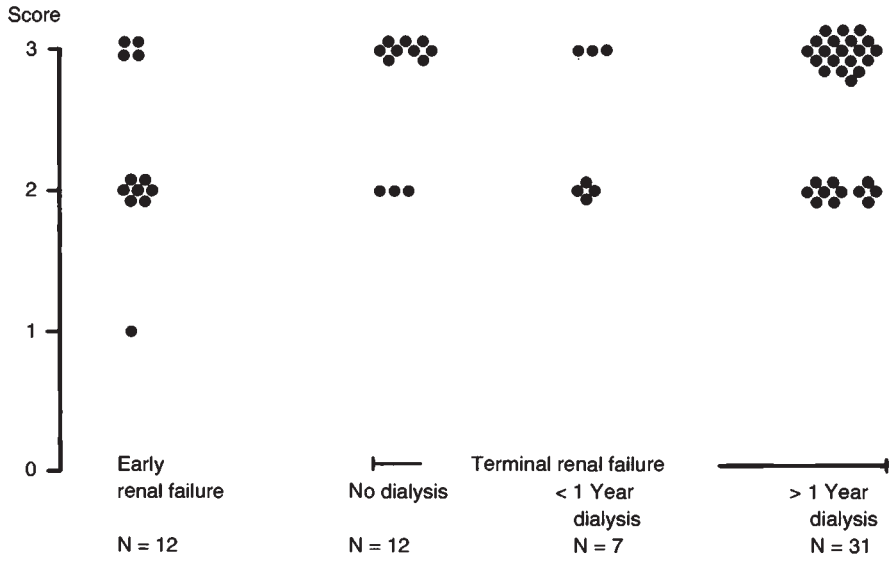

Fig. 6. *Interstitial fibrosis in patients with ADPKD in early and terminal renal failure.*

our impression that vascular sclerosis was more severe in ADPKD patients than in patients with comparable renal function who suffered from glomerular disease. Two factors (which are not mutually exclusive) may be involved. Long-standing and severe hypertension is common in patients with ADPKD, even at normal GFR. Gabow [26] found hypertension in 48% of ADPKD patients with normal S_{Cr}. Furthermore, when examining prepubertal children with ADPKD, we found higher blood pressure values as compared to their non-affected siblings or age-matched local controls [27]. Although blood pressure is definatly elevated, the reaction of renal vessels to elevated blood pressure may also be abnormal. If this is the case, however, the vascular reaction must be restricted to the kidney, since vascular lesions in the liver and the pancreas were considerably less severe. Severe vascular hypertrophy and vascular lesions were found in transgenic mice expressing the human renin gene despite no elevation in systemic blood pressure [28] consistent with a role of renin in the vascular changes. It is therefore of interest that plasma renin activity after acute administration of captopril is high in ADPKD patients [29]. In our patients the number of juxtaglomerular apparatuses expressing the renin-epitope as well as the number of renin positive cells per juxtaglomerular apparatus were increased. The finding may indicate that renin positive cells were recruited through metaplasia. These findings are consistent with the observations of Graham and Lindrop [30]. Of particular note is the observation of renin expression in arterioles remote from glomeruli, but adjacent to large cysts. This finding would be consistent with metaplasia of vascular smooth muscule cells by mechanical stretch, although other possibilities are not excluded. Our observations of immunoreactive renin in tubular epithelial cells is in agreement with the previous observations of Torres et al [31].

The second key finding in this study was the demonstration of marked interstitial fibrosis, even in patients with normal renal function. Interstitial fibrosis has previously been commented upon by others [12]. Its molecular basis may be, at least in part, stimulation of interstitial fibroblasts by PDGF aberrantly expressed by tubular epithelial cell as suggested by cell co-culture experiments [32]. Fibrosis was more severe with advancing renal failure. Interstitial infiltrates were scarce and consisted of lymphocytes and macrophages. The presence of macrophages is of interest in view of the suspected role of cytokines in the genesis of interstitial fibrosis [33–35]. Previous authors speculated whether extravasation of sterile tubular or cyst fluid can contribute to interstitial fibrosis. To the extent that extravasation is indicated by interstitial deposition of Tamm-Horsfall protein, our observations argue against this possibility. Cortical ischemia is suggested by the severity of vascular lesions and may play a role in genesis of interstitial fibrosis. The distribution of fibrosis did not follow vascular territories. Of note was the prominence of fibrosis around cysts [36]. It is perhaps of interest that at the twelfth week of gestation interstitial fibrosis was absent in the fetal ADPKD kidneys despite the presence of cysts [2], suggesting that fibrosis is a late consequence and is not related to the primary steps of cyst formation.

Franz and Reubi [4] advanced the proposal that progression of renal failure in ADPKD was related to compression of renal parenchyma by expanding cysts. Tubular atrophy, interstitial fibrosis and global glomerular sclerosis may occur next to renal masses, and all these lesions are found even in patients with ADPKD and normal renal function. Intense tubular atrophy was found, however, only in close vicinity to renal cysts. Furthermore, deroofing, that is, surgical decompression of cysts, which should relieve interstitial pressure, fails to improve GFR [37]. In view of these observations, pressure atrophy of renal parenchyma is not likely to make a major contribution to progression.

We are aware of the limitations of our purely descriptive approach, but the above findings do not provide strong support for glomerular mechanism of progression to renal failure in ADPKD. Progression was paralleled by more severe vascular and interstitial lesions in the kidneys, but not in extrarenal organs, and this may indicate that these lesions play a role in progression.

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Reprint requests to Martin Zeier M.D., Department of Medicine/ Nephrology, Bergheimerstrasse 56a, 6900 Heidelberg, Germany.

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