The Effect of Uninephrectomy on Progression of Renal Failure in Autosomal Dominant Polycystic Kidney Disease[1]

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ABSTRACT

The evolution of renal failure was compared in 47 patients (21 male, 26 female) with autosomal dominant polycystic kidney disease (ADPKD) in Germany, France, Spain, and Portugal who had undergone uninephrectomy (UNX) (median age at uninephrectomy, 41 yr; range, 22 to 54) and 47 non-UNX matched controls. UNX was usually performed because of uncontrolled urinary tract infection ($N = 30$), stones ($N = 8$), trauma ($N = 2$), or hemorrhage ($N = 7$). Median serum creatinine at UNX was 2.1 mg/dL (0.9 to 4.3). Twenty-eight of the 47 uninephrectomized patients progressed to end-stage renal failure. When the age at renal death was evaluated by survival analysis, only minor and nonsignificant acceleration was seen in the uninephrectomized patients (median, 50 yr; p25 = 43.6 yr; p75 = 58.3 yr, where p is the percentile) compared with non-UNX patients matched for age, sex, and serum creatinine at the time of UNX in the propositus (51.2 yr; p25 = 48.6 yr; p75 = 56.1 yr). In addition, the median interval for serum creatinine to rise from 4 to 8 mg/dL was similar in UNX (21.3 months) versus nonuninephrectomized ADPKD patients (21.9 months). Renal survival differed in the two genders. In females, no significant difference of age at renal death was found between UNX (median age, 51.6 yr) and non-UNX ADPKD patients (53.7 yr). In male UNX patients, age at renal death was slightly (but not significantly) less than in non-UNX patients (median age, 47.3 versus 52.7 yr). All male patients reaching end-stage renal failure before age 44 were severely hypertensive.

Key Words: *progression of renal failure, autosomal dominant polycystic kidney disease, uninephrectomy, hypertension*

In various animal models of renal failure, *e.g.*, streptozotocin diabetes (1–3) or immune injury of the kidney (4,5), uninephrectomy (UNX) has been shown to accelerate the progression of renal failure. In humans, the evidence is less impressive. In life donors of kidney transplants, long-term follow-up showed little (6–8), if any, albuminuria and no development of renal failure, although this may occur after more severe reduction of renal mass (9). In uninephrectomized individuals, a high incidence of *de novo* hypertension has been noted (10–13), particularly in patients with a family history of hypertension (14). The mechanisms of progression of renal failure in autosomal dominant polycystic kidney disease (ADPKD) have not been clarified. Histologic studies had demonstrated no evidence of focal glomerulosclerosis in ADPKD patients (15,16). We reasoned that analysis of the evolution of renal failure in ADPKD patients after UNX might be informative, because accelerated progression would be predicted by the hyperperfusion theory (17). In the past, UNX was often required in patients with ADPKD for cyst infection and septicemia, because the antibiotics then available did not penetrate into the cyst fluid (18).

This enabled us to collect a total of 47 ADPKD patients who had undergone UNX between 1965 and 1991. The subsequent course of renal failure in these patients was compared with a cohort of ADPKD patients in southern Germany who were matched for age, gender, and renal function at baseline.

PATIENTS AND METHODS

Data were collected retrospectively by a standardized questionnaire. European centers were contacted and asked to report all known patients with ADPKD

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[2] This study was done with the participation of Dr. Almeida, Lisboa, Portugal; Dr. Birnbaum, Berlin, Germany; Prof. Bösken, Trier, Germany; Dr. Gladziwa, Aachen, Germany; Prof. Stein, Jena, Germany; and Dr. Theodorakis, München, Germany.

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and UNX before end-stage renal failure from 1970 onward and for whom follow-up information was available. A total of 47 cases were collected. The following data were collected: serum creatinine, age at UNX, indication for UNX, presence of proteinuria, blood pressure, and blood pressure medication. All patients were monitored until March 1991 or ESRD.

As a control group, we selected patients who were comparable with respect to gender and age and who had the same creatinine concentrations (within 10%) at an age corresponding to the age of the propositus at the time of UNX. The controls were selected from a total of 429 patients out of 57 families in southwest Germany. These German patients had been examined because they were relatives of propositi who had reached end-stage renal failure and were treated in one of three regional dialysis programs. This examination was part of a systematic study of all members in the respective ADPKD families. Family members had blood pressure measurements, measurements of serum creatinine, and renal sonography. The diagnosis of ADPKD was verified by renal ultrasonography in all control patients. Cross-national comparisons showed that the proportion of dialysis patients reaching end-stage renal failure because of ADPKD (19) and the median age at which end-stage renal failure occurred (20,21) were comparable in Germany, France, Spain, and Portugal, *i.e.*, the countries from which the propositi of this study were recruited. Because of the homogeneity of the renal prognosis in the different European countries, we feel that the local controls were appropriate for the propositi recruited from all over Europe.

STATISTICAL METHODS

The increase in serum creatinine was used to evaluate the rate of progression of renal failure. All of the patients who reached a renal endpoint (serum creatinine >8 mg/dL or dialysis) were included if at least two serum creatinine values between 4.5 and 7.5 mg/dL were available. Because the starting point of the observation periods were not uniform with respect to renal function (*i.e.*, because observation started at different serum creatinine values), we normalized the data as described earlier (22). In brief, to allow a graphical plot of the change of serum creatinine versus time of observation, we arbitrarily chose the time at which serum creatinine had reached 6 mg/dL (Figure 1) as time zero. The curves of the individual patients, thus standardized with respect to time zero, were overlaid, and median and quartile curves were calculated for the groups of uninephrectomized and nonuninephrectomized ADPKD patients, respectively. The plot of serum creatinine versus normalized time was performed as described earlier (23).

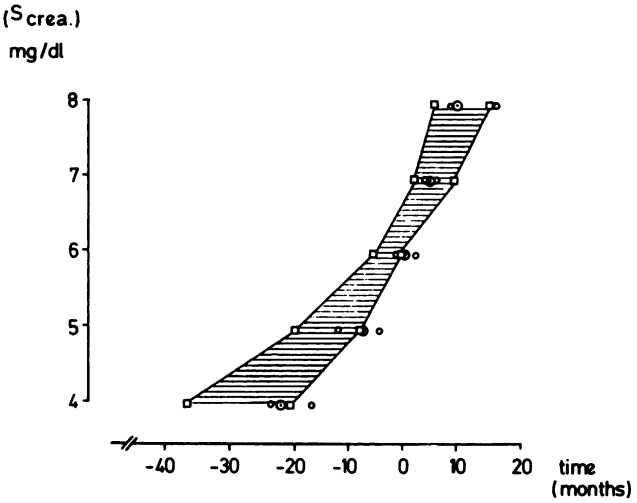

Figure 1. Cumulative time interval for the increase of serum creatinine (S_{crea}) from 4 to 8 mg/dL, for patients who reached end-stage renal failure. Circles, uninephrectomized patients (25th and 75th percentile); ovals with dots, uninephrectomized patients (median); boxes, nonuninephrectomized matched control patients (25th and 75th percentile). Note: The control patients had similar serum creatinine (within 10%) at an age that corresponded to the age of the matched propositus at UNX. By statistical chance, and because patients were not matched for age when serum creatinine had reached 6 mg/dL, the median observation time at serum creatinine of 6 mg/dL in controls was not exactly zero.

Kaplan-Meier (24) analysis was performed to compare age at renal death between the two groups, *i.e.*, UNX versus non-UNX patients (SAS statistical package; SAS Institute, Cary, NC) (23, 25). None of the patients had died before reaching renal death. Data are given as median, p25 (= 25th percentile), and p75 (= 75th percentile.)

RESULTS

Patient Characteristics

The patients' characteristics at the time of UNX are listed in Table 1. UNX was performed because of uncontrolled infection (N = 30), stones (N = 8), trauma (N = 2), or uncontrolled renal bleeding (N = 7). It is remarkable that none of the patients had renal cell carcinoma. None of the patients had diabetes mellitus. In eight patients, narrowly spaced, complete, perioperative serum creatinine values were available and rose from 2.5 (0.8 to 4.0) to 2.8 mg/dL (1.2 to 4.5) postoperatively. Patients could be monitored until March 1991, with a median follow-up of 115 months (34 to 252). Median follow-up for patients who reached a renal endpoint was 101 months (34 to 252) and for those who did not, it was 94

TABLE 1. Patients' characteristics

	UNX	Matched Controls
No. of Patients	47	47
Age at UNX (yr)	41.6 (22.2–62.6)	42.3 (21.5–65.3)
Male/Female	21/26	22/25
Serum Creatinine (mg/dL) at time of UNX[a]	2.1 (0.9–4.3)	2.3 (0.8–4.9)
Follow-Up Period (months)	115 (34–252)	98.2 (19.2–185)
End-stage Renal Failure at Last Observation[b]	m/f, 14/14	m/f, 14/14
Serum Creatinine at Last Observation in Renal Survivors (mg/dl)	2.56 (0.9–7.8)	2.86 (1.0–5.7)

[a] Or at corresponding age of the matched controls.

[b] Serum creatinine >8 mg/dL or renal replacement therapy.

months (19 to 192). Age at last follow-up for patients who reached a renal endpoint was 52.4 yr (30.8 to 73.3) and for those who did not, it was 51.1 yr (47.2 to 57.5). Twenty-eight patients (15 male, 13 female) had progressed to end-stage renal failure, *i.e.*, serum creatinine above 8 mg/dL or renal replacement therapy.

Blood pressure medication comprised mainly propranolol, nifedipine, clonidine, prazosin, and furosemide. None of the patients were treated with angiotensin-converting enzyme inhibitors.

Rate of Progression of Renal Failure and Survival Analysis

Figure 1 gives the rise of serum creatinine for both groups as a function of time of observation (normalized so that the time at which serum creatinine was 6 mg/dL is time zero). It is immediately obvious that the rate of progression in UNX patients was similar to that in the 47 matched, nonuninephrectomized patients. The median time required for serum creatinine to rise from 4 to 8 mg/dL was 21.3 months in the uninephrectomized and 21.9 months in the nonuninephrectomized ADPKD patients (difference not significant).

Survival analysis calculated for all patients (Figure 2a through c) showed no significant difference (by Kaplan-Meier analysis) between the uninephrectomized ADPKD patients and the matched controls.

With the given group size of 47 patients, the procedure had a power of 80% at a two-sided significance level of $P < 0.05$ to detect a difference of 20% (*i.e.*, 75% of patients not being in end-stage renal failure after 3 yr in one group versus 95% in the other group) (26).

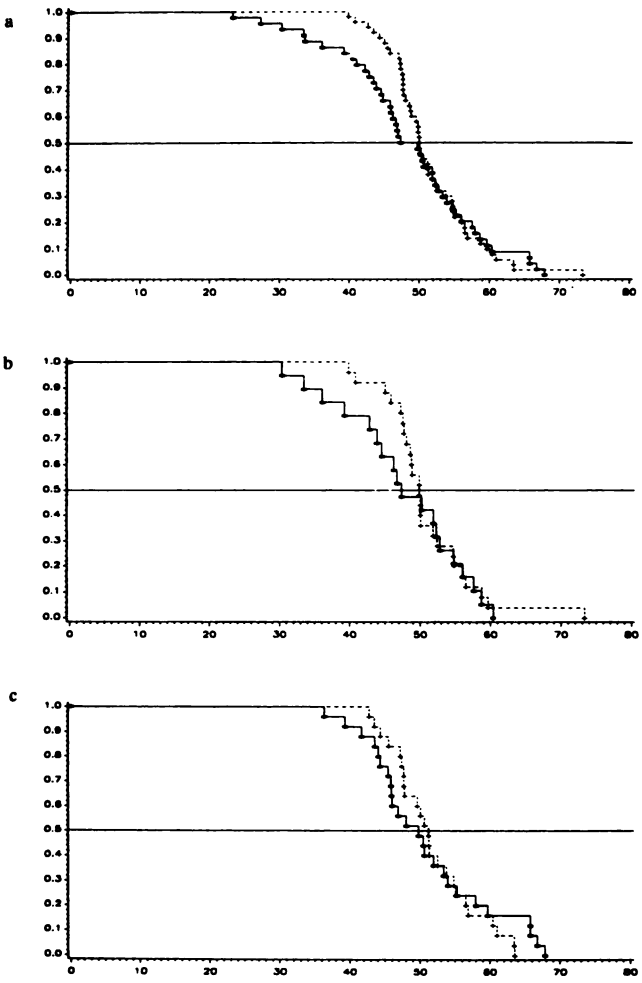

Figure 2. Kaplan-Meier analysis of uninephrectomized versus nonuninephrectomized patients (all patients; N = 47). * Uninephrectomized patients; † nonuninephrectomized patients. Panel a, all patients; panel b, male patients; panel c, female patients.

As described earlier (22,27) survival differed between the two genders. There was a suggestive deflection of the survival curve in uninephrectomized males indicating that some UNX males reached end-stage renal failure at relatively early age (Figure 2b and c). Analysis of the individual cases showed that all of these patients had further surgical loss of renal mass, infection of the remnant kidney, or uncontrolled hypertension (Table 2).

Thus, median age at the time of end-stage renal failure was somewhat less in uninephrectomized male patients (median age at end-stage renal failure, 47.3 yr [p25 = 39.3 yr; p75 = 55.7 yr]) as compared with non-UNX males (52.7 yr; p25 = 49.3 yr; p75 = 56.5 yr), but the difference was statistically not sig-

TABLE 2. Clinical details of UNX patients with fast progression to renal failure[a]

Age at Renal Failure (yr)	Blood Pressure (mm Hg)	Remarks/Cause of Death
46	190/100 at SCr of 2 mg/dL	Additional resection of remaining kidney
46	180/100 at SCr of 3 mg/dL	
43	180/110 at SCr of 2.5 mg/dL	
40	170/115 at SCr of 3 mg/dL	Cyst bleeding in remaining kidney
36	170/110 at SCr of 2 mg/dL	
33	160/110 at SCr of 2.5 mg/dL	Hematuria; *Escherichia coli* infection in the remaining kidney
30	180/100 at SCr of 2 mg/dL	

[a] End-stage renal failure before age 47 yr. All patients described in this table were male. SCr, serum creatinine.

nificant. Female uninephrectomized patients reached end-stage renal failure at 51.6 yr (p25 = 46 yr; p75 = 59.6 yr) versus non-UNX female ADPKD patients (median age, 53.7 yr; p25 = 48.7 yr; p75 = 59.2 yr) (difference not significant).

DISCUSSION

This retrospective study examined the evolution of renal failure in ADPKD patients subsequent to UNX. It does not provide evidence for significantly accelerated progression of renal failure when uninephrectomized patients were compared with matched nonuninephrectomized ADPKD patients (in the few patients in whom complete data are available, no evidence of aggravation of proteinuria was noted). Two different indicators of progression were used (*1*) the rate of increase of serum creatinine from 4 to 8 mg/dL and (*2*) analysis of probability of renal survival. With both measures of outcome, similar conclusions were reached. An important consideration from a statistical viewpoint is the ability of the study to recognize an existing difference. This study had an 80% power to recognize a difference of renal survival of 36 months at a *P* value of 0.05. We emphasize, however, that not all patients progressed to end-stage renal failure after UNX. Indeed, only 28 of the 47 patients progressed to end-stage renal failure within a median follow-up period of 115 months. Also instructive is a case of a 55-yr-old female ADPKD patient of our outpatient clinic, not included in this series, who has unilateral renal agenesis but still has normal serum creatinine; we also monitor an ADPKD patient who had been uninephrectomized at the age of 8 yr whose renal function is still normal at the age of 28 yr.

UNX was performed in early renal failure—predictively, it caused a modest rise in serum creatinine. Because controls, however, were matched for postoperative serum creatinine values, this should not have interfered with the analysis of the subsequent renal course.

The marked heterogeneity of renal outcome in a disease with (presumably) uniform genetic basis has been widely interpreted to suggest an important influence of environmental factors (although other explanations are not excluded). In this context, we emphasize that our patients were collected in different European countries with widely varying protein and salt intakes, different medical systems with different modalities of outpatient follow-up, different antihypertensive strategies, *etc.* These and other important variables that may be of potential influence for progression were not adequately controlled. It is thus even more remarkable that renal survival was almost superimposable in the 47 patients collected in five different European countries on the one hand and a homogeneous group of matched local controls in southwest Germany on the other hand. The highly predictable course of renal function in ADPKD is further emphasized by comparison of Figure 1 of our previous article concerning 58 patients with ADPKD (22 with this series, *i.e.*, Figure 2a through c).

Ablation of renal mass is a maneuver that causes marked acceleration of progression in various models of renal diseases. This is usually thought to result from "glomerular strain" in residual nephrons. This study fails to provide evidence of similar acceleration of progression of renal failure in ADPKD after UNX. The results suggest that pathomechanisms other than "glomerular strain" must be involved in the progressive loss of renal function in this inherited renal disease that leads to renal failure during adult life, although abnormal renal architecture is evident even in early fetal life (28). The above observation is more consistent with the role of nonglomerular

mechanisms in the progression of ADPKD to end-stage renal failure, *e.g.*, progressive vascular and interstitial fibrosis, as suggested by histologic comparison of ADPKD kidneys without impairment of renal function and with terminal renal failure (16).

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REFERENCES

1. **Steffes MW, Buchwald H, Wigness BD, *et al.*:** Diabetic nephropathy in the uninephrectomized dog: Microscopic lesions after one year. Kidney Int 1982;21:721–724.
2. **Steffes MW, Brown DM, Mauer SM:** Diabetic glomerulopathy following unilateral nephrectomy in rats. Diabetes 1978;27:35–41.
3. **Steffes MW, Brown DM, Matas AJ, Mauer SM:** Effects of pancreatic islet transplantation upon the increased urinary albumin excretion rates in intact and uninephrectomized rats with diabets mellitus. Diabetes 1978;27:959–964.
4. **Neugarten J, Feiner HD, Schacht RG, Gallo GR, Baldwin DS:** Aggravation of experimental glomerulonephritis by superimposed clip hypertension. Kidney Int 1982;22:257–263.
5. **Baldwin DS, Neugarten J:** Role of hypertension in the evolution of renal diseases. Contrib Nephrol 1987;54:63–76.
6. **Robitaille P, Lortie L, Mongeau J-G, Sinnassamy P:** Long term follow-up of patients who underwent unilateral nephrectomy in childhood. Lancet 1985;1:1297.
7. **Miller I, Riggio RR, Suthanthiran M, *et al.*:** The impact of renal donation: Long term (clinical and biochemical) follow up of living donors in a single center. Kidney Int 1984;25:346.
8. **Weiland D, Sutherland DER, Chavers B, Simmons RL, Ascher NL, Najarian JS:** Information of 628 living-related kidney donors at a single institution, with long-term follow-up in 472 cases. Transplant Proc 1984;16:5–7.
9. **Novick AC, Guz B, Steinmuller DR, Streem SB:** Long-term renal function after partial nephrectomy in a solitary kidney. N Engl J Med 1991; 325:1058–1062.
10. **Hakim RM, Goldzer RC, Brenner BM:** Hypertension and proteinuria: Long-term sequelae of uninephrectomy in humans. Kidney Int 1984;25: 930–936.
11. **Talseth T, Fauchald P, Skrede S, *et al.*:** Long-term blood pressure and renal function in kidney donors. Kidney Int 1990;29:1072–1076.
12. **Miller IJ, Suthanthiran M, Riggio RR, *et al.*:** Impact of renal donation: Long-term clinical and biochemical follow-up of living donors in a single center. Am J Med 1985;79:201–206.
13. **Oberle G, Neumann HPH, Schollmeyer P, Boesken WH, Stahl RAK:** Mild proteinuria in patients with unilateral kidney. Klin Wochenschr 1985;63:1048–1051.
14. **Minetti L, Grillo C, Guidi E, Civati G, Rovati C:** Renal hemodynamics after uninephrectomy. Contrib Nephrol 1987;54:86–94.
15. **Zeier M, Geberth ST, Ritz E, Jäger T, Waldherr R:** Adult dominant polycystic kidney disease-clinical problems. Nephron 1988;49:177–183.
16. **Zeier M, Fehrenbach P, Geberth ST, Waldherr R, Ritz E:** Mechanisms of progression in autosomal dominant polycystic kidney disease—a histological study [Abstract]. J Am Soc Nephrol 1990;1:297.
17. **Brenner BM, Meyer, TW, Hostetter TH:** Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation and intrinsic renal disease. N Engl J Med 1982;307:652–659.
18. **Muther RS, Bennett WM:** Cyst fluid antibiotic concentrations in polycystic kidney disease: Differences between proximal and distal cysts. Kidney Int 1981;20:519–522.
19. Proc Eur Dial Transplant Assoc 1978;15: 36–86.
20. **Gonzalo A, Rivera M, Quereda C, Ortuno J:** Clinical features and prognosis of adult polycystic kidney disease. Am J Nephrol 1990;10: 470–474.
21. **le Goff JY, Simon P, Thebaud HE, Ladaique JM, Drouet D, Petiot JF:** Development rate of ESRD is comparable whatever the age of discovery of autosomal dominant polycystic kidney disease [Abstract]. J Am Soc Nephrol 1990;1:301.
22. **Gretz N, Zeier M, Geberth ST, Strauch M, Ritz E:** Is gender determinant for evolution of renal failure? A study in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1989;14: 178–183.
23. **Gretz N, Strauch M:** Survival analyses in the SAS-System: A survey. Proc SAS Eur User Group Int 1986;4:3–10.
24. **SAS Institute.** Introduction to survival analysis procedure. In: SAS/STAT User's guide: Release 6.03. Cary, NC: SAS Institute; 1988:87–89.
25. **SAS Institute.** SAS User's guide: Statistics, Release 6.03. Cary, NC: SAS Institute; 1990.
26. **Machin D, Campbell MJ.** Statistical tables for the design of clinical trials. Oxford: Blackwell Scientific Publications; 1987:115–120.
27. **Gabow PA, Johnson AM, Kaehny WD, *et al.*:** Factors affecting the progression of renal disease on autosomal dominant polycystic kidney disease. Kidney Int 1992;41:1311–1319.
28. **Waldherr R, Zerres K, Gall A, Enders H:** Polycystic kidney disease in the fetus. Lancet 1989; 2:274–275.