Renal Function 16 to 26 Years After the First Urinary Tract Infection in Childhood

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Objective: To evaluate renal function in a population-based cohort with urographic renal scarring after childhood urinary tract infection (UTI).

Design: Follow-up investigation 16 to 26 years after the first recognized UTI.

Setting: Outpatient university clinic for children with UTI serving the local area.

Patients: From the original cohort of 1221 consecutive children with first UTI diagnosed during 1970 to 1979, 57 (41 females and 16 males; mean age, 24.5 years) of 68 with nonobstructive renal scarring participated as well as 51 (38 females and 13 males; mean age, 24.9 years) matched subjects without scarring.

Main Outcome Measure: Glomerular filtration rate (GFR) measured by chromium 51–EDTA clearance, expressed as milliliters per minute per 1.73 square meters.

Results: Median GFR was 99 in both those with and without renal scarring. In patients with unilateral scarring, the total GFR remained unchanged over the years whereas the individual GFR of the scarred kidneys declined significantly from 46 to 39. In 7 patients with bilateral scarring, the GFR declined from 94 to 84 (P = .14); compared with those with unilateral scarring, the GFR was significantly lower at follow-up (P = .007). Median urinary albumin-creatinine ratio was 1.2 and 0.6 mg/mmol in those with scarring and those without, respectively (P = .30).

Conclusions: The GFR 2 decades after the first recognized UTI in childhood was well preserved. However, a significant reduction of individual renal GFR in the unilaterally scarred kidneys indicates that further follow-up is required. Although there were few patients with bilateral scarring, a more serious prognosis can be expected among them.


Editor’s Note: The results of this study are encouraging. However, because there is evidence that individual affected organ dysfunction exists, later follow-up might have different results. Keep the study flowing.

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RESULTS

STUDY GROUP WITH UROGRAPHIC SCARRING IN CHILDHOOD

Of the 68 patients with renal scarring, 57 (84%) (41 females and 16 males) participated in the follow-up investigation (50 with unilateral lesions and 7 with bilateral lesions). The median time after the first recognized UTI was 22 (range, 16-26)
PATIENTS AND METHODS

PATIENTS

During 1970 to 1979, 1221 children (989 girls and 232 boys) were registered at the single children’s hospital in Göteborg, Sweden, with their first known symptomatic UTI. They were aged 0 to 15 years, residents of the city, and attended a special UTI clinic with regular checkups according to a standardized protocol. All children younger than 2 years and all with febrile infections were recommended to undergo imaging of the urinary tract (during the 1970s, urography and voiding cystourethrography) after the first infection. Children with nonfebrile infections were investigated if other signs suggested renal involvement or if recurrent infections appeared. Initially during the 10-year period all children were followed up for 3 years. However, from 1975 on, those with a single UTI without fever or other signs of renal involvement were followed up for only 3 months.

In 652 children the index infection was febrile and 545 (84%) of them were investigated by urography. This investigation was also performed in 37% (208/569) of those with a nonfebrile index UTI. Of 753 children investigated by urography, 21 had obstructive malformation and they were excluded from further analyses.

Nonobstructive renal scarring was ultimately found in 74 children—21 boys with a median age of 0.25 years and 53 girls with a median age of 2.8 years at first recognized UTI. Ten of these 74 patients had bilateral scarring. Three children underwent nephrectomy and 3 underwent heminephrectomy, including 1 with bilateral scarring, and were therefore excluded from the study. The intention was to observe all children with renal scarring until 16 years of age. However, follow-up was discontinued in 17 of the 68 remaining patients (15 families moved from the area and 2 were lost). To evaluate renal function, patients with renal scarring were compared with individuals from the original cohort of children who had normal kidneys at urography. The comparison group was selected individual for individual by minimizing the maximal values between the scarring and the comparison group over the variables sex, age, calendar year, and characteristics of first UTI (febrile/nonfebrile).

The follow-up investigation was performed from 1995 to 1997 at the children’s hospital. The total group of 68 patients (18 males and 50 females) with renal scarring who were not operated on, and the matched group without scarring were searched for through the Swedish Central Registry of Inhabitants. They were contacted by letter and thereafter informed consent was obtained by telephone. The study was approved by the Ethics Committee of the Medical Faculty of Göteborg University.

DEFINITIONS

A diagnosis of UTI required significant bacteruria, ie, more than 10^5 colony-forming units per milliliter of a single species in 1 midstream or 2 bag urine samples, or any growth of bacteria in urine obtained by suprapubic bladder aspiration. A child with a temperature of 38.5°C or higher was considered to have febrile infection.

Renal scarring on urography was defined as a reduction of parenchymal thickness with corresponding caliceal deformation. Primary scarring was defined as damage identified on the first urogram. This group also included kidneys with isolated caliceal deformity or isolated parenchymal thinning that later developed into classic renal scarring according to Hodson. Acquired scarring was defined as damage developing in a previously normal kidney. Isolated parenchymal thinning was defined as reduction of the parenchyma to more than 2.5 SDs below the normal mean.

A technetium Tc 99m succimer (DMSA) scan was considered abnormal when focal or generalized uptake defects were noticed or if the relative uptake of DMSA in 1 of the kidneys was less than 45% of the total glomerular filtration rate (GFR). The relative uptake was calculated in the posterior view after background subtraction.

Vesicoureteral reflux was classified into 5 grades according to an international grading system. When referring to VUR observed during childhood, the maximum grade of the damaged kidney was used.

FOLLOW-UP INVESTIGATIONS

Renal Function

The GFR was determined using a multisample plasma clearance method with chromium 51–labeled EDTA (\(^{51}\)Cr–EDTA), expressed as milliliters per minute per 1.73 square meters. Split renal function and identification of renal damage was determined by DMSA scan with posterior, anterior, and posterior oblique views. Individual kidney GFR was estimated by multiplying the total GFR by the percentage side function using the posterior view. In patients with bilateral scarring, the kidneys with the lowest function were chosen to analyze the correlation between individual clearance of the scarred kidneys and grade of VUR.

The results of the follow-up investigation were compared with those of the last \(^{51}\)Cr–EDTA investigations performed during childhood, registered in 50 children at a median age of 15 (mean, 14; range, 5–17) years. Split renal function at that time was determined by probe renography with iodohippurate sodium 131 (\(^{131}\)I–hippuran).

Albumin Excretion

In samples of first morning urine, albumin was measured by an immunoenzymatic assay and creatinine was determined according to the method of Jaffe. Urine albumin excretion was expressed as the quotient of albumin (milligrams per liter) and creatinine (millimoles per liter). An albumin-creatinine ratio greater than 2.0 mg/mmol was considered abnormal.

Identification of Renal Damage

DMSA scanning was performed in all patients as well as in all subjects in the matched group. Urography was repeated at the follow-up only in those not found to have DMSA scan lesions corresponding to the scarring on the previous urogram. In the matched group, a new urogram was obtained if DMSA scan results were abnormal. Evaluation of the renal status was done without knowledge of clinical data.
years. Median age at investigation was 24.6 (mean, 24.5; range, 16.5-33.8) years. Of the 11 patients not participating, 5 had moved abroad and could not be traced (4 with unilateral scarring and 1 with bilateral scarring) and 6 declined participation (5 with unilateral scarring and 1 with bilateral scarring). Determination of GFR was unsuccessful in 1 individual because of technical problems.

Of the 57 patients, 53 had uptake lesions on DMSA scans, all corresponding to previous urographic findings. Four patients had normal DMSA scan results but unchanged findings on repeated urography: symmetrical bilateral scarring of mild degree in 1 patient, a scarred duplex kidney in 1 patient, and minimal unilateral scarring in 2 patients. No patients had evidence of new scarring in a previously unscarred kidney.

In 43 (77%) of 56 cases investigated by voiding cystourethrography, VUR to the scarred kidney was found during childhood; in 13 (23%) no VUR was found. Vesicoureteral reflux was maximally grade I in 5 (9%), grade II in 14 (25%), grade III in 13 (23%), grade IV in 9 (16%), and grade V in 2 (4%).

MATCHED GROUP WITHOUT UROGRAPHIC SCARRING IN CHILDHOOD

A total of 66 matched subjects participated in the follow-up investigation; 15 were found to have uptake defects on DMSA scanning and are therefore presented as a separate group (adults with defects on DMSA scan).

The distributions of the matching variables for the 51 subjects with normal DMSA scan results and the 57 patients with renal scarring were nearly the same: 75% vs 72% females, 92% vs 91% with febrile first UTI, and 53% vs 54% presenting during the first half of the period 1970 to 1979. Mean age at first UTI was 2.8 years in both groups.

Adults With Defects on DMSA Scan

In 8 of 15 subjects, minor uptake lesions or split renal function discrepancy (42%-44% side function) was found on DMSA scan but the repeated urogram was normal. The remaining 7 patients showed abnormalities on DMSA scans and urography. Four males had parenchymal thinning without caliceal deformation; the relative uptake of DMSA was 43% in 2 kidneys and 44% and 46% in 1 each. Three female patients had classic urographic scarring; 2 had unilateral damage with side function of 39% and 45%, respectively, and 1 had bilateral damage. Follow-up at the children’s hospital had been discontinued in these 3 females, and the last urographic examination had been performed at the age of 4 years in 2 of them and at 11 years in 1.

During childhood VUR was shown in 7 (47%) of 15 subjects: 8 (53%) had no VUR, 2 (13%) had grade I, 3 (20%) had grade II, and 2 (13%) had grade III. One of the 3 female patients with urographic scarring had VUR (grade II).

Adults With Normal DMSA Scan

Fifty-one of the 66 matched subjects had normal kidneys on DMSA scan. In this group, VUR had been shown in 22 subjects (43%) during childhood: 29 (57%) had no VUR, 2 (4%) had grade I, 17 (33%) had grade II, and 3 (6%) had grade III.

RENAL FUNCTION

GFR Results

The Figure shows the GFR of all patients and subjects in the follow-up investigation. There were no significant sex differences within the subgroups.

The median GFR in the 56 patients with renal scarring was 99 (mean, 99; range, 69-134) compared with 99 (mean, 101; range, 79-128) in the 51 subjects with normal DMSA scan findings at follow-up.

Unilateral Scarring

The median GFR at follow-up was 101 (mean, 101; range, 69-134). Comparison with a previous investigation performed at a median age of 15 years in 43 patients showed
no significant change (median of 103 compared with 101 at follow-up; Table 1).

Bilateral Scarring

There was a decline of GFR from the last investigation in childhood until follow-up (median GFRs, 94 and 84, respectively), but the difference was not significant (Table 1). Compared with those with unilateral scarring, the median GFR was significantly ($P = .007$) lower at the follow-up investigation; at the childhood investigation significance was not reached ($P = .06$).

GFR < 80

Eight individuals had a GFR of less than 80—6 patients in the scarring group and 2 subjects in the matched group. In the first group, 2 male patients had bilateral (GFRs, 74 and 79) and 4 female patients had unilateral scarring (GFRs 69, 73, 73, and 79). These 6 children presented with a febrile UTI before age 6½ years and VUR was demonstrated in 4 of them (maximally grade I in 1, grade III in 2, and grade V in 1). Recurrent febrile UTI was documented in 4 of 6 during childhood—a single recurrence in 2 patients, and 2 and 4 recurrences in 1 each. No one in this group had febrile recurrences recognized during adulthood.

In the matched group, a female patient with bilateral scarring had a GFR of 69. She presented with a febrile UTI at 2½ years of age and had a febrile recurrence at 4 years of age but after that she was lost from follow-up. No scarring or VUR was demonstrated at radiological investigation 1 month after the second infection. A second febrile recurrence was registered at another hospital when she was 6 years old. During the present study, urography that had been performed at the age of 10 years showed bilateral renal damage. Another female patient with normal DMSA scan results at follow-up had a GFR of 79. She presented at age 1 year with a febrile UTI but had no recurrence or VUR.

Individual Kidney Function

The distribution of individual GFR in damaged kidneys at the follow-up investigation is shown in Table 2; in 31 patients individual GFR was less than 40 in 1 of the kidneys. In Table 3 current individual kidney GFR in the group with unilateral scarring is compared with function during childhood. In the scarred kidneys the reduction from a median GFR of 46 in childhood to 39 at follow-up was significant. In the contralateral unscarred kidneys, the clearance remained stable (GFRs 60 and 61, respectively). The difference between scarred and unscarred kidneys was significant ($P < .001$) both at last childhood and at follow-up investigation. The individual GFR in the unscarred kidneys (median, 61; mean, 62) of those with unilateral scarring was significantly higher than in the kidneys with the highest function of the matched group with normal DMSA scan results (median, 53; mean, 53) ($P < .001$).

In the scarring group, a negative correlation was found between individual GFR of scarred kidneys and VUR grade to the corresponding kidney ($P = .047$, $r = −0.27$). The mean GFR of 14 kidneys with nonrefluxing ureters, of 17 kidneys with grade I to II refluxing ureters, and of 24 kidneys with grade III to V refluxing ureters was 41, 39, and 35, respectively.

Primary vs Acquired Scarring

In Table 3 the scarred kidneys of patients with unilateral damage have also been subdivided into primary and acquired scarring. The reduction in individual kidney GFR was significant in both subgroups ($P = 0.002$ and $P = 0.04$, respectively). However, the difference in individual kidney GFR between the subgroups was not significant, neither at childhood nor at follow-up investigation.
In the patients with bilateral scarring, all males (n = 4) had primary and all females (n = 3) had acquired scarring.

**Albumin Excretion**

Samples of first morning urine were obtained from 55 patients in the scarring group and 51 matched individuals with normal DMSA scans. One patient in each group had bacteriuria and these patients were therefore excluded. Median albumin-creatinine ratio was 1.2 (mean, 0.6; range, 0.2-32) mg/mmol and 0.6 (mean, 0.5; range, 0.2-2.3) mg/mmol, respectively (P = .30). Pronounced albuminuria (32 mg/mmol) was found in 1 male patient with bilateral scarring and a GFR of 84. Minimal albuminuria (2.4 and 2.3 mg/mmol, respectively) was found in a male patient with unilateral scarring and a female patient without scarring, both with normal GFRs.

Most children with febrile UTI in Göteborg are diagnosed at the children’s hospital. A study of the files of all pediatric outpatient units in the area for the years 1979 to 1981 showed that only 14% of the cases with first recognized febrile UTI were identified outside the hospital. In the present study, 84% of the 68 patients with urographic scarring participated in the follow-up investigation 22 years after the first known UTI in childhood.

The most widely used method for detection of renal scarring today is the DMSA scan. Therefore, this technique was used at the follow-up investigation in contrast to the 1970s when urography was the method of choice. The DMSA scans were evaluated as normal in 4 of 57 patients with childhood urographic scarring. In 2 of them a repeated urogram showed symmetrical bilateral scarring and a scarred duplex kidney, respectively, which are known causes of misinterpretation of the DMSA scan. Split renal function was assessed by 131I-hippuran renography during the 1970s as compared with DMSA scan at the follow-up investigation. It has been shown, however, that the correlation between relative uptake, determined by these two methods, is good.

Some patients with renal scarring probably escaped detection in childhood. This is illustrated by the findings in the matched group of subjects with normal urograms in childhood. Of 66 participating in the follow-up investigation, 15 had uptake defects or individual renal function less than 45% of the total GFR on the DMSA scan. However, 12 had minor lesions and only 3 girls had classic scarring on a new urogram. The latter 3 had all discontinued follow-up at the children’s hospital and the last urogram was performed at 4, 4, and 11 years of age, respectively. None of the patients had acquired a scar in a previously unscarred kidney after completed checkups during childhood. Thus, the risk of developing late renal scarring is small, which has been shown previously. That minor lesions on DMSA scan would be seen among the subjects in the matched group was expected since this technique is more sensitive for detection of damage than urography.

In the patients with renal scarring, the renal function was well preserved; the median GFR was 99. There was in fact no difference between the 56 patients and the matched group of 51 subjects with normal DMSA scans. Only 6 of 56 patients had GFRs of less than 80 and the reduction of function was small, with values in the range of 69 to 79. Thus, the long-term outcome concerning total renal function in patients with pyelonephritic scarring was favorable 22 years after the first recognized UTI. The GFR remained stable from the last childhood investigation in patients with unilateral scarring, although there was a significant decline in individual function of the scarred kidneys from a GFR of 46 to a GFR of 39. This decline was correlated to the VUR grade observed during childhood. The individual function of the unscarred kidneys in the patients with unilateral scarring was significantly higher than in the matched group with normal DMSA scans as an indication of compensatory hypertrophy. It is important to observe these patients for longer periods to determine whether progressive deterioration of function will occur. For those with bilateral scarring, there was a decline in GFR from 94 to 84. The number of patients was small (n = 7) and the difference did not reach statistical significance.

We found that 54% (40/74) of the patients with scarring had acquired scarring, ie, there was at least 1 urogram without signs of renal damage. The GFR in kidneys with primary scarring was not different from that of those with acquired scarring. In this context it is important to notice that our definition of “primary” does not necessarily mean congenital.

In the literature there is considerable variation in the frequency of chronic renal insufficiency and terminal renal failure in patients with pyelonephritic scarring. Several factors must be taken into consider-
ative study by Martinell et al,34 more favorable results were
had occurred in one third of the kidneys. In a prospec-
tive study by Martinell et al,34 more favorable results were
demonstrated. A group of 54 female patients with renal
scarring, of whom 19 had severe scarring, were fol-
lowed up continuously from their first known UTI in
childhood. They had rapid access to medical care for treat-
ment of recurrent UTI, both during childhood and adul-
tood. After 15 years of follow-up, the GFR was signifi-
cantly lower (96) in those with severe scarring compared
with controls, but there was no difference between those
with moderate scarring and controls. The GFR was less
than 80 in 4 patients with severe scarring but not less
than 70 in any patient. Consequently, close supervision
seems important for minimizing deterioration of renal
function in patients with renal scarring. This is also in
accordance with our results, where almost all patients were
followed up at least up to 16 years of age.

In a recent follow-up report by Smellie et al,25 226
patients (189 females and 37 males) were reinvestigated
at a mean age of 27 years. They were followed up pro-
spectively, from a mean age of 5 years, throughout child-
hood because of recurrent UTI and VUR. Radiological
renal scarring was found in 85 patients before the age of
10 years and none developed new scars thereafter. Dur-
ing childhood low-dose antibacterial prophylaxis was
given to all with scarring or persistent VUR, but during
adulthood checkups were rare. At follow-up investiga-
tion, renal function measured by plasma creatinine level
was impaired in 9 (11%) of those with scarring, all but 1
of whom had bilateral scarring. Two patients under-
go transplantation and 1 had died because of ma-
lignant hypertension. In the scarring group, markedly
raised albumin excretion was found in 3% and micro-
albuminuria in 13%. At a further follow-up by postal ques-
tionnaire at a median age of 35 years, there were no
additional patients with impaired renal function or end-
stage renal disease. Although these patients were origi-
nally referred, ie, selected, they were under close super-
vision during the rest of their childhood, and in contrast
to the study by Jacobson et al,35 no significant radiologi-
cal deterioration was seen in those who had repeated uro-
graphy. This is in accordance with a report by Berg36 show-
ing that reduction in renal function occurred early after
pyelonephritis and that further reduction was slow in chil-
dren followed up continuously. On the other hand, the
patients described by Smellie et al27 differed from ours
in that they were of an older age at detection and that

Jacobson et al8 investigated 30 (26 females) pa-
tients 27 years after the detection of nonobstructive py-
elonephritic scarring. Three patients had developed end-
stage renal failure and the remaining had significantly
lower GFRs (mean, 90) than 13 healthy control sub-
jects. Their patients were selected retrospectively through
the department of pediatric radiology, where urograms
were obtained. In a prospective or retrospective study design, extent of scarring, and follow-up time.

Several reports on adults with pyelonephritic scar-
ing have been presented, although the accuracy of GFR
estimation was low in most of them.28-31,33 Impaired re-
nal function was found in 18% to 38%. In general, renal
scarring was extensive and it was shown that bilateral
scarring is a risk factor for declining renal function. How-
ever, some authors pointed out that patients with uni-
lateral scarring are also at risk of decreasing function, pre-
sumably secondary to hypertensive vascular damage.28,31
In studies with this type of design, females presenting with
UTI are the dominant group while the smaller group of
males frequently presents with features of renal dam-
age, such as hypertension, proteinuria, or symptoms of
renal failure.30,35 Thus, reports of studies in adults have
shown that patients with renal failure as a consequence
of pyelonephritic scarring are not a neglectable group.
Most were not under medical supervision until progres-
sive deterioration of renal function was inevitable and
bilateral scarring was frequent but not a prerequisite for
impairment of renal function. In our study there were
only 7 patients (12%) with bilateral scarring. Although
not significant, their median GFR decreased from 94 to
84 during the 10-year period between 15 and 25 years
of age. However, none had progressive renal deterioration,
neither those with bilateral nor those with unilat-
eral scarring.

In our study, pronounced albuminuria was found
in only 1 male who had bilateral scarring and a GFR of
84. A negative correlation between GFR and urinary al-
bumin excretion in patients with pyelonephritic scar-
ing has been described previously.17 Proteinuria, as an
indication of glomerular lesions, has been reported to be
a constant finding in such patients with progressive de-
terioration of renal function.30 Consequently, the low fre-
quency of albuminuria in our study, where no one had a
GFR less than 69, was not surprising.

Although nonobstructive renal scarring is still a
global major cause of end-stage renal disease in chil-
dren,39 the frequency has decreased during the past de-
cades in some countries with modern medical care.40 In
Sweden there has not been registered any child during
1952 to 1970, were followed up for 24 years. Two (2
males) of the 4 patients with bilateral scarring had renal
insufficiency, but in the others the GFR was not less
than 70. At the same center, 24 patients with end-stage
reflux nephropathy, in the same age span and during
the same period, entered the renal replacement pro-
gram. In contrast, the latter group presented later and
were not regularly followed up. Thus, also in this study
the benefit of early detection and continuous follow-up
was suggested.

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the last decade,41 and in adulthood the incidence of end-


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