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Effect of vesicoureteral reflux on renal function in children with recurrent urinary tract infections

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Effect of vesicoureteral reflux on renal function in children with recurrent urinary tract infections. The functional damage caused by vesicoureteral reflux (VUR) has been examined by unilateral clearance studies in 22 children with recurrent urinary tract infection (UTI) and representing 23 kidneys with large VUR, 7 kidneys with small to moderate VUR and 14 kidneys without VUR. Inulin clearance, Na^+ excretion and glucose reabsorption were determined. In kidneys without or with small and moderate VUR, UTI had no effect on renal function if treated. In kidneys with large VUR extending into the pelvis and dilating the ureter, there was a gradual deterioration of glomerular filtration rate (GFR) that was accelerated after the age of 6 yr. Before puberty more than 50% of renal function was lost despite strict medical care of the UTI. If this functional loss was unilateral, hyperfunction of the contralateral kidney was generally observed. Maximal glucose reabsorption was depressed in proportion to GFR. In kidneys with unilaterally low GFR, the fractional Na^+ excretion was consistently increased as compared to the contralateral kidney with normal GFR. This adaptive increase in Na^+ excretion must therefore be of intrarenal origin.

Effet du reflux vésico-urétéral sur la fonction chez l'enfant atteint d'infection urinaire récidivante. L'altération de la fonction rénale déterminée par le reflux vésico-urétéral (VUR) a été étudiée par clearance unilatérale chez 22 enfants atteints d'infection urinaire récidivante (UTI). L'étude a porté sur 23 reins avec reflux importants, 7 reins avec reflux minime ou moyen et 14 reins sans reflux. La clearance de l'inuline, l'excrétion de Na et la réabsorption de glucose ont été déterminés. L'infection urinaire récidivante n'a pas d'effets sur la fonction des reins sans reflux ou avec reflux minime ou moyen. Dans les reins avec reflux important atteignant le bassinet et dilatant l'uretère on observe une détérioration progressive de la filtration glomérulaire, détérioration qui est plus rapide après l'âge de 6 ans. Avant la puberté, plus de 50% de la fonction rénale sont perdus malgré un traitement strict de l'infection urinaire récidivante. Quand cette diminution de la fonction est unilatérale, une augmentation de la fonction controlatérale est habituellement observée. La réabsorption maximale de gluclose est diminuée en proportion du débit de filtration glomérulaire. L'excrétion fractionnelle de sodium par les reins dont la filtration glomérulaire est diminuée est nettement plus grande que celle du rein controlatéral dont la filtration glomérulaire est normale. Il semble donc que cette adaptation dans l'excrétion du sodium doive être d'origine intrarénale.

Retrospective studies on the outcome of recurrent urinary tract infection (UTI) in children [1] as well as in adults [2, 3] have consistently shown that it will only rarely result in renal failure. Since recurrent UTI is in most cases a benign disorder, it is now often suggested that asymptomatic bacteriuria should not generally be treated. It has thereby become increasingly important to trace the small group of patients in whom recurrent UTI could result in end-stage renal failure. Most likely this group will consist mainly of patients that have had vesicoureteral reflux (VUR) in childhood [4]. The causal relationship between VUR and renal functional damage has, however, not yet been established.

Since VUR is often unilateral, only selective renal function studies are useful in evaluating the functional damage caused by the reflux. Unilateral clearance studies during external ureteral compression have previously been used in this laboratory and the reliability of the method has been found to be satisfactory [5]. This method has now been applied to children with different degrees of unilateral or bilateral VUR. The children have been selected so that their past history of recurrent UTI is fairly homogenous.

Patients

Twenty-two girls with VUR, aged 3 to 13 yr, were subjected to selective studies of renal function. Micturition cystourethrography was performed in all children within six months prior to the study. The refluxes were classified into three groups: grade I, representing reflux into the ureter not reaching the pelvis; grade II, reflux extending into the pelvis but without dilatation of the ureter; and grade III, reflux extending into the pelvis with dilatation of the ureter. The dilatation did, however, generally not exceed 1.5 cm. In 14 kidneys there was no reflux in the ureter. In 2 kidneys there was grade I VUR, in 5 kidneys there was grade II VUR and in 23 kidneys there was grade III VUR.

An i.v. urogram was performed in all children

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Table 1. Follow-up in grade III VUR

	VUR III (age, 2 to 4 yr)	VUR III (age, 5 to 7 yr)	VUR III (age, 8 to 12 yr)	No VUR (age, 8 to 12 yr)
Yr since diagnosis of first UTI	2.5 ± 0.8	4.7 ± 0.5	4.3 ± 2.3	5.0 ± 2.0
Yr since first MCU[a]	2.0 ± 0.8	4.5 ± 0.8	3.6 ± 2.5	3.3 ± 2.1
Mean age, yr	3.3 ± 0.5	5.8 ± 0.8	9.9 ± 1.7	9.8 ± 1.9
N	6	7	10	9

[a] Micturition cystourethrography.

within six months prior to the study. A varying degree of renal scarring and parenchymal reduction could be demonstrated. The area of the renal parenchyma was, however, correlated well with the glomerular filtration rate (GFR; correlation coefficient, 0.84) [5]. The radiologic examination gave in no case evidence for renal malformation or urinary tract obstruction. None of the patients studied have been subjected to any urologic operation prior to the study. The age at diagnosis of the first UTI for kidneys with grade III reflux is given in Table 1. Radiologic examinations were carried out at varying time intervals after diagnosis of the first UTI. In all cases the first radiologic examination included both i.v. urogram and micturition cystourethrography. In all but one patient (a 6-yr-old child that had previously had a grade I to II VUR), the existence of grade III VUR was observed already on the first micturition cystourethrography that was carried out in the patient. The age at diagnosis of the VUR is also included in Table 1.

Following diagnosis of the first UTI, all patients have been followed with urine cultures every two to three months. In addition, a urine culture has always been performed if there have been any symptoms of UTI. In each case of significant bacteriuria (> 100,000 bacteria/ml of freshly voided urine), antimicrobial therapy has been used. In each case the bacteria cultured were sensitive either to sulphonamides, ampicillin or nalidixic acid. The relapse frequence following treatment was 9% in the case of no VUR and 8.5% in the case of grade III VUR. All patients with unilateral or bilateral grade III reflux and generally also those patients with grade I or II reflux have received long-term treatment with nitrofurantoin, 1 mg/kg/day, if the frequency of UTI has exceeded one a year. Seventy-three percent of the patients with no reflux to one kidney and 75% of the patients with grade III reflux to one or both kidneys had at one time received long-term treatment for at least one year. The average frequency of UTI to which the kidneys with different degrees of VUR have been exposed is listed in Table 2. In patients with no reflux to one kidney, the UTI was due to *Escherichia coli* in 88% of the cases. In the remaining 12% it was due to either *Enterococci* or *Staphylococcus albus*. The bacteria cultured from patients with unilateral or bilateral grade III VUR were *E. coli* in 75% of cases and *Enterococci* in 16% of cases. In the remaining cases *Staph. albus*, *Aerobacter* and *Proteus* were cultured.

Methods

All patients were subjected to unilateral clearance studies with determination of glomerular filtration rate (clearance of inulin, C_{In}), fractional sodium excretion (C_{Na}/C_{In}) as well as maximal tubular reabsorption of glucose ($Tm_{glucose}$).

On the day of the study, the patients were given a standard breakfast meal and were allowed a free water intake. Standard clearance technique was used. This includes a continuous infusion of 10% inulin (Laevasar-Gesellschaft), 0.001 g/min/kg of body wt after the priming dose of 0.05 g of inulin/kg of body wt. The continuous infusion was started at least one hour before the study. For urine sampling the bladder was catheterized with a double lumen polyethylene catheter enabling a continuous suction. Blood samples were obtained in the middle of each urine collection period. With the double purpose of determining $Tm_{glucose}$ and ensuring a constant diuresis, the patients were given a constant infusion of 20% glucose starting 30 min prior to the first urine collection period. For the unilateral clearance studies, external ureteral compression technique was used

Table 2. Number of yearly infections

	No VUR	VUR I	VUR II	VUR III
	1.28 ± 0.98	1.90 ± 1.25	1.73 ± 0.94[a]	1.54 ± 0.93
Compared to no VUR	—	$0.4 > P > 0.3$	$0.4 > P > 0.3$	$0.5 > P > 0.4$

[a] Mean ± 1 SD.

[5, 6]. The pressure was applied on the anterior abdominal wall pressing the ureter against the posterior brim of the pelvic inlet. The complete ureteral occlusion by this technique as well as the adequacy of urine sampling was continuously checked by high amplifying fluoroscopy. For this purpose an i.v. injection of 60% Urografin (Schering), 0.5 to 1 ml/kg of body wt, was given five minutes before compression. The duration of the ureter compression never exceeded 15 min allowing for two to three clearance periods.

The chemical analyses of inulin in serum and urine were carried out with the anthrone method [7]. Before the analysis 0.09 g of Baker's yeast (0.3 ml of a 30% yeast suspension) was added to the samples (0.2 ml of plasma) in order to eliminate the interference with glucose. The sodium concentration in serum and urine was analyzed by a flame photometer (Eppendorff). Glucose in serum and urine was determined with the glucose-oxidase method.

Results

Glomerular filtration rate. The reliability of the method for selective renal function studies can easily be evaluated by comparing the GFR obtained when no ureteral compression was used with the sum of GFR obtained from each kidney during unilateral ureteral compression. In these cases, where the total GFR obtained without compression deviated more than ±15% from the sum of GFR obtained during compression, the results were discarded and the patients have not been included in this report. In one patient, however, renal functional data were obtained only from one side during ureter compression. The GFR in 13 kidneys with no ureteral reflux was 66 ± 18 ml/1.73 m² of body surface/min (mean ± 1 SD). The GFR in kidneys with grade I and grade II ureteral reflux was 61 ± 13 ml/1.73 m² of body surface/min, and in 23 kidneys with grade III reflux, 38 ± 19 ml/1.73 m² of body surface/min. The normal value for GFR in healthy young adults under water diuresis was in this laboratory found to be 109 ± 12.7 ml/1.73 m²/min, which yields for one kidney 54.5 ± 6.4 ml/1.73 m²/min [8]. One factor that was thought to have contributed to the fairly large scatter of data was the duration of the reflux. To examine this possibility the GFR in each group has been related to the age of the patients. The exact time of onset of the reflux was unknown in most cases, but the age of the patient was thought to be a fairly good index of how long-standing the ureteral reflux had been. The relationship between the GFR and age is given in Fig. 1. In the kidneys without VUR, the GFR in relationship to body surface was constant from the age of 3 to

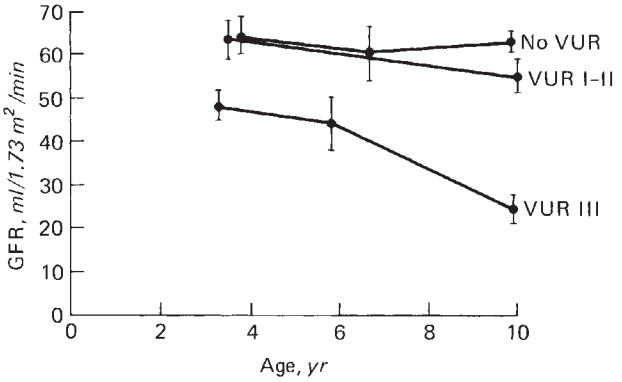

Fig. 1. *GFR in relation to age in kidneys without VUR, with grade I-II VUR and with grade III VUR.* The *closed circles* represent the mean values and the *bars* the SEM.

10 yr. The existence of grade I and II VUR did not appear to affect renal function. When grade III VUR was present, however, there was a gradual decline in the GFR with increasing age. Already in 3- to 5-yr-old children, the GFR was somewhat lower in kidneys with grade III VUR. The difference was almost significant ($0.05 > P > 0.02$). In 8- to 12-yr-old children, however, the GFR in kidneys with grade III VUR was less than 50% of that found in control kidneys and the difference was highly significant ($P < 0.001$). The rate by which the GFR in VUR III kidneys falls appears to be accelerated after the age of 5 yr.

Figure 2 examines how the deterioration of renal function caused by unilateral VUR III will affect the contralateral kidney. As a rule the GFR in the con-

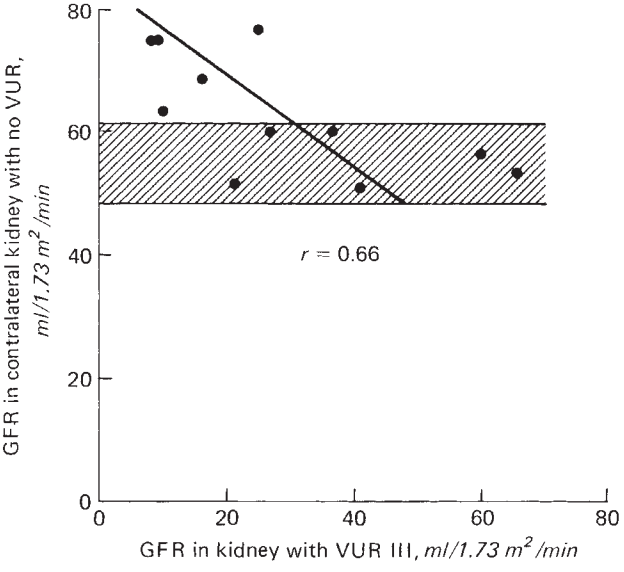

Fig. 2. *The relationship between the glomerular filtration rates in the two kidneys in patients with unilateral grade III VUR.* The *shaded area* represents the normal GFR for one kidney (mean ± 1 SD).

tralateral kidney was increased above normal when the GFR in the VUR III kidney was below 25 ml/1.73 m^2/min.

Renal tubular function. It is generally considered that the maximal reabsorptive capacity for glucose is reached when the blood glucose value exceeds 300 mg/100 ml. It was found, therefore, justified to use the calculated amount of reabsorbed glucose as the maximal glucose reabsorptive capacity ($Tm_{glucose}$) when the blood glucose values ranged between 320 and 600 mg/100 ml. Table 3 gives the $Tm_{glucose}$ per unit of filtered load in those studies. There was no significant difference between the groups. In addition, the $Tm_{glucose}$ per unit of filtered load has been compared between the two kidneys in patients with unilateral grade III ureteral reflux. The difference of mean was not significant ($P > 0.2$).

The Na^+ excretion in relationship to the filtered load (C_{Na}/C_{In}) was determined in each case. Due to the fairly large range of the blood glucose values in the various studies, the patients were under different degrees of osmotic diuresis. The average fractional Na^+ excretion was therefore not calculated. In each individual patient, however, the blood glucose concentration was fairly constant during the entire course of the study. Thus, the fractional Na^+ excretion could be compared in the kidneys of the same patient. The relationship between fractional Na^+ excretion and GFR in patients with unilateral grade III ureteral reflux and reduction of GFR is demonstrated in Fig. 3. It is apparent that the fractional salt excretion is consistently higher in the kidney with low GFR. In fact, the relationship between the fractional salt excretion and GFR is almost constant in the different patients studied.

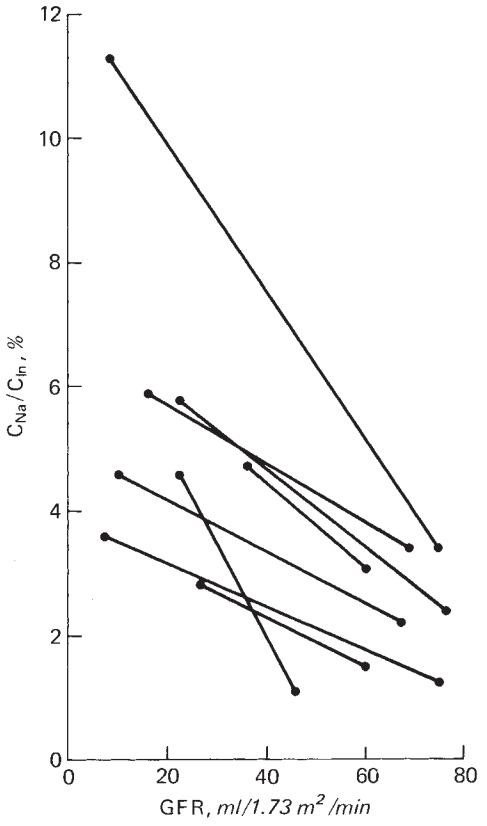

Fig. 3. *The relationship between fractional Na^+ excretion and GFR in patients with unilateral grade III VUR and reduced GFR.* The *thin lines* connect the two kidneys in each patient.

Discussion

Previously the effect of VUR on renal function has generally been evaluated by following the changes in renal parenchyma as judged from the i.v. urogram [9-11]. The size of the renal parenchyma as it appears on the radiologic film is, however, in this particular disorder a good index of GFR [12]. The radiologic evidence for a close association between VUR and progressive renal scarring is strong when data from children are reviewed. VUR occurs in 26% of children with recurrent UTI but only in 5% of adults [13]. It is considered to be self-restoring in most cases. Since VUR is almost always diagnosed on the first radiologic examination of children with UTI, many authors believe that it is congenital [14]. Others state that a UTI is needed to create a reflux in a predisposed ureter. Under all circumstances the onset of VUR is in most cases in very early life and the age of the patient will therefore be a good index of the duration of the reflux. The present study thus confirms the previous radiologic impression that renal function declines progressively with the duration of a large VUR.

When attention was first drawn to the association of reflux with renal infections [15], it was suggested that recurrent UTI was mainly responsible for the renal damage. The results from the present study indicate that medically controlled UTI will not interfere with renal function in kidneys without VUR but will not prevent functional damage in kidneys with large VUR. It should, however, be remembered that the diagnosis of UTI has been made on the basis of significant bacteriuria. The degree of bacterial invasion of the renal parenchyma might therefore be

Table 3. $Tm_{glucose}$, mg/100 ml of glomerular filtrate

	No reflux	Grade I to II reflux	Grade III reflux
Mean	264	243	259
SD	39	47	50
N	11	6	20

quite different in kidneys with VUR III as compared to kidneys with no VUR. Whether it is the VUR alone or the VUR in combination with UTI that has caused the damage is therefore impossible to tell from the present results. Findings of animal experiments on the effect of sterile reflux on renal function are contradictory [16, 17]. In clinical practice this question is of less importance, since sterile refluxes are diagnosed only rarely. The large majority of children in whom VUR is diagnosed have a past history of UTI similar to that which was found in the present subjects. In those patients a progressive deterioration of renal function can be expected to result in a 50% loss of GFR before puberty. Even if the combination of UTI and VUR is needed to initiate the functional damage, it should be noted that strict medical care alone will not prevent renal functional loss, since most patients in the present study have been followed for several years with urine cultures every second month and in the case of more than one infection yearly have received long-term treatment. On the basis of the present results, it can therefore be suggested that children with histories of UTI and persisting grade III VUR should be considered for antireflux operation before their sixth year of life. Of equal importance is that an early radiologic examination including a micturition recording is made in children with recurrent UTI. By those means most cases of renal failure resulting from UTI should be prevented.

In addition to GFR, two aspects of tubular function have been evaluated, namely glucose and Na^+ reabsorption. The reabsorptive capacity for glucose is generally considered to be a fairly stable process levelling off at a constant value ($Tm_{glucose}$) when a sufficiently high blood glucose concentration is reached [18]. $Tm_{glucose}$ has therefore sometimes been used as a measurement of the reabsorptive sites of the proximal tubular lumen [19]. In the present study GFR and Tm were reduced to the same extent indicating a homogenous loss of glomerular and proximal tubular function. On the other hand, the reabsorptive capacity for Na^+ is known to adjust to physiological needs [20]. In the present study the fractional Na^+ excretion was uniformly increased in kidneys with low GFR. In fact, C_{Na}/C_{In} was inversely correlated to GFR in patients with unilateral grade III refluxes. The increase in Na^+ excretion per unit of filtered load in kidneys with low GFR might be interpreted as an adaptation to keep the basal salt excretion rate constant. An enhanced natriuretic response to saline loading has previously been observed from the diseased kidney in dogs with unilateral pyelonephritis [21].

In patients with large unilateral refluxes and concomitant functional loss, the GFR on the contralateral side was, generally but not always, higher than normal. Thus, the renal functional loss in the kidneys with large refluxes will generally initiate a compensatory hyperfunction in the contralateral kidney. In two patients the GFR in the large reflux kidney was below 10 ml/1.73 m^2/min. In both those patients the GFR of the contralateral kidneys was 75 ml/1.73 m^2/min, which is close to the GFR values found in nephrectomized patients in whom the contralateral kidney has been regarded as normal postoperatively [22]. The fact that not all of the patients with unilateral grade III VUR and reduced GFR were able to increase the GFR to the same degree in the contralateral kidney is of clinical importance. When a patient with recurrent UTI and unilateral grade III reflux is to be operated, nephrectomy might be considered if there is a very substantial loss of renal parenchyma. However, failure of the contralateral kidney to respond with a compensatory increase in function is indicative of a defect in this kidney as well. Under these circumstances, it is of the utmost importance that as much functional renal parenchyma as possible be preserved.

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