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Preservation of renal function in the modern staged repair of classic bladder exstrophy

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Abstract

Objective—To compare the estimated glomerular filtration rate (eGFR) in bladder exstrophy patients with published normative GFR estimates.

Patients and Methods—eGFR was calculated using the Schwartz formula at three timepoints, with mean eGFR at each timepoint compared to normative values.

Results—At primary closure (n = 53) the mean eGFR (ml/min/1.73 m^2) in exstrophy patients was similar to norms at 0–7 days (exstrophy vs norm: 42.5 vs 40.6, $p > 0.05$) and after 2 years of age (108.8 vs 133, $p > 0.05$). However, the mean eGFR in exstrophy patients was significantly lower than norms between 8 days (44.8 vs 65.8, $p < 0.0001$) and 2 years of life (68 vs 95.7, $p = 0.01$). At bladder neck reconstruction (n = 13) no statistically significant difference existed between the exstrophy and normative eGFR values (137.1 vs 133, $p > 0.05$). Similarly, among 27 patients with at least 1 year follow-up after bladder neck reconstruction, the mean exstrophy eGFR was no worse or higher than normative values (2–12 years: 124.5 vs 133, $p > 0.05$; males ≥ 13 years 175.6 vs 140, $p = 0.04$; females ≥ 13 years 128.8 vs 126, $p > 0.05$).

Conclusion—The staged reconstruction of exstrophy does not appear to negatively impact renal function in most patients. As eGFR detects only significant changes, surgical reconstruction may still cause more subtle renal damage.

Keywords

Bladder Exstrophy; Estimated Glomerular Filtration Rate; Modern Staged Repair of Exstrophy

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INTRODUCTION

The modern reconstruction of bladder exstrophy has focused on providing good functional and cosmetic outcomes. A primary functional outcome of the staged reconstruction as described by Jeffs has been the preservation of renal function[1]. Factors that can impact renal function in children with bladder exstrophy include increases in outlet resistance that occur following initial closure and bladder neck reconstruction (BNR), vesicoureteral reflux, and possible complications of surgical reconstruction, including urethral strictures, bladder prolapse and recurrent infections.

Most studies of long-term outcomes in children with bladder exstrophy have used ultrasound to evaluate upper tract dilatation as a presumptive indicator of renal injury[2–5]. Ultrasounds are a useful means to evaluate the gross renal structure and follow patients non-invasively over time. Although upper tract dilatation can imply renal injury, it lacks functional information to determine true renal compromise. Ebert et al. evaluated serum creatinine measurements in 17 adult male patients treated with a single-stage reconstruction, and found that all patients had normal serum creatinine values (≤ 0.85 mg/dL)[6]. Conversely, Gobet et al. measured glomerular filtration rate (GFR) in 13 adult exstrophy patients with intact ureterosigmoidostomies, and found the mean GFR to be below normal in most cases[7].

Patients who undergo the Modern Staged Repair of Exstrophy are at increased risk for renal deterioration if they experience postoperative complications such as urethral stricture following primary closure or epispadias repair or if their urethral outlet provides too much resistance following bladder neck repair. However, no studies to date have evaluated GFR in patients who have been reconstructed with this approach. We hypothesized that the estimated GFR in children with exstrophy is no different to the normative values at birth, at BNR, and after BNR. The aim of this study was to determine if increasing urethral outlet resistance by performing a BNR leads to worsening renal function.

PATIENTS AND METHODS

After institutional review board approval, a centralized exstrophy database was used to identify patients who had undergone primary bladder closure, epispadias repair, and BNR at our institution. For inclusion in this study, patients had to meet the following criteria: all three surgeries performed at this institution as part of the Modern Staged Repair of Exstrophy, serum creatinine and height measurements to calculate GFR at one or more pre-specified timepoints, and at least 12 months of follow-up after BNR. Retrospective chart review was utilized to capture demographic, medical, surgical, radiologic, and continence data. Patients were excluded if they were premature or had any stage of reconstruction performed at an outside institution. Total continence was defined as being dry at night and continent for at least 6 h during the day, whereas partial continence was defined as being dry for at least 3 h during the day with occasional nighttime leakage. Incontinence was defined as leakage or urinary bother severe enough to warrant further reconstruction.

Ureteral reimplantation was performed as part of the BNR procedure in most patients. If patients remained incontinent after bladder neck repair and subsequently underwent an augmentation cystoplasty, the last creatinine value measured before augmentation was used as their post-BNR follow-up value.

The Schwartz formula (GFR = constant * height (cm) / serum creatinine (mg/dL)) was used to estimate GFR (in ml/min/1.73 m^2)[8]. For these calculations, the constants 0.45 (for day of life 0 through 2 years of age), 0.55 (for 2–12 years of age and females 13 years of age or older), and 0.70 (for males 13 years of age or older) were used[8–10]. Normative GFR values from the National Kidney Foundation are defined for male and female children at 0–7

days of life, 8–56 days of life, 57 days of life to 2 years, 2–12 years of life, and males >12 years of life and females >12 years of life[11].

We calculated eGFR values prior to bladder closure, at the time of BNR, and at least 1 year following BNR. However, to allow for comparison with the normative values, we further divided our exstrophy patients into groups based on their age and gender at the time of GFR estimation. Within each group, the mean eGFR was calculated and compared to the normative eGFR values using a one-sample t-test. To determine if eGFR was different between continent and incontinent patients after BNR, the Wilcoxan rank-sum test was used to compare eGFR values among continent patients (either totally or partially continent) with those of incontinent patients. A two-sided p-value < 0.05 was considered significant. Stata 10 statistical software was used for all analyses (StataCorp LP, College Station, TX, USA, 2007).

Ultrasound studies obtained at post-BNR follow-up were reviewed for hydroureteronephrosis and when present the degree was documented. Radionuclear renal scans were not routinely performed.

RESULTS

Eighty-five patients were identified as potential candidates. Of these, 57 had sufficient data to calculate GFR. The characteristics of the study population are shown in Table 1. Forty-three (75%) patients were males, and 53 (93%) patients were white.

Comparison of patients with exstrophy to age- and gender-based norms is demonstrated in Table 2. At primary closure, the mean eGFR at 0–7 days of life was no different than norms, as was the mean eGFR between 2 and 5 years of life. However, at the time of primary closure the mean eGFR in children with exstrophy was significantly lower than age-based norms between 8 and 56 days of life and from 57 days to 2 years of life.

Thirteen patients were evaluated at BNR. The mean age of this group was 5.8 years (range: 2.1–11.3 years). There was no difference in the mean eGFR between exstrophy patients at the time of BNR and age-based norms.

After BNR, 21 males and 6 females with a mean follow-up of 9.3 (range: 1.6–20.9) and 11.3 (range:1.6–23.5) years, respectively, had evaluable data. Nine patients were 12 years of age or younger at post-BNR follow-up (mean age: 8.9 years). As shown in Table 2, the mean eGFR of these exstrophy patients was no different than normal. Three exstrophy females ≥13 years old similarly had a mean eGFR that was no different than normal females. However, 15 exstrophy males ≥13 years old had a mean eGFR that was significantly higher than that of normal males.

Although 27 patients had post-BNR eGFR values, only 10 patients had data to longitudinally follow eGFR from BNR to post-BNR in individual patients. Only 1 patient, whose case is discussed below, had a worsening of eGFR from an age-defined normal value to well below normal (61ml/min/1.73 m^2). All the other patients had eGFR values that stayed within 1 or 2 SDs of the normative values.

As urinary continence and increased outlet resistance following BNR could impair renal function, continent patients following BNR were compared to incontinent patients following BNR. Among the 9 patients ≤ 12 years old, 3 were dry at night and continent for at least 6 h during the day (totally continent), 2 were continent for at least 3 h during the day with occasional nighttime leakage (partial continence), and 3 were incontinent and underwent augmentation cystoplasty. Continence data were not available for 1 patient. No difference

was found when comparing the mean eGFR between total or partially continent and incontinent patients in this group ($p = 0.19$). Among the 15 exstrophy males with post-BNR follow-up, 7 were totally continent, 5 had partial continence, and 3 were incontinent and underwent augmentation cystoplasty. No difference was found comparing the mean eGFR in older totally or partially continent males to the mean eGFR in older incontinent males just prior to their augmentation ($p = 0.19$). As all 3 females who underwent BNR were totally continent, no comparisons of eGFR between continence states could be made.

Twenty-two out of 27 patients with post-BNR follow-up had ultrasound information (at a mean of 9.9 years after BNR) available for review. Among these 44 representative renal units, 35 had no hydronephrosis, 2 had mild, 5 had moderate, and 2 had severe hydronephrosis. One patient who had chronic urinary retention following BNR had moderate right and severe left hydroureteronephrosis and worsening renal function, as described below. Otherwise, in this limited dataset there was no correlation between the presence or degree of hydronephrosis, continence status, and impaired eGFR.

Of the 27 evaluable patients after bladder neck repair, only 1 (4%) met criteria for Stage 2 chronic kidney disease (eGFR 60–89 ml/min/1.73 m^2)[11]. This patient had his first episode of urinary retention within 6 weeks of his bladder neck repair, which prompted institution of a clean intermittent catheterization (CIC) regimen. Although moderate bilateral hydronephrosis and left renal cortical thinning were present at least 1 year prior to his BNR, this progressed to left moderate and right severe hydroureteronephrosis after his continence surgery. Eventually, poor compliance with the CIC regimen led to bladder perforation 10 years after his outlet procedure. By this time, however, his eGFR had decreased from 155 ml/min/1.73 m^2 at bladder neck repair to 61 ml/min/1.73 m^2. The patient also had hypertension, which was controlled with one oral anti-hypertensive agent.

DISCUSSION

Preservation of renal function is a primary aspect of the functional reconstruction of children with bladder exstrophy. In describing the technique of staged reconstruction, Jeffs considered renal deterioration a failure of reconstruction[1]. No long-term outcome studies in exstrophy, however, provide sufficient evidence to determine the ultimate renal function in patients treated with the modern staged approach.

Gobet et al. recently reported the long-term nephrourological outcomes of 21 individuals with over three decades of follow-up treated with ureterosigmoidostomies in Switzerland[7]. Of the 10 patients with ureterosigmoidostomies still in place, the mean eGFR was below 90 ml/min/1.73 m^2 in all patients. However, the inherent difference in reconstruction method makes comparison of these results to our patient population difficult. Ebert et al. recently reported long-term outcomes of patients treated with a functional single-stage reconstruction technique[6]. The mean age of the 17 male exstrophy patients in this study was 23.4 years. Though eGFR was not calculated, the authors report that the mean serum creatinine was normal at 0.85 mg/dl, and no patients showed radiographic evidence of upper tract dilatation. However, because it can underestimate the level of renal impairment, serum creatinine concentration alone may not be an ideal indicator of renal function[11]. With short-term follow-up in a group of 22 patients having undergone the complete primary repair, Gargollo reports that 22% of patients showed evidence of renal scarring by DMSA scan; no creatinine or GFR data are available.[2]. As DMSA scans are sensitive in detecting renal scarring which may have negative implications for renal function, this study provides reassuring 5-year follow-up data in this group. However, more mature radiological follow-up and GFR data to assess the renal function of this cohort in the future will be needed to validate this early promising data. Together, these short- and long-term follow-up studies

report varied measures of renal health in exstrophy, but due to the lack of GFR measurements one cannot make a definitive conclusion as to the ultimate renal health in patients treated with modern approaches.

This is the first study of renal function as measured by eGFR in children who have undergone the staged repair of exstrophy. In an effort to determine if staged reconstruction preserves renal function and thereby fulfills Jeffs' criteria for functional success, we calculated estimated GFR values in our population and compared them to normative values.

An unexpected finding was a reduction in mean eGFR in some patients at the time of primary closure. Further work will be needed to verify this finding, but these data might suggest that in-utero bladder development and cycling promotes renal maturation. Moreover, if exstrophy is associated with impaired renal function at birth, additional stress such as post-closure outlet obstruction, bladder prolapse, or urinary tract infections may lead to further renal compromise. This highlights the importance of a complication-free initial closure and close follow-up.

A primary goal of this study was to determine if increasing urethral outlet resistance by performing a BNR leads to worsening renal function. In a small and select group of patients, compared to normative values, our data suggest no difference in mean eGFR in our patients (irrespective of continence status) after BNR. As increased outlet resistance in continent patients could lead to more renal impairment than in incontinent patients, these two patient groups were compared and no difference in mean eGFR was found.

No correlation between ultrasonographic evidence of hydronephrosis and continence status or eGFR was found during our nearly full decade of follow-up. There is the possibility that hydronephrosis is a predictor for renal impairment and that longer term follow-up with serial ultrasounds and eGFR measurements is needed to detect such differences. For this reason, ultrasounds will continue to be used in our practice as they are a useful non-invasive modality that can, at the very least, heighten the provider's suspicion for potential obstructive uropathy.

Importantly, 1 patient with normal renal function at the time of BNR progressed to Stage 2 chronic kidney disease over a 10-year period of urinary retention requiring CIC. Though present in only 1 of our 27 patients, this highlights the risk of continence surgery and the importance of close follow-up.

This study should be viewed in light of its limitations, including its relatively small sample and the retrospective study design. This limits assessing pertinent clinical findings such as the number of urinary tract infections, detailed continence status, impaired bladder emptying, and other non-urologic causes of kidney damage. Further, serum and urine tests and radionuclear scans were only performed in select patients based on individual clinical scenarios. Thus, we cannot determine the number of patients with Stage 1 chronic kidney disease (individuals with an eGFR > 90 ml/min/1.73 m^2 but with evidence of renal impairment such as proteinuria or uremia) or with a normal eGFR but evidence of renal scarring. Importantly, the exact timing and clinical setting of the creatinine and height measurements in our study were not controlled, and this introduces variability in calculating GFR estimates. As the technique for measuring serum creatinine has also changed since the inception of the Schwartz formula, the equation has been shown to overestimate GFR, particularly with decreasing GFR levels[11]. Though this may lead to an underestimate of the proportion of our patients with impaired renal function, most of our patients had eGFR values above normal. Given the limitations of the 'classical' Schwartz formula, future investigations should include newer, more precise and comprehensive measures of GFR that minimize overestimation[12]. Estimated GFR values are useful in assessing the functional

status of the kidneys, yet significant insults may be required before decrements in renal function can be expected. More specifically, subtle renal damage that is not seen in children with normal eGFR values could have occurred as a result of reconstructive surgery. Thus, as more sensitive modalities for detecting mild-to-moderate renal impairment, DMSA scans and ultrasounds should be considered to detect more subtle renal injury.

This is the first and largest report of long-term renal function as measured by eGFR in patients who have undergone the modern staged repair of exstrophy. In comparison to normal values, our evidence from a select group of patients suggests that, in general, there is no impairment in eGFR through at least young adulthood in the reconstructed exstrophy patient. That is, these findings imply that continence can be achieved without harming the kidneys in the majority of patients. However, less severe renal impairment that is outside the detection limits of eGFR changes may still result from exstrophy reconstruction. Further prospective studies would aid in correlating ultrasound findings, radionuclear scans, and physiologic renal function measurements to more completely evaluate renal health in the reconstructed and aging exstrophy population.

CONCLUSION

Exstrophy patients undergoing the modern staged repair maintain consistent renal function through at least young adulthood. Although limited to a small and select group of patients undergoing the staged approach, the surgical reconstruction of exstrophy (in particular increasing the bladder outlet resistance by performing a BNR) does not appear to negatively impact renal function in most patients. As eGFR detects only significant changes in renal function, surgical reconstruction may still cause more subtle renal damage.

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Ethical approval

This study was approved by the Institutional Review Board of our institution.

BIBLIOGRAPHY

1. Jeffs RD. Exstrophy and cloacal exstrophy. Urol Clin North Am. 1978; 5:127–140. [PubMed: 644708]
2. Gargollo PC, Borer JG, Diamond DA, Hendren WH, Rosoklija I, Grant R, et al. Prospective followup in patients after complete primary repair of bladder exstrophy. J Urol. 2008; 180:1665–1670. discussion 70. [PubMed: 18715576]
3. Shnorhavorian M, Grady RW, Andersen A, Joyner BD, Mitchell ME. Long-term followup of complete primary repair of exstrophy: the Seattle experience. J Urol. 2008; 180:1615–1619. discussion 9–20. [PubMed: 18710721]
4. Mouriquand PD, Bubanj T, Feyaerts A, Jandric M, Timsit M, Mollard P, et al. Long-term results of bladder neck reconstruction for incontinence in children with classical bladder exstrophy or incontinent epispadias. BJU Int. 2003; 92:997–1001. discussion 2. [PubMed: 14632863]
5. Shaw MB, Rink RC, Kaefer M, Cain MP, Casale AJ. Continence and classic bladder exstrophy treated with staged repair. J Urol. 2004; 172:1450–1453. discussion 3. [PubMed: 15371867]

6. Ebert AK, Schott G, Bals-Pratsch M, Seifert B, Rosch WH. Long-term follow-up of male patients after reconstruction of the bladder-exstrophy-epispadias complex: psychosocial status, continence, renal and genital function. J Pediatr Urol. 2010; 6:6–10. [PubMed: 19596609]
7. Gobet R, Weber D, Renzulli P, Kellenberger C. Long-term follow up (37–69 years) of patients with bladder exstrophy treated with ureterosigmoidostomy: uro-nephrological outcome. J Pediatr Urol. 2009; 5:190–196. [PubMed: 19136304]
8. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976; 58:259–263. [PubMed: 951142]
9. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr. 1984; 104:849–854. [PubMed: 6726515]
10. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr. 1985; 106:522–526. [PubMed: 3973793]
11. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. Pediatrics. 2003; 111:1416–1421. [PubMed: 12777562]
12. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20:629–637. [PubMed: 19158356]

Table 1

Characteristics of study population

	No. of Patients* (%)	Mean Age (SD)	Range
Sex			
Male	43 (75)		
Female	14 (25)		
Race			
White	53(93)		
Black	2 (3.5)		
Other	2 (3.5)		
Primary Closure			
GFR within 0–7 days	20	2 days (2)	0–5 days
GFR 8–56 days	20	24 days (17)	8–54 days
Delayed Primary Closure			
GFR 57 days–2 years	9	214 days (203)	59–699 days
GFR > 2 years	4	4.2 years (1.3)	2.1–5.4 years
Bladder Neck Reconstruction	13	5.8 years (2.6)	2.1–11.3 years
Post-BNR Follow-up			
Males	21	15.1 years (5.6)	5.5–25.1 years
Females	6	14.8 (7.5)	6.8–26.8 years

* Four patients had GFR values only at post-BNR follow-up.

Table 2

Comparison of estimated GFR values between exstrophy patients and normal children

Evaluation timepoint	Age at GFR measurement	Exstrophy mean eGFR (SD) (ml/min/1.73 m^2)	Population mean eGFR (SD)[11] (ml/min/1.73 m^2)	p-value
Primary Closure	0–7 days (n=20)	42.5 (14.5)	40.6 (14.8)	0.55
	8–56 days (n=20)	44.8 (12.0)	65.8 (24.8)	< 0.0001
	57 days – 2 years (n=9)	68.0 (24.8)	95.7 (21.7)	0.01
	>2 years (n=4)	108.8 (56.1)	133 (27)	0.45
BNR	2–12 years (n=13)	137.1 (49.6)	133 (27)	0.77
Post-BNR follow-up	2–12 years (n=9)	124.5 (23.3)	133 (27)	0.31
	Males ≥ 13 years (n=15)	175.6 (61.2)	140 (30)	0.04
	Females ≥ 13 years (n=3)	128.8 (27.2)	126 (22)	0.87