

Original Article

Urinary Albumin and Interleukin-8 Levels are not Good Indicators of Ongoing Vesicoureteral Reflux in Children who have no Active Urinary Tract Infection

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Abstract

Introduction: Vesicoureteral reflux (VUR) is a risk factor for kidney scarring, hypertension and declining renal function. Standard diagnostic methods are invasive and can cause exposure to radiation and urinary tract infections (UTIs). We aimed to investigate urine albumin and interleukin-8 levels as markers of ongoing VUR and renal damage in children without UTIs.

Methods: Random urine samples were collected from 51 children, including 16 children with VUR (group A), 17 children with resolved VUR (group B) and 18 normal children (group C). The diagnosis of VUR or resolved VUR was confirmed by voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRNC). All children had normal kidney function and had no evidence of UTI in the preceding three months. Random urine specimens were assayed for albumin (Alb), creatinine (Cr) and interleukin-8 (IL-8) and mean values were compared by one way ANOVA.

Results: In groups A and B, the mean age at first UTI was 31.7 ± 2.4 and 27 ± 2.0 months respectively. In group A, the mean duration between VUR diagnosis and study entrance was 30 ± 9.1 months. In group B, the mean duration between VUR diagnosis and recovery was 19.9 ± 1.3 months. Overall, 76.4% of affected children had bilateral VUR and 41.2% had severe VUR. There were no significant differences in urinary Alb, IL-8, Alb/Cr and IL-8/Cr between the three groups.

Conclusion: The current study does not support the hypothesis that microalbuminuria or urinary IL-8 are good indicators of ongoing VUR and renal injury in children.

Keywords: Children; Interleukin-8; Microalbuminuria; Vesicoureteral Reflux.

The authors declared no conflict of interest

Introduction

Vesicoureteral reflux (VUR) is one of the most common contradictory dialogues in pediatric nephrology and urology. VUR has been reported to be present in 30–50% of children with recurrent urinary tract infections (UTIs) [1]. It is a dilemma for physicians, patients and their parents because of invasive diagnostic procedures, the need for long term follow up, potential complications and controversial treatment [2]. The close association between VUR, UTIs and renal scarring indicates that VUR can induce scar formation in the kidney. Reflux of infected urine may cause scarring in susceptible kidneys with the potential to compromise renal function. This supposition has become the starting point for existing therapeutic modalities intended to avoid renal parenchymal damage [3].

Dimercaptosuccinic acid (DMSA) renal scan is the primary diagnostic tool for the detection of renal scarring. Previous studies that used DMSA scans did not support the concept that VUR predisposes patients with acute pyelonephritis to renal scarring [4, 5]. Up to now, plenty of efforts have been undertaken to elucidate the association between measurement of IL6, IL8 and microalbuminuria and renal involvement in UTIs [4-7]. However, less is known about their role after the acute infection has resolved.

The term "microalbuminuria", defined as an increased urine albumin excretion above the expected reference range for a healthy population, was first introduced in medical literature about 30 years ago when Liberty and Svendsen explained the significance of urinary albumin values below the detection limit of standard dipstick testing [8]. After that, the predictive value of microalbuminuria

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has been shown for several diseases such as diabetic nephropathy [9], cardiovascular mortality in patients with type II diabetes [10] and cardiovascular and renal disease in both diabetic and non-diabetic patients [11, 12]. Recently, Basic *et al* demonstrated that albumin excretion was significantly increased and creatinine clearance was significantly reduced in patient with severe VUR (grade IV-V) [13].

Interleukin-8 (IL-8) is a pro-inflammatory protein mainly involved in the initiation and amplification of acute inflammatory reactions and in chronic inflammatory processes [5]. It has been reported to be associated with different infectious, malignant and neurological diseases. Different studies demonstrated that IL-8 is present only in trace amounts in the urine of healthy subjects, while in children and adults with various forms of UTIs the urinary levels of these cytokines are significantly increased [4-6]. More recently, it was reported that urine IL-8 levels remain elevated in infants with VUR even in the absence of UTI [14]. It seems that measuring urinary IL-8 is potentially useful in assessing the localization and severity of inflammation within the urinary tract [15].

In this study we aimed to investigate the mean random urine albumin and IL-8 levels in children with VUR and resolved VUR in the absence of UTIs.

Methods

This cross-sectional study was performed in 17 Shahrivar Children's Hospitals in Iran. Random urine samples were collected from 51 children, including 16 children with VUR (group A), 17 children with resolved VUR (group B) and 18 normal children (group C).

Inclusion criteria for children in groups A and B were age between 2-10 years, no history of UTI in the preceding three months, confirmed diagnosis of VUR or resolved VUR by voiding cystourethrogram (VCUG) or direct radionuclide cystography (DRNC) and normal kidney function. Absence of UTI was confirmed by supra-pubic aspiration in non-toilet trained children and midstream collection in continent children. Informed consent was obtained from parents. The Ethics Committee of Guilan University of medical sciences (Rasht, Iran) approved the study protocol.

Data such as age, sex, unilateral or bilateral reflux was extracted from children files and the severity of reflux was defined by VCUG or DRNC. Grades 1 and 2 of VUR were considered as mild, grade 3 as moderate and grades 4 and 5 as severe VUR. DMSA scan was used to evaluate renal scars. Random urine specimens were collected and the levels of urine albumin (Alb), creatinine (Cr) and interleukin-8 (IL-8) were measured in

a single laboratory. Albumin concentration was measured by turbidometric method using Hitachi autoanalyzer and IL-8 concentration was measured by radioimmunoassay (RIA).

Mean values for urine Alb and IL-8 as well as Alb/Cr and IL-8/Cr ratios in the three groups were compared by one way ANOVA test using SPSS Version 15 (SPSS Inc., Chicago, IL, USA). P value less than 0.05 was considered to indicate statistical significance.

Results

Fifty-one children with a mean age of 5.7 ± 2.5 years were entered in this study (Table-1). In groups A and B, the mean age at first UTI was 31.7 ± 2.4 and 27 ± 2.04 months respectively. In group A, the mean duration between VUR diagnosis and study entrance was 30 ± 9.1 months. In group B, the mean duration between VUR diagnosis and recovery was 19.9 ± 1.3 months.

Overall, 76.4% of affected children had bilateral VUR and 41.2% had severe VUR (Table-2). DMSA scan demonstrated renal scarring in four children; including three children in group A and one child in group B.

There were no significant differences in urinary Alb, IL-8, Alb/Cr and IL-8/Cr between the three groups (Table-3).

Discussion

VUR occurs in approximately one percent of newborns, and its incidence is as high as 30 to 45 percent among young children with urinary tract infection (UTI). The present medical and surgical treatment modalities for VUR are based on the hypothesis that it can be detrimental to the kidneys because it will transfer bacteria from the lower urinary tract to the kidneys. Subsequent hypertension, decreased renal function, proteinuria, and end-stage renal disease (ESRD) may result from widespread renal scarring [2, 3].

The most important presentation of VUR is UTI, so radiological surveillance by VCUG or DRNC of each child aged less than 5 years after his/her first febrile UTI is mandated. These diagnostic methods are invasive and can cause exposure to radiation and UTIs. To date, several attempts were done to replace VCUG and DRNC by other non-invasive diagnostic methods. Different substances have been evaluated in urine for this purpose, including IL-6 and soluble TNF receptor-1 [16].

Smellie *et al* believe that sterile reflux cannot harm kidneys [3], but Galankis and colleagues suggest that the inflammatory process in VUR continues even after UTI has resolved [14]. Their supporting evidence was urine IL-8 levels that remained elevated in infants with VUR

Table-1: Demographic characteristics of the study population

	VUR (A)	Unresolved VUR (B)	Controls (C)
Number	16	17	18
Age (mean \pm SD, years)	5.8 \pm 3.1	6.3 \pm 2.4	5.1 \pm 2.0
Males/Females (N)	2/14	1/16	11/7

Table-2: Types and severity of VUR in groups A and B

	VUR (group A)		Resolved VUR (group B)	
	N	%	N	%
Types of reflux				
Bilateral	9	56.3	13	76.4
Unilateral	7	43.7	4	23.6
Severity of reflux				
Mild	8	50.0	7	41.2
Moderate	5	31.3	3	17.6
Severe	3	18.8	7	41.2

Table-3: Mean values of urinary Alb, IL-8, Alb/Cr and IL-8/Cr in the three studied groups

	VUR (A)	Resolved VUR (B)	Controls (C)	P value
Alb (mean \pm SD)	19.7 \pm 13.4	25.4 \pm 12.5	17.1 \pm 11.1	0.1
Alb/Cr (mean \pm SD)	5.1 \pm 4.7	5.7 \pm 7.5	5.2 \pm 4.4	0.9
IL-8 (mean \pm SD)	23.0 \pm 40.4	11.6 \pm 10.2	43.8 \pm 140.7	0.5
IL-8/Cr (mean \pm SD)	1.2 \pm 2.9	0.2 \pm 0.1	1.6 \pm 5.2	0.5

VUR: vesicoureteral reflux, Alb: albumin, IL-8: interleukin-8, Cr: creatinine

even in the absence of UTI [22]. Similar results were also reported by other authors [14, 17, 18]. These results are different from our findings which revealed no significant differences in IL-8 urinary concentration in children with and without VUR in the absence of UTI. Lack of association between urinary IL-8 and VUR was also reported by Jutley *et al* [19]. One potential explanation for this discrepancy may be that the inflammatory process in VUR takes a while to subside after an episode of UTI. In this study, we excluded patients who had an episode of UTI over the preceding three months.

Microalbuminuria was introduced in different branches of medicine over the last three decades as a marker of different diseases [8-11]. VUR has been proposed to be included in this list and Basic *et al* found elevated levels of urinary albumin excretion in patients with high

grade VUR [13]. Our results are not consistent with their findings. The absence of significant differences in urinary albumin excretion between patients with and without VUR in this study may indicate that microalbuminuria is not an accurate indicator of ongoing damage in these patients or that ongoing injury ceases after resolution of an acute UTI episode. Nevertheless, we must consider the possibility that albumin excretion has some racial and age related diversity [20].

Conclusion

The current study does not support the hypothesis that microalbuminuria or IL-8 are good indicators of ongoing VUR and renal injury in children.

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