

Urinary Tumor Necrosis Factor-Alpha a Good Indicator for Inflammatory Response in Pyelonephritis

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ABSTRACT

Background: TNF- α is one of the most potent cytokines in proinflammatory reactions.

Objectives: This article contributes to evaluate the correlation between urinary TNF- α and inflammatory response markers in children with acute pyelonephritis.

Patients and Methods: This cross sectional study, was performed on children with acute pyelonephritis. Fresh random urine samples were obtained before treatment of pyelonephritis. Urine samples were tested for TNF- α and creatinine. We also evaluated our patients with routine biochemical studies.

Results: One hundred and twenty children with acute pyelonephritis were evaluated. Urinary TNF- α /Cr was 0.0051 ± 0.00083 Pg/g creatinine. The authors found out a significant difference in urinary TNF- α /Cr between patients who have normal and abnormal levels of urine leukocytes, urine protein, urine culture, erythrocyte sedimentation rate and C- reactive protein. This study revealed a significant correlation between urinary TNF-alpha and urine WBC ($r = 0.36$, P value = 0.02), ESR ($r = 0.75$, P value = 0.03) and CRP ($r = 0.58$, P value = 0.02).

Conclusions: We concluded that urinary TNF- α /Cr might be a good indicator for inflammatory response in children with acute pyelonephritis.

Keywords: Tumor Necrosis Factor-alpha; Pediatrics; Pyelonephritis

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► Implication for health policy/practice/research/medical education:

Urinary tract infection (UTI) is one of the most commonest infections in children. Current researches try to detect the infection and differentiate between upper and lower UTI by evaluation of urinary proteins.

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1. Background

Urinary tract infection (UTI) is by far the most common serious bacterial infection in febrile young infants (1). UTI may cause inflammation of the renal parenchyma and may lead to impairment in renal function and scar formation. Among the immunocytes involved in the defense against UTI, granulocytes play a crucial role (2, 3). Now a days analysis of urinary inflammatory cytokines and mediators are important areas for nephrologic researches. Cytokines are small proteins which are important for the orchestration of inflammatory processes (4). The results of previous researches suggest that urinary cytokines may be elevated in urinary tract infections and may play a key role in defining pyelonephritis (5-9). TNF- α is one of the most important and most potent cytokines in proinflammatory reactions. Role of TNF- α in monitoring the therapeutic response to BCG in bladder cancer (10), in evaluation of pediatric febrile infections (11), in shistosoma haematobium-induced urinary-tract morbidity (12, 13), in glomerulonephritis (14-16) and in pathogenesis of allograft rejection (17) has been reported before. Recent studies show the role of TNF- α in apoptosis and pathogenesis of pediatric renal diseases (18, 19), in the pathogenesis and progression of renal injury in diabetes mellitus, as an accurate marker for diagnosis of acute pyelonephritis (20, 21) and as a pathogenic indicator of multidrug resistance *E. coli* in urosepsis (22). A great majority of these studies have been done on serum level of TNF- α ; however, few researchers have studied the changes in the urinary level of TNF- α in UTI. Some of these studies have reported no change in the urinary level of TNF- α in children with UTI (23, 24) and some showed an increased level of urinary TNF- α in pediatric UTI (25, 26).

2. Objectives

This article aims to evaluate the correlation of urinary TNF- α with inflammatory response markers in children with acute pyelonephritis documented by dimercaptosuccinic acid scintigraphy (DMSA).

3. Patients and Methods

This cross sectional study was conducted from March 2006 to April 2011 on children with acute pyelonephritis

admitted in Mofid children's hospital. The diagnosis of acute pyelonephritis was confirmed based upon standard criteria [fever (more than 38 ° C), abdominal pain, anorexia, dysuria, leukocyturia (more than 5/Hpf), positive urine culture, increased ESR (erythrocyte sedimentation rate > 20 mm/hr), positive CRP (C-reactive protein \geq 1+) and abnormal DMSA scan findings in favor of pyelonephritis (27). Our patients have been previously healthy with no signs of any nephrologic or urologic problems. We excluded patients with recent history of antibiotic consumption, (during previous 7 days) and patients with renal insufficiency or any kind of known kidney or urinary tract disorders or other accompanying infections. Fresh random urine samples were obtained at admission and were tested for TNF- α (ELISA colorimetric, SANQUINE, USA) and creatinine (Jaffe reaction, auto analyzer, RA 1000). All patients were treated with 75 mg/kg/day intravenous ceftriaxone with or without 15 mg/kg/day intravenous amikacin based on antibiogram results). We also evaluated our patients with routine biochemical studies and inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The ethics committee of the Shahid Beheshti medical university and pediatric infectious research center approved this study.

Data were expressed as mean \pm SD. Mann-Whitney U test and Pearson's correlation coefficient was used for analysis. Statistic test was two-tailed and was considered significant when $P \leq 0.05$.

4. Results

One hundred and twenty children (84% female) with acute pyelonephritis, mean age 38 ± 35 months were evaluated. The demographic data and clinical features of study group are shown in *Tables 1* and *2*. Urinary TNF- α /Cr on admission was 0.0051 ± 0.00083 Pg/g creatinine.

This research revealed a significant correlation between urinary TNF-alpha and urine WBC ($r = 0.36$; P value = 0.02), ESR ($r = 0.75$; P value = 0.03) and CRP ($r = 0.58$; P value = 0.02). Furthermore, our study showed a significant difference between the level of urinary TNF- α /Cr in patients with normal and abnormal urine leukocytes, urine protein, urine specific gravity, urine culture, ESR and CRP (all P values were < 0.001; See *Table 3*).

Table 1. Demographic Data of Study Group (mean, Standard deviation)

	Minimum	Maximum	Mean	SD
Age, mon	1	132	38.14	34.96
Body weight, Kg	3	47	13.81	9.46
White blood cell, No/micL	3200	29000	15830	10000
ESR, mm/hr	2	102	45.16	31.47
CRP, mg/dL	2	80	45	20
Urine WBC, No/micL	2	30	19.45	10.84
Urine TNF- α /Cr, Pg/g creatinine	0.0041	0.064	0.005114	0.000834

Table 2. Clinical and Paraclinical Features of Study Group

Clinical features	Frequency, %
Hematuria	2.6
Fever	51.5
Dysuria	12.6
Vomiting	13.9
Abdominalpain	7.6
Abnormal CRP	40
Abnormal ESR	80
Leukocyturia	100
Proteinuria	30
Nitrite positive	36.2
Positive urine culture	85.7
Ecoli	69.2
Klebsiella	9.8
Enterococ	1.7
Pseudomonas	3
Enterococ	2

Table 3. Comparison of TNF- α /Cr in Children With Pyelonephritis With Different Levels of Other Inflammatory Markers.

	Urine TNF- α /Cr (pg/g; mean \pm SD)	P Value
Urine leukocytes		< 0.001
Abnormal	0.0045 \pm 0.0009	
Normal	0.0015 \pm 0.0006	
Urine protein		< 0.001
Abnormal	0.0039 \pm 0.0008	
Normal	0.0016 \pm 0.0009	
Urine specific gravity		< 0.001
Abnormal	0.0043 \pm 0.0007	
Normal	0.0013 \pm 0.0005	
Urine culture		< 0.001
Positive	0.0039 \pm 0.0009	
Negative	0.0015 \pm 0.0009	
ESR		< 0.001
Abnormal	0.0040 \pm 0.0003	
Normal	0.0014 \pm 0.0004	
CRP		< 0.001
Abnormal	0.0039 \pm 0.0002	
Normal	0.0014 \pm 0.0006	

It means that the level of urinary TNF- α /Cr were significantly higher in patients with abnormal urine leukocytes, urine protein, urine culture, ESR and CRP than who have normal range of these examinations in children

with acute pyelonephritis.

5. Discussion

In the present study, we sought to gain more insight into the correlation of urinary TNF- α with inflammatory factors in children with acute pyelonephritis. Our research revealed a significant correlation between Urinary TNF-alpha and urine WBC ($r = 0.36$), ESR ($r = 0.75$) and CRP ($r = 0.58$). Cytokines and cytokine receptors are involved in the systemic and local inflammatory response in patients with urinary tract infections (28). TNF- α is rapidly recruited to the bladder in urinary tract infection and contributes directly to the innate defense against various viral and bacterial infections (29). Biyikli et al. showed that TNF- α , renal tissue malondialdehyde and myeloperoxidase levels are elevated in rats with acute and chronic pyelonephritis (30) and Wolfs determined the role of TNF- α in immunosurveillance during inflammation at the site in which ascending bacteria enter the kidney tissue, the collecting ducts and the distal part of the nephron (31). Florquin reported that the production of tubular epithelial urokinase receptor was strongly up-regulated after stimulation with TNF- α during urosepsis (32). Author's previous study reported that urinary TNF- α -creatinine ratio was significantly increased in pediatric acute pyelonephritis and it decreased after appropriate therapy (25). Tullus showed that urinary soluble TNF receptor levels were higher during acute pyelonephritis (33) and Davidoff showed U TNF- α is significantly elevated in patients with microhematuria and cystitis compared to normal (26). Sadeghi et al. revealed an increased level of urinary cytokines like TNF- α during bacteriuria in kidney transplant patients (34).

Regardless of these results Dariusz reported that concentrations of TNF- α in serum and urine were below the limit of detection in the vast majority of controls and pyelonephritic patients, and no significant differences were found between the two groups; Kim et al's study showed the same results (24-25). Larger studies of the role of this factor in pyelonephritis and the correlation between its level and other investigations of pyelonephritic patients such as imaging studies have not been performed so far. According to our results, there is a significant correlation between the level of urinary TNF- α /Cr and inflammatory markers such as ESR, CRP, urinary leukocytes and even urine culture in patients with acute pyelonephritis. De Man has reported the correlation between the level of circulatory tumor necrosis factor with fever, increased ESR and CRP in acute symptomatic UTI (35) but few studies have been performed on correlation between urinary TNF- α and inflammatory markers of pyelonephritis.

Ultimately the results of these studies might reveal the efficacy of urinary TNF- α /Cr in anticipation of the inflammatory factors in pyelonephritis. Our findings have addressed the real role of urinary TNF- α in better and faster diagnosis of pyelonephritis and for follow up of these pa-

tients. The authors recommend more and wide researches to get more information for better circumlocution of this fact.

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Authors' Contribution

None declared.

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