RESEARCH ARTICLE

Diagnostic Values of Some Immunological Markers in Patients With Urinary Tract Infection

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ABSTRACT

The study was carried out in Tikrit city from January 1st to July 1st 2015. These patients admitted to Sallah Al-Deen general hospital and primary health care centers in Tikrit city. The number of patients with Urinary tract infection was 300 patients whom their ages ranged from 2 months to 70 years. The control group included 100 individuals who appeared healthy with no history of UTI. A urine direct and indirect examination was held for all the patients and control. The result showed 70 % positive specimens in culture media. Most isolates were *Staph. aureus* with 25%. *Staph. saprophyticus* 24% , *E. coli* 16%, *K. pneumoneae* 5% . *Pseudomonas aeruginosa*, and *Proteus* Spp. and *Citrobacter frundii* were present in about 5% and 7%, respectively. A member of (yeast-like fungi) *Candida Spp.* was also found in the ear in about 11%. Blood analysis showed that there was a significant increase in WBC, ESR, neutrophil, and CRP in UTI patients compared to the control group. Serum cytokines showed that the mean level of serum IL-1 family (IL-1α & IL-1β), IL-6, and IL-8 in addition to TNF-α, all were significantly higher in UTI patients than in the control group. Also, results showed a significant increase in serum cytokines in UTI patients with gram-negative bacteria in comparison with gram-negative bacteria.

Conclusion: A significant difference was found between patients with UTI and control group regarding some immunological markers. They are also can differentiate between gram-positive and negative UTI.

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial diseases in men, women of all ages. Early diagnosis and proper antimicrobial treatment are required to minimize renal complications and in extent kidney damage. Bacteria are the main reason of infection but we cannot overlook the role of fungi and viruses as a causative agents. However, the role of viral and fungal UTI is considered to be rare phenomena. Though the infection may seem to be harmless in the initial stages of infection, the patient may show a variety of symptoms as the stage progresses, and it may lead to death in rare circumstances where the infection is severed.

Urine analysis is one of the most important and essential tests that is regularly used in clinical laboratories in the diagnosis and follow up of UTI.[1] Urine sedimentation test has been the most used methodology for examining urine cells and microorganisms. Screening test with dipstick reagents is mostly used as a complement to urinalysis examination tests.

Cytokines are small proteins produced by a broad range of cells in response to infections and inflammation. Interleukin-6 is a pro-inflammatory cytokine, which is an important mediator of acute phase response in an early stage of bacterial infection[2] Interleukin-1 family is a group of eleven cytokines that plays a distinctive role in the regulation and initiation of the immune response.[3]

Interleukin-8 is a chemokine produced by macrophages, epithelial, and endothelial cells, and its main role is the migration of neutrophils to the place of inflammation and induces phagocytosis once they arrived.[4] Increased serum concentrations IL-6 and IL-8 were detected during the acute phase of UTI. Thus, cytokines and acute-phase inflammatory cells synergistically reflect the inflammation associated with UTI. The authors also concluded that cytokine responses to

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UTI have different responses regarding the severity of the infection and diversity of host, and the unstable nature of microbes can affect cytokine activation.[5]

Aim

This study aims at determining the diagnostic values of some immunological markers in patients with UTI.

The objectives of this study were to evaluate the diagnostic levels of cytokines and pro-inflammatory factors (WBC, ESR, CRP, IL-1 family including (IL-1α & IL-β), IL-6, IL-8, and TNF-α) in diagnosis of urinary tract infection. And to assert if there is organism-specific response.

MATERIAL AND METHOD:

This cross-sectional study was effectuated through the period of 1st January 2018 to 1st July 2018 on the patients admitted to Sallah Al-Deen hospital and health centers in Tikrit city. The patients' age ranged between two months and seventy years. The study included 300 patients with 210 culture-positive UTI and one hundred age and sex-matched healthy participants as a control group.

UTI was diagnosed according to clinical symptoms and urine analyses (direct examination, Microscopic examination, and culturing).

Urine samples were collected by either mid-stream technique or by using a sterile urine bag for infants. The samples were examined within thirty minutes of collection. After direct urine culture (physical appearance, rabid urine dipstick and microscopic examination) the samples were conducted to culturing as well.

Serum samples were obtained from both patients and control and stored at -20°C until they were tested. Concentrations of IL- 1 family, IL-6, IL-8, and TNF-α, were measured by ELISA (Komabiotech- technology, France). And the results were read in an automated microplate reader (Anthos Labtec Instruments, Austria).

Data analysis and statistics by The Mann-Whitney U test and Pearson's correlation test were used. A p-value less than 0.05 was considered statistically significant.

RESULTS

Out of the 210 culture proved UTI, 130 of them were females and 80 males distributed into five age groups, Table 1. The mean age of UTI patients was 26.004 ± 22.663 years, compared to the control group 20.236 ± 20.126 years (p= > 0.05), as shown in Table 2. Gram-positive bacteria in urine culture were found in (52%) of the cases with UTI, while Gram-negative bacteria were found in (25%) while yeast was found in (11%) of the cases.

Staph. aureus was the most common bacterial species isolated from urine in addition to *Staph. Saprophyticus* , *E. coli* , *K. pneumonia* and *Citrobacter frundii* also a positive result for yeast, specifically *Candida albicans* was also found on culture media. Table 2 shows that there was a significant increase in WBC, ESR, neutrophil and CRP in patients with UTI in comparison to control group ($P = 0.001$).

The mean level of serum IL-1α (10.691 ± 2.342), IL-1β (10.948 ± 2.982), IL-6 (30.710 ± 7.874), IL-8 (245.607 ± 116.041) and TNF-α was (2.974 ± 0.723) were statistically higher in UTI patients than in control group, as it is shown in Table 3. Also,

Table 1: Distribution of patients among different age groups

No. of group	*Age groups in years*	*Female*		*Male*		*Total*	
		No.	*%*	*No.*	*%*	*No.*	*%*
1	≤ 2 month	15	6.92	8	10	23	10.95
2	5 - 15	24	18.46	20	25	44	20.05
3	15 - 30	66	50.76	31	38.75	97	46.19
4	30 - 50	18	13.84	11	13.75	29	13.80
5	50 - 70	7	5.38	10	12.5	17	8.09
	Total	130	100	80	100	210	100

Table 2: Comparison between laboratory and clinical data of the studied group

Parameters	*Patients with UTI (No. = 210)*	*Control group (No. = 100)*	*p-value*
Age (1-70 years)	26.004 ± 22.663	20.236 ± 20.126	> 0.05
Gender (male/female)	80/130	40/60	
CBC			
HB (g/dl)	12.187± 1.766	11.919 ± 1.846	> 0.05
RBCs (x10*9/L)	4.633 ± 0.844	4.439 ± 0.835	> 0.05
WBCs (x10*9/L)	11.367 ± 3.339	6.711 ± 1.545	< 0.001*
Neutrophil %	76.64 ± 10.465	58.33 ± 7.455	< 0.001*
CRP (mg/dl)	25 ± 17.581	10 ± 1.665	< 0.001*
ESR (1st hour)	30.8 ± 5.329	13.1 ± 2.807	< 0.001*
Urin analysis			
Pus cells	41 ± 14.552	7.45 ± 3.299	< 0.001*
RBCs	6 ± 1.491	2 ± 1.252	< 0.001*

*significant

Table 3: Comparison between cytokines in patients with and without UTI.

Parameters	*Patients with UTI (No.= 210)*	*Control group (No.= 100)*	*P- value*
IL- 1 α	10.691 ± 2.342	0.754 ± 0.852	< 0.001*
IL- 1 β	10.948 ± 2.982	0.945 ± 0.794	< 0.001*
IL- 6	30.710 ± 7.874	6.451 ± 1.419	< 0.001*
IL- 8	245.607 ± 116.041	20.44 ± 16.793	< 0.001*
TNF- α	2.974 ± 0.723	1.531 ± 0.971	< 0.001*

*Significant

Table 4 shows a significant increase in serum cytokines in UTI patients with gram-negative bacteria in comparison with gram-negative bacteria.

Correlation between serum cytokines and systemic inflammation markers are presented in Table 5.

DISCUSSION

Results showed that UTI infection samples gave about 210 positive bacterial culture, and about 90 of samples registered as a negative bacterial culture even after 48 hours, which may be due to the consumption of antibiotics by the patients or the presence of another type of causative agents.

Study groups of patients with UTI were divided into five age groups according to age and gender. The infection was more frequent at the age between 5 and 30 years old and was more frequent in females, as shown in table 2. UTI is more common in women than men, as well as young children of both genders. There are risk determinants in this age group include physiologic and anatomic factors, such as estrogen deficiency and obstructing lesions, genetic factors, such as antibiotic consumption or functional status, and blood group secretor status.[6]

Cytokines are inflammatory mediators which are produced as a response to infections and inflammations in different sites of the body. IL-6 and IL-8 are two of the most important cytokines.[7] IL-6 is a pro-inflammatory cytokine that plays a significant role in responding to microbial infections. Interleukin 8 (IL-8) is another inflammatory cytokine secreted by macrophage and endothelial cells and works as a chemoattractant for neutrophil during infectious diseases in response to IL-1 and tumor necrosis factor-α.[8,9] IL-8 also plays a role in T cell and B cell proliferation and the secretion of C-reactive protein and immunoglobulins.[10-13]

Certain types of bacteria, specifically opportunistic bacteria, can bind different host cytokines[14-20] and increase their growth as an immune response[14,21,22] forming biofilms or changing virulence characteristics.[15,16,23]

Researchers of the several studies think that invasion of P fimbriae and lipid A axial part of the endotoxin present in *E. coli* and other types of gram-negative bacteria induce inflammatory response and elicit the release of IL-1, IL-6, and IL-8 cytokines in the site of the infected area, and subsequently increase these types of cytokines in urine infection.[24,25,26] Among the several mechanisms that microorganisms have developed to evade host defense mechanisms,[27] there is a recent report indicates that pathogenic *Escherichia coli* may find the presence of IL-1β as a growth factor for itself.[28] Although the increase in nosocomial infections might be due to impaired host defense response. An alternative theory says that the host immune response may enhance the environment for bacterial growth.

A study was done by Gurgoze *et al*.,[29] on 76 children infected with UTI showed that inflammatory parameters such as ESR, C-reactive protein, WBC, neutrophil, PCT, IL-1β, and IL-6 were significantly higher in patients with upper UTI than lower UTI. Gurgoze *et al*.,[29] then proved that there was a positive significant correlation between upper UTI and IL-1β and PCT, but not with IL-6.

Table 4: Comparison between serum cytokines and patients with gram positive and negative UTI

Parameters	*Patients with UTI*		*Control group*	*P- value*
	Gram-positive	*Gram-negative*		
IL- 1 α	9.402 ± 4.812	11.569 ± 2.410	0.754 ± 0.852	< 0.001*
IL- 1 β	9.720 ± 10.703	10.462 ± 2.991	0.945 ± 0.794	< 0.001*
IL- 6	19.21 ± 7.618	26.56 ± 10.917	6.451 ± 3.419	< 0.001*
IL- 8	129.34 ± 103.381	263.90 ± 198.641	20.44 ± 16.793	< 0.001*
TNF- α	2.702 ± 0.521	2.140 ± 0.138	1.531 ± 0.971	< 0.001*

*significant

Table 5: Comparison of serum cytokines between patients with upper and lower UTI

Parameters	*Patients with UTI*		*Control group*	*P- value*
	LUTI	*UUTI*		
IL- 1 α	8.044 ± 2.514	11.349 ± 2.609	0.754 ± 0.852	< 0.001*
IL- 1 β	8.442 ± 1.105	10.392 ± 2.325	0.945 ± 0.794	< 0.001*
IL- 6	18.050 ± 4.541	24.531 ± 7.624	6.451 ± 3.419	< 0.001*
IL- 8	106.72 ± 89.281	197.82 ± 123.918	20.44 ± 16.793	< 0.001*
TNF- α	1.862 ± 0.714	2.341 ± 1.610	1.531 ± 0.971	< 0.001*

*significant

Also in the study of Sheu *et al*.,[24] on children of one to 121 months old have a UTI showed that the values of inflammatory parameters such as CRP, WBC, IL-6 and IL-8 in patients with UUTI were higher than that in LUTI patients.

Increased urinary TNF- α, IL-1 (IL-1α & IL-1β), IL-6, and IL-8 levels have been reported in patients with UTI compared to a control group and those with LUTI.[10,30-34] Similarly, urinary IL-1, IL-6, and IL-8 found to be in high concentrations during the acute infection compared to a healthy control group.

Additionally, varies researches showed instant removal of urinary cytokines after the beginning of antibiotic treatment. Therefore, defining urinary interleukins is helpful for treatment evaluation in UUTI, and significant elevation in the concentrations of urinary interleukins is an indication of treatment modifications.[11,35,36] Subsequently, an increase in urinary interleukins levels may decrease antibiotic treatment and was taken into consideration for therapeutic follow-ups in UTI patients.[30]

A significantly positive correlation was found between the cytokine response and the severity of infection.[35] A significantly correlated was also found between IL-1α, WBC, and CRP in a study of Sheu *et al*.[10] TNF-α was the additionally evaluated mediator of bacterial infections in this study, and it is considered to be one of the most rapid and reliable tests for the diagnosis of UUTI.[37,38] It is notably decreased after antibiotic treatment.[39] Anyhow, TNF-α concentrations didn't give significant changes in Lins study,[40] which is not compatible with the results of our current study.

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