ORIGINAL ARTICLE

Evaluation of oxidant-antioxidant balance and total antioxidant capacity of serum in children with urinary tract infection

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ABSTRACT

Background: Urinary tract infection (UTI) is the most common bacterial infections in children. This studyaimed to investigate the oxidative and antioxidate status of plasma in patients with UTI and to compare them with those of the controls. **Methods:** This case–control study of 50–75 children in the given order was performed in 2013 at the Pediatric Clinic of infections in Zahedan Hospital of Ali Ibn Abi Talib. The antioxidative status of plasma were evaluated by measuring the total antioxidant capacity (TAC) The oxidative status of samples was assessed by measuring the total peroxide and the oxidative stress index (OSI) levels. The means of the parameters were compared and the relationship among them was determined. Data were analyzed using SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Student's *t*-test and Mann–Whitney U-test were applied in various situations of our questions; 95% confidence interval was considered for the level of significance. **Results:** The results showed that total oxidant serum status in UTI patients was higher compared to controls when total antioxidant serum was lower. The balance of oxidant-antioxidant serum was in favor of oxidant serum and this term was confirmed by OSI. **Conclusion:** Our results showed that the plasma levels of TAC in patients with UTI were decreased compared to controls, and oxidant-antioxidant balance and OSI caused increased OS in patients.

Key words: Children, oxidant-antioxidant balance, oxidative status, total antioxidant capacity, urinary tract infection

INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial diseases in children.[1] The prevalence of UTI has been estimated that 7% of girls and 2% of boys will be experienced at least one episode of UTI before 6 years of age.[2] Moreover, *Escherichia coli* are responsible for about 80% of febrile and afebrile UTIs.[3] This disease is running-in with kidney, urinary tract, and bladder.[4] Its clinical symptoms are dysuria, frequency and urgency abdominal and flanks pain with or without fever.[5] UTI sometimes do not show specific signs in children unlike adults and occurs with unusual signs such as weight loss, failure to thrive, anorexia, jaundice, and fever with the unknown resource. Diagnosis and proper treatment are very important because of early complications such as sepsis, bacteremia, and late complications such as hypertension and chronic renal failure (RF).[6] Despite of close relation between urinary system and the outside circumstances of the body and the entrance of pathogenic bacteria into the urinary system, there are several factors to clean up and defend against these pathogens.[1] ROS interferes in host defense mechanisms and causes cell damage. Producing ROS is low typically, and this low-levels are necessary

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for several biologic processes including intracellular differentiation, cell production, and arrest of cell growth, immunity, and defense against micro-organisms.[7,8,25] In human body, there is a fine and precise balance between the production and elimination of ROS.[6] External antioxidants such as Vitamins E and C and endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase have role in inhibition of some oxidants such as hydroxyl radicals, superoxide.[7] Increase of ROS with or without a reduction in antioxidant defenses is defined as oxidative stress (OS) and causing the destruction of biologic macromolecules means that the pathogenesis of many involved.[5] In other words, OS is resulted by an imbalance between oxidant and antioxidants.[7] To reduce OS in body, antioxidants act as cleaning-free radicals and are thought to have a role in complete safety.[7] This study aimed to evaluate the antioxidant capacity of plasma levels of total antioxidant capacity (TAC) and oxidant-antioxidant balance in children with UTI in comparison with controls.

METHODS

This case–control study was conducted on children <15-year-old who were referred to Pediatric Nephrology Clinic due to the complaints of UTI symptoms. Sample size was determined as 125 in which 50 patients and 1.5 times for controls.[7] The local Ethical Committee (code number 5795) of Zahedan University of Medical Sciences approved the study protocol, and written informed consent was obtained from the parents. For suspected cases, urine culture and urinalysis were performed. Patients with the following criteria were included in the study: Positive reaction for leukocyte esterase in urine test strip and/or pyuria (microscopic examination of urine sediment: ≥10 white blood cells). UTI was diagnosed when there was significant bacteriuria (>100.000 colony-forming units/mL) in midstream flow by clean – catch or 10^3 in using catheter or suprapubic method in the urine culture. Exclusion criteria included of refusing cooperation' received antibiotics in the last week and anti-inflammatory drug during the 3 days and vitamins within a week, underlying rheumatic and inflammatory diseases and urinary tract malformation. The control groups were selected from those who referred for check up to the same health centers. About 3 ml of blood sample was collected from each individual test tube without anticoagulant. To evaluate the oxidant-antioxidant balance and TAC of serum in children following methods were used: Total antioxidant assay based on ferric reducing ability of plasma by method Benzie and Strain.[9] Total oxidant assay by using the ferric-xylenol orange method,[13] OS index (OSI), which is an indicator of the degree of OS, was calculated as the percent ratio total oxidants to total antioxidants OSI = (TOX [μM]/TAO [μM]) × 100[10] and prooxidant – antioxidant balance assay was performed according to Sharifian, *et al*.[4] SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used with *t*-test when the distribution of data was normal and if not, Mann–Whitney U-test was used to compare the means or ranks in two groups. The significant level considered in 0.05.

RESULTS

In our study, 125 children were entered in the division of 50 and 75 for patients and control groups, respectively. In both groups, the variables of age, gender, weight, serum total oxidant, serum total antioxidant, oxidant-antioxidant balances, and OSI were measured. The case group consisted of 50 patients, 13 (26%) male and 37 (74%) were female. The control group included 75 patients, 35 (47%) males and 40 (53%) were female (Pearson Chi-square = 17.415, $P < 0.001$). The mean age of patients was 4.36 ± 3.58 years compared to 4.77 ± 2.90 years in control group and observed that the difference was not statistically significant ($P = 0.144$). The means of weight were 15.83 ± 9.02 kg and 15.25 ± 5.1 kg for case and control groups, respectively, with no statistically significant difference ($P = 0.41$).

Table 1 shows that our important variables are distributed normally. All variables have normal distribution accordance to Kolmogorov–Smirnov *Z*-test and *P* value of (1.210, 0.051), (0.949, 0.329), (0.519, 0.950), and (0.960, 0.315) for oxidant, antioxidant, balance of oxidant-antioxidant, and OSI, respectively.

The results of comparison in parameters in the study revealed that the oxidant, any oxidat means of TAC plasma level were 615.57 ± 213.80 μM and 814.92 ± 217.05 μM in the groups of case and control, respectively, which was statistically significant ($P < 0.001$) observed [Table 2].

The mean plasma levels of total oxidant in patients were 93.28 ± 31.6 when in the control group was 82.53 ± 16.84, which was statistically significant ($P = 0.014$) [Table 3].

Table 1: The results of one sample of Kolmogorov–Smirnov *Z*-test for normality

Statistics	Oxidant	Antioxidant	Balance of oxidant-antioxidant	Oxidative stress index
n	125	123	113	121
Normal parameters				
Mean±SD	87.01±24.578	698.23±235.874	65.63±18.303	8.26±2.932
Most extreme differences				
Absolute	0.124	0.086	0.049	0.087
Positive	0.124	0.086	0.039	0.087
Negative	−0.119	−0.061	−0.049	−0.063
Kolmogorov–Smirnov *Z*-test	1.210	0.949	0.519	0.960
P	0.051	0.329	0.950	0.315

SD – Standard deviation

Table 2: Results of comparison in parameter

Variables	Case	Control	Significant level (*P*)
Total antioxidants	615.57±213.8	814.92±217.05	<0.001
Total oxidants	93.28±213.8	82.53±16.84	0.014
Balance of oxidant-antioxidant	70.6±20.46	62.70±16.35	0.026
Oxidative stress index	9.37±3.04	7.51±2.62	0.001

Table 3: Demographic characteristics

Characteristic	Case	Control	*P*
Mean of age	3.58±4.36	2.9±4.77	0.144
Mean of weight	9.02±15.83	5.1±15.25	0.41

The means of oxidant -antioxidant balance in patients and in control were 70.60 ± 20.46 and 62.7 ± 16.35, respectively. The difference was statistically significant ($P = 0.026$).

OSI in patients was 9.37 ± 3.04 in the control group 7.51 ± 2.62, which was statistically significant ($P = 0.001$).

DISCUSSION

This study aimed to assess the balance of oxidant-antioxidant serum and antioxidant capacity in children with UTI. To achieve this goal, the total oxidant, TAC, oxidant-antioxidant balance, and OSI in children with UTI and control groups were measured. The results indicated that OS was higher in the patient group. Serum antioxidant statuses in patients have decreased equilibrium between oxidants and antioxidants in favor of oxidants and OSI and were higher in patients than controls. In a relative study by Kurutas *et al*., the status of OS urinary infection was evaluated and concluded that the levels of lipid peroxidation level were increased whereas CAT and SOD activity were decreased in positive urine culture compared to negative culture. In addition, it was observed that UTI causes OS and increased lipid, and antioxidant enzymes may lead to insufficiency of antioxidant enzymes.[5] In urine samples of both patients and controls, the levels of CAT, SOD, and malondialdehyde (MDA) were measured and compared and significant differences ($P < 0.01$) were found. The level of CAT and SOD was increased, when antioxidant MDA levels were decreased.[5] Although this study was conducted on urine samples, it showed that OS in UTI leading to insufficiency of antioxidant enzymes.

Ciftci *et al*. measured antioxidant status in urine and serum by TAC and plasma Vitamin C levels as well oxidative statuses with total peroxide and OSI.[7] The means of parameters were compared, and the relationships between them were determined. Total peroxide and OSI levels were found to be lower, and TAC was found to be higher in the urine of patients with UTI. In this study, it was observed that plasma Vitamin C concentration and TAC of serum were lower (both with $P < 0.001$) and total peroxide and OSI levels were higher in patients than controls ($P < 0.001$). We also concluded similar results in comparison with Vitamin C in which we did not use it. In a study, urinary levels of 8-hydroxy-2-deoxyguanosine (8-oxodG) and TAC were checked as markers of OS and antioxidant capacity in children with UTI. Patients with positive dimercaptosuccinic acid (DMSA) had higher levels of urinary 8-oxodG ($P = 0.003$) and TAC ($P = 0.001$) compared to patients with normal DMSA.[14]

It was included that pregnancy may aggravate OS[15,16] Various diseases accompany many inflammatory conditions and influence the endogenous antioxidant. Pavlova *et al*. studied the dynamics of OS in the blood and urine of children with kidney diseases such as glomerulonephritis, pyelonephritis (PYN), RF, and lower UTIs. They confirmed that products of lipid peroxidation and enzyme antioxidant capacity were proper test in combination with clinical parameters for the dynamics of OS and markers of intoxication in children with inflammatory and immunological active parenchymal kidney disorders.[17]

Ece *et al*. studied the level of total antioxidants, peroxides, total peroxide, and OSI in patients with nephrotic syndrome and reported an increase in OSI. Although our study was performed on other illness, results were same.[18]

Petrovic *et al*. reported that the parameters total antioxidant status (TAS) and OSI change with the duration of inflammation while only OSI reflected changing in the oxidative-antioxidant balance at discharge from the hospital. However, none of the examined parameters were changed according to the acute changes in kidney function.[24]

Hashemi *et al*. concluded that TAC showed a significant decrease in the relative deficit balance resulting from oxidant-antioxidant in patients with nephrotic syndrome.[8] Although our study population was not the patients with nephrotic syndrome, the TAC was significantly lower in the group with UTI.

Plotnikov *et al*. showed that OS in pyelonephritic kidney was accompanied by a reduced level of mitochondrial B-cell lymphoma 2. Importantly, renal cell death and animal mortality were both alleviated by mitochondria-targeted antioxidant 10 (6'-plastoquinonyl) decyl rhodamine 19 (SkQR1). They suggested that PYN can be treated by reducing mitochondrial ROS and thus by protecting mitochondrial integrity and lowering kidney damage.[19]

Gorukac evaluated the effects of rolipram, a phosphodiesterase four enzyme inhibitor, on *E. coli*-induced renal oxidative damage in an acute PYN rat model. Tissue MDA and nitric oxide levels and SOD and CAT activities were significantly increased in the kidneys from the PYN

groups. However, rolipram administration reduced renal MDA, nitric oxide levels, and enhanced SOD and CAT activities. The histopathology examinations demonstrated that rolipram treatment reduced the inflammation grade in the kidney specimens.[20]

The activities of the antioxidant enzymes, CAT, SOD, glutathione peroxidase (GSH-Px), and xanthine oxidase (XO) were also elevated by *E. coli*. However, caffeic acid phenethyl ester (CAPE) (phosphodiesterase four inhibitors) administration reduced MDA and no levels as well as XO activity when it is a cause of increasing SOD and GSH-Px activities. Histopathological examination showed that CAPE reduced the inflammation grade induced by *E. coli*. They recommended CAPE administrations decrease the oxidative damage occurring in PYN and, therefore, could be used for medical management of bacterial nephropathy.[21]

Some treatments applied to decrease oxidative damage in UTI. Acute renal inflammatory injury can be prevented much more effectively by combination therapy rather than by conventional therapy alone. Görür S, *et al*. investigated the involvement of OS in the pathogenesis of acute PYN and evaluated the impact of meloxicam and/or L-carnitine in addition to conventional antibiotic treatment. L-carnitine and meloxicam alleviated OS, probably by decreasing lipid peroxidation and enforcing antioxidant defense system.[20]

Treatment by thymoquinone (TQ) before or during *E. coli* inoculation prevents oxidative damage in acute PYN in an ascending obstructive rat model. It has been indicated that TQ administration is attenuated the oxidative damage. The oxidative damage occurred in PYN and, therefore, it could be used as a supportive agent to protect the kidneys from oxidative damage caused by PYN.[22,23]

The limitations of our study were small size of population and indirect measures of renal parenchymal inflammation. The controls have strengthened the findings and solved the first limitation. Employing direct assessment with upper urinary tract imaging studies such as scintigraphy, association between the oxidative status parameters, direct assessment of renal inflammation, and subsequent scarring is necessary.

CONCLUSION

According to our findings, OS is higher in patients. We also found a decrease in serum antioxidant status in patients. Equilibrium between oxidants and antioxidants is in favor of oxidants, and the OSI was higher in patients compared to their counterparts in control group. UTI may causes OS and increases lipid peroxidation level that leading to insufficiency of antioxidant enzymes. Many studies revealed that the majority of antioxidants such as ROM, TOS, BAP, TAS and TTP reducing oxidative stress.[10-12]

We can conclude that TAS and OSI, as markers of OS during UTI, are sensitive in accompanying inflammatory conditions. However, none of the examined parameters were sensitive to acute changes in kidney function.

Further investigations are needed to evaluate whether TAS, TOS, and OSI could be used to monitor disease severity in children with UTI. Given that there are no adequate studies in this area; therefore, more studies are recommended to be done first on a comprehensive sample from some different societies with various circumstances. It could be useful for results generalization. Comprehensive and general results would be the tools for acquired decisions by planners in the field of health policies. Second, a few studies are needed to be done on the status of OS and antioxidant balance before and after the consumption of some antioxidants such as Vitamin C and Vitamin E. Perhaps, in the future, we can suggest that patients with UTI may benefit from antioxidant treatment as additives drug.

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Conflicts of interest

There are no conflicts of interest.

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