Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

The role of oxidative stress in pediatric urinary tract infections: a systematic review

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ARTICLE INFO

Article type
Systematic review article

Article history
Received: 28 Feb 2015
Revised: 13 Apr 2015
Accepted: 23 Apr 2015

Keywords
Antioxidants
Oxidative stress
Urinary tract infection

ABSTRACT

Introduction: Urinary tract infection (UTI) that can affect any part of the urinary tract and may subsequently lead to kidney infection is linked with variety of causative factors such as oxidative stress. In this study, we aimed to systematically review the literatures to evaluate the effects of oxidative stress on UTI.
Method: PubMed and Google scholar were searched systematically using the key terms, "oxidative stress" and "urinary tract infection" in the title, keywords, and abstract on February 2015 to find articles in which the oxidative stresses had been evaluated in children with urinary tract infection (UTI). Papers were excluded if they were unrelated to the purpose of this study, or in language other than English. Full texts of the relevant documents were fully reviewed for data extraction.
Result: Of overall 50 articles from PubMed, and 6 records found in Google scholar, only 8 articles met the inclusion criteria for further assessment. Additionally, three papers were omitted due to full texts unavailability or language irrelevancy, and five articles, which fully met the inclusion criteria, were used for data extraction. The results showed that the level of antioxidant decreases significantly in patients with UTI, while the markers of oxidative stress increases.
Conclusions: The results of the studies showed that the level of antioxidants decreases in patients with UTI, while lipid peroxidase and the level of oxidative stress biomarkers such as malondialdehyde and reactive oxygen species increase. These findings are suggestive of an association between oxidative stress and UTI.

Please cite this paper as:
Delshad M, Fesharakinia A, Eghbal S. The role of oxidative stress in pediatric urinary tract infections: a systematic review. Rev Clin Med. 2016;3(1):43-47.

Introduction

There are three forms of acute urinary tract infection (UTI) including cystitis, pyelonephritis, and asymptomatic bacteriuria, which typically start in the lower urinary tract and damage the kidneys, ureters, bladder, and urethra. urinary tract infections are usually caused by a variety of bacteria, especially gram-negative bacteria such as Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae and different types of fungi and viruses (1,2). Several other factors, such as kidney stones also increase the risk of UTI. UTI is the second most prevalent bacterial infection in human after respiratory tract infection (3), and it is suggested that almost 10% of people experience UTI during their lifetime (4,5).

It is now suggested that childhood UTI can be considered as the main cause of acute morbidity and chronic medical conditions, such as hypertension and renal insufficiency in adulthood (6,7).

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However, UTI is more common in adults compared to children, the frequency of UTI in children is almost 1% in males and 1 to 3% in females (8). UTI has been predominantly reported in girls and women compared to boys and men (9). It has been also reported that UTI is more common in uncircumcised male children (10). Findings revealed that more than 1.1 million hospital visits are due to the infections of urinary tract in children (6). The first UTI in girls usually occurs by the age of 5, but mostly occurs in the first year of life in boys. Three initial UTIs in children include pyelonephritis, cystitis, and asymptomatic bacteriuria. Viral infections, especially infections with adenovirus are the main cause of urinary cystitis. Pyelonephritis is a specific type of UTI, and is the most serious infections in febrile infants under 2 years of age (11). Moreover, acute pyelonephritis could lead to renal scars.

Three factors are involved in the inflammatory process of tubulointerstitial diseases caused by infections including the anatomy and function of the urinary tract, virulence of the bacteria and the host innate immune system; in addition, kidney damage is the final outcome of this process (12). Since inflammation causes oxidative stress (OS), extensive studies have been performed on oxidative damage and human diseases to achieve an effective and safe therapy for better treatment of associated diseases (13). However, few studies have been conducted on the relationship between OS and UTI in human, and most of the theories are often based on animal studies. Thus, the presence of OS in UTI may suggest possible treatment of the disease with antioxidants and anti-inflammatory medications in combination with antibiotics to accelerate the healing process and reduce the risk of renal scarring in children. Therefore, in present study, we aim to systematically review the literatures to find and explain the possible relationship between UTI and the presence of OS in pediatric patients.

Methods

Literature search strategy

PubMed and Google scholar were thoroughly searched to find articles in which the oxidative stresses had been evaluated in patients with UTI. Literature search was performed in these databases to find articles in English language, using the key terms, "oxidative stress" and "urinary tract infection" in the title, keywords, and abstracts on February 2015 by two independent reviewers. Relevant articles with the following search terms (oxidative stress) AND (urinary tract infection OR UTI) were selected and used for data extraction. Papers were omitted if they were unrelated to the purpose of this study. The reference lists of articles were also searched to include other potentially relevant articles and minimize the possibility of bias or any missing data.

Study selection

There was no time limitation for the included articles. In order to avoid any misinterpretation of data in further processes of data extraction, only articles in English language were included in the study. Various types of the articles with varied study design were included in this literature review. Review articles were excluded. Inclusion criteria were documents in which the oxidative damage or indexes of OS were studied in patients with UTI. Moreover, only studies conducted on children under the age of 13 were included and used for data extraction, and articles in which the biochemical markers of OS had been evaluated in adult patients or animal models were excluded from further assessment. Duplicated and irrelevant papers were omitted in the first step by reviewing the title, keywords, and abstract of papers. Papers were also excluded if OS or indexes of OS had been evaluated in patients with disease other than UTIports. Articles which induced mild hypothermia and the rewarmed patients were also excluded from the results.

Data synthesis

Data including the name of first author, country of origin, publication date, study design, and concluded results were extracted and tabulated based on the main purpose of this study. All available data including total number of participants, demographic data, and biochemical markers were obtained as possible. Data were categorized based on the results reporting the association between OS and UTI in children. All processes of data extraction and study selection were based on the recommendation of PRISMA 2009 checklist (14).

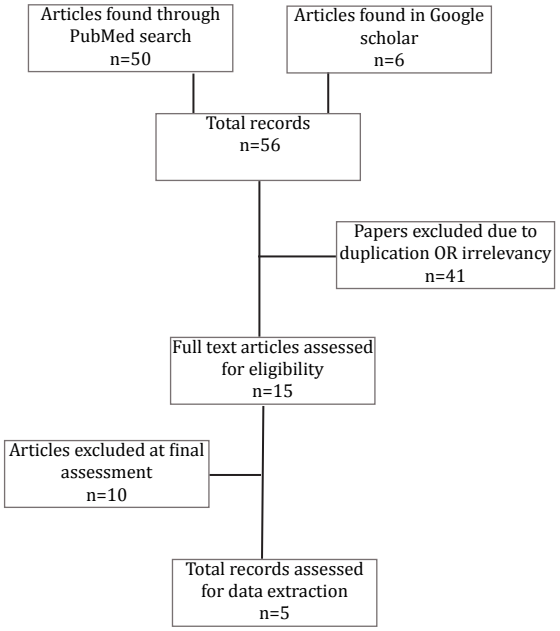
Results

search results

From overall 50 article found in PubMed search, and 6 papers in Google scholar, 41 articles were excluded in the first step due to irrelevancy or duplication, and only 15 articles seemed to be relevant to the purpose of this study. Publications in which the relationship between UTI and OS had been evaluated in adults were excluded. After careful review of the included articles, only 8 papers met the inclusion criteria for further assessment. Of these, 3 articles were also omitted due to full text unavailability or language irrelevancy. Finally, full texts of 5 articles which fully met the inclusion criteria were obtained and

data were extracted based on the main purpose of this study. Figure 1 shows step by step selection process of included articles.

Figure 1. Flowchart of selection of studies



Literature search strategy

The total number of participants in the reviewed literatures, measuring the biomarkers of OS in children with UTI, was 183. Minimum age of the patients in the included studies was three weeks in a case reports and the maximum age was 17 years. In the selected studies, different biochemical methods including thio-butyric acid methods, biochemical kits, nephelometric and spectrophotometric methods were used to measure OS biomarkers. The markers of OS evaluated in these studies were malondialdehyde (MDA), total antioxidant capacity (TAC) and reactive oxygen species (ROS).

Study results

Data showed that antioxidant level decreased significantly in patients with UTI. On the other hand, the indexes of OS increased in these patients. Results showed that UTI could change the balance between oxidants and antioxidants levels. It is also demonstrated that MDA increased in UTI patients, while the level of serum cations such as zinc, copper, and calcium decreased. In all included studies, the markers of OS were evidently high in patients with UTI. According to the results of the studies, reduction in the level of TAC increased OS in patients with UTI. Therefore, a close relationship was suggested between OS and UT infection, especially in pediatric patients. (Table 1)

Table 1. Data extracted from included studies

Author Country, Year Reference	Study design	Study population	Number of patients	Oxidative stress marker	Results
Petrovic Serbia, 2014 (15)	POCS[1]	UTI[2]	50	TOS[3],TAS[4], OSI[5], CRP[6]	TAS and OSI higher in subjects groups
Pavlova Bulgaria, 2005 (16)	RS[7]	KD[8]	39	CRP, primary LPO[9], TAC[10]	Total antioxidant activity increased in all groups
Luk USA, 1991 (17)	CR[11]	UTI	3	Met-Hg[12]	Methemoglobinemia
Teslariu Romania, 2012 (18)	PS[13]	UTI	18	MDA[14],TAC	Serum level of cations and plasma TAC decreased and MDA level increased in patients
Chien Taiwan, 2014 (19)	PS	UTI	73	8-oxodG[15], TAC	Plasma TAC increased

[1]POCS: Prospective observational cohort study; [2]UTI: Urinary tract infections; [3]TOS: Total oxidant status; [4]TAS: Total antioxidant status; [5]OSI: Oxidative stress index; [6]CRP: C-reactive protein; [7]RS: Retrospective study, [8]KD: Kidney disease; [9]LPO: Lipid peroxidation; [10]TAC: Total antioxidant activity [11]CR: Case report; [12]Met-Hg: Methemoglobinemia; [13]PS: Prospective study; [14]MDA: Malondyaldehide;[15]8-oxodG: 8-hydroxy-2'-deoxyguanosine

Limitations included the small number of studies conducted on children with UTI. Moreover, in some studies, demographic data did not mention or categorize according to the purpose of the study.

Discussion

Studies have provided evidence that OS, which is defined as the production of extremely reactive oxygen species or depletion of reducing agents such as glutathione and metal ions, is the most important leading cause of several infectious diseases such as UTI. OS is also involved in several biological processes such as oxidative damage to hemoglobin, damaging ion channels and cytotoxicity by triggering ROS production. Comprehensive studies have been conducted on the effect of oxidative stress on different diseases such as diabetes, urinary tract, and renal infections. It has been shown that in patients with diabetes who have UTI, the level of antioxidants decreases, while lipid peroxidase and OS biomarkers rise (20,21). Furthermore, it is shown that lipid peroxidase biomarker such as malondialdehyde is involved in UTI and chronic renal disease (16,22). Moreover, the results of a study in which the level of OS biomarkers was evaluated in children with renal disease showed that the TAC significantly increased in all groups of patients with renal and UT infections (16). Assessment of ROS and lipid peroxidase level showed that the levels of these markers were higher in patients with UTI. Results also showed that high level of methemoglobin could lead to low oxygen concentration in tissues resulting in oxidative stress. Hence, methemoglobinemia could result in OS and could affect UT infections in children.

Animal studies showed that bactofection-mediated gene delivery for reducing bacterial colonization decreased OS, and therefore protected kidney and urinary tracts from oxidative damage (23). Similarly, it is shown that renal cell death is associated with reduced level of mitochondrial B-cell lymphoma 2 (Bcl-2) leading to OS and inflammatory response of kidney and urinary tract (24). Studies on human showed that medications and herbal medicines that reduced OS, had protecting effects on renal and UTI (25). Other studies in adult patients with UTI strongly supported the association between UTI and OS (26). The level of catalase and superoxide dismutase significantly decrease in adult patients with UTI, while lipid peroxidase increase, demonstrating that inefficacy of antioxidants results in increased formation of ROS and decreased antioxidant defense leading to UTI and kidney damage (27,28). Other reports in children with UT infection demonstrated that increasing total antioxidant capacity led to bacterial infections and leukocyte aggregation, the most important leading cause of infection in the urinary tract and kidney (15). Therefore, the results of this study showed a strong association between OS and the infection in urinary tracts and kidneys, especially in pediatric patients, suggesting possible detoxifying and further management of the disease with antioxidants.

Conclusion

The results of included articles showed a strong association between the infection in urinary tract and kidney in children (and even adults) and OS. Moreover, it is shown that there is a significant reduction in antioxidant level, while OS biomarkers increase in patients with UTI. Hence, this systematic literature review provides evidence on association between the incidence of OS and UTI, and suggests the theoretical effectiveness of antioxidants in the treatment of UTI.

Acknowledgement

We would like to thank Clinical Research Development Unit of Ghaem Hospital for their assistant in this manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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