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Secretory Immunoglobulin A (sIgA): is it an early marker for UrinaryTract Infections (UTI)?

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ABSTRACT

Urinary tract infections (UTIs) are among the most common bacterial infections, affecting 150 million people worldwide each year. Although both men and women may become infected, UTIs are traditionally thought of as a disease of women, among whom 50% will be affected across their life span. Approximately 25% of women presenting with a first episode of bacterial cystitis go on to suffer recurrent UTI within 6 months, some having 6 or more infections in the year following the initial episode. IgA is the most abundant antibody isotype in the body, comprising almost 70 % of the body's total immunoglobulins. The majority of IgA is found in the various mucous secretions, including saliva, milk, colostrum, tears, and secretions from the respiratory tract, genitourinary tract, and prostate. Several studies have manifested that every change in sIgA levels may be associated with UTI. Finding rapid techniques to diagnose the patients with UTI is so important. In this case control study, we investigated secretory IgA as an early marker of urinary tract infection.

Keywords: *Urinary tract infections, IgA, marker*

1. Introduction

Urinary tract infection occur when a microbe infects any component of the urinary system (urethra, bladder, ureter, and kidney), overcoming the host defense barrier and colonizing the urinary tract. UTIs range from simple self-limiting illness to severe sepsis, with a death rate of 20-40% ***(Das., 2020).***

Adult women have much more UTIs than males, presumably due to their shorter urethra, which allows germs from the intestine to pass through more easily. UTI is the second-most prevalent community-acquired illness in older women, and the leading cause of hospital-acquired infection in long-term care residents ***(Guglietta .,2017).***

UTI is mostly caused by bacteria, however other micro-organisms such as fungi and viruses are rare etiologic agents ***(Olin and Bartges., 2015).*** In both community and hospital infections, E.coli is the commonest uropathogen (75–90 %), while other pathogenic microorganisms like Proteus mirabilis, Staphylococcus saprophyticus (frequent isolation from younger females), Enterococcus faecalis, Klebsiella pneumoniae, and Pseudomonas aeruginosa are each less relevant ***(Sheerin and Glover .,2019).***

Recurrent UTIs cause personal and social burdens. The social burden comprises clinical and economic costs, while the personal burden includes social and psychological impacts that reduce quality of life (QoL). The high incidence of recurrent UTIs is a modifiable determinant of social and personal burdens, emphasizing the need for illness prevention. They are linked to an increased rate of morbidity and mortality among the elderly, who are the most susceptible to UTIs ***(Urology., 2018).***

The significant role of TLR4 gene polymorphisms in immune imbalanced patients and its effect on the used therapies had been clarified in previous studies **(Abdelsalam etal.,2021).** Mechanical mechanisms, like the physical flushing of organisms from the urinary tract by urine flow, along with the innate immune response are both involved in the host antimicrobial defense in the lower urinary tract. When bacteria attach to superficial bladder epithelial cells, Toll-like receptor 4 (TLR4), a member of the Toll/IL-1 receptor (TIR) domain superfamily, signals an innate immune response. cytokines and chemokines like IL-6, IL-8, and antimicrobial peptides are secreted by these activated uroepithelial cells ***(Köves and Wullt., 2016)***. IL-8 is a potent chemoattractant that attaches to neutrophil CXC chemokine receptor type 1 (CXCR1) and CXCR2 receptors, causing neutrophil recruitment and migration across the uroepithelium, in which they phagocytose uropathogens. Genetic variants that cause innate immune system receptor malfunction may increase susceptibility to many types of UTIs ***(Ambite et al., 2017).***

Immunoglobulin A (IgA) is the most common immunoglobulin in the body, contributing to more than 70% of total immunoglobulin and playing a key role in mucosal immunity. It can be detected as a dimer in tissues and secretions of gastrointestinal and respiratory systems, as well as saliva, tears, and breast milk. IgA plays a critical role in the first-line mechanisms that contribute to the establishment of tolerance and infection protection ***(Swain et al., 2019).***

IgA production is higher than all other antibodies indicating its significance in host-pathogen defense. During various infectious disorders, pathogen-specific IgA exists on mucosal surfaces and in the serum, but its exact function is unknown. For diseases involving respiratory and reproductive systems, like Mycobacterium tuberculosis (Mtb), HIV-1, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, IgA has been shown to have both passive immunity and immune activating capabilities ***(Magri and Cerutti., 2020);(Chao et al., 2020).***

IgA immune complex production takes place when IgA aggregates are produced. This occurs when invading bacteria get opsonized with IgA, during secondary infection, or due to cross-reactivity of antibodies to pathogen components ***(Bunker et al., 2017).*** FcαRI attaches monomeric and dimeric IgA with moderate affinity,

while IgA immune complexes attach to FcαRI, which upon attaching activates classic immunoreceptor tyrosine-based stimulation motif (ITAM) signaling. FcαRI activation does not directly promote cytokines formation, despite the fact that IgA immune complexes can stimulate effector actions like phagocytosis and degranulation. Instead, by collaborating with PRRs, FcαRI greatly enhances inflammatory responses. Accordingly, the production of IgA immune complexes serves as a warning signal that increases inflammation in various organs ***(Hansen et al., 2019).***

Several studies have shown that fluctuations in sIgA levels are linked to urinary tract infections. It's thus critical to develop quick methods for diagnosing UTI sufferers ***(SS D,et al.,2004).***

The presence of sIgA has been linked to UTIs in both children and adults; however, sIgA has been shown to be manipulative of the infective agent and can be used to identify infection types. As a result, evaluating urine antibody levels can provide another indication of host responses to infection, which can be used as a basic screening test or to aid in the development of an assessment when combined with additional trials ***(Navidinia, et al., 2018).***S-IgA has been found to prevent E. coli adherence to urinary epithelial cells in UTIs ***(Deo and Vaidya., 2004).***

This study investigated if sIgA is an early marker of UTI or not.

2. Material and methods

A case-control association study was conducted upon 44 clinically diagnosed urinary tract infection (UTIs) patients with age more than 18 years old, with further subdivision into two equal groups (22 UTIs patients with cancer and 22 UTIs patients without cancer). In addition, age and sex matched 44 apparently healthy subjects were selected to act as a control group.

This study was carried out at Mansoura University Hospital and Mansoura Oncology Center in the period between November 2019 and November 2020 at Dakahlia Governorate, Egypt , after getting approved by the local health committee Faculty of Medicine with approval number (R.19.03.531)

Inclusion criteria:

Patients with urine analysis showing pus cells >20 HPF and symptoms of UTIs; including pain or a burning feeling during urination, feeling of urgency, or feeling the need to urinate frequently, altered appearance of the urine (either bloody (red) or cloudy containing pus), passing only a tiny amount of urine even when the urge to urinate is strong, tiredness and confirmed by urine culture.

Exclusion criteria :

Patients with Immune deficiency diseases either congenital or acquired and patients with autoimmune diseases to exclude any pathological effect on sIgA level.

1. Sampling:

- **Blood sample:**

  blood samples were collected for measurement of serum creatinine level and for complete blood count.

- **Urine samples:**

Early morning mid-stream urine samples at were collected in sterile container under strict aseptic precautions for urine culture done within one hour then rest of the urine samples were used to evaluate IgA levels by ELISA technique (CKbio-11964).

2. Microbiological examination of urine:

1. Urinalysis: to detect number of pus cells in urine.
2. Culture and colony count were done CLED agar
3. Identification of bacteria: Bacterial growth was identified by colony morphology, gram stain then followed by biochemical reactions manual and automated Vitek II system.
4. Antibiotic sensitivity was done by manual disk diffusion for some selected antibiotics Interpreted according to laboratory standard recommendations of Clinical and Laboratory Standards Institute (CLSI)guidelines **(Kumar et al., 2014).**

3. Enzyme-linked immunosorbent assay (**ELISA**)

The kit of Shanghai Coon Koon Biotech., Ltd with Cat. No (CKbio-11964) was used to test the level of Human Immunoglobulin A (IgA), based on the principle of biotin double antibody sandwich technology enzyme linked immunosorbent assay (ELISA). The sample was added to the wells that pre-coated with IgA monoclonal antibody, then incubated. After incubation, biotin-labeled anti- IgA antibody was added and bound to streptavidin-HRP to form an immune complex; and then incubated. Then washed for removal of unbound enzyme, and then the substrate A and B were added, then the solution turned blue and finally changed into yellow by the effect of acid. The color depth or light was positively correlated with the concentration of IgA.

Statistical Analysis

Data analysis was performed using statistical software program (SPSS for Windows, version 21, USA). The categorical variables were presented as number (percentages). However, numerical data were presented as means ± standard deviation. Chi-square test was used to assess the distribution of such nominal data between the selected patients. To compare the complete blood picture between control, patients with urinary tract infection (UTI) and patients with UTI and cancer, One Way Anova test was performed. To compare the creatinine level and IGA level between each of control and patients with UTI, control and patients with UTI and cancer, and patients with UTI and patients with UTI and cancer, independent t test was conducted. Furthermore, to evaluate the correlation between creatinine level and IGA level in patients with UTI and patients with UTI and cancer, Pearson correlation test was done. Moreover, frequency distribution of isolated bacteria from Patients with UTI and Patients with UTI and cancer was done and expressed as number (percentages). Likewise, the antibiotic profile of E. coli, Klebsiella pneumonia, Pseudomonas aeruginosa, and coagulase positive staphylococcus isolated from urine samples obtained from patients with UTI only (n = 18 isolates) and patients with UTI and cancer was conducted and expressed as number (percentages) and chi-square test was used to compare between the obtained percentages. In all statistical analyses, the results were statistically significant at $p < 0.05$.

Results

The study included 44 adult healthy volunteers (control group) and 44 adult patients; 22 patients were suffering from UTI only and the other 22 patients had UTI and cancer in the period from 2019 to 2020, with no significant difference in the gender and age between the studied groups.

In UTI group, the recorded clinical symptoms were frequent urination (95.5 %), urgency (95.5 %), burning sensation (95.5 %), lower abdominal pain (54.5 %), cloudy urine (54.5 %), pus cells in urine examination (100 %). In UTI and cancer group, the recorded clinical symptoms were frequent urination (77.3 %), urgency (72.7 %), burning sensation (77.3 %), lower abdominal pain (50 %), cloudy urine (63.6 %), and pus cells in urine (100 %).

There was a significant increase in WBCs count in both patients groups in comparison with control group. Moreover, there was a significant increase in WBCs count in patients with UTI and cancer compared with patients with UTI only. However, there was a significant decrease in RBCs, hemoglobin level, and platelets count in both patients groups in comparison with control group. Moreover, there was a significant decrease in RBCs and hemoglobin level in patients with UTI and cancer when compared with patients with UTI only.

There was a significant increase in Creatinine level in both patients' groups in comparison with control group.

There was a significant decrease in IgA level in both patients with urinary tract infection (UTI) and patients with UTI and cancer in comparison with control group. There were non-significant differences in IgA level between patients with UTI and cancer and patients with UTI only (table 1).

Table (1). IgA in Patients with Urinary Tract Infection (UTI) and Patients with UTI and cancer

	IgA level	**t-value**	**P-value**
Control group (n = 44)	11.16 ± 2.16	- 6.748	**0.001**
UTI group (n = 22)	7.81 ± 1.20 **		
Control group (n = 44)	11.16 ± 2.16	- 6.582	**0.001**
UTI with cancer group (n = 22)	7.77 ± 1.51 **		
UTI group (n = 22)	7.81 ± 1.20	0.103	**0.919**
UTI with cancer group (n = 22)	7.77 ± 1.51		

Table (2). Correlation between creatinine level and IgA level in Patients with Urinary Tract Infection (UTI) and Patients with UTI and cancer

	IgA level	**Creatinine level**
Creatinine level	r = - 0.233 P = 0.029 *	

IgA level		r = - 0.233 P = 0.029 *

There was a significant ($p < 0.05$) negative correlation between creatinine level and IgA level in Patients with Urinary Tract Infection (UTI) and Patients with UTI and cancer (table 2).

Table (3). Frequency distribution of isolated bacteria from Patients with Urinary Tract Infection (UTI) and Patients with UTI and cancer

	UTI group	**UTI with cancer group**	**Total**
***Escherichia coli* (n = 29)**	18 (81.8 %)	11 (50 %)	29 (65.9 %)
***Klebsiella pneumonia* (n = 6)**	3 (13.6 %)	3 (13.6 %)	6 (13.6 %)
***Pseudomonas aeruginosa* (n = 4)**	1 (4.5 %)	3 (13.6 %)	4 (9.1 %)
***Coagulase positive staphylococcus* (n = 5)**	0 (0 %)	5 (22.7 %)	5 (11.4 %)
Total	**22 (100 %)**	**22 (100 %)**	**44 (100 %)**

In patients with UTI infection, the chief isolation percentage of bacteria was recorded for *Escherichia coli* (81.8%), then *Klebsiella pneumonia* (13.6 %), then *Pseudomonas aeruginosa* (4.5 %). In patients with UTI infection and cancer, the chief isolation percentage of bacteria was recorded for *Escherichia coli* (50%), then coagulase positive staphylococcus (22.7 %), then *Klebsiella pneumonia* and *Pseudomonas aeruginosa* (13.6 %, for each). (table 3).

Table (4). IgA level in patients with UTI and Patients with UTI and cancer related to the isolated organisms

	UTI group (n = 22)	**UTI with cancer group (n = 22)**	**t-value**	**P-value**
Escherichia coli	7.95 ± 1.14	7.79 ± 1.40	0.341	0.736
Klebsiella pneumonia	6.89 ± 1.60	7.07 ± 1.54	- 0.135	0.899
Pseudomonas aeruginosa	7.99 ± 0.00	7.27 ± 3.05	0.205	0.856
Coagulase positive staphylococcus	-	7.44 ± 0.43	-	-

There was a non-significant difference in IgA level in ***Escherichia coli***, ***Klebsiella pneumonia, Pseudomonas aeruginosa***, and ***Coagulase positive staphylococcus*** infection between patients with UTI and Patients with UTI and cancer (table 4)..

Discussion

Antibody analysis by serological techniques had been studied in many years and had been important role in virological diagnosis. This non-invasive method for collecting samples is easy for pediatric and old age patients, where blood collection is difficult. Also, it is not expensive and had lower risk than venipuncture method. The good stability of urinary antibodies at room temperature makes the sample transport easier. All these advantages can make urine an ideal sample for diagnosis **(Mohandas etal.,2022).**

The presence of antibodies in urine was first reported by finding poliovirus neutralizing antibodies (NAbs)Lerner *et al*[14] were the first to report in human urine when they observed neutralizing antibodies (NAbs) to poliovirus in patient's urine (Lerner and Remington 1962) .

Urinary tract infections (UTIs) currently rank among the most prevalent infectious diseases globally, with chronic and recurrent infections ***(Navidinia et al., 2014).***Secretory IgA (sIgA) is a dominant Ig in mucosal secretions. Besides, small concentrations of sIgA also exist in the serum ***(Oortwijn et al., 2008).***

The presence of urinary secretory IgA (sIgA) is one of the defense mechanisms against UTI, and its role in UTI episodes has been reported ***(Deo and Vaidya., 2004).*** It has been advocated that sIgA might have a pathogenic role in IgA nephropathy (IgAN). There is evidence that serum sIgA was increased among IgAN cases ***(Oortwijn et al., 2008)*** and sIgA deposition of in glomeruli was revealed among some patients with IgA nephropathy ***(Zhang et al., 2008).***

The present study aimed to measure secretory IgA in urine of patients with (UTI) in comparison to healthy subjects.

In the UTI group, females represented 72.7% of the group. This may be due to short urethra and bacteria which may rise from the perianal region, possibly leading to UTI (***Al-Badr and Al-Shaikh., 2013).***

In the cancer group, male represented 59.1% of the group while females represented 40.9% of the group, this may be due to severe immunosuppression as after cancer treatment strategies is associated with the risk of opportunistic infections. Infection is a serious complication and is a major cause of morbidity and mortality among cancer persons (***See et al., 2012).*** There are many risk factors that facilitate the acquisition of infection. These include neutropenia and long-term catheterization ***(Custovic et al., 2014).***

In the present study, the percentage of isolated bacteria was ordered as Escherichia coli (65.9 %), then Klebsiella pneumonia (13.6 %), then Pseudomonas aeruginosa (9.1 %), and coagulase positive staphylococcus (11.4 %). In agreement with our result, a previous study showed that; E. coli was the most prevalent bacteria with an isolation rate of 48.6%. Klebsiella pneumoniae was the second most predominant organism (14.3%) and Staphylococcus aureus accounted for the 4th cause of bacteriuria ***(Tchente Nguefack., 2019).*** Also, some reports revealed S. aureus to be the commonest microorganism ***(Tadesse et al., 2014) (Onu et al., 2015).*** Variation in geographical location and antimicrobial use can be responsible for such differences.

In our study, there was a significant decrease in RBC and hemoglobin level in both patients with UTI and patients with UTI and cancer in comparison with control group. Moreover, there was a significant decrease in RBCs and hemoglobin level in patients with UTI and cancer when compared with patients with UTI only.

This may be due to increased destruction of RBCs. Several cytokines, such as tumor necrosis factor α, interleukin-6 and interleukin1β, could also cause increased destruction of red blood cells ***(Pierce and Larson., 2005).***

In the present study, there was no significant difference between patients with (UTI) and patients with UTI and cancer as regard IgA level. There was a significant decrease in IgA level in both patients with (UTI) and patients with UTI and cancer in comparison with control group which was explained by ~~a~~ previous study, demonstrated that; the presence of low urinary sIgA could be the cause or the consequence of UTI. Likewise, luminal infections (negative antibody coating) could interfere with local sIgA production (***Navidinia et al., 2018).***

In contrary, ***Deo and Vaidya., 2004*** study showed that; sIgA increased significantly in adults with UTIs compared to control group

In our study there was a significant ($p < 0.05$) negative correlation between creatinine level and IgA level in Patients with Urinary Tract Infection (UTI) and Patients with UTI and cancer.

A previous study showed a significant association between urinary sIgA concentrations, serum creatinine, and urea concentrations as well as extent of kidney fibrosis was also revealed. This indicated the presence of positive relation between the degree of kidney injury and urinary sIgA concentrations, where sIgA might serve as a marker for real injury ***(Krawczyk et al., 2019).***

A basal sIgA concentration might have protective role against bacterial infection and decreased concentrations have been proposed to be correlated with an increased risk of UTI (***Yan et al., 2002).***

Renal diseases usually are associated with decreased tubular flow due to reduced GFR. This could result in an enhanced risk of ascending UTI and, therefore, it appears likely that polymeric Ig receptor induction in the injured kidney might be protective against bacterial infection. In this context, it has been demonstrated that sIgA reduces the adhesion of *E. coli* to urothelial cells (***Krawczyk et al., 2019***).

In Chinese study ,level of urinary sIgA was increased in patients with IgA nephropathy and was related to disease phenotypes of the. Their results supported the notion that sIgA might related to pathogenesis of IgAN. They recommended The urinary sIgA as a reliable non-invasive biomarker for kidney injury and disease severity in patients with IgAN. **(Tan etal.,2009).**

Conclusion

Urine could be used as a diagnostic sample for finding antibodies because of its unique advantages in comparison with invasive samples. In this study we recommended using of sIgA as an early biomarker for UTI being non invasive economic and easy way for sample collection. But Its role as a diagnostic sample has many limitations due to decreased level of antibodies, difference in results due to physiological variations, methods of collection and presence of chemicals and drug.

Recommendations:

Further studies are necessary to elucidate the local role of IgA(s) in the genitourinary tract. Since IgA does pot fix complement it may act together with some other immunoglobulins or chemical factor to exert its effect on local defense mechanisms.Screening for UTI among cancer patients is recommended as impaired immunity is risk factor for recurrent UTI.Further studies to evaluate the negative correlation between sIgA and serum creatinine among UTI patients.

Disclosure

The author reports no conflicts of interest in this work.

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