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Research article

Relationship between Bacterial Urinary Tract Infections and Levels of Basic Inflammatory Indicators in Patients with Rheumatoid Arthritis.

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ABSTRACT

Rheumatoid arthritis (RA) is considered one of the complex autoimmune diseases that affects not only the body's joints but can also affect various organs of the body. There are several inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) used to estimate the activity and progression of the disease (RA). The current study aims to highlight the effect of bacterial urinary tract infections (UTIs) on the level of some inflammatory indicators (ESR and CRP), in addition to the level of antinuclear antibodies (ANA) in the peripheral blood of patients with RA. The present study included 70 patients suffering from (RA) divided into two groups, the first group contained 40 patients (24 female and 6 male) with RA and UTI; the second group, 29 patients suffering from RA (24 female and 5 male) without bacterial UTIs, and 30 healthy control cohorts. The study showed that the levels of ESR, CRP, and ANA in the group of patients suffering from RA and bacterial UTI were not statistically different from their levels in patients suffering from RA only (without bacterial UTIs). The bacterial species (UTIS) did not affect the levels of ESR, CRP, and ANA in patients with RA and UTIs. The current study showed that bacterial infection of the urinary tract does not affect the level of basic inflammatory indicators (ESR and CRP) in patients with RA. It also does not affect the level of ANA. The study showed that the age factor and the period of treatment that a patient with RA undergoes do not affect the incidence of bacterial UTIs.

Keywords: ANA, CRP, ESR, Rheumatoid arthritis, Urinary tract infection.

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1. INTRODUCTION

Rheumatoid arthritis is a chronic autoimmune disorder that primarily affects the joints, leading to pain, inflammation, and joint damage. It is characterized by the immune system mistakenly attacking healthy joint tissues, resulting in chronic inflammation. RA often leads to joint deformities and can affect various other organs and systems such as the skin, lungs, and heart. Early diagnosis and management are crucial in preventing joint damage and improving the quality of life for those affected by this condition. t is a multifactorial disease with It is a multifactorial disease with genetic and environmental factors contributing to its occurrence and expression, and most of these factors are likely to be associated with both disease occurrence and severity [1]. Severe extra-articular disease manifestations are a major determinant of cardiovascular morbidity in rheumatoid arthritis, and this association is not due to differences in age, sex, smoking, rheumatoid factor, or erosive joint damage [2]. Urinary tract infections (UTIs) are often associated with morbidity and mortality, and this study found that

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that the most common pathogen causing UTIs is *Escherichia coli*, which has high resistance to commonly used antibiotics [3]. The previous study highlighted three independent routes of recurrence of UTIs: (i) following an intestinal bloom of uropathogenic bacteria and subsequent bladder colonization, (ii) reinfection of the urinary tract from an external source, and (iii) bacterial persistence within the urinary tract [4]. The susceptibility to a UTI is influenced by dysfunctions of the urinary tract and by genetic mechanisms that control the innate immune response to infections [5]. Inflammation of the lower urinary tract occurs frequently in people. The causes remain obscure, with the exception of urinary tract infections. Another study proved the role of infected urinary tract with bacterial especially gram-negative bacteria stimulating the local and systemic inflammation in the host body such as autoimmune cystitis and elevating the inflammation markers because of the effect of bacterial lipopolysaccharide or LPS [6]. UTIs are more common in people with RA than in people without RA. This is likely due to the immunosuppressive effects of RA medications. Immunosuppressive medications weaken the immune system, making it more difficult for the body to fight off infections. UTIs are infections of the urinary tract, which includes the bladder, ureters, kidneys, and urethra. UTIs are caused by bacterial infections which are more common in women than in men [7].
Inflammation markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and antinuclear antibodies (ANA), are often elevated in people with both RA and UTIs. Inflammation markers are substances in the blood that indicate the presence of inflammation. ESR and CRP are two common inflammation markers. ESR measures the rate at which red blood cells settle to the bottom of a test tube. CRP is a protein that is produced by the liver in response to inflammation. ANA are antibodies that attack the body's own cells and tissues [8]. It is important for people with RA to be aware of the signs and symptoms of UTIs and to seek medical attention promptly if they suspect they have an infection. UTIs can be treated with antibiotics, but it is important to start treatment early to prevent complications. The present study aims to evaluate the effect of suffering from UTIs in patients with RA on the inflammation markers in the human body who receiving the treatments and suffering from RA for several years.

2. MATERIAL AND METHODS

2.1. Patients' samples

The 100 cohorts in the current investigation included 30 healthy control volunteers and 69 RA patients divided into two groups, The first group contained 40 patients (24 female and 6 male) with RA and UTI; the second group, 29 patients suffering from RA (24 female and 5 male) no UTI was identified. The patients were indoor patients receiving treatment and medicine at Baghdad Teaching Hospital in Baghdad, Iraq [1. Enbrel and Methotrexate (50 mg/ week), 2. Enbrel (50 mg/ week), 3. Methotrexate (25 mg), 4. Humira (40 mg/ week) and methotrexate (25 mg/week, 4. Rituximab (500 mg/week)]. The volunteer health group (hospital visitors and regular employees of the University of Baghdad in Baghdad, Iraq) joined this study post taking their written acceptance in terms of they were signed the concern forms. Rheumatologists in specialized hospitals adhered to 2010 RA classification standards [9]. The patients hadn't used any corticosteroids or disease-modifying medications in the month before the current study's time point. The patients and healthy control group ages were 48.1 ± 5.1 years (mean + SD), and 46.2 ± 4.1 respectively. The disease activity score 28 (DAS28) [10] of patients was 4.88±0.94 (mean SD), and IgM rheumatoid factor positivity of 52.8% and anti-CCP positivity of 71.4%, respectively. The levels of DAS28 were measured using the previous studies [9,10].

2.2. Bacteriological examination

A urine sample was obtained from 100 cohorts, and it was immediately sent to the lab (using sterile screw cups and ice box). The urine samples were inoculated onto MacConkey agar and blood agar and then incubated at 37°C for 18 h in aerobic conditions. To determine the staphylococcus species, the chosen colonies were re-cultured on mannitol salt agar. The morphological features of bacterial cells and colonies were examined [10]. For each isolate, the Gram stain slides were created using the Gram stain kit in accordance with the standard Gram stain protocol. This stain is often the first differential test for bacterial identification according to the bacterial cell shape and the stain color [11]. The pure culture of bacterial isolates was cultivated onto nutrient agar slant (sterile tube) and stored at 4 ^{o}C for a medium-term (a month). Pure colonies were cultivated at 37 °C for 18 hours into nutrient broth containing 15% glycerol in order to preserve bacteria for a long period (a year), by keeping them at -20 °C for a year.

2.3. Experiment

In the current study, the ESR, CRP, and ANA were measured in two patient groups (RA+UTI and RA without UTI) and a healthy control group [12]. In this study, the effect of the infection of the urinary tract of patients with RA by different bacterial species on the level of the (ESR, CRP, and ANA) was evaluated. Also, this study evaluates the effect of the duration of treatment and the age of patients on the possibility of infection with UTI.

2.4. Statistical analysis

The statistical analysis and graphs were done by using Origin 8 software. The data was expressed as means ± sd. The differences were evaluated by using the student t-test and one-way ANOVA. A value of $P<0.05$ was considered to be statistically significant.

3. RESULTS

3.1. Bacterial isolates

Of 70 patients with RA, only 40 cases suffered from urinary tract infection (UTI). The results showed the highest rate of bacterial infection that isolated from RA patients was found in the case of Staphylococcus aureus followed by *E. coli*, while the lowest bacterial infection rate was found in the case of Klebsiella pneumonia and Micrococcus luteus, with one case to each one Table 1. The highest rate of bacterial infection of the urinary tract of the healthy control group (who not suffering from RA 30 volunteers) was found in the case of *S. haemolyticus* followed by *E. coli.*

3.2. Inflammation markers, ANA, Age, and duration of treatment of patients with RA

In the present study, there is no significant difference in the level of ESR, CRP, ANA, ages, and duration of treatment in the patients with RA and suffering from UTI as compared with patients with RA who do not suffer from UTI. The present study proved that bacterial infection of the urinary tract does not change the level of inflammation markers such as ESR and CRP and also does not affect the level of ANA. Moreover, it was

observed the age of the patients and the duration of treatment do not affect the infection of the urinary tract with pathogenic bacteria (Table 2).

Table 1. *Incidence of bacterial isolation in the urine of patients suffering from RA and healthy control group.*

Bacterial species	Patient		Control	
Enterococcus faecium	2	5.26	0	0
Escherichia coli	4	10.52	4	36.36
Klebsiella pneumoniae	1	2.63	0	0
Micrococcus luteus	3	7.89	0	0
Staphylococcus aureus	16	42.10	2	18.18
Staphylococcus epidermidis	2	5.26	0	0
Staphylococcus haemolyticus	7	18.42	5	45.45
Streptococcus spp	3	7.89	0	0
Total	38	100	11	100

Table 2. The levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-nuclear antibody (ANA), ages, and duration of treatment in patients with rheumatoid arthritis (RA) and suffering from urinary tract infection (RA-UTI) and patient suffering from only RA.

	RA-UTI	RA	P value
ESR	46.6 ± 16 mm/h	42.1±15 mm/h	P=0.48
CRP	15±4.9 mg/l	9.6± 9.2 mg/l	P=0.11
ANA	0.35±0.05 U	0.21±0.06 U	p=0.104
Age	49.9±12.2 Years	54.2±10.2 Years	p=0.06
duration of treatment	6.8±5.6 Years	6.8±5.7 Years	p=0.485

3.3. Effect of age on the UT bacterial infection

The effect of age of patients on the possibility of infection of the urinary tract with different bacterial species. The results showed that the age of patients with RA did not affect the rate of infection of different bacterial species (*S. epidermidis, E. coli, S. aureus*, and *S. haemolyticus*) (Fig 1).

3.4. Effect of bacterial species on ESR

The present study showed the effect of infection of the urinary tract of patients with RA with different species of pathogenic bacteria (*S. epidermidis, E. coli, S. aureus*, and *S. haemolyticus)* on the level of ESR. The results showed that there is no significant difference (P>0.05) between the level of ESR in patients with RA and suffering from bacterial UTI with different bacterial species as compared with the levels of ESR in all patients with RA who suffered from UTI (38 patients) and the patients who urinary tract dose not infected with pathogenic bacteria (32 patients) (Fig 2).

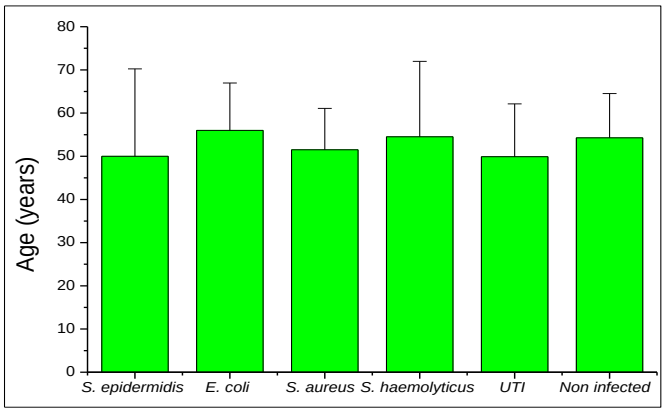

Fig. 1. The effect of the age of patients on the infection of the urinary tract (UT) with different bacterial species.

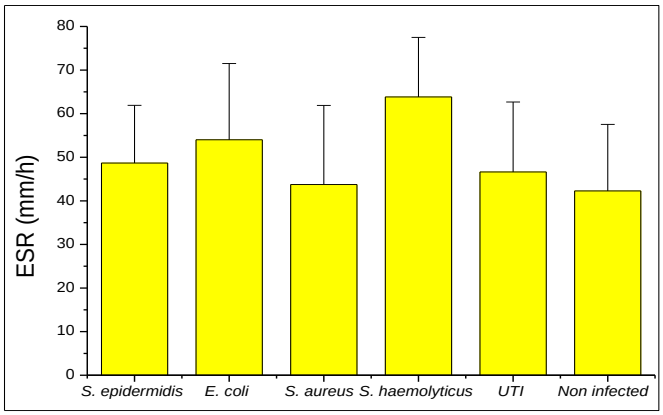

Fig. 2. The effect of infection of the urinary tract with different species of bacteria on the level of ESR in patients with RA.

3.5. Effect of bacterial species on CRP

Fig. 3 shows the effect of infection of the urinary tract of patients with RA with different species of pathogenic bacteria (*S. epidermidis, E. coli, S. aureus*, and *S. haemolyticus)* on the levels of CRP. The results showed that there is no significant difference (P>0.05) between the level of CRP in patients with RA and suffering from bacterial UTI with different bacterial species as compared with the levels of CRP in all patients with RA who suffered from UTI (38 patients) and the patients who urinary tract dose not infected with pathogenic bacteria (32 patients).

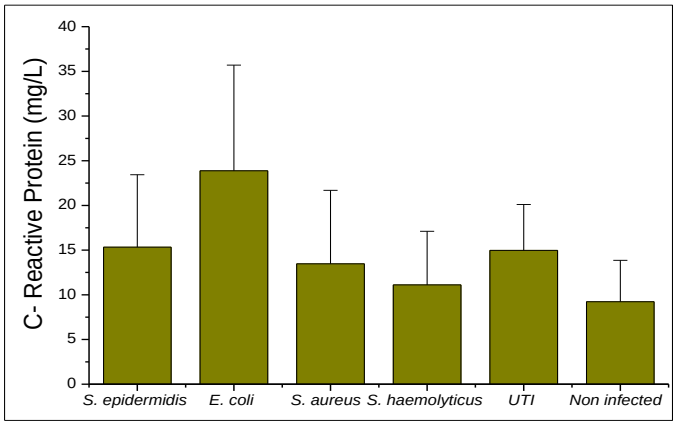

Fig. 3. The effect of infection of the urinary tract with different species of bacteria on the level of C-reactive protein (CRP) in patients with RA.

3.6. Effect of infection with different species of bacteria on ANA

In the current study the effect of infection of the urinary tract of patients with RA with different species of pathogenic bacteria (*S. epidermidis, E. coli, S. aureus*, and *S. haemolyticus)* on the levels of ANA (IU). The results of the effect of the infection with each bacterial species on the level of ANA were compared with the levels of ANA in the sera of all patients with RA who suffered from UTI (38 patients) and the patients whose urinary tract was not infected with pathogenic bacteria (32 cohorts). The results showed that there is no significant difference (P>0.05) between the level of CRP in patients with RA and suffering from bacterial UTI with different bacterial species as compared with the levels of CRP in all patients with RA who suffered from UTI or not suffering from UTI (Fig. 4).

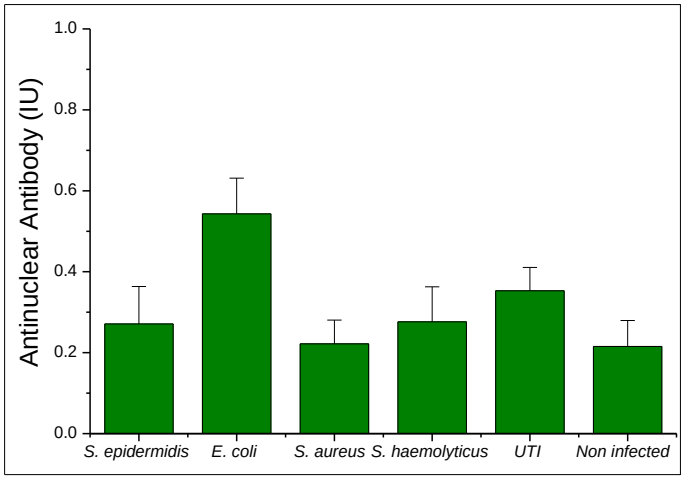

Fig. 4. The effect of infection of the urinary tract with different species of bacteria on the level of C-reactive protein (CRP) in patients with RA.

4. DISCUSSION

The incidence of UTIs in patients with RA is a subject of clinical interest and research due to the potential links between autoimmune diseases like RA and an increased susceptibility to infections. RA, as a chronic autoimmune disorder, affects not only the joints but also various aspects of a person's immune system and overall health. Several previous study highlighted the relationship between the suffering with RA and the inflammation markers in terms of ESR, and CRP in patients' blood circulation [7,8]. Moreover, other studies showed that infection with UTIs is related to elevation in the inflammation of blood markers such as ESR and CRP [13]. The research studies dealing with the effect of UTIs on the levels of ESR and CRP and other markers in patients with RA are scanty in the literature.

Therefore, the current study attempted to fill the knowledge gap related to the effect of two factors, first suffering from bacterial UTIs and RA, on the levels of the inflammation markers (ESR, and CRP) and ANA in the blood of patients with RA. In the current study, the ESR level was estimated in two groups of RA (those suffering from UTIs and those not suffering from UTIs) and the healthy control group. The results showed that the bacterial urinary tract infection does not affect the level of inflammatory indicators (ESR, and CRP), as there are no significant differences between those two groups with UTIs and those not infected their urinary tract with pathogenic bacteria. Moreover, the present study showed no effect of the infection with a particular species of bacteria (UTI) on the levels of ESR and CRP [Only the high-incidence bacteria were (*E. coli, S. aureus, S. epidermidis,* and *S. haemolyticus*) included in the study because bacterial species that isolated less than three isolates were not included because it is difficult to calculate statistically]. Our current study also confirmed that age and the treatment period do not affect the levels of ESR and CRP in the above groups of RA.

Bacterial infections play an important role in stimulating the inflammatory immune response and contribute to increasing the body's inflammatory response mediators, which depends largely on the increase in gamma-globulin proteins, especially as this is reflected in the increase in the ESR [14]. Bacterial infections contribute to the release of CRP from the liver of the host and this makes the ratio of these factors high [15]. The body of bacterial cells contains a number of antigens and proteins that contribute to the stimulation of inflammation response, including LPS [6], as well as proteins of the bacterial envelope that stimulate the immune cells responsible for the inflammation immune response to increase their effectiveness and thus increase the level of inflammatory indicators such as ESR and CRP [13, 16].

5. CONCLUSION

The current study showed that bacterial infection of the urinary tract does not affect the level of basic inflammatory indicators (ESR and CRP) in patients with RA. It also does not affect the level of ANA. The study showed that the age factor and the period of treatment that a patient with RA undergoes do not affect the incidence of bacterial UTIs.

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Conflict of interest

The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the Scientific Committee of the Ministry of Higher Education, Baghdad, Iraq (No 189, 2022).

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