Research Article

Assessment The Correlation Between Interleukin-22 And Ribonuclease-7 In Patients With Acute, Recurrent, And Chronic Urinary Tract Infections In Kirkuk City

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Abstract

Background
Urinary tract infections (UTIs) are among the most common types of infections. They place a huge burden on healthcare systems and represent a significant problem worldwide. The most serious issue is the recurrence of infections, which in many cases can develop into chronic conditions
Aim
This study aimed to evaluate the correlation between IL-22 and RNase7 in patients with acute, recurrent, and chronic urinary tract infections.
Materials and Method
This study was conducted on 151 urine samples from individuals suspected of having urinary tract infections (UTIs), selected according to established criteria. The sample consisted of 62 males and 89 females, collected between December 2022 and November 2023 in Kirkuk Governorate. The patients, whose ages ranged from 21 to 78 years, were diagnosed by a specialist physician. Interleukin-22 and ribonuclease-7 levels were measured in the urine of patients with acute, recurrent, and chronic UTIs. The tests were performed using enzyme-linked immunosorbent assay (ELISA) for each variable under investigation
Results
The concentration levels of the two variables were measured in urine. A correlation was performed between IL-22 and RNase 7, and the results showed a significant positive correlation between the two variables in acute cases, reaching ($r = 0.8521$) at a significance level of ($P<0.0001$). As for patients with recurrent urinary tract infections, the results showed a correlation of ($r = 0.3$) at a probability level of
($r = 0.0413$). Regarding patients with chronic urinary tract infections, the results showed an inverse correlation of ($r = -0.4$) between IL-22 and RNase 7 at a probability level of ($p<0.001$)
conclusion
The study showed a positive correlation between IL-22 and RNase7 enzyme in acute and recurrent cases, and an inverse correlation in chronic cases. This may indicate a possible role for these two factors in different stages of the disease, as they change according to disease progression and may play a role in the worsening and progression of the condition.

Keywords : Interleukin-22 , Ribonuclease-7 , Acute, Recurrent, and Chronic UTI.

Introduction

Urinary tract infections (UTIs) are infections affecting any part of the urinary system, such as the kidneys, ureters, bladder, and urethra. They typically cause a significant burden on individuals and are associated with high healthcare costs(1). Individuals of all ages, including women, men, children, and the elderly, are affected. Some suffer from acute or recurrent infections leading to serious complications. Symptoms vary depending on the

location and severity of the infection. In some cases, UTIs can be serious if left untreated. Therefore, UTIs have a negative impact on patients' lives (2). They are also more common in females than males due to anatomical and physiological reasons. Approximately 50% of women experience at least one UTI at some point in their lives (3).About 25% of women with cystitis experience recurrent UTIs within 6 months. Some women experience up to six recurrent infections per year.

Regarding chronic urinary tract infections (UTIs), persistent microbial infection is a rapidly expanding problem due to increasing antimicrobial resistance. This trend is particularly concerning because of the role chronic infections may play in cancer and chronic inflammatory diseases. Recurrent infections can become chronic, and early, effective intervention is key to preventing UTIs (4).

IL-22 is a cytokine produced by immune cells with bispecific function depending on the tissue in which it is expressed. IL-22 possesses antimicrobial properties and can reduce bacterial infection. It also stimulates pro-inflammatory responses, which can have serious consequences for disease progression. Conversely, this interleukin can also promote epithelial cell repair and regeneration, restoring mucosal function. It has a wide-ranging effect in maintaining homeostasis in mucous surfaces colonized by commensal microorganisms, such as those found in the urinary tract. Thus, IL-22R signaling in epithelial cells leads to the expression of genes involved in antimicrobial host defense (5). AMPs play a pivotal role in the innate immune system as a first line of defense against microbial infections and can serve as biomarkers and alternative antibiotics, thereby overcoming mortality associated with multidrug-resistant pathogens in urinary tract infections (6).

Ribonuclease 7 (RNase 7) is an important member of the RNAase family. Eight catalytically active subtypes (numbered 1–8) have been identified, each with a unique tissue distribution. First identified in normal human skin, it exhibits potent antimicrobial activity in vitro against Gram-positive and Gram-negative bacteria and fungi (7). This enzyme is involved in a wide range of biological processes, including the regulation of intracellular and extracellular RNA metabolism. RNase 7 exhibits antiviral, antibacterial, antifungal, neurotoxic, proliferative, antiapoptotic, and immunomodulatory activities. It is expressed by the interstitial cells of the renal collecting ducts and the lower urinary epithelium of the ureter and bladder, which are major sources of its production. It is also the most abundant enzyme in the urinary tract (8).

Materials and Methods

1. Study Area

This study was conducted in Kirkuk Governorate among patients attending private clinics on Doctors' Street.

2. Patient Selection

The clinical conditions required in this study were diagnosed by a urologist, specifying whether the condition was chronic, acute, or recurrent. A total of 151 samples were collected, ranging in age from 21 to 78 years. The sample consisted of 62 males and 89 females.

3. Urine Sample Collection

Samples were collected in sterilized screw-capped plastic tubes. Patients were instructed on the correct method for collecting urine samples, specifically a clean-catch midstream urine sample, to avoid contamination by the normal flora present in this area.Five milliliters of urine were collected and placed in sterile tubes within a centrifuge. The filtrate was isolated, and one milliliter of the supernatant was placed in each Eppendorf tube and frozen pending immunoassay for the desired variants. The sediment was examined microscopically by placing a drop onto a sterile glass slide and examining it under a light microscope for the presence of pus cells, epithelial cells, and red blood cells, which are indicators of urinary tract infection.

4- Interleukin-22 Urine Test

The test was performed according to the instructions of the supplier, BT LAB Bioassy Technology, for the KIT Human Interleukin-2 (IL-22) ELISA kit, which included a set of solutions and reagents.

5-Test RNASE7 in Urine

The test was performed according to the instructions of the manufacturer, ELK Biotechnology, for the Human RNASE7 test kit. The kit included a set of solutions and reagents, The ELISA assay was performed.

The data were statistically analyzed using Prism software, and the results were presented as the mean and standard deviation. Correlation between parameters was also analyzed using the Pearson Correlation Coefficient

test. Pearson's test was used to investigate the correlations between different factors and to explain the nature and strength of the relationship between the studied variables. The p-value was used to determine statistical significance levels: significant ($p<0.05$) and highly significant ($p<0.01$).

Results and Discussion

1-Numbers and percentages of samples by gender

In the current study, the number of male patient samples was 62 samples, representing (41.1%), while the number of female samples was 89, representing (58.9%), as shown in Figure (1).

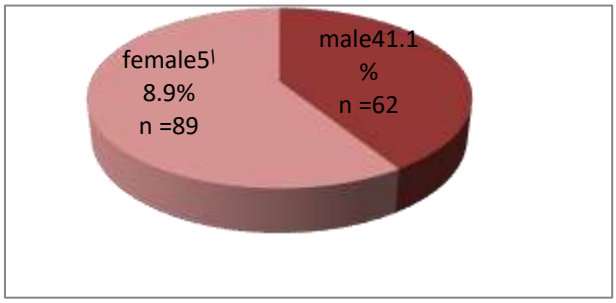


Figure (1) Numbers and percentages of samples by gender

The result was consistent with a study conducted in Kirkuk Governorate (9), where the percentage of males was 23.4%, while the percentage of females was 6.76%. It was also consistent with a study conducted in Najaf (10). Females are generally more susceptible to urinary tract infections due to anatomical and physiological differences in the urinary system between males and females, which increases the chance of rapid access of intestinal bacteria to the bladder (11). Hormonal fluctuations and estrogen deficiency contribute to an increased rate of urinary tract infections in females. Childbirth, pregnancy, methods of delivery, methods of contraception, and repeated intrauterine examinations (12) are all factors that increase the incidence of infection in females. Furthermore, the reproductive tract is constantly exposed to contamination by various types of bacteria and the natural flora of that area, i.e., changes in the Microflora (13).

Regarding males, the prostate gland plays a role in eliminating microorganisms and producing antibacterial substances in prostatic fluid. Additionally, the physiology of the male reproductive organs and the lower rate of urethral colonization in men, due to differences in the environment surrounding the urethra, contribute to reducing infection rates (14) .

2- Distribution of clinical cases by number and percentage

The number of samples for patients with acute urinary tract infections was 91 samples, recurrent urinary tract infections were 54 samples, while chronic infections numbered only 6 samples, with percentages of (60.3%), (35.8%), and (3.9%) respectively, as shown in Figure 2. A study conducted by (Bahragava). in 2022 (15)indicated that 40-60% of females suffer from acute urinary tract infections at least once in their lives. Pregnancy, childbirth, sexual activity, hormonal changes, menstruation, menopause, immune status, genetic predisposition, unhealthy lifestyle, poor personal hygiene, and a weak innate or adaptive immune response, in addition to bacterial isolates and their virulence, may all play a role in the development of urinary tract infections (UTIs). Recurrent infection occurs with two episodes within 6 months or more than three episodes within 12 months (16). UTIs are more frequent in women than men, with women experiencing 50% more recurrent UTIs than men due to differences in the anatomical structure of the female urinary system compared to males, family history, and hormonal changes (17The causes of recurrent infection may result from continuous exposure to bacterial strains transmitted from the gastrointestinal tract, or the infection may be present within the bladder epithelium and reappear periodically, causing recurrent infections. A high rate of recurrent infection and antibiotic aversion are also associated with the presence of quiescent bacteria. Intracellular Reservoirs (QIRs) within the epithelium (18)

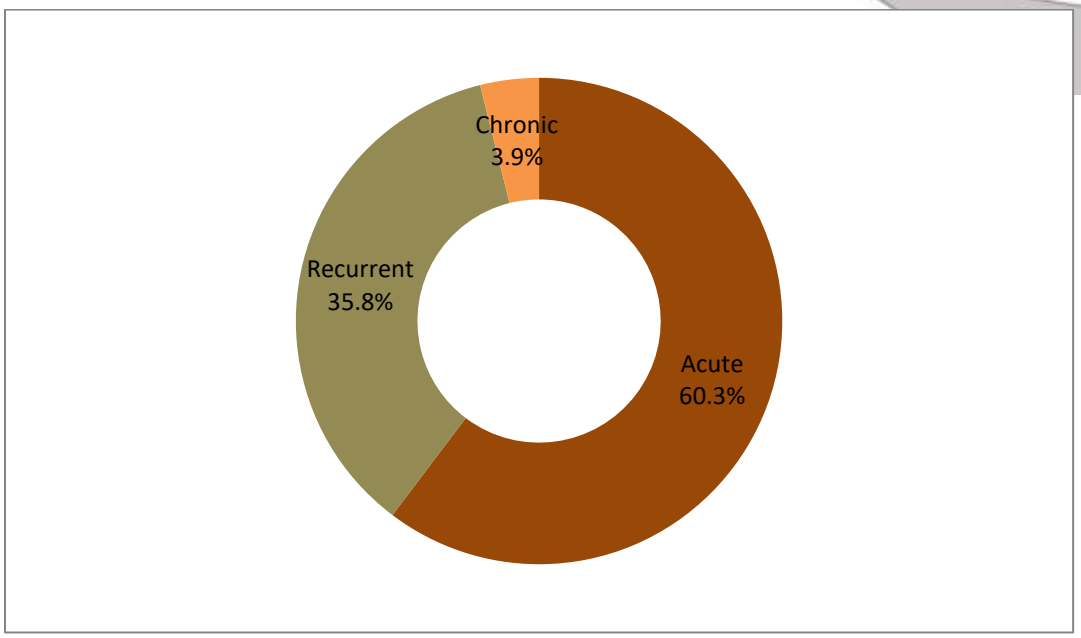


Figure (2) Distribution of Samples by Clinical Status

Immune disorders play a significant role in recurrent infection, and the condition can progress to a chronic state (19).

In patients with chronic urinary tract infections, only 6 samples were collected. The limited number of samples was due to the difficulty in diagnosis, as the condition requires a very long time to be diagnosed. Chronic cases are difficult to diagnose, patients often do not respond to treatment, and bacterial culture is challenging, with 90% of culture results being negative. The physician relies on long-term treatment, administering antibiotics for 383 days. (20)

Due to deficiencies in diagnosis and progression of the condition, poor management of previous episodes, and non-compliance with proper treatment, the condition worsens, bacterial resistance is enhanced, and the immune system is evaded. It is crucial to take medications precisely and without interruption, following the doctor's instructions and taking nutritional supplements. Furthermore, it is preferable to refer patients to a center specializing in urological diseases rather than a general gynecology clinic.

3-IL-22 concentration in urine

Regarding interleukin-22 (IL-22), In acute cases the results obtained in this study showed a significant difference at the ($P > 0.05$) level between patients and the control group. The concentration levels in both groups were (211.41±33.15) and (96.32 ± 19.48) pg/ml, respectively.IL-22 has both a protective and pathogenic role (21). It may play a pathogenic role or a positive one by promoting the integrity of the epithelial barrier and providing protection against acute urinary tract injuries (22). This cytokine targets epithelial cells and regenerates tissues after injury (23). A study measuring serum and urine levels of IL-22 indicated a high concentration in urine.(16.999 ± 0.6)pg/ml compared to its serum concentration (24). Another study indicated that IL-22 levels increased after 16 hours in infected mice, and that IL-22 levels also rise in the early stages of infection (25).

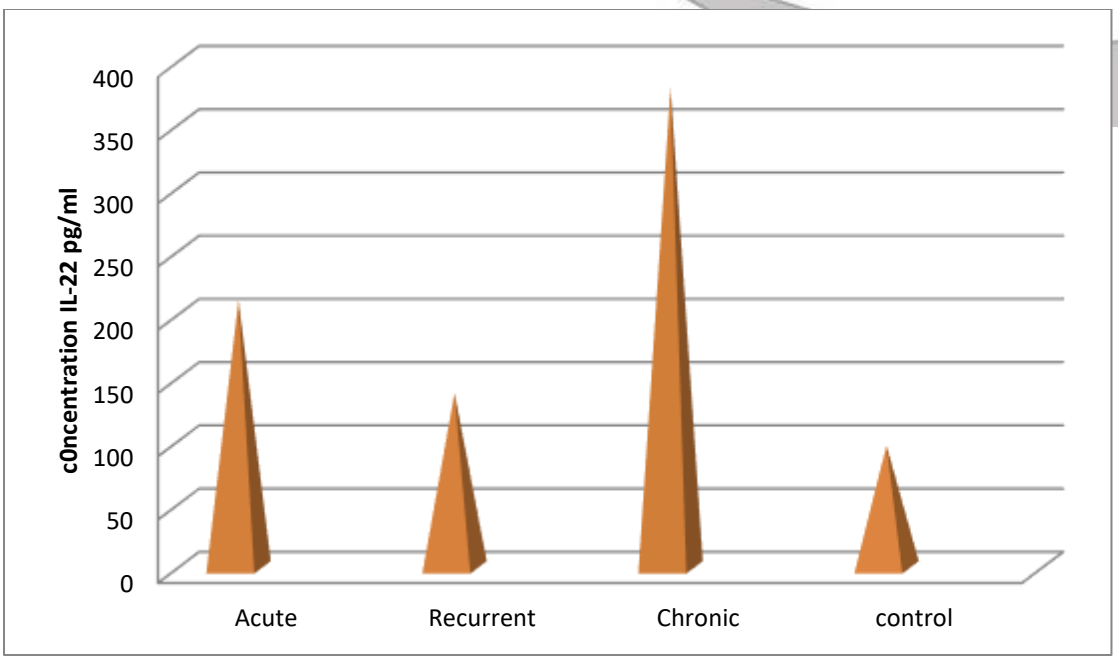


Figure (3) IL-22 concentration levels in patients with acute, recurrent, and chronic urinary tract infections

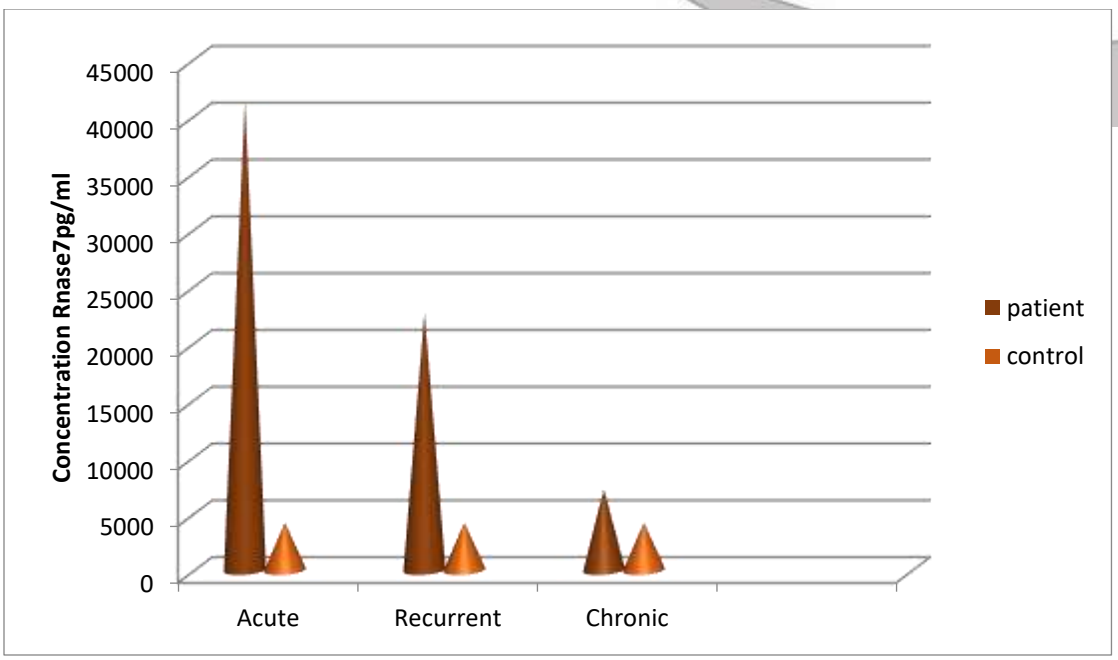
Regarding IL-22, In recurrent cases the results of this study showed a significant difference at the probability level ($P < 0.05$) between the patient group and the control group.

The concentration levels for both groups were(137.91 ±28.64)pg/ml and(96.32 ± 19.48)pg/ml, respectively. IL-22 is essential for protection against pathogens (26).A study revealed that IL-22 concentration was also high in patients with urinary tract infections, reaching 318 pg/ml (27). The potentially conflicting roles of IL-22 in some disease states raise questions about the therapeutic value of targeting this cytokine.

Regarding IL-22 In chronic cases, a highly significant difference ($P<0.01$) was observed between the patient and control groups, with concentration levels reaching(379.16 ± 46.59) and,(96.32 ± 19.48) respectively. IL-22 secretion may be beneficial or harmful depending on the site and context of its expression. Beneficial effects include the release and regulation of antimicrobial peptides (AMPs) and cell repair and regeneration IL-22 induces a pro-inflammatory response that may have serious consequences for the disease (5)Studies have confirmed the protective effect of IL-22 deletion in the acute phase, which is associated with a reduction in chronic disease (28). Research has also indicated the involvement of IL-22 in promoting inflammation and in several diseases, such as kidney cancer (29). IL-22 is a cofactor that exacerbates acute kidney injury, meaning it increases the severity of the condition. Deletion of IL-22 and its receptors in the kidneys of mice leads to improved nephropathy (28). A significant increase in IL-22 levels may play a role in disease progression; the increase in acute cases may have worsened the condition, leading to chronicity. T cells are also involved in IL-22 production ((30)

4. Level of ribonuclease7 enzyme concentration

n this study, the concentration of the RNase7 enzyme was measured in urine samples collected from patients with acute, recurrent, and chronic urinary tract infections. The results showed a statistically significant increase ($P<0.05$) between the patients and the control group. The concentration in the patients was (41329.44 ± 779.40)pg/ml, while in the control group it was (4190.45 ± 222.84)pg/ml, as shown in Figure 4.RNase7 plays an important role in regulating innate immune responses. A study demonstrated an increase in the concentration of this enzyme in acute infections (31).



Figure(4) RNASE7 enzyme concentration levels in patients with acute, recurrent, and chronic urinary tract infections

Another study also indicated elevated levels of RNase7 enzyme in urine (32). Furthermore, an increase in RNase7 concentration was observed in patients with urinary tract infections, meaning it is secreted in large quantities and released into the urine (Bender et al., 2021).RNase7 enzyme is produced by epithelial cells in the urinary tract, specifically the ureter and bladder epithelium, and is secreted into the urethra (33). A study suggested that RNase7 could be a therapeutic target for preventing urinary tract diseases (32). This increase may play a role in protecting against urinary tract infections. The antimicrobial mechanisms of bacterial membrane disruption differ significantly from those of antibiotics, which typically exert antibacterial effects by inhibiting cell wall synthesis, DNA replication, RNA transcription, or protein synthesis. These unique mechanisms offer potential insights into the development of AMPs such as RNase7, which represent a new class of therapeutic agents against urinary tract infections and play an important role in innate immunity (34).

Regarding patients with recurrent urinary tract infections, the results showed a significant increase ($P < 0.05$) when compared to the control group. The concentration levels in both groups were (22650.19 ± 520.11) and (4190.45 ± 222.84), respectively.

The enzyme RNase 7 plays a role in the recurrence of urinary tract infections (UTIs) in patients with recurrent UTIs, as it helps prevent excessive damage resulting from repeated infections (35). In this patient group, RNase 7 levels were lower than in patients with acute UTIs, possibly due to recurrent infections, bacterial isolates, health status, age, or sex—all of which may have influenced this finding.However, in patients with chronic UTIs,

the results of this study showed no significant difference or significant increase ($P > 0.05$) between the diseased and control groups. Silencing RNase 7 makes cells more susceptible to UPEC, and a decrease in RNase 7 levels for any reason increases the risk of UTIs (32). In one study, RNase 7 levels were found to be low in chronic infections (36). RNase 7 can be considered a warning sign of inflammation and a therapeutic target for bacterial infections. The severity of the disease and the duration of the infection may play a role in the decrease of RNase 7 levels. Understanding the underlying immune mechanisms and making progress in this area, and translating the findings into clinical treatments for RNase 7, is crucial. In this study, RNase 7 levels varied: they were high in acute cases, and as is known, RNase 7 has a protective role in repairing damage resulting from infection. However, in recurrent cases, levels were lower, perhaps contributing to recurrence. The low concentration in chronic cases may contribute to increased disease severity, or the patient's condition and the chronic infection itself may play a role

The differences between these variables in all cases are an important tool for diagnosing UTIs and a significant indicator of progression to a chronic condition. Regardless of the type of bacteria or sex, cytokine concentrations in urine can serve as a decision-supporting tool in the clinical diagnosis of the disease. Urine was chosen as the research material in this study because urinary tract diseases are under evaluation. The use of this biological material and its easy availability during illness may greatly facilitate matters for patients. Dysfunction and damage to the urinary tract play a role in the release of inflammatory proteins into the urine. Furthermore, chronic infections can be predicted early by identifying certain biomarkers and cytokines in urine.

5-The correlation between IL-22 and RNase7 in patients with acute urinary tract infections

After obtaining the results and identifying the levels and concentrations of the variables measured in the urine, a correlation was performed between these variables. The results showed a positive correlation ($r = 0.8521$) at a probability level ($P<0.01$) between IL-22 and RNase7 in patients with acute urinary tract infections, as shown in Figure 5

IL-22 acts as a protective agent through its role in AMP release and is elevated in acute pyelonephritis (37). RNase7 increases with infection and is considered the most potent human AMP (38). One study indicated that IL-22 induces epithelial cell proliferation, contributes to tissue repair, and stimulates AMP production. It also plays a protective and antifungal role (39).

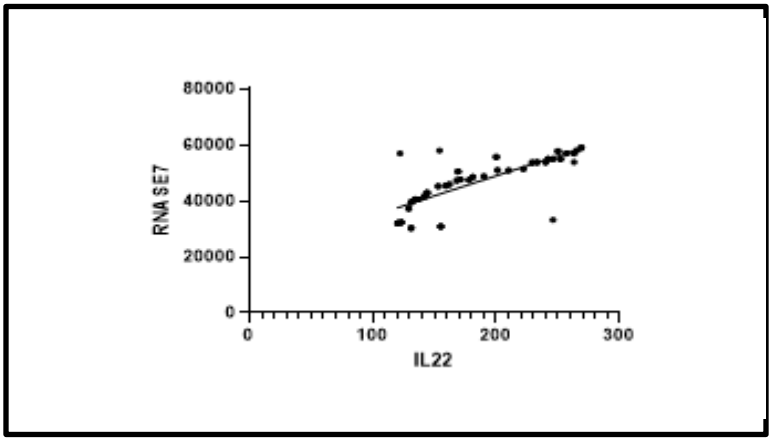


Figure (5) The Relationship between IL22 and RNase7 in patients with acute urinary tract infections

IL-22 is involved in AMP production and maintaining epithelial homeostasis (40). IL-22 increases and stimulates ribonuclease 7 in the early stages of the disease, and its concentration is high. It regulates immune defenses by producing peptides that are antimicrobial against Citrobacter rodentin. (41)

6-The correlation between IL-22 and RNase7 in patients with recurrent urinary tract infections

The results of this study showed a correlation ($r = 0.3$) at a probability level ($P<0.05$) between IL-22 and RNase7. As shown in Figure (6), although Interleukin-22 was significantly increased in the results obtained in this study, it was less than in acute cases. This may have affected the concentration of RNase7, which was lower than in acute cases

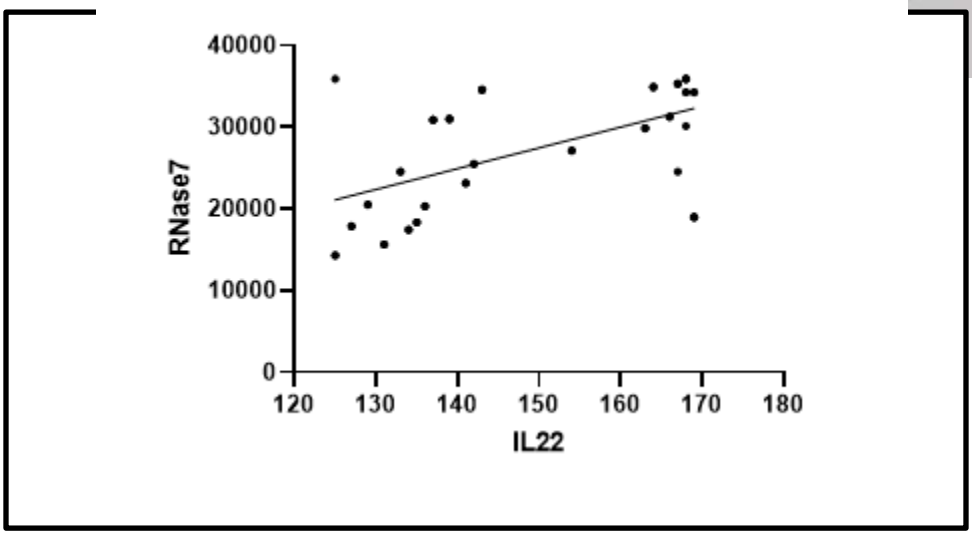


Figure (6) The Relationship between IL22 and RNase7 in patients with recurrent urinary tract infection

. Therefore, age, sex, recurrent disease condition, and types of isolates in this group may play a role in this. Histological analysis indicated that mice with a deficiency in IL-22 levels had more epithelial damage and an increased bacterial burden in the surrounding tissues, indicating penetration of the epithelial layer and bacterial spread (42).

7-The correlation between IL-22 and RNase7 in patients with chronic urinary tract infections

The results showed an inverse correlation (r = 0.4) between IL-22 and RNase 7 at a probability level (P<0.05), as shown in Figure7. In this study, the RNase 7 concentration was low in the group of patients with chronic urinary tract infections. This may be due to excessive IL-22 concentration, which could have a detrimental effect on the disease and its progression. The effect of IL-22 is not always protective, and it is believed that excessive activation and epithelialization play a role in some cases (43

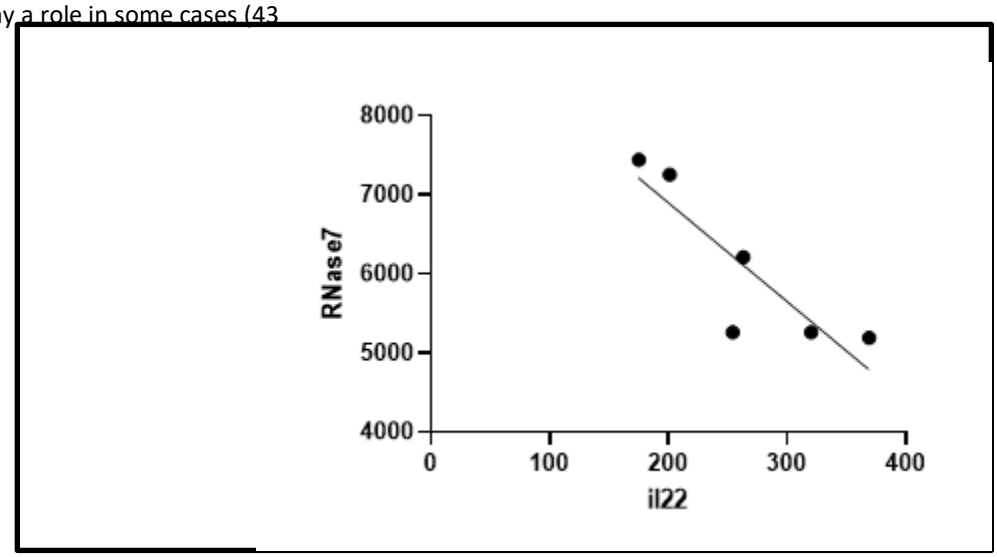


Figure (7) The Relationship between IL22 and RNase7 in patients with chronic urinary tract infections

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IL-22-dependent AMP promotes the anatomical containment of commensal bacteria and thus reduces inflammation. However, due to the low RNase 7 enzyme level, this led to an increase in inflammation (44).

The decrease in RNase 7 in chronic infection may be explained by the role of variables and their interaction, as well as the relationship between acute elevations of these variables and their effect on the decrease in RNase 7. Further research is needed. Basic and clinical research evidence is needed to determine whether this is a cause or a consequence of the disease.

Current treatments for chronic urinary tract infections are often unsuccessful. Therefore, further research could lead to easier treatment methods, such as intravesical drug delivery, thereby shortening recovery times and resulting in significant cost savings.

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