Biochemical changes in the renal function markers due to urinary tract infections.

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Abstract:

UTIs are a dominant clinical disorder that can substantially impact renal function, particularly in instances of recurrence or severe illness. These infections are primarily attributed to uropathogens including Escherichia coli, Klebsiella spp., and Proteus spp., while Enterococcus spp. and Staphylococcus saprophyticus, also significantly contribute in some demographics. Urinary tract infections provoke inflammatory responses that disrupt normal renal physiology, leading to biochemical alterations in renal function indicators. Primary indicators consist of elevated serum creatinine and BUN levels, signifying glomerular filtration rate and tubular dysfunction. Moreover, glomerular filtration rate typically diminishes during infection due to inflammation and decreased renal perfusion, highlighting the reduction in renal function. Other prevalent electrolyte imbalances, such as hyperkalemia and hyponatremia, also signify tube damage and dysfunction in the management of fluids and electrolytes.

Severe infections, particularly pyelonephritis, exacerbate these biochemical abnormalities and may result in acute kidney injury or chronic kidney diseases, if not addressed. Chronic infection leads to oxidative stress, tubular injury, and renal scarring, which progressively deteriorate kidney function. Comprehending these biochemical alterations is crucial for early diagnosis and care to avert prolonged renal problems resulting from UTIs. This review has examined the correlation between urinary tract infections and alterations in renal function indicators, emphasizing the necessity of prompt and efficient treatments. Moreover, analyzing these biochemical indicators enables the clinician to evaluate the infection's severity and customize suitable therapy approaches to mitigate renal damage and maintain renal health.

Key words: Urinary tract infections, CKD, renal markers, BUN, serum creatinine.

Introduction:

Urinary tract infections (UTIs) rank among the most commonly diagnosed infections in outpatient settings across the United States. UTIs are increasingly prevalent with advancing age, with the exception of young women aged 14-24 years. [1] Women aged over 65 have a prevalence of over 20%, in contrast to 11% in the general population. Approximately 50% to 60% of adult women may encounter at least one urinary tract infection during their lifespan, with approximately 10% of postmenopausal women indicating a UTI in the preceding year. [2]

The etiology of UTIs is considered predictable as a result of the consistent variety of microorganisms involved in these conditions. Nonetheless, the emergence of less common infections as significant contributors to the disease has transpired as a result of progress in medical treatments and pharmacology, alongside the increasing prevalence of immunosuppressed patients, whether due to disease or iatrogenic factors. [3, 4]

This review aims to determine the biochemical changes induced by urinary tract infections in renal function markers. This study aimed to obtain current data on the impact of UTIs on biomarkers such as electrolytes, glomerular filtration rate (GFR), BUN, and serum creatinine. This review will examine the fundamental mechanisms driving these changes, focusing specifically on renal stress, bacterial toxins, and inflammation. Acquiring insight into these alterations is essential for improving diagnosis, evaluating disease severity, and optimizing treatment.

Urinary tract infections classification and the microorganisms related to it:

Urinary tract infections can be classified based on severity and clinical manifestation into multiple groups. Complicated UITs occur in individuals with structural or issues affecting the normal functioning of the urinary system, including but not limited to nephrolithiasis, neurogenic bladder, and the use of indwelling catheters, as well as in those with predisposing factors such as diabetes and immunosuppression. [5, 6]

Acute uncomplicated cystitis is the predominant kind of urinary tract infection, found in otherwise healthy, nonpregnant, premenopausal women with the infection confined to the bladder. [2,7] Acute uncomplicated pyelonephritis is a more severe condition affecting the kidneys, characterized by systemic symptoms such as fever, flank pain, chills, and nausea, necessitating systemic antibiotic therapy for treatment. [8, 9]

Asymptomatic Bacteriuria (ASB) is the presence of significant levels of bacteria in the urine with the absence of illness symptoms. [10] The presence of two or more episodes within a period of six months or three or more episodes within a period of one year is indicative of recurrent urinary tract infections that are not classified as complex, [11] (table 1)

Table [1]: classification of UTIs [2].

Classification	Definition
Uncomplicated UTI	A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk of developing serious complications
Acute uncomplicated cystitis	A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute uncomplicated pyelonephritis	An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C)
Asymptomatic bacteriuria	A positive urine culture (>10^5 colony-forming units/ml) in the absence of urinary symptoms
Recurrent uncomplicated UTIs	A recurrent UTI refers to the occurrence of ⩾2 symptomatic episodes within 6 months or ⩾3 symptomatic episodes within 12 months

UTI, urinary tract infection.

Members of the Proteae tribe, including Proteus, Providencia, and Morganella species, and the Enterobacterales order, which includes Gram-negative bacteria such as Escherichia coli, Klebsiella spp., and pathogens from the CES group [Citrobacter-Enterobacter-Serratia], are the predominant pathogens in urinary tract infections (UTIs). Additional causal agents comprise non-fermenting Gram-negative bacteria (Pseudomonas spp. and Acinetobacter spp.), atypical microorganisms (Mycoplasma and Ureaplasma species), and yeasts (Candida spp.). [12, 13, 14]

Several phylogenetically different taxa within the Firmicutes class are Gram-positive, facultative anaerobic cocci. Various bacterial orders are associated with distinct streptococci; the Bacillales order encompasses Staphylococcus spp., the Lactobacillales order comprises Enterococcus spp., and the Streptococcus order includes Groups A, B, C, and G according per Lancefield classification.[3, 15] Staphylococcus aureus was formerly considered an infrequent causative agent in ascending urinary tract infections among outpatients; nevertheless, it may assume a more prominent role in hospitalized, immunocompromised individuals. [16, 17]

It is essential to enforce stringent procedures to prevent and monitor UTIs to avert negative impacts on renal graft performance, as complicated UTIs adversely affect renal function. Tacrolimus may influence eGFR by a deficiency in antimicrobial defense against urinary tract infections, perhaps resulting in decreased eGFR. [18]

Understanding Renal Function Markers:

Renal function markers are essential indicators in the evaluation and diagnosis of renal diseases. Essential indicators comprise BUN, serum creatinine, GFR, and electrolytes including salt, potassium, and bicarbonate. Each one illustrates specific elements of renal physiology and disease. [19]

BUN reflects the blood concentration of urea nitrogen, a byproduct of protein metabolism. Elevated levels indicate either diminished renal filtration capacity or enhanced protein catabolism. [20] Creatinine,

a byproduct of muscle creatine phosphate degradation, is another significant indication. Its serum levels rise with compromised kidney filtration, making it an effective measure of renal function. The GFR, assessed through creatinine levels, provides a direct indicator of renal filtration efficiency and is the predominant metric utilized for staging chronic kidney disease (CKD). [21, 22, 23]

Sodium and potassium are electrolytes essential for fluid equilibrium, neural transmission, and muscular activity. Alterations in their levels typically indicate renal impairment, as the kidneys govern their excretion and reabsorption. Bicarbonate levels are crucial for maintaining acid-base equilibrium, and deviations typically indicate metabolic acidosis in renal failure. [24, 25]

These markers are analyzed in relation to baseline levels. The normal range for BUN is 7-20 mg/dL, whereas serum creatinine levels for people typically range from 0.6-1.2 mg/dL, however these values may fluctuate based on age, gender, and muscle mass. GFR values over 90 mL/min/1.73 m^2 signify normal renal function, while decreasing values suggest advancing stages of chronic kidney disease (CKD). Electrolyte ranges, including 135-145 mmol/L for sodium and 3.5-5.0 mmol/L for potassium, serve as standards for identifying imbalances. [26]

Physiologically, these markers are crucial for assessing renal health and diagnosing illness. BUN and creatinine assess waste excretion efficiency, while GFR evaluates filtration capacity. Electrolytes will reflect the kidneys' regulatory activities in preserving homeostasis. These markers collectively establish a complete framework for evaluating renal function, thereby facilitating early intervention and personalized treatment in kidney disorders. [19, 23, 25]

Mechanisms of Renal Dysfunction During UTI

Urinary tract infections can lead to considerable renal impairment, particularly if they ascend to the upper urinary system and cause pyelonephritis. [27] The pathogenesis commences with microbial invasion of the lower urinary tract, typically instigated by Escherichia coli or other uropathogens that rise to the kidneys. [28, 29] The bacteria provoke a robust local immune response in the renal parenchyma, characterized by tissue inflammation, neutrophil infiltration, and the release of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These variables contribute to tissue damage and compromise renal function. [30, 31]

A key mechanism of renal impairment during urinary tract infections is modified renal blood flow. Inflammatory mediators provoke vascular alterations, such as vasoconstriction and heightened vascular permeability, which impair perfusion. This results in hypoxia within the renal tissue, compromising its capacity to filter blood efficiently. The ensuing a state of stress intensifies tissue damage, leading to acute kidney injury in severe instances. [32, 33]

Inflammation is regarded as the primary factor in the modulation of renal impairment in urinary tract infections (UTIs). [34, 35] Bacterial toxins and the host's immunological response impair glomeruli and tubular structures, diminishing the kidneys' ability to reabsorb essential nutrients and regulate waste products. [36, 37]

Moreover, inflammation elevates oxidative stress, leading to cellular damage and impairing renal filtration. The sustained presence of inflammation, resulting from recurrent infections or inadequate treatment, fosters fibrosis, scarring, and chronic renal impairment. [38, 39, 40]

The severity of the infection correlates closely with the degree of kidney impairment. Minor infections may result in temporary disruptions in renal function, whereas severe or repeated urinary tract infections can cause irreversible harm, including renal scarring and the loss of

functional nephrons. Obstruction, diabetes, and impaired immunity are risk factors that increase susceptibility to renal failure. [41]

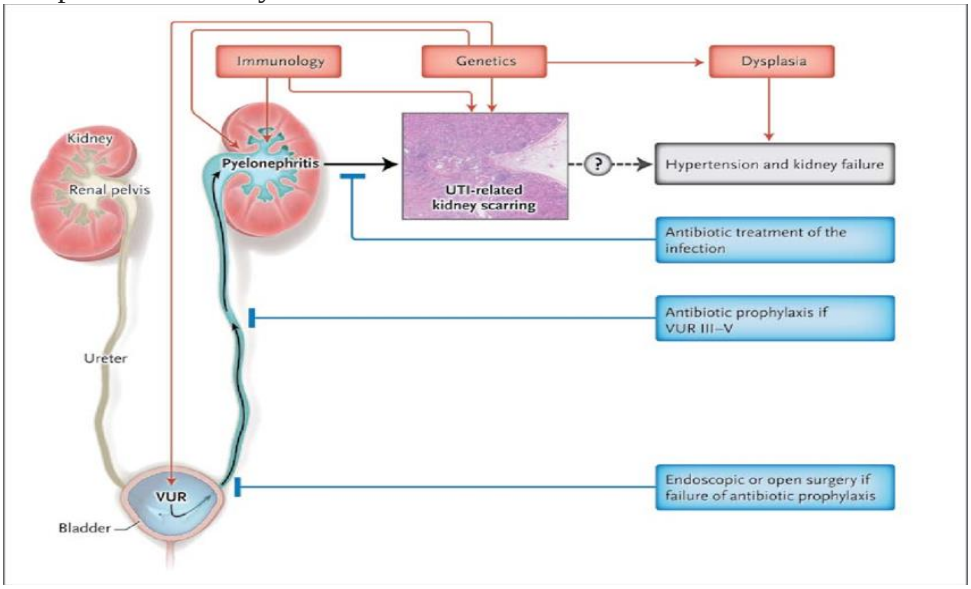

Figure [1]: mechanism of renal dysfunction during UTIs [41].

Role of Microorganisms in Renal Biochemical Alterations:

Pathogenic bacteria, particularly microorganisms, contribute to the alteration of renal biochemical indicators during urinary tract infections (UTIs). [42] The kidneys regulate homeostasis by managing electrolytes, excreting waste products, and balancing fluids. Urinary tract infections, induced by bacteria including Escherichia coli, Proteus mirabilis, and Klebsiella pneumoniae, can provoke inflammatory and oxidative stress responses, resulting in compromised renal function. [43, 44, 45]

Bacterial invasion leads to the secretion of cytokines and chemokines, inducing inflammation in renal tissues and causing tubular damage. This inflammation can elevate blood urea nitrogen and creatinine levels, which are significant indicators of renal impairment. [46, 47]

Pathogen-derived toxins, specifically Shiga toxins such hemolysins and proteases, directly impair renal cells, augmenting the permeability of the glomerular membrane and modifying filtration rates. [48, 49]

Certain bacteria, such as Proteus mirabilis, synthesize urease, which catalyzes the hydrolysis of urea into ammonia, hence elevating the pH of urine and facilitating stone formation. This activity disrupts normal metabolic processes, contributing to tubular blockage and renal stress. [50, 51, 52].

Biochemical Changes in Specific Renal Function Markers

Urinary tract infections, particularly severe or recurrent forms, induce significant biochemical alterations in renal function indicators, indicating the effects of infection and inflammation on kidney health. [53]

Serum creatinine typically rises with urinary tract infections, indicating a reduction in renal filtration efficiency. Creatinine is a byproduct of muscle metabolism that is primarily excreted through glomerular filtration. Infections that compromise renal blood flow or damage filtration structures result in elevated serum creatinine levels. [54, 55] This rise is significant as it directly impacts the calculation of GFR, a crucial indicator of renal function. A reduced GFR during UTIs indicates suboptimal kidney function,

typically signifying acute or chronic injury. [54, 56]

Blood Urea Nitrogen (BUN) levels increase due to renal stress induced by urinary tract infections (UTIs). BUN denotes the concentration of blood urea nitrogen, a waste product resulting from amino acid metabolism, eliminated through the kidneys. [57, 58] The kidneys' inability to eliminate urea during infection is due to variables including compromised renal perfusion, inflammation, and tubular dysfunction; thus, urea accumulates in the bloodstream. [59] Elevated BUN frequently coincides with increased creatinine levels, forming the foundation for assessing renal function in infection-related contexts. [60, 61]

Another significant biochemical alteration with urinary tract infections is the imbalance of electrolytes. Sodium, potassium, and chloride levels may fluctuate due to compromised tubular reabsorption and secretory functions resulting from infection and inflammation. [62] Hyponatremia may occur from tube malfunction or excessive water reabsorption. [63] Hyperkalemia frequently arises from diminished potassium excretion in critical situations and can result in potentially fatal cardiac problems. [64] Likewise, disruptions in chloride equilibrium may signify acid-base imbalances, such as metabolic acidosis, frequently associated with advanced renal impairment. [65]

Finally, a reduction in GFR during urinary tract infections is indicative of compromised renal filtration. This drop may result from reduced renal blood flow, glomerular inflammation, or urinary tract obstruction. Although a decrease in GFR is typically acknowledged as a characteristic of acute renal impairment, chronic kidney disorders may develop following sustained decreases, particularly in cases of recurrent or inadequately managed infections. [54, 66, 67]. Consequently, these biochemical indicators facilitate the evaluation of renal impairment during urinary tract infections by tracking their concentrations and suggesting additional therapeutic measures.

Impact of UTI Type and Severity on Renal Biochemical Markers

The intensity and classification of urinary tract infections significantly affect alterations in renal biochemical markers, indicating the degree of kidney involvement and systemic effects [68, 69] Lower urinary tract infections (cystitis) primarily affect the bladder and typically exhibit minor or transitory alterations in renal indicators. These infections rarely induce major alterations in serum creatinine or blood urea nitrogen levels, since renal function remains predominantly intact. [34, 70]

In upper UTIs, pyelonephritis affects the renal parenchyma and can lead to substantial elevations in creatinine and BUN due to compromised glomerular filtration and heightened renal stress. In pyelonephritis, inflammatory indicators and electrolyte equilibrium are more significantly disrupted due to systemic inflammation and tubular injury. [71, 72]

The progression from acute to chronic urinary tract infection highlights alterations in biochemical markers. In acute infections, modifications in renal markers, such as elevated serum creatinine or potassium levels, are typically reversible with prompt intervention. [73, 74]
Chronic or recurring infections may lead to irreversible renal impairment. Chronic urinary tract infections cause prolonged inflammation, scarring, and fibrosis, resulting in enduring decreases in glomerular filtration rate and persistent electrolyte imbalances. Over time, this may lead to chronic kidney disease, accompanied by progressively deteriorating biochemical imbalances. [75, 76]

Complications from urinary tract infections include renal abscess formation and sepsis, which exacerbate alterations in renal biochemical indicators. Abscesses can impede normal renal function and induce localized ischemia, resulting in a significant

increase in creatinine and BUN levels. In sepsis, systemic inflammatory reactions can lead to extensive organ failure, including acute kidney injury (AKI). This condition is marked by abrupt declines in GFR, significant hyperkalemia, and metabolic acidosis resulting from the kidneys' inability to manage electrolytes and acid-base equilibrium. [77, 78, 79, 80, 81]

Renal Function Markers as Prognostic Indicators in UTI

Renal function markers are crucial as prognostic indicators in urinary tract infections, offering insights into potential consequences and informing treatment strategies. [82] Serum creatinine and GFR are critical indicators of renal function, and deviations in these levels may indicate filtration impairment related to infection. [83] Elevated creatinine levels or a declining GFR during a UTI indicate significant renal involvement, such as pyelonephritis or acute kidney injury (AKI). An persistently elevated creatinine level will forecast the advancement to chronic kidney disease in instances of recurrence or insufficient infection management. These markers additionally identify patients susceptible to systemic problems such as sepsis, facilitating prompt management. [84, 85, 86, 87]

The BUN-to-creatinine ratio can assist in distinguishing between prerenal causes of acute kidney injury, such as diminished renal perfusion during sepsis, and intrinsic renal damage. [88] Electrolyte imbalances, including hyperkalemia, hyponatremia, and metabolic acidosis, are essential for evaluating UTI severity and forecasting consequences. Severe hyperkalemia may signify critical renal impairment, while hyponatremia frequently suggests tubular injury or significant fluid retention [89, 90]

Renal markers are dynamic indicators that inform the therapy of UTIs and assess the therapeutic response. These markers facilitate clinical decisions about supportive care, which may encompass hydration, dialysis in severe cases, and modifications in drugs that could potentially induce renal damage. [34, 91, 92, 94]

Conclusion:

Urinary tract infections are prevalent and clinically important contributors to renal dysfunction, particularly in cases of recurrent or severe infections. Approximately 50-60% of women will experience a urinary tract infection. The incidence markedly increases in elderly individuals. Escherichia coli are the predominant causative agent of urinary tract infections; however, Klebsiella, Proteus, and Gram-positive cocci, including Staphylococcus saprophyticus and Enterococcus spp., are emerging as uropathogens. Inadequate filtration and tubular injury from UTIs can elevate serum creatinine and blood urea nitrogen levels.

Infection frequently reduces GFR, an indicator of renal efficiency, owing to inflammation and decreased renal blood flow. Hyperkalemia and hyponatremia are further manifestations of tube damage and electrolyte imbalance. These anomalies are exacerbated by renal damage resulting from severe conditions such as pyelonephritis. Chronic inflammation, oxidative stress, and fibrosis contribute to renal impairment, particularly in cases of recurrent urinary tract infections, diabetes, or obstruction. Early detection of UTIs is essential to avert renal complications and to comprehend the biochemical alterations that facilitate treatment.

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