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Title: **Evaluating the Risk Factors and Bidirectional Association of Urinary Tract Infections in Diabetes Mellitus**

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Evaluating the Risk Factors and Bidirectional Association of Urinary Tract Infections in Diabetes Mellitus

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ABSTRACT

Background. Urinary tract infections (UTIs) are the most predominant among people with diabetes mellitus (DM), with significant implications for morbidity and mortality. Various microbial agents, including bacteria, fungi, and viruses, contribute to UTIs in diabetic patients.

Objective. This review aims to examine the association between UTIs and DM, focusing on pathogenic mechanisms, risk factors, and clinical implications.

Methods. A comprehensive literature review was conducted to gather data on UTIs in diabetic patients. Relevant articles gathered from various databases, such as PubMed, Google Scholar, Semantic Scholar, and ScienceDirect were analyzed for insights into microbial colonization, pathogenic mechanisms, and epidemiological trends.

Results. Microorganisms commonly implicated in diabetic UTIs include *Escherichia coli, Proteus mirabilis, Enterobacter* spp*.,* and *Klebsiella spp*. Elevated urinary glucose levels provide a conducive environment for microbial growth, contributing to increased infection rates. Risk factors such as female sex, obesity, glycosuria, immunosuppression, and diabetic complications (such as nephropathy and cystopathy) further exacerbate susceptibility.

Conclusion. The incidence of UTIs in diabetic populations is rising globally, provoked by antibiotic resistance among uropathogens such as Gram-negative bacteria including *Escherichia coli* (65-80%), trailed by *Pseudomonas aeruginosa*, *Proteus mirabilis* (2-6%), and *Klebsiella* spp. (3.5-13%). Whereas, Gram-positive bacteria include *Staphylococcus* spp. (4-6%), GBS (3%), *Enterococcus faecalis* (4-7%), and *Candida* (1%).

Keywords: antibiotic resistance, diabetes mellitus (DM), prevalence, urinary tract infections (UTIs), uropathogens

Highlights

- UTIs are more common in diabetic patients which requires attention.
- Multidrug resistance may play a crucial role in developing UTIs among diabetic patients.

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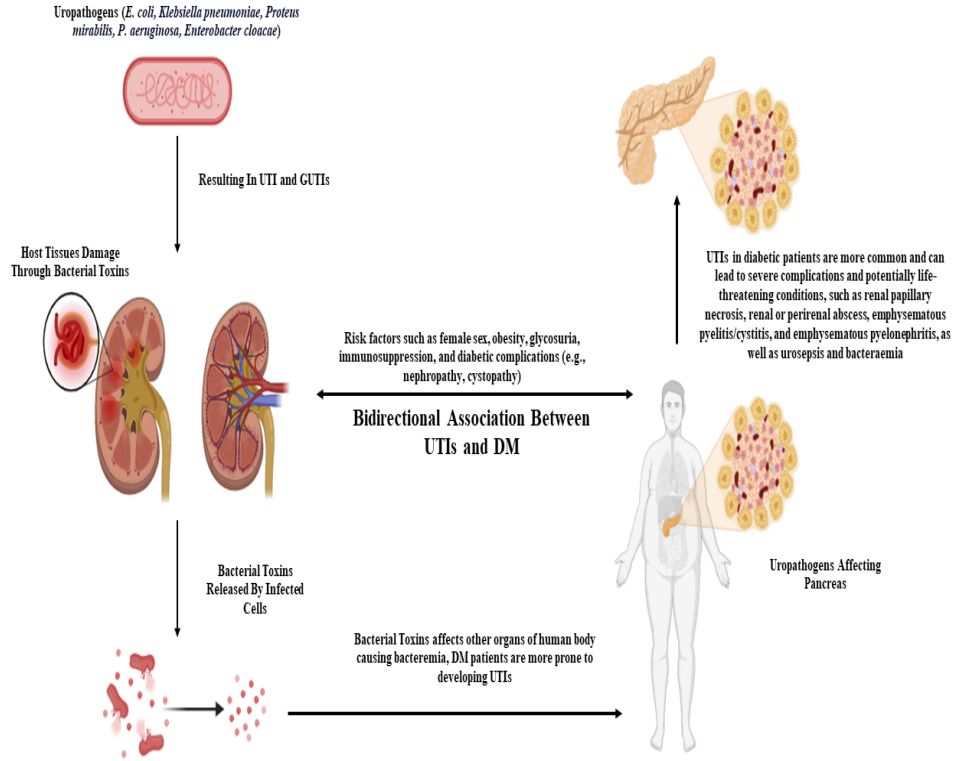
- The unknown pathogenic mechanism of uropathogens requires attention for designing therapeutic strategies.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Diabetes mellitus (DM) is a long-lasting metabolic disease and is one which contributes high frequency of illness worldwide [1]. Immune system dysfunction is greatly associated with DM, which results in repeated infections prone to/among the affected individuals, particularly those with the infections of genitourinary tract [2].

Urinary tract infections (UTIs) can be described as/comprise the disorders caused by microbial colonization of the human genitourinary tract. They contribute to frequently acquired bacterial infections and account for approximately 25-40% of the nosocomial infections [3].

UTIs may be asymptomatic or symptomatic. Symptomatic UTIs include urgency, lower abdomen cramping, burning micturition, chill, fever, nausea, fatigue, weakness, vomiting, mental irritability, dysuria, and back pain [2]. DM appears to upsurge/increase the danger of developing the complications of/complicated UTIs or infrequent infectious forms. Else, rare problems, such

as emphysematous cystitis and pyelonephritis, renal papillary necrosis, xanthogranulomatous pyelonephritis, and abscess formation have been associated with DM in some case reports [4].

There is a reason that DM alters the host defense system and frequently results in the development of UTIs. It includes the attachment of pathogenic microorganisms to urinary epithelial cells and granulocytes dysfunction, which possibly results in intracellular calcium metabolism impairment [5]. Urogenital infections together with UTIs, balanitis, male accessory gland infections, vaginitis, and balanoposthitis, express an increased risk of incidence in individuals with DM than in the non-diabetic patients [6]. Patients with both UTIs and DM face greater complications and disease severity. There are several factors involved in the higher frequency of these infections in diabetic people, including neuropathy, poor metabolic control, and weak immunity [7].

The most prominent pathogen responsible for developing UTIs is *E. coli.* It contributes 80-85% of these infections. It is trailed by *Staphylococcus saprophyticus,* which contributes 5-10% of such infections. Besides these bacterial pathogens, *Pseudomonas, Proteus, Klebsiella,* and *Enterobacter* spp. are also associated with UTIs. The bacteria can enter the bladder through the urethra and the infection can also be contracted through lymph and blood [8].

The classification of UTIs is based on their severity (complicated or uncomplicated) and location (upper and lower). Complicated UTIs are more severe and present unembellished clinical features. Their treatment is not easy. Whereas, uncomplicated UTIs are milder than complicated UTIs and commonly occur in women. These do not require the necessary treatment through antibiotic therapy [7].

Complicated UTIs can be described as symptomatic. These UTIs are caused in patients by structural or functional abnormalities; or in patients having systemic diseases such as renal insufficiency and immunodeficiency. Moreover, patients having had urinary instrumentation, or those undergone organ transplantation tend to develop these infections. The presence of leukocytes in the urine is known as pyuria [9]. UTIs can be caused by various reasons and DM is one of them, which occurs due to the alteration in the immune system of diabetic patients, for instance, granulocyte dysfunction. They can be caused by microbial growth, such as the growth of bacteria, fungi, or viruses and their colonization inside the urinary tract. However, UTIs caused by fungi and viruses have a low incidence [7, 10].

The pathogenesis mechanism for this association is not fully explained, however, it has been suggested that the higher amount of glucose in the urine may favor the growth of pathogenic microorganisms [11]. While the exact mechanism remains unknown, several possibilities have been proposed to describe the relationship among UTIs and DM [12]. For example, any injury in the genitourinary system as a result of diabetic neuropathy can lead to bladder dysfunction, thus providing development opportunity for UTIs. The increased concentration of glucose in urine can be another pathway for the development of UTIs which amplifies bacterial growth and produces a favorable environment for infections [13].

There are several uropathogens found in diabetic patients' infections. Among them, the most common uropathogens isolated from diabetic patients are

Klebsiella spp., *Candida albicans, Escherichia coli,* and *Staphylococcus aureus* [14].

The biological mechanisms of increased UTIs danger between the diabetic patients remain unknown but are expected to include glycemic control in response to immune mechanisms [15]. UTIs alone are not frequent in DM patients. Rather, they may lead to the development of emphysematous pyelonephritis, acute papillary necrosis, bacteremia with metastatic localization to other body parts, and increased morbidity [16]. UTIs are the utmost mutual infections in the patients with DM and are accountable for significant/severe illness, if left unidentified or untreated [17]. Diabetic patients are at a higher risk for infections, which include UTIs, soft tissue infections, community acquired pneumonia, bloodstream infections, and necrotizing otitis externa infections [18].

Patients with or without DM have many risk factors which include female sex, obesity, prostate syndrome in males. Moreover, immunocompromised, glycosuria, and bladder dysfunction are associated with DM and are particular UTI risk factors [17].

Besides these risk aspects, the patient-related factors which increase the hazard of developing UTIs in diabetic patients include age, cystopathy, primarily diabetic nephropathy, metabolic control, and long-term complications [12]. Furthermore, there are several clinical risk factors for developing UTIs in patients with DM including the duration of disease, poor glycemic control, impaired leukocyte function in hyperglycemia, diabetic microangiopathy, structural and functional abnormalities of the urinary tract, and recurrent vaginitis [4].

The frequency of UTIs depends on various risk factors including advanced age, DM, neurological disorders, urinary tract obstruction, and immunosuppression [19]. This increase in frequency has been also due to the developing antibiotic resistance in the urogenital pathogenic bacteria [19].

According to an estimation by the International Diabetics Federation in 2017, about 451 (8.4%) million individuals worldwide between 18 to 99 years of age were living with DM. Moreover, about 5 million people between 20 to 79 years of age had died because of this disease. This number is predicted to increase to 693 million (9.9%) by 2045 [10]. Globally, UTIs have been estimated to infect 150 million people per year [20]. Presently, DM affects approximately 366 million people internationally, but this number is projected to rise. In 2030, it is projected that about 552 million individuals will have DM [13]. Currently, about 420 million people have DM, worldwide. It is projected that this number will double by 2025, while unreasonably distressing the working age individuals [21].

The treatment choice remains the same in both non-diabetic or diabetic patients and depends upon the local resistance forms of the frequently found uropathogens [22]. There is a frequency of the most commonly prescribed antimicrobial resistance like; nitrofurantoin, amoxicillin, ciprofloxacin, sulfamethoxazole and trimethoprim in the isolates form the diabetes mellitus patients having urinary tract infections [22]. The optimum period of treatment for UTIs in diabetic patients remains unclear. Generally, patients with a complicated UTI can be treated for a period of 7 to 14 days [22]. To enable appropriate treatment, accurate screening for UTIs in diabetic

patients is necessary to avoid complications [20].

In the case of Gram-negative pathogenic bacteria, tazobactam and ceftolozane show effective activity against them. These drugs are approved by the European Medicine Agency and United States Food and Drug Administration for the treatment of patients who have complicated intra-abdominal infections. Metronidazoleis is used in combination with these drugs for the treatment of UTIs, including pyelonephritis [23].

There are several antibiotic drugs used for treatment including cotrimoxazole, penicillin, gentamicin, imipenum, amikacin, newer fluorinated quinolone (ciprofloxacin, ofloxacin), cephalosporins, and nalidixic [24].

2. ASSOCIATION BETWEEN DM AND UTIS

Diabetes Mellitus Type 2 is a chronic disorder which has many complications resulting from inflammation, hyperglycemia, and immune system abnormalities. Moreover, to the macro and micro vascular injury, type 2 DM is also related with higher risks of UTIs, non-sexually transmitted genital infections (including balanitis, vulvovaginal infections), and asymptomatic bacteriuria [25]. The urinary tract infection is an infection which can be caused by the existence and progression of microorganisms anywhere within the urinary tract. This is particularly because of the bacteria from the digestive tract which scrambles the urethral opening and begins to multiply which starts to cause the infection [26].

Diabetic patients are more likely to get infections, with the urinary tract being their most common location. Various UTIs show no symptoms and remain asymptomatic. It is not known whether the symptomatic UTIs are headed by asymptomatic bacteriuria [27].

Even among individuals who are non-diabetic, an enormously common UTI consisting of/causing both uncomplicated and complicated cases is triggered by Gram-negative bacteria including the uropathogen *Escherichia coli* (65-80%), trailed by *Pseudomonas aeruginosa, Proteus mirabilis* (2-6%), and *Klebsiella* spp. (3.5-13%). While, the remaining percentage of cases is caused by Gram-positive bacteria, including *Enterococcus faecalis* (4–7%), GBS (3%), *Staphylococcus* spp. (4-6%), and *Candida* (1%) [28, 29].

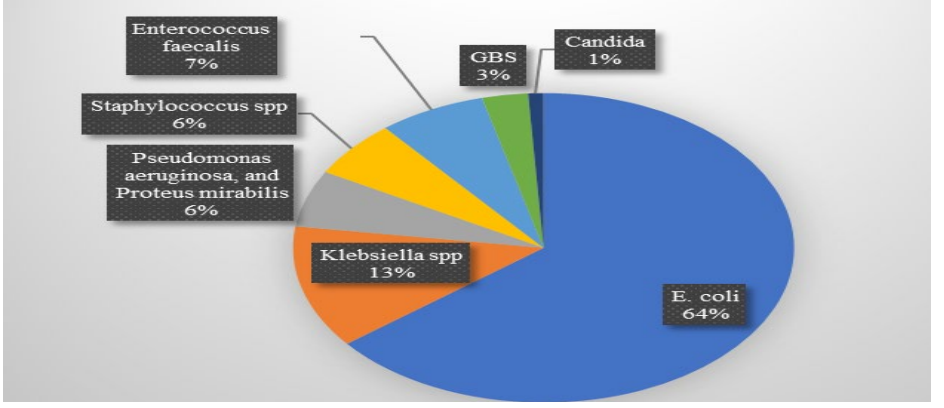


Figure 1. Percentage of Microorganisms Causing UTIs

DM is a significant risk issue for the growth of UTIs. It is also linked with the higher risk of complicated UTIs including xanthogranulomatous pyelonephritis, emphysematous cystitis, emphysematous pyelonephritis, emphysematous pyelitis, renal papillary necrosis, and renal or perianal abscess. These conditions are possibly life-threatening and need prompt management and evaluation [30].

Individuals with type 2 DM are at a higher risk of experiencing UTIs and recurrent UTIs, as compared to those without the condition. Type 2 DM increases the likelihood of various genitourinary infections (GUIs), including UTIs and genital infections, across all age groups. SGLT2 inhibitors, a newer class of anti-hyperglycemic medication, have been linked to a higher risk of GUIs. Effective management of diabetes, along with lifestyle modifications centered on the patient, is crucial for preventing serious and long-term complications, including those related to genitourinary health [31].

It has been shown that diabetes has secondary effects on the urogenital system that result in a greater possibility of the patient contracting UTIs [27]. A relationship between DM and UTIs was observed in an autopsy series reported in the 1940s. The principal site of infection in diabetes is the urinary tract. Variations in the host defense mechanism, diabetic cystopathy presence, and microvascular diseases in the kidney may have a role in the increased occurrence of UTIs in diabetic patients [32]. Poor white blood cell circulation and elevated blood glucose levels are the common reasons [33]. Another reason is inappropriate bladder emptying because of autonomic neuropathy, which causes the urine to remain in the bladder for extended periods of time and turns it into a bacterial breeding ground [34, 35].

Patients with hyperglycemia have elevated levels of glucose (glycosuria) in their urine which makes it favorable for microbes to grow. Such conditions interfere with the antimicrobial function by neutralizing glucose-6-phosphate dehydrogenase (G6PD), inhibiting polymorphonuclear leukocyte movement through the endothelium, and also enhancing polymorphonuclear leukocyte apoptosis [37, 38].

A study by Karslıoğlu, M. and M. O. Yılmaz (2024) emphasized that individuals with diabetes, especially women and those taking SGLT-2 inhibitors, face a heightened risk of UTIs. The researchers suggested that it is essential to implement careful monitoring and customized strategies to manage UTIs in diabetic patients, taking into account gender and the particular treatment administered for diabetes [39].

Shahsavari et al. [40] conducted a study on diabetic patients who frequently suffer from UTIs. They examined how glycemic control impacts UTIs rates, the pathogens involved, and the prevalence of multidrug-resistant (MDR) and extensively drug-resistant organisms, as well as the connection between these infections and diabetes. The study involved 500 diabetic patients, of which 189 (37.2%) tested positive for UTIs. Among those with poor glycemic control, 130 patients reported the highest number of UTIs, as compared to 59 patients with well-managed blood sugar levels. Additionally, the prevalence of UTIs was significantly higher in female patients than in male patients in both diabetic groups, with rates of 88.4% for the former and 11.6% for the latter. The most

frequently isolated bacterium, *E. coli*, showed a 58.4% rate of multidrug resistance [40].

Shalgam et al. [41] proposed that type 2 DM primarily affects middle-aged and older individuals, who experience persistent hyperglycemia due to their poor dietary habits and lifestyle choices. In their study, *E. coli* accounted for 67% of the bacterial isolates found in the urine of type 2 DM patients with UTIs. The research revealed that *E. coli* showed a high sensitivity rate of 97% to nitrofurantoin, erythromycin, tetracycline, oxyacillin, vancomycin, teicoplanin, and imipenem. However, the bacteria exhibited complete resistance (100%) to moxifloxacin, meropenem, tigecyclin, ampicillin, cefazolin, ceftriaxone, ertapenem, cefoxitin, and nalidixic acid [41].

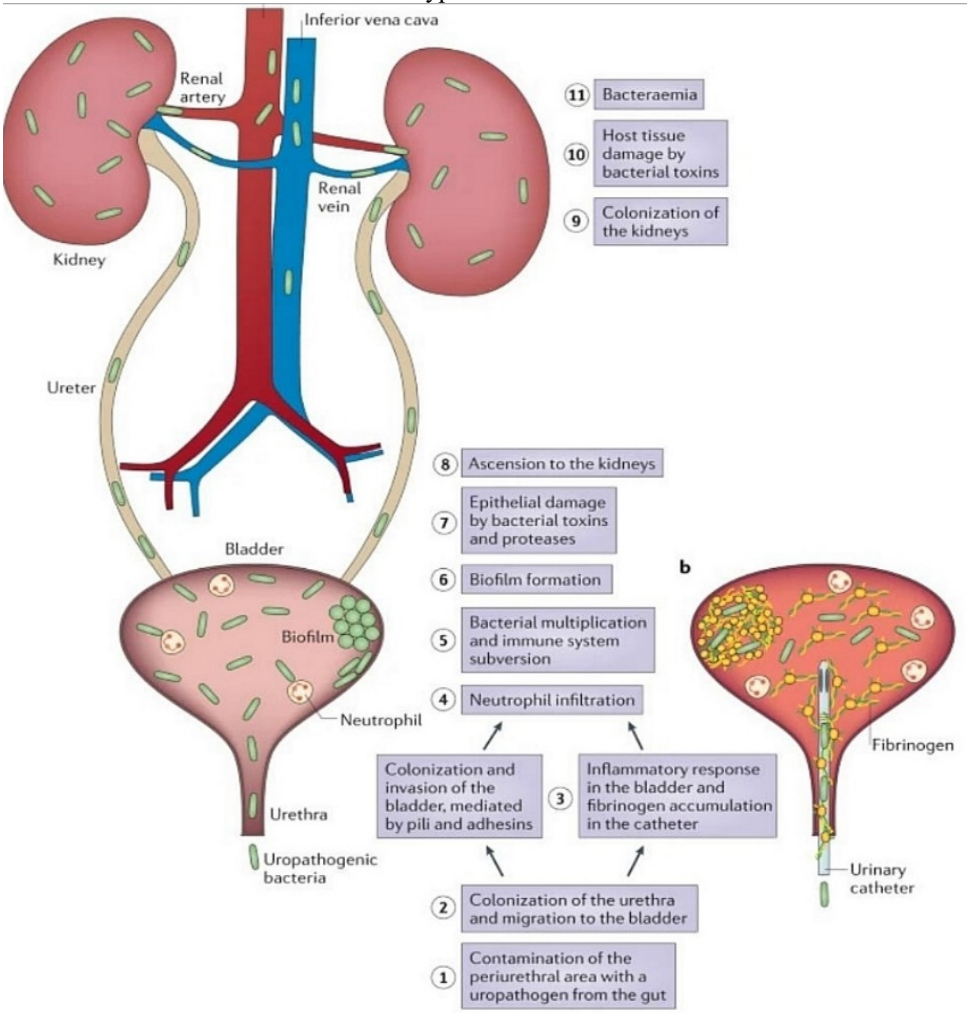


Figure 2. Pathogenesis of UTIs [36]

Table 1. UTIs in Diabetic Patients along with Their Causative Agents and Risk Factors

Year	Infection	Causative agent	Risk Factors	References
1957	Cystitis and Urethritis Emphysematos	Diabetes	Diarrhea, weakness, and anemia	[42]
1961	Cystitis emphysematous	Diabetes	Old age, hyperglycemia	[43]
1973	Renal emphysema	Diabetes	Arteriosclerotic heart disease, chronic pancreatitis, and parathyroid adenoma	[44]
1978	UTI	Diabetes	Neuropathy, Nephropathy	[35]
1997	Body infections	Diabetes	Polymorphonuclear neutrophils	[33]
2001	Emphysematous pyelonephritis	*K pneumoniae, P mirabilis, E. coli*	Hyperglycemia	[45]
2002	UTI	Gram negative pathogen, *E. coli*, *candida species*	Pyelonephritis	[4]
2002	UTI	*E. coli*	Diabetes	[27]
2004	Emphysematous cystitis	Gas fermenting bacterial and fungal pathogens	Diabetes	[46]
2007	UTI	Diabetes	Ketoacidosis, Host defense	[38]
2007	emphysematous cystitis	*E. coli*	Middle-aged diabetic women	[47]
2008	UTI	*E. coli*	Glucosuria, hyperglycemia	[22]
2009	UTI	*E. coli*	Poor glycemic control	[30]
2009	Emphysematous pyelonephritis	Diabetes	Ureteric obstruction	[48]
2010	UTI	Diabetes	Insulin intolerance	[15]
2010	Emphysematous pyelonephritis	Diabetes	ketoacidosis	[49]
2011	Xanthogranulomatous pyelonephritis	Diabetes	Long-term urinary tract obstruction	[50]
2012	Nosocomial UTIs	*Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *E. coli*, *Proteus mirabilis*, *Klebsiella pneumoniae, Enterococcus faecalis*	Catheters and urethral stents or sphincters	[3]
2012	Diabetes mellitus	Type 2 DM	Obesity	[34]
2012	UTI	Diabetes	Low T cells response, neutrophil function, and	[37]

Year	Infection	Causative agent	Risk Factors	References
			humoral immunity diseases	
2013	UTI	Bacteriuria	Diabetes	[11]
2013	Upper UTI	*E. coli*	Poor glycemic control	[18]
2013	UTI	Gram negative bacteria	Pregnancy, diabetes, old age	[32]
2014	UTI	Bacteriuria	Old age women	[9]
2014	UTI	Type 2 DM	Diabetic neuropathy, bladder dysfunction	[13]
2014	UTI/GUTI	Type 2 DM	Glucosuria, immune dysfunction and bacterial attachment to the uroepithelium.	[25]
2015	UTI	Multidrug resistant (MDR) uropathogenic strains	Female sex, and prostate syndrome in men, Obesity, low immunity	[17]
2015	UTI	*E. coli, Klebsiella, Proteus species, pneumoniae, Staphylococcus aureus, Enterobacter, Pseudomonas aeruginosa, group Streptococci, Serratia species Enterococcus faecalis,*	Host defense, neuropathy, bladder emptying, cystopathy and micro-vascular disease	[26]
2016	UTI	Diabetes	Host defense, bladder dysfunction	[20]
2017	UTI	*Klebsiella, Proteus, Pseudomonas* and *Enterobacter*	Microbial colonization to UT, Diabetes	[8]
2017	UTI	Bacterial species	Diabetes, postmenopausal period, antihyperglycemic sodium-glucose cotransporter-2 inhibitors	[16]
2017	UTI	*E. coli, Enterobacter, Klebsiella spp, Candida albicans,* and *S. aureus*	hyperglycemia, elevated HbA1c, glycosuria, albuminuria	[21]

Year	Infection	Causative agent	Risk Factors	References
2017	UTI	Multi drug resistance bacteria	Diabetes	[23]
2018	UTI	Diabetes	Age, sex and high blood glucose	[14]
2018	UTI	*E. coli, Proteus, Klebsiella, Streptococcus* and *Staphylococcus epidermis*	Sexual behavior, diabetes mellitus, postmenopausal women, urinary retention, poor bladder function, and occlusion in the urinary system that results in insufficient voiding	[24]
2019	UTI/GUTI	*E. coli*	Immune system dysfunction	[2]
2019	GUTI	Bacterial colonization to UTI	Granulocyte dysfunction, abnormal intracellular calcium metabolism	[5]
2019	UTI	Diabetes mellitus	Drugs	[6]
2019	UTI	*Enterobacter spp, Proteus mirabilis, Klebsiella spp, E. coli,* and *Pseudomonas aeruginosa*	Old age, urinary tract obstructions, immunocompromised, and neurological disorders	[19]
2020	UTI	Diabetes mellitus	Immunosuppression	[1]
2020	UTI	*Klebsiella* spp., *Enterobacter* spp, *Mycoplasma* spp, *Escherichia coli*	Diabetes	[7]
2020	UTI	Type 2 DM	Age, metabolic control	[12]
2021	UTI	Gram-negative bacteria	Host defense, high glucose concentration	[10]
2024	UTI/GUTI	Type 2 DM	SGLT2 inhibitors	[31]
2024	UTI	Type 2 DM	Old age	[51]
2024	UTI	Diabetes Mellitus	Frequent in women's than in men	[39]
2024	UTI	Diabetes Mellitus	MDR *E. coli,* higher in women's than in men	[40]
2024	Emphysematous pyelonephritis	Type 2 DM	Chronic kidney disease	[52]

UTI: Urinary tract infection, GUTI: Genitourinary tract infection, MDR: Multi-drug resistance, *E. coli; Escherichia coli,* Spp: Species, DM: Diabetes Mellitus, *P. mirabilis: Proteus mirabilis, K. pneumoniae: Klebsiella pneumonia*

3. CONCLUSION

Diabetic patients are at a higher risk of developing UTIs. These infections are severe and may lead to very severe complications. If not treated, they may even result in death. Complications include urgency, lower abdomen cramping, burning micturition, chill, fever, fatigue, weakness, vomiting, mental irritability, dysuria and back pain, abscess formation, pyelonephritis, emphysematous cystitis, and renal papillary necrosis. The exact pathogenesis mechanism remains unknown, but there are some studies which describe the association between developing these UTIs in diabetic patients/how these UTIs develop in diabetic patients. However, there are no random trials that suggest the best treatment strategy, although some medications, such as amoxicillin, nitrofurantoin, trimethoprim/sulfamethoxazole, ciprofloxacin, and ceftolozane, in combination with metronidazole, penicillin, cotrimoxazole, gentamicin, and amikacin are used for the treatment of UTIs in diabetic patients. Alternative strategies should be targeted to combat with antibiotic resistance including herbal treatments, as well as the designing of protein motif which targets the resistance gene or protein and results in contending with emerging microbial resistance.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILTY STATEMENT

The data associated with this study will be provided by the corresponding author upon request.

FUNDING DETAILS

No funding has been received for this research.

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