Exploring the alliance: Urinary Tract Infections in Diabetic Patients

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Abstract: Urinary tract infections (UTIs) are a common and significant complication in diabetic patients, posing a considerable challenge to healthcare providers. This review article aims to provide a comprehensive analysis of the current understanding of UTIs in diabetic patients, exploring the prevalence, pathogenesis, risk factors, and management strategies. We discuss the interplay between diabetes and UTIs, highlighting the role of hyperglycemia, immune dysfunction, and other diabetes-associated factors in predisposing individuals to UTIs. Furthermore, we examine the challenges in diagnosis, given the atypical presentation and asymptomatic bacteriuria often observed in diabetic patients. We also delve into the various therapeutic approaches, emphasizing the importance of individualized treatment plans and the need for prompt intervention to prevent complications. Finally, we underscore the necessity for preventative measures, patient education, and ongoing research to improve the overall management of UTIs in this vulnerable population.

1. Keywords: Urinary tract infection (UTI), Antibiotic therapy, Prevalence

Introduction:

Urinary tract infections (UTIs) are a common and significant health concern for diabetic patients. The prevalence of UTIs in individuals with diabetes is higher compared to the general population, and these infections can lead to severe complications if left untreated. This article aims to provide an in-depth understanding of the relationship between diabetes and UTIs, the risk factors for developing UTIs, symptoms, diagnosis, treatment, and prevention strategies.

Diabetic patients experience several impacts on their immune system, which can increase their susceptibility to infections and impair their ability to recover from illnesses. Some key aspects of the immune system that are affected in diabetic patients include impaired immune cell function, decreased circulation, chronic inflammation, glycation of proteins and compromised barrier function.

Diabetic neuropathy: Diabetic neuropathy is a common complication of diabetes, resulting from long-term high blood sugar levels, which can damage nerves throughout the body. While diabetic neuropathy typically affects nerves in the hands, feet, and legs, it can also impact the nerves controlling the urinary system, leading to an increased risk of urinary tract infections (UTIs) in diabetic patients.

In diabetic patients with neuropathy of the urinary system, the bladder may be affected in several ways such as bladder dysfunctions, loss of sensations, weakened immune response, increased glucose in urine and autonomic neuropathy.

To reduce the risk of UTIs in diabetic patients with neuropathy, it is essential to manage blood sugar levels effectively, practice good hygiene, and maintain a healthy lifestyle. Additionally, patients should consult their healthcare providers for regular check-ups and discuss any urinary symptoms to ensure timely diagnosis and treatment of UTIs.

Additionally, diabetes itself can contribute to kidney damage through diabetic nephropathy, which is a complication that affects the small blood vessels in the kidneys [4]. This further increases the risk of kidney disease development in diabetic patients who experience UTIs [1][2].
Early detection and treatment of UTIs in diabetic patients are crucial to prevent kidney damage and complications. This includes proper management of diabetes, maintaining good blood sugar control, and seeking medical attention if UTI symptoms occur [1].

**Diabetic and Non-Diabetic UTIs:**

**Severity and frequency of infections:** In diabetic patients, the severity and frequency of urinary tract infections (UTIs) can be significantly higher compared to non-diabetic individuals. There are several factors contributing to this increased risk and severity:

1. Impaired immune system: As mentioned earlier, diabetes can weaken the immune system, making it less effective at identifying and fighting off infections. This can lead to more frequent UTIs and a higher likelihood of complications, such as kidney infections or sepsis.
2. Increased glucose in urine: High blood sugar levels can result in increased glucose in the urine, creating a favorable environment for bacterial growth. This can promote more frequent UTIs and make them harder to treat.
3. Diabetic neuropathy: Diabetic neuropathy affecting the urinary system can lead to bladder dysfunction and incomplete emptying, which can increase the risk of UTIs and make them more severe due to the prolonged presence of bacteria in the bladder.
4. Reduced blood flow: Diabetes can cause damage to blood vessels, leading to reduced blood flow and oxygen delivery to tissues, including the urinary tract. This can impair the immune system's ability to reach and effectively combat infections, potentially making UTIs more severe and difficult to treat.
5. Recurrent infections: Diabetic patients who have experienced a UTI are at a higher risk for recurrent infections. This can be due to the factors mentioned above, as well as antibiotic resistance, which can make UTIs more challenging to treat effectively.

The severity and frequency of UTIs in diabetic patients can have significant consequences, such as increased hospitalizations, higher healthcare costs, and a diminished quality of life. To reduce the risk and severity of UTIs, diabetic patients should focus on effective blood sugar management, maintaining good hygiene, and seeking prompt medical attention if they suspect a UTI. Regular consultations with healthcare providers can also help monitor and manage any urinary symptoms and complications.

**Predisposition to complicated UTIs:** Diabetic patients are predisposed to complicated urinary tract infections (UTIs) due to several factors that increase their risk of infection and make it more challenging to treat. These factors include impaired immune system, increased glucose in urine, diabetic neuropathy, reduced blood flow, antibiotic resistance and presence of comorbidities.

**Risk Factors for UTIs in Diabetic Patients**

1) **Lifestyle Factors**

**Age and gender:** Age is a well-known risk factor for bacteriuria in nondiabetic females, and advanced age has been widely accepted as a risk factor for patients with type 2 diabetes [1]. Older diabetic individuals, particularly women, are more susceptible to UTIs due to factors such as weakened immune systems, poor blood sugar control, and age-related changes in the urinary system [5].

Gender also impacts UTI risk in diabetic patients. Women are generally more prone to UTIs than men, which can be attributed to anatomical differences such as a shorter urethra, making it easier for bacteria to enter the urinary tract [6]. However, age and gender can influence the prevalence of different bacteria causing UTIs. For example, E. coli is less prevalent in males over 60 and in those under 14, while P. mirabilis is more prevalent in the latter group [7].

Considering age and gender is important when determining the causative uropathogen and providing appropriate treatment for UTIs in diabetic patients [3]. This helps healthcare professionals to tailor treatment plans and preventive strategies for individuals who are at higher risk for UTIs and its complications, such as kidney damage.

**Use of urinary catheters:** The use of urinary catheters significantly increases the risk of urinary tract infections (UTIs) in diabetic patients, as well as in the general population [1][2][3]. Bladder-inserted catheters can lead to nosocomial UTIs by allowing microorganisms to enter the bladder during insertion or manipulation of the catheter [2]. Daily incidence of bacteriuria is 3-10% after catheter placement, which can be asymptomatic [2]. In diabetic patients, the risk is further elevated due to compromised immune systems and poor blood sugar control [1].
E. coli is the most common organism found in these infections, followed by Pseudomonas species and Enterococcus species [2]. Longer duration of catheterization, colonization of the drainage bag, diabetes, and errors in catheter care are some risk factors for bacteriuria [2].

Prevention measures include limiting catheter use and promptly discontinuing catheters when it is clinically feasible to do so [8]. Guidelines recommend minimizing catheter use and avoiding their use for treatment of incontinence [2]. Antibiotics should not be routinely used to prevent catheter-associated UTI [2]. Infection control programs must monitor catheter use and implement strategies to prevent infection, while technical advances in catheter materials are necessary to prevent biofilm formation [3].

**Hygiene practices:** Hygiene practices play a crucial role in preventing urinary tract infections (UTIs) in diabetic patients. Proper hygiene can help minimize the introduction of bacteria into the urinary tract, reducing the risk of infection. Diabetic patients, who are already at a higher risk of UTIs due to factors like impaired immune function and increased glucose in urine, can benefit significantly from good hygiene practices. Some essential hygiene practices for diabetic patients to prevent UTIs include:

1. **Regular bathing:** Bathing regularly, especially around the genital and perianal areas, helps remove bacteria and prevent their transfer to the urethra.
2. **Proper wiping technique:** After using the toilet, it is important to wipe from front to back to avoid introducing bacteria from the rectal area to the urethra.
3. **Clean underwear:** Wearing clean, breathable, and moisture-wicking underwear helps prevent the growth of bacteria and reduces the risk of UTIs. Changing underwear daily, or more often if necessary, can also help maintain cleanliness.
4. **Hydration:** Drinking plenty of water encourages regular urination, which helps flush bacteria out of the urinary tract and reduce the risk of infection.
5. **Urination habits:** Urinating when needed, rather than holding it in, can help prevent the buildup of bacteria in the urinary tract. Additionally, completely emptying the bladder when urinating can also reduce the risk of UTIs.
6. **Proper catheter care:** If a diabetic patient uses a catheter, strict hygiene practices must be followed while inserting, cleaning, and removing the catheter to minimize the risk of UTIs.

By following these hygiene practices, diabetic patients can significantly reduce their risk of developing UTIs and maintain better overall urinary health. It is essential for diabetic patients to maintain good blood sugar control and work closely with their healthcare providers to address any urinary symptoms or concerns.

**Medical Factors**

**Duration of diabetes:** The duration of diabetes plays a significant role in the development of UTIs in diabetic patients. Patients who have had diabetes for five or more years have two times the odds of experiencing UTIs compared to those with a shorter duration of diabetes [5]. This increased risk is associated with the longer duration or greater severity of the disease [2]. As diabetes progresses over time, it weakens the immune system and reduces blood circulation [3], making it more challenging for the body to fight off infections like UTIs. Consequently, diabetic patients with a longer history of the condition are more susceptible to UTIs, which could further complicate blood sugar control and reduce their quality of life [3].

**Glycemic control:** Glycemic control plays a crucial role in preventing UTIs in diabetic patients. Poor glycemic control can increase the risk of UTIs, as high blood sugar levels impair the immune system's ability to fight off infections [3]. In a study analyzing urine samples from 722 adult diabetic patients, UTIs were more prevalent in those with uncontrolled glycemia [6].

To maintain good glycemic control, diabetic patients should regularly monitor their blood sugar levels and follow their healthcare provider's recommendations for medication, diet, and exercise. By effectively managing blood glucose levels, diabetic patients can reduce the risk of UTIs and associated complications [3]. Implementing proper diabetes management techniques not only helps to prevent UTIs but also improves overall health and quality of life for diabetic patients.

**Presence of diabetic complications:** The presence of diabetic complications can significantly impact the risk, severity, and management of urinary tract infections (UTIs) in diabetic patients [1][2]. These complications include diabetic neuropathy, nephropathy, and impaired immune function [1][2].

Diabetic neuropathy, particularly autonomic neuropathy, can lead to bladder dysfunction, incomplete bladder emptying, and urinary retention, which predispose patients to UTIs [1][3]. Moreover, diabetic nephropathy, which affects the kidneys, may impair the body's ability to concentrate urine and excrete waste products, increasing the risk of UTIs and other infections [1][3].
Impaired immune function in diabetic patients is another crucial factor that can exacerbate UTIs [2]. High blood sugar levels can impair the function of white blood cells, which are essential in fighting bacterial infections [1][2]. Consequently, diabetic patients may have difficulty clearing bacteria from the urinary tract, leading to more frequent, severe, and recurrent infections [2][3].

**Concurrent medical conditions:** Concurrent medical conditions can play a significant role in increasing the risk and complicating the management of urinary tract infections (UTIs) in diabetic patients. Some medical conditions can impair immune function, affect urinary tract anatomy, or contribute to urinary stasis, making it more challenging for the body to fight off infections. Common concurrent medical conditions that can impact UTIs in diabetic patients include:

1. Kidney disease: Diabetic patients are at a higher risk of developing kidney disease, which can lead to impaired kidney function and urinary stasis, increasing the risk of UTIs.
2. Neurological disorders: Diabetes can cause neuropathy, leading to bladder dysfunction and urinary retention. Conditions such as multiple sclerosis, Parkinson's disease, or spinal cord injuries can also affect bladder function, increasing the risk of UTIs.
3. Benign Prostatic Hyperplasia (BPH): BPH, or an enlarged prostate, can cause urinary retention and incomplete emptying of the bladder in men, increasing the risk of UTIs.
4. Immunodeficiency: Conditions that weaken the immune system, such as HIV/AIDS or treatments like chemotherapy, can make it more difficult for the body to fight off infections, including UTIs.
5. Urinary tract abnormalities: Structural abnormalities, such as vesicoureteral reflux, kidney stones, or bladder diverticula, can contribute to urinary stasis and increase the risk of UTIs in diabetic patients.
6. Use of indwelling catheters: Patients with concurrent medical conditions that require the use of indwelling catheters are at a higher risk of UTIs due to the increased chance of introducing bacteria into the urinary tract.
7. Obesity: Obesity can impair immune function and make it more difficult for diabetic patients to maintain proper hygiene, increasing the risk of UTIs.

It is essential for diabetic patients with concurrent medical conditions to work closely with their healthcare providers to manage these conditions effectively and minimize the risk of UTIs. Preventative measures, such as proper hygiene practices, maintaining good blood sugar control, and addressing urinary symptoms promptly, can help diabetic patients reduce the risk of UTIs and maintain better overall urinary health.

**Symptoms and Diagnosis of UTIs in Diabetic Patients**

**Dysuria:** Dysuria is the medical term for painful or difficult urination, which is a common symptom of urinary tract infections (UTIs) in diabetic patients. When a UTI occurs, bacteria, most commonly Escherichia coli (E. coli), enter and multiply in the urinary tract, causing inflammation and irritation of the urethra, bladder, or kidneys.

In diabetic patients, dysuria in UTIs can be attributed to several factors:

1. Inflammation and irritation: The presence of bacteria in the urinary tract leads to inflammation and irritation of the affected tissues, causing pain and discomfort during urination.
2. Increased sensitivity: Diabetic patients may have heightened sensitivity due to the effects of high blood sugar levels on nerve function, making them more susceptible to pain and discomfort during a UTI.
3. Impaired immune function: Diabetes can weaken the immune system, making it more challenging for the body to fight off infections. As a result, UTIs in diabetic patients may be more severe or long-lasting, causing more pronounced dysuria.
4. Glycosuria: High blood sugar levels can result in glucose being excreted in the urine (glycosuria). This excess glucose can provide a favorable environment for bacterial growth, exacerbating UTIs and potentially increasing the severity of dysuria.

It is essential for diabetic patients experiencing dysuria to consult their healthcare provider promptly, as early diagnosis and treatment of UTIs can help alleviate symptoms and prevent complications. Treatment may involve antibiotics to eliminate the infection, along with proper hydration and pain relief medications to manage symptoms. Additionally, maintaining good blood sugar control and practicing proper hygiene can help diabetic patients reduce the risk of UTIs and dysuria.

**Urgency and frequency:** Urgency and frequency are common symptoms of urinary tract infections (UTIs) in diabetic patients, as well as in the general population [1][3].

Urgency refers to a sudden, strong, and often overwhelming need to urinate, which can be difficult to postpone [1]. This occurs because the infection causes inflammation and irritation of the bladder and urethra, leading to increased sensitivity and the urgency sensation [3]. In diabetic patients, impaired bladder function due to diabetic neuropathy may exacerbate the feeling of urgency [2].
Frequency is characterized by the need to urinate more often than usual, even when the bladder is not full [10]. This increased frequency can be due to the infection causing inflammation and irritation of the bladder, which reduces its capacity to hold urine [3]. Additionally, in diabetic patients, high blood sugar levels can lead to increased urine production and more frequent urination, further contributing to the increased frequency [2].

Both urgency and frequency can be uncomfortable and disruptive for patients, emphasizing the importance of prompt diagnosis and treatment of UTIs in diabetic patients [3]. Proper management of blood glucose levels and preventive measures, such as maintaining good hygiene and staying well-hydrated, can help reduce the risk of UTIs in this population [3].

**Hematuria**: Hematuria, or the presence of blood in the urine, can occur in UTIs among diabetic patients [2]. It is one of the symptoms that may indicate a UTI and can manifest as either microscopic (only visible under a microscope) or gross (visible to the naked eye) hematuria [2].

In diabetic patients, high blood sugar levels can weaken the immune system and impair the body's ability to fight off infections, including UTIs [3]. Inflammation and infection in the urinary tract can cause damage to the lining of the bladder or urethra, resulting in bleeding and the presence of blood in the urine [3].

If a diabetic patient experiences hematuria along with other UTI symptoms, such as dysuria (painful urination), urgency, or frequency of urination [9], they should consult their healthcare provider for a proper diagnosis and treatment. It is essential to address UTIs promptly in diabetic patients to minimize complications and maintain overall health.

**Lower abdominal pain**: Lower abdominal pain is a common symptom of urinary tract infections (UTIs) in diabetic patients, which is often caused by the inflammation and irritation of the bladder or urethra. When a UTI occurs, bacteria, most commonly *Escherichia coli* (E. coli), enter and multiply in the urinary tract, leading to an infection in the lower urinary tract (cystitis) or upper urinary tract (pyelonephritis).

In diabetic patients, lower abdominal pain in UTIs can be attributed to several factors:

1. Inflammation and irritation: The presence of bacteria in the urinary tract leads to inflammation and irritation of the affected tissues, particularly the bladder. This inflammation can cause lower abdominal pain, often described as aching, cramping, or pressure.
2. Bladder spasms: UTIs can cause involuntary contractions or spasms of the bladder muscles, leading to pain and discomfort in the lower abdomen.
3. Impaired immune function: Diabetes can weaken the immune system, making it more difficult for the body to fight off infections. As a result, UTIs in diabetic patients may be more severe or long-lasting, causing more pronounced lower abdominal pain.
4. Increased sensitivity: Diabetic patients may have heightened sensitivity due to the effects of high blood sugar levels on nerve function, making them more susceptible to pain during a UTI.

It is essential for diabetic patients experiencing lower abdominal pain to consult their healthcare provider promptly, as early diagnosis and treatment of UTIs can help alleviate symptoms and prevent complications. Treatment may involve antibiotics to eliminate the infection, along with proper hydration and pain relief medications to manage symptoms. Additionally, maintaining good blood sugar control and practicing proper hygiene can help diabetic patients reduce the risk of UTIs and lower abdominal pain.

### 3 Diagnostic Tests

**Urinalysis**: Urinalysis is a laboratory test used to evaluate the physical, chemical, and microscopic components of urine, which can help diagnose urinary tract infections (UTIs) in diabetic patients. It is an essential diagnostic tool, as UTIs can have more severe consequences in diabetic individuals due to impaired immune function and increased susceptibility to infections.

A urinalysis for diagnosing UTIs in diabetic patients generally involves the following steps:

1. Collection of a clean-catch midstream urine sample: The patient is instructed to collect a midstream urine sample after cleansing the genital area to minimize contamination. This sample is then sent to the laboratory for analysis.
2. Physical examination: The urine sample's appearance, color, and odor are evaluated to detect any abnormalities. UTIs may cause the urine to appear cloudy, dark, or have a strong odor.
3. Chemical examination: A chemically treated test strip (dipstick) is dipped into the urine sample, which tests for the presence of various substances, including glucose, protein, white blood cells (leukocyte esterase), and nitrites. In diabetic patients, the presence of glucose in the urine (glycosuria) is common, and elevated levels of leukocyte esterase or nitrites may indicate a UTI.

4. Microscopic examination: A small amount of urine is examined under a microscope to identify any cellular components, such as red and white blood cells, bacteria, or crystals. In UTIs, an increased number of white blood cells and the presence of bacteria are typical findings.

If the urinalysis results suggest a UTI in a diabetic patient, the healthcare provider may order a urine culture to identify the specific bacteria causing the infection and determine the appropriate antibiotic treatment. It is crucial for diabetic patients with UTIs to seek prompt medical care, maintain good blood sugar control, and practice proper hygiene to reduce the risk of complications and recurrent infections.

**Urine culture**: A urine culture test is an essential diagnostic tool for detecting urinary tract infections (UTIs) in diabetic patients [1]. This test checks a urine sample for the presence of microorganisms, such as bacteria and yeast, which can cause UTIs [1]. The urine culture helps healthcare providers identify the specific bacteria or yeast present and determine the appropriate treatment for the infection [7].

Diabetic patients are at an increased risk of developing UTIs due to complications such as diabetic neuropathy, impaired immune function, and nephropathy [2]. Consequently, prompt diagnosis and treatment are crucial in managing UTIs in this population. Overall, urine culture tests play a critical role in diagnosing and treating UTIs in diabetic patients, helping to ensure appropriate and effective management of these infections [1][2].

**Kidney function tests**: In diabetic patients with suspected urinary tract infections (UTIs), kidney function tests are essential to assess the overall health of the kidneys and detect any complications due to diabetes or the infection. These tests typically include urine and blood tests[3].

Blood tests, such as creatinine, glomerular filtration rate (GFR), and blood urea nitrogen (BUN) levels, help evaluate kidney function[3]. Increased levels of these markers can indicate reduced kidney function or potential kidney damage due to diabetes or the UTI.

In summary, kidney function tests in diabetic patients with UTIs are crucial for detecting any kidney damage or complications. Early detection and appropriate treatment can help prevent further deterioration of kidney function and overall health.

**Treatment of UTIs in Diabetic Patients**

**Antibiotic Therapy**: The choice of antibiotics in treating urinary tract infections (UTIs) in diabetic patients plays a critical role in the successful management of the infection and the prevention of complications. Diabetic patients are more susceptible to UTIs due to factors such as impaired immune function, increased glucose levels in the urine, and potential nerve and kidney damage related to long-standing diabetes. Therefore, the appropriate selection of antibiotics is essential to ensure a positive outcome.

Several factors influence the choice of antibiotics for UTIs in diabetic patients:

1. Bacterial susceptibility: A urine culture and sensitivity test is performed to identify the specific bacteria causing the UTI and determine their susceptibility to various antibiotics. This information guides the healthcare provider in selecting the most effective antibiotic for the patient.
2. Severity of infection: The severity of the UTI, whether it is an uncomplicated lower urinary tract infection (cystitis) or a more severe upper urinary tract infection (pyelonephritis), impacts the choice of antibiotics. Cystitis may be treated with oral antibiotics, while pyelonephritis may require intravenous antibiotics and hospitalization.
3. Patient factors: The choice of antibiotics also depends on the patient's medical history, including allergies, previous antibiotic use, and any underlying health conditions such as kidney disease or pregnancy. These factors help determine the safest and most effective antibiotic for the individual patient.
4. Local resistance patterns: Knowledge of local antimicrobial resistance patterns is essential, as it helps healthcare providers choose an antibiotic that is most likely to be effective in their geographic region.
5. Duration of treatment: Diabetic patients may require a longer duration of antibiotic treatment compared to non-diabetic individuals, as their immune system may be less capable of fighting off the infection.

Some commonly prescribed antibiotics for UTIs in diabetic patients include trimethoprim-sulfamethoxazole, nitrofurantoin, fluoroquinolones, and beta-lactams such as cephalosporins and amoxicillin-clavulanate. The healthcare provider will consider the factors mentioned above to select the most appropriate antibiotic, ensuring the infection is treated effectively, and minimizing the risk of complications and recurrent UTIs.

**Duration of treatment:** The duration of treatment for UTIs in diabetic patients depends on several factors, including the severity and type of infection, presence of symptoms, and whether the infection is localized or systemic [1][2]. Generally, treatment involves the use of antibiotics, and the specific duration of therapy may vary [1][3].

For uncomplicated cystitis (infection of the bladder), a typical course of antibiotics may last for 7-10 days [2][3]. Asymptomatic bacteriuria in diabetic patients should also be treated for about 10 days [3]. In more severe infections, such as pyelonephritis (infection of the kidneys) or complicated UTIs, the duration of antibiotic treatment may be longer, sometimes extending up to 14 days or more [1][2]. In these cases, parenteral antibiotics might be needed, and hospital admission may be required [3].

The choice of antibiotics and the duration of treatment should be guided by factors such as antibiotic sensitivity tests, the patient's overall health, and the presence of any other complications [1][2]. It is essential for diabetic patients to complete the prescribed course of antibiotics to ensure effective treatment and prevent the development of antibiotic-resistant infections [1][3].

Additionally, it is crucial for diabetic patients to manage their blood glucose levels, maintain good hygiene, and stay well-hydrated to reduce the risk of recurrent UTIs [1][2].

**Antibiotic resistance:** Addressing antibiotic resistance in UTIs among diabetic patients is crucial to ensure effective treatment and prevent complications. The prevalence of antibiotic-resistant urinary tract infections is higher in people with type 2 diabetes mellitus (T2DM), doubling the likelihood of such infections compared to those without the condition [2].

In diabetic patients, the immune system is weakened due to high blood sugar levels, making them more susceptible to infections and complications [3]. With the increasing prevalence of antibiotic resistance among uropathogens causing UTIs, it's essential to monitor and treat these infections carefully in diabetic patients [3].

**Conclusion**

Urinary tract infections pose a significant threat to the health and well-being of diabetic patients. By understanding the risk factors, recognizing symptoms, seeking prompt diagnosis and treatment, and implementing preventive measures, diabetic individuals can minimize their risk of developing UTIs and related complications. Healthcare providers must take a proactive approach to educate diabetic patients about the importance of UTI prevention and management to ensure optimal patient outcomes.

**References:**