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Review Paper

Immune homeostasis, the key to controlling the urinary tract infections in diabetic patients

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ABSTRACT

Diabetes mellitus is one of the most common endocrine diseases and is characterized by elevated blood glucose levels. Hyperglycemia affects many body systems, including the urinary system. Patients with diabetes are more likely to develop urinary tract infections (UTIs), which are often more frequent and severe. In these patients, the diversity of pathogenic bacteria and the expression of their virulence factors may also increase. This study explores the complex relationship between diabetes and the immune response to UTIs, with emphasis on the impact of diabetes on bacterial diversity, virulence factor expression, and cytokine production. Diabetes disrupts the effectiveness of immune cells and cytokine-mediated responses, contributing to impaired immune function. The prevalence and virulence of opportunistic bacteria may increase in diabetic patients compared with healthy individuals because of the multiple virulence factors produced by these pathogens. The diversity of virulence factors can stimulate cytokine production, disturb immune balance, and potentially affect the overall health of patients. The immune response to UTIs represents a complex interaction between innate and adaptive immunity. This interaction normally ensures effective protection against microbes; however, in conditions such as diabetes or immunodeficiency, this response may be impaired, requiring supportive medical interventions. Therefore, understanding the dynamics of this response may contribute to improved prevention and treatment strategies.

Keywords: *Cytokines, Diabetes mellitus, Innate immune, Interleukins, Virulence factors*

1 INTRODUCTION

Urinary tract infections (UTIs) are among the most prominent diseases associated with diabetes mellitus [1]. UTIs are caused by a variety of bacteria, and their severity varies depending on the individual immune response [2]. Dysregulation of the immune response affects susceptibility to infection by creating an imbalance between immune cells and cytokines [3]. Cytokines are protein mediators secreted to maintain immune homeostasis and respond to changes caused by different factors, including bacterial infection [4]. Studies have shown that cytokine levels, such as interleukin-6 (IL-6), IL-8, and IL-1β, are elevated in patients with UTIs, indicating an active inflammatory response [5].

High glucose levels in urine affect the local environment of the urinary tract in patients with diabetes. This promotes bacterial growth and increases the risk of infection [6]. Furthermore, patients with diabetes may exhibit an imbalanced immune response, with reduced

cytokine expression and impaired neutrophil infiltration, which can weaken the body's ability to eliminate infecting bacteria [7]. Some studies indicate that measuring urinary cytokine levels may be a promising diagnostic tool for identifying UTIs in patients, especially in cases associated with fever [8]. For example, one study demonstrated that urinary IL-6 and IL-8 levels were significantly higher in children with UTIs compared with healthy controls [9].

Therefore, developing effective diagnostic and therapeutic strategies requires understanding the relationship between cytokines and UTIs in patients with diabetes. This review aimed to analyze the impact of diabetes on immune system function, including innate and adaptive immune responses, and to identify the mechanisms of immune dysfunction that increase susceptibility to infection. It also aimed to highlight the stages of the immune response during UTIs in diabetic patients and identify immune weaknesses at each stage. In addition, this review discusses the bacterial species that may cause UTIs in diabetic patients, with emphasis on clinical characteristics and changes in bacterial flora. It also examines bacterial diversity and virulence factors in strains isolated from diabetic patients and compares them with those observed in non-diabetic patients. Finally, this review explores the relationship between pathogen type and cytokine profile to better understand the impact of bacterial variation on the nature and severity of the inflammatory response.

2 METHODOLOGY AND REVIEW STRATEGY

2.1 Clear definition of the objective

The objective of this article was clearly defined as the analysis of the interaction between diabetes, immune response, and microbial response in urinary tract infections, with emphasis on clinical and immunological characteristics.

2.2 Search strategy

The review process was conducted by searching several reliable scientific databases, including PubMed, Scopus, Web of Science, Google Scholar, and local journals, to identify relevant studies. The search period was set between 2010 and 2025 to ensure comprehensive coverage of the available evidence.

2.3 Study selection

The study selection process was based on clear inclusion criteria. First, the studies had to be published in English. Second, the full text had to be available. Third, the studies had to use a clear and reliable research methodology. Exclusion criteria included studies that had not undergone peer review, studies that did not address the variables under investigation, and studies that lacked sufficient descriptive or quantitative data for analysis. All titles and abstracts were initially screened, followed by full-text examination of studies that met the final inclusion criteria.

2.4 Descriptive and analytical approach

This review combined descriptive and analytical approaches. After examining the relationship between diabetes and UTIs, as well as associated immune changes, microbial changes, and virulence factors, the clinical and immunological features were described in detail.

2.5 Linking clinical and laboratory data

Clinical information, such as symptoms and complications, was linked with laboratory information, including cytokine analysis and bacterial virulence factors.

2.6 Future practical applications

The findings of this review are directed toward future practical applications. The article is not limited to theoretical analysis but also provides diagnostic and clinical recommendations that may be useful in medical research and clinical practice.

3 EFFECT OF DIABETES ON IMMUNE CELLS

The immune system represents the body's main complex defense system against pathogens, foreign bodies, and invading non-self cells. The effectiveness of this system depends on the coordinated activity of specialized immune cells, including T cells, B cells, neutrophils, and macrophages, along with chemokines and other immune mediators [10]. However, diabetes, through metabolic dysfunction and hyperglycemia, negatively affects this delicate system and exposes diabetic patients to multiple bacterial infections [11].

Neutrophils are among the most important innate immune cells. They engulf and destroy pathogenic bacteria and secrete several antimicrobial compounds, such as α-defensins (Figure 1) [12]. In diabetic patients, the efficiency of these cells in fighting invading bacteria decreases when their chemotactic ability to migrate to the site of infection is impaired [13]. As a result, delayed

infection clearance and an increased risk of skin infections and UTIs may occur [14].

In healthy individuals, phagocytic cells and dendritic cells contribute to microbial recognition and antigen presentation on their cell surfaces. These cells serve as a link between innate and adaptive immunity. However, in diabetic patients, their efficiency is reduced, weakening immune system effectiveness [15, 16]. This may include changes in cell count, impaired antigen presentation and immune activation, altered secretion of antibacterial proteins and cytokines, and effects on immune tolerance and autoimmunity [17].

Natural killer cells recognize and target virus-infected cells, certain intracellular pathogen-infected cells, and cancer cells [18]. In diabetic patients, the activity of cytotoxic immune cells and their secretion of cytotoxic molecules, such as perforin and granulysin, are reduced, potentially leading to impaired resistance to infection [19]. Diabetes can also cause chronic inflammation, even in the absence of infection, because of continuous stimulation of innate immune cells and excessive secretion of inflammatory cytokines [20]. This weakens immune regulation and increases the risk of cardiovascular disease and other associated conditions [21].

The adaptive immune system, which represents the body's second line of defense, is characterized by its ability to accurately recognize pathogens and form long-term immunological memory through interactions between T cells and B cells [22, 23]. In diabetic patients, an ineffective immune response may result from an imbalance in T-cell subsets, particularly between Th1 and Th2 cells [24]. There may also be a reduced ability of T cells to proliferate and interact with antigens [25]. Several studies have indicated that deficiency in regulatory T cells (Tregs) increases the risk of chronic inflammation and autoimmune disorders, as shown in Figure 2 [26].

The ability of B cells to produce antibodies and maintain antibody diversity may also be affected by diabetes, leading to a weaker response during infection or after vaccination [27]. In addition, decreased efficiency of innate and adaptive immune cells has been observed in diabetes, particularly impaired maturation of B cells in the lymph nodes. As a result, the body's ability to fight infection is weakened, while the risk of complications is increased [28, 29]. Understanding these changes is essential for developing effective therapeutic and preventive strategies for people with diabetes [30]. Therefore, improving blood glucose control is a key step in maintaining immune function in diabetic patients.

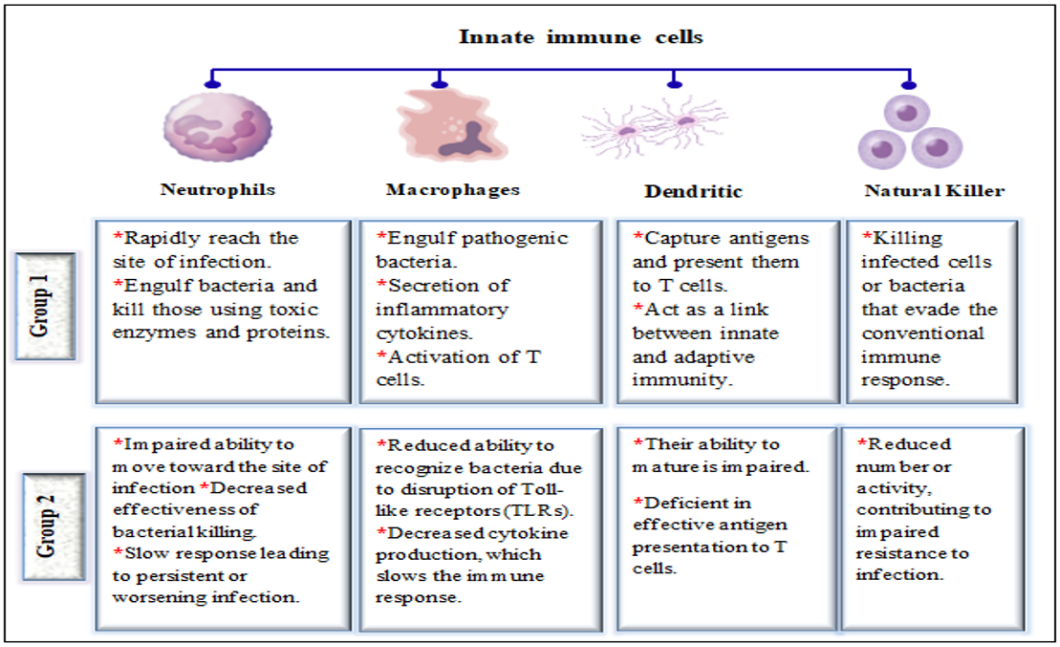

Fig. 1 Comparison of the activity and efficiency of innate immune cells (Neutrophils, Macrophage, Dendritic and Natural Killer) between two groups of patients: Group 1: Patients with a urinary tract infection (UTI) only. Group 2: Patients with a urinary tract infection (UTI) and diabetes.

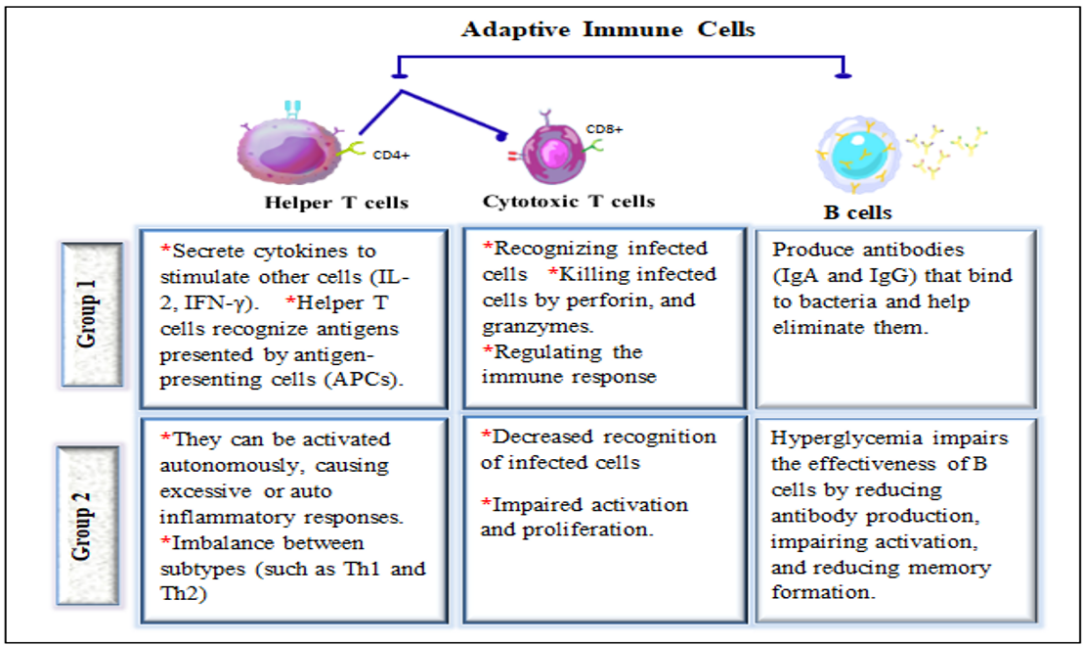

Fig. 2 Comparison of adaptive immune cells (such as T cells and B cells) in: Group 1: Patients with a urinary tract infection (UTI) only. Group 2: Patients with a urinary tract infection (UTI) and diabetes.

4 STAGES OF THE IMMUNE RESPONSE

4.1 Immune response to urinary tract infections: sequence of stages and integration of innate and adaptive immunity

Urinary tract infections (UTIs) are commonly classified as ascending infections, often beginning in the urethra and reaching the bladder, with possible extension to the kidneys [31]. *Escherichia coli* *E. coli* is the most common causative agent [32]. In response to this threat, the body relies on a coordinated immune response that includes innate immunity as the first line of defense and adaptive immunity as a specific response [33].

The first stage is pathogen recognition. Bacteria are recognized through receptors on host-cell surfaces, such as Toll-like receptors (TLRs), especially TLR4 [34]. Bladder epithelial cells begin releasing alarm signals, triggering a series of early immune reactions [35].

The second stage is the innate immune response. This stage involves the recruitment of neutrophils and macrophages to phagocytose and kill bacteria. It also includes activation of innate immunity through cytokine release, such as IL-6 and TNF-α, which attract additional immune cells [36]. Antimicrobial peptides, such as defensins, are produced by epithelial cells and directly inhibit bacterial growth [37].

The third stage involves dendritic cell activation and antigen presentation. Dendritic cells capture bacterial antigens at the infection site and migrate to regional lymph nodes [38]. There, they process and present antigens to T cells, including CD4+ and CD8+ cells, marking the transition toward adaptive immunity [39].

The fourth stage is the adaptive immune response. T cells proliferate and secrete additional cytokines, such as IFN-γ, to promote bacterial elimination [40]. B cells differentiate into plasma cells and begin producing specific IgA and IgG antibodies, which bind to bacteria and facilitate their elimination. If infection extends to the kidneys, CD8+ cells may contribute to the elimination of infected host cells [41].

The fifth stage involves immune memory, regulation, and termination of the response. Some T and B cells differentiate into memory cells capable of responding rapidly to recurrent infection [42]. Thus, the severity of future infections may be reduced, and long-term protection may be promoted [43]. Once

the pathogen is removed, regulatory T cells (Tregs) reduce the immune response to avoid excessive tissue damage [44]. Tissue repair and restoration of homeostasis then begin in the urinary system [45].

4.2 Stages of the immune response in UTIs among diabetic patients

Diabetes, especially uncontrolled diabetes, weakens the immune system and makes the body more susceptible to infections such as UTIs [46]. Diabetes affects all stages of the immune response, from infection recognition to pathogen elimination, thereby increasing the severity and frequency of infection [47]. Diabetes affects the first stage, the recognition stage, by altering the expression or function of receptors such as TLR4. This may delay the initial immune response and allow bacteria to spread [48]. Its effect is more pronounced in the second stage, the innate response stage, in which neutrophils and macrophages lose part of their ability to phagocytose and kill bacteria [49]. The hyperglycemic environment also reduces the secretion of antimicrobial peptides by bladder epithelial cells, making the mucosal barrier easier to penetrate and facilitating ascending infection to the kidneys [50].

The effect on the third stage involves impaired activation and recruitment of dendritic cells. In diabetic patients, dendritic cell number and maturation may decrease, reducing their efficiency in presenting antigens to T cells [51]. This impairment may delay adaptive immune activation and consequently contribute to persistent infection [52].

Diabetes also affects the adaptive immune response by influencing both T and B cells. T cells may show weak responses and limited proliferation, while some regulatory T cells may be deficient or ineffective [53]. B cells may produce fewer antibodies, and their response to vaccines may be limited. Together, these changes result in poor infection control, prolonged disease duration, and increased risk of recurrence [54].

Diabetes also affects the fifth and final stage, which includes termination of the immune response and prevention of chronic inflammation [55]. When regulatory cells are insufficiently active, urinary tissue damage and recurrent chronic inflammation may occur because of persistent inflammatory activity. Consequently, complications such as pyelonephritis or sepsis may develop [56]. Overall, all stages of the immune response, from recognition to termination of infection, may be impaired by chronic hyperglycemia. This explains the overlap between diabetes and increased susceptibility to UTIs [57]. Understanding these changes is essential for developing preventive and therapeutic strategies tailored to this patient population.

5 ANALYSIS OF THE RELATIONSHIP BETWEEN CYTOKINE LEVELS AND UTIs

The immune system is directly affected by hyperglycemia in diabetic patients. As a result, these patients become more susceptible to infections, especially UTIs [58]. Cytokines play a fundamental role in regulating the immune response. Many studies have shown that diabetic patients may produce heterogeneous cytokine patterns during infections, affecting disease severity and response to treatment [59]. Cytokines are commonly divided into pro-inflammatory cytokines, such as IL-6, TNF-α, and IFN-γ, and anti-inflammatory cytokines, such as IL-10 and TGF-β [60]. In the context of UTIs, the most prominent cytokines include IL-6, which is a strong inducer of the inflammatory response and an indicator of infection severity [61]; IL-8, which attracts neutrophils to the site of inflammation [62]; and TNF-α, which enhances the inflammatory response and increases vascular permeability [63, 64].

Studies have shown that diabetic patients with UTIs have elevated levels of IL-6, IL-8, and TNF-α in blood or urine compared with non-diabetic patients [65]. Oda et al. (2023) demonstrated that serum interleukin-35 and macrophage migration inhibitory factor (MIF) levels were significantly higher in diabetic children with UTIs than in non-diabetic children [3]. Another study published in Pediatric Nephrology demonstrated that IL-8 is a strong predictor of UTIs in patients with unexplained fever [66]. Oudah et al. (2023) reported that

cytokine regulation in diabetic patients differs significantly from that in healthy individuals, potentially explaining the increased incidence and recurrence of infections [67]. Table 1 focuses on different cytokines involved in the immune response and shows changes in cytokine levels between healthy individuals and patients with UTIs. These changes help explain the effect of UTIs on cytokine secretion in diabetic patients compared with healthy individuals. Understanding the relationship between cytokines and UTIs in diabetic patients is important for clarifying infection dynamics. Changes in cytokine patterns may reflect impaired immune regulation and contribute to the complexity of the clinical condition. In this vulnerable population, such knowledge may support the development of more accurate diagnostic and prognostic methods and improve therapeutic interventions.

Table 1 Comparison of inflammatory and anti-inflammatory cytokine levels among healthy individuals, patients with UTIs only, and patients with UTIs and diabetes

Cytokine	Sample type	Healthy individuals	Ref.	Patients with UTIs	Ref.	Patients with diabetes + UTIs	Ref.
IL-6	Serum	186.01 pg/mL	[68]	286.65 pg/mL ↑	[68]	129.91 pg/mL ↓	[69]
IL-8	Plasma	9.48 pg/mL	[70]	16.80 pg/mL ↑	[70]	15.86 pg/mL ↑	[70]
TNF-α	Serum	3.7 pg/mL	[71]	8.9 pg/mL ↑	[71]	59.13 pg/mL ↑	[69]
TGF-β	Serum	13.45 ng/mL	[72]	32.35 ng/mL ↑	[72]	42.04 ng/mL ↑	[73]
IL-35	Serum	5.514 ng/mL	[67]	There is no study		10.42 ng/mL ↑	[67]
MIF	Serum	2.16 ng/mL	[74]	There is no study		29.68 ng/mL ↑	[3]
	Urine	211.45 pg/mL	[75]	1082.82 pg/mL ↑	[75]	There is no study	

6 EFFECT OF BACTERIAL DIVERSITY AND VIRULENCE FACTORS IN UTIS ON THE IMMUNE RESPONSE

Several types of bacteria can cause urinary tract infections (UTIs), and their prevalence varies according to the patient's age, sex, health status, and predisposing factors [76]. Common causative agents include Gram-negative bacteria, such as *Escherichia coli E. coli, Klebsiella spp., Proteus mirabilis*, and *Pseudomonas aeruginosa*, as well as Gram-positive bacteria, including *Staphylococcus saprophyticus, Enterococcus faecalis*, and *Streptococcus agalactiae* [77]. Some species, such as *Proteus* spp. and *Pseudomonas* spp., are associated with more complicated infections, especially in patients with diabetes or those with urinary catheters [78]. *S. saprophyticus* is commonly associated with UTIs in young sexually active women [79]. A variety of bacterial virulence factors contribute to the development of UTIs by enabling bacteria to adhere to urinary tissue, resist host immunity, and multiply within the host [76]. Virulence factors are bacterial properties or mechanisms that enable pathogens to cause disease. The main bacterial virulence factors involved in UTIs include the following.

Fimbriae or pili: These are protein appendages that enable bacteria to adhere to urothelial cells. The most important include type 1 fimbriae, which bind to mannose-containing receptors in the bladder, and P fimbriae, which bind to receptors on kidney and bladder cells and contribute to ascending infection [80]. The urinary tract is normally protected by continuous urine flow, which helps flush bacteria from the urinary system [81]. Therefore, for bacteria to survive and multiply, they must possess effective mechanisms for attachment to epithelial cells [82]. When fimbriae bind to their receptors on urothelial cells, signaling pathways are activated within host cells, stimulating the release of inflammatory cytokines, such as IL-6 and IL-8 (Figure 3A). These cytokines attract immune cells, especially neutrophils, and contribute to the initiation of the innate immune response [83].

Toxins: Toxins are among the most important virulence factors contributing to bacterial pathogenicity. They play a dual role in the relationship between bacteria and the host [84]. First, they can stimulate the innate immune response by activating pattern recognition receptors (PRRs) and inducing cytokine secretion, including IL-1β, IL-8, and TNF-α. Second, they can disrupt immunity by causing cell death or inhibiting cell function, thereby weakening the body's ability to control infection [85]. The interaction between immune activation and immune inhibition may lead to uncontrolled inflammation and tissue damage in the urothelium, especially in severe cases [86]. Important examples include α-hemolysin, which can damage urothelial cells, and cytotoxic necrotizing factor 1 (CNF-1), which

modulates host-cell signaling and contributes to cellular injury [87].

Degradative enzymes: Degradative enzymes are important virulence factors used by pathogenic bacteria to cause infections, including UTIs [2]. These enzymes help bacteria degrade host-cell components, overcome immune defenses, and create a suitable environment for growth and reproduction [88]. Various bacteria produce these enzymes, but *P. mirabilis* and uropathogenic *E. coli* (UPEC) are among the most recognized examples in this context [89]. Proteases can degrade defensive proteins, such as IgA, one of the most important antibodies in urine, thereby reducing the effectiveness of local immune protection in the urinary tract [90]. Some proteases also help break down proteins between cells, allowing bacteria to penetrate tissues more easily [91].

Lipopolysaccharide: Lipopolysaccharide (LPS), also known as endotoxin, is found in the outer membrane of Gram-negative bacteria. It stimulates immune receptors, such as TLR4, leading to the release of inflammatory cytokines, including IL-6 and TNF-α (Figure 3A) [92]. LPS is responsible for strong inflammatory responses and may contribute to complications of severe UTIs, including pyelonephritis and urosepsis [80].

Iron acquisition systems: Iron is an essential element for the growth and reproduction of most microorganisms, including bacteria in the urinary tract environment [93]. In the human body, free iron is present in low amounts because it is strongly bound to proteins such as lactoferrin and transferrin [45]. To overcome this limitation, pathogenic bacteria, such as UPEC, have developed sophisticated iron acquisition systems that are considered important virulence factors. These systems help bacteria survive within the host and cause UTIs [94].

Siderophores are small molecules secreted by bacteria to capture iron from the surrounding environment [3]. Enterobactin is one of the most potent siderophores secreted by UPEC. Aerobactin is particularly effective in lactoferrin-rich environments and helps UPEC colonize the bladder [95]. After siderophores bind to iron, they are recognized by specialized receptors on the bacterial cell surface, and the complex is internalized for iron utilization [92]. Some bacterial strains also possess surface receptors that bind directly to host iron-carrying proteins, such as transferrin or hemoglobin [96]. This mechanism allows bacteria to utilize iron sources available in the human body [93].

Biofilm formation: A biofilm is a bacterial community attached to a surface, such as the bladder wall or a urinary catheter, and surrounded by a sticky extracellular polymeric substance (EPS) secreted by the bacteria. EPS consists mainly of polysaccharides, proteins, and nucleic acids [91]. Biofilm formation is one of the most important virulence mechanisms that enables bacteria to survive in hostile environments within the human body [97]. In UTIs, biofilms represent both protective and pathogenic mechanisms used by bacteria such as UPEC, *P. mirabilis*, and *Klebsiella pneumoniae* to evade the immune system and resist antibiotics, especially in chronic or catheter-associated infections [98]. Biofilm presence can lead to persistent immune stimulation and chronic inflammation through cytokine release, including IL-6 and TNF-α, without effective elimination of the infection. This process may further damage bladder or kidney tissue [95].

Motility: Motility is an important physiological characteristic of some pathogenic bacteria and helps them reach infection sites in the human body [99]. In UTIs, bacterial motility plays a pivotal role in bacterial ascent from the urethra to the bladder and, in some cases, to the kidneys, making it an important virulence factor in infection development [100]. Bacterial motility, particularly flagella-mediated motility, activates innate immune receptors such as TLR5, leading to secretion of inflammatory cytokines such as IL-8, which attracts neutrophils and other immune cells to the infection site [101]. However, some bacteria can reduce flagellin expression after infection begins to avoid immune detection (Figure 3B) [102].

The diversity of virulence factors among bacteria causing UTIs is a crucial factor in determining infection severity and the nature of the host immune response. These factors stimulate innate immune

responses by activating PRRs, such as Toll-like receptors (TLRs), on the surface of epithelial cells and immune cells. When these receptors are activated, cytokine production is stimulated. These cytokines include IL-6 and IL-8, which are among the most important neutrophil-attracting cytokines, as well as TNF-α and IL-1β. They attract immune cells, such as neutrophils and macrophages, to the infection site, causing inflammation and contributing to infection control. However, some virulence factors may weaken or hinder this response. For example, hemolysin and CNF-1 can cause cell damage and interfere with immune-cell function. Thus, the diversity of virulence factors not only increases bacterial aggressiveness but also modifies the nature of the immune response and the severity of inflammation. This may explain differences in clinical presentation between mild infections, such as dysuria, and severe infections that may progress to pyelonephritis or urosepsis. In this context, cytokines play a pivotal role in regulating the inflammatory response. However, the type of bacteria causing the infection may lead to variation in the cytokine pattern produced, thereby affecting infection severity and clinical outcomes.

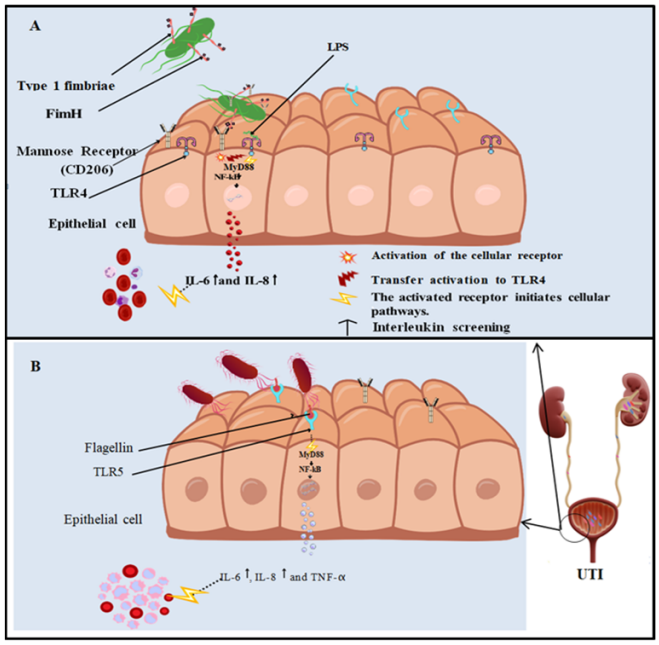

Fig. 3 Mechanism of the effect of bacterial virulence factors on inducing the immune response. A: Fimbriae and their relationship in activating their response with Lipopolysaccharide (LPS). B: Flagellum in pathogenic bacteria .Created in Canva.Toll-like receptors (TLR), Cluster of Differentiation 206 (CD206), Urinary tract infection (UTI), Myeloid differentiation primary response 88 (MYD88) and Nuclear factor kappa B (NF-KB)

7 DIABETES, BACTERIAL DIVERSITY, AND VIRULENCE FACTORS IN UTIS

Diabetes is a major factor that increases susceptibility to bacterial infections, particularly UTIs [46]. The immunological and environmental changes associated with hyperglycemia affect microbial flora composition and virulence factor expression, thereby increasing infection severity [57]. High glucose levels in urine and surrounding tissues may cause an imbalance in the microbiome, with increased growth of opportunistic bacteria such as *E. coli* and *Klebsiella* spp. [70]. Atypical species, such as *Streptococcus oralis* and *Kocuria kristinae*, have also been observed in patients with diabetes, suggesting a shift in the microbial spectrum because of immunological and environmental changes [3].

Diabetes may also influence bacterial virulence factors. For example, *E. coli* isolates from diabetic patients may show increased production of adhesins, which enable bacteria to adhere to bladder cells [81]. Increased expression of biofilm-forming genes has also been reported, conferring greater antibiotic resistance [8]. The immune response is influenced by bacterial virulence factors [98], and this may coincide with heterogeneous cytokine responses, such as elevated IL-6 and TNF-α and decreased IL-10. This pattern indicates uncontrolled inflammation [63]. Such a response may be a prominent feature of complex UTIs in diabetic patients [60].

Changes in bacterial diversity and increased virulence contribute to diagnostic and therapeutic complexity and may increase the risk of antibiotic resistance [103]. Understanding these changes can assist in selecting targeted antibiotics, improving infection control, and preventing recurrence [104]. UTIs in

diabetic patients may therefore differ fundamentally from those in non-diabetic individuals because of the overlap between diabetes-related immune dysfunction and specific bacterial changes [105]. Careful evaluation of the isolated bacterial species and analysis of virulence factors are required to support a more precise and effective therapeutic approach [106].

8 CONCLUSION

Urinary tract infections are among the most prevalent bacterial infections. Their development is supported by several bacterial virulence factors that enable pathogens to adhere, invade, evade immunity, and survive in the hostile urinary environment. These factors include fimbriae, which promote adhesion; degradative enzymes, which break down host-cell barriers; toxins, which damage host cells; and iron acquisition systems, which provide bacteria with essential resources for growth. In addition, biofilm formation and bacterial motility contribute to infection persistence and antibiotic resistance.

The immune response plays a dual role in UTIs. It contributes to resistance against infection by activating cytokines and immune cells; however, some virulence factors can disrupt or inhibit this response, leading to chronic or recurrent infections. These challenges become more complex in diabetic patients because elevated urinary glucose levels promote bacterial growth and diversity while weakening immune function. As a result, bacteria may further activate their virulence mechanisms, making diabetic patients more susceptible to acute, chronic, and recurrent UTIs.

Therefore, understanding virulence mechanisms, bacterial diversity, and immune responses in vulnerable populations, particularly diabetic patients, is essential. Such knowledge may support the development of more effective preventive and therapeutic strategies, including antibiofilm agents, virulence inhibitors, and potentially targeted vaccines.

Suggested recommendations

Medical Care: Periodic follow-up of diabetic patients using urine tests and early detection of infections, even in the absence of symptoms. Prioritizing blood glucose control to reduce bacterial proliferation and strengthen the immune response. Using targeted antibiotics based on urine culture and antimicrobial susceptibility testing and avoiding empirical or random antibiotic use that may increase resistance.

Prevention: Educating patients and their families about personal hygiene, adequate fluid intake, and regular bladder emptying. Using appropriate vaccines, such as pneumococcal and influenza vaccines, especially for patients with significant immune deficiency. Monitoring neuro-urological problems in diabetic patients, such as diabetic cystopathy, which may contribute to urinary stasis and increased infection risk.

Diagnosis and Laboratory Analysis: Using immunological cytokine tests, such as IL-6, IL-10, and TNF-α, as potential indicators of inflammation severity or pathogen-associated immune response. Studying bacterial virulence factors, such as biofilm-associated genes, to identify potentially complicated infections early. Adopting molecular biological tests to identify bacterial species more rapidly and accurately.

Research: Conducting broader studies on patients with diabetes to investigate different infection patterns and immune responses. Developing specialized models to predict infection risk based on immune markers, genetic markers, and bacterial species. Expanding research on immunotherapy and the microbiome to improve prevention of chronic UTIs in diabetic patients.

Author contributions

NAO: Supervision and writing—original draft the review. ZAM. FAA: Validation and editing. RAA and SAH: Software and data curation.

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N/A

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