CLINICAL AND THERAPEUTIC TREATMENT APPROACH BETWEEN DIABETES MELLITUS AND URINARY TRACT INFECTION

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ABSTRACT

Diabetes Mellitus is a metabolic syndrome of multiple origins, caused by the insulin absence in the bloodstream and/or by the inability of insulin to adequately exert its effects, causing hyperglycemia and subsequent complications in the body's organic systems. Urinary tract infection (UTI) is one of the most frequent due to the glucose increase in blood circulation and the impairment of cellular immunity, creating a favorable environment for the bacteria proliferation at the inflammation spots. This review describes the clinical and therapeutic aspects of diabetes mellitus and urinary tract infection, with guidelines on glucose management in these events. A non-systematic review was carried out in the Virtual Health Library, PubMed, Scielo, and Google Academic databases with the descriptors Diabetes mellitus, Urinary Tract Infection, Hyperglycemia, Bacteriuria, and Urinary Incontinence. The most relevant articles were selected. Pertinent clinical and therapeutic issues were discussed, covering the diabetes factors that contribute to the onset of UTI; urinary tract infection complications in patients with diabetes mellitus; asymptomatic bacteriuria, recurrent urinary tract infections, and urinary incontinence in people with diabetes; treatments for diabetes and urinary tract infection; and the relationship between glucose-lowering medications and UTI. Given the greater susceptibility of people with diabetes to acquire UTI, the combined insight into these diseases is crucial, both for better UTI prevention in diabetics and for the treatment of both.

Keywords: Diabetes mellitus; Urinary tract infection; Hyperglycemia; Bacteriuria; Urinary incontinence.

Introduction

Insulin, a hormone produced by the pancreatic β-cells, is responsible for glucose control. The lack of this hormone leads to a deficit in glucose metabolism and, consequently, to increased blood glucose levels,

resulting in a metabolic syndrome, Diabetes Mellitus (DM). This syndrome has multiple origins and may be caused by the lack of insulin and/or the insulin's incapacity to adequately exert its effects[1].

DM can be classified as type 1, type 2, gestational (Table 1), and other types, including genetic defects, medication use, and an association with other diseases. Type 1 DM (DM1) is present mainly in childhood and adolescence, occurs in about 5% to 10% of diabetics, and is caused by a defect in the immune system in which autoantibodies destroy insulin-producing β-cells. Type 2 diabetes (DM2), also known as non-insulin-dependent diabetes, affects approximately 90% of diabetics and is related to overweight and bad eating habits; it occurs due to insulin resistance, where the organism does not adequately utilize the produced insulin. Another relevant point, some people develop DM2 through an autoimmune process, damaging the pancreatic β-cells, called Latent Autoimmune Diabetes in Adults (LADA)[2]. In contrast, gestational diabetes occurs due to temporary hyperglycemia during pregnancy, affecting between 2 and 4% of all pregnant women[3].

Table 1. Classification and etiology of the metabolic syndrome.

Diabetes Mellitus			
	Type 1	**Type 2**	**Gestational**
Etiological factors	ICA, IAA, anti-GAD	Overweight, poor eating habits, insulin resistance, autoimmune process	Hyperglycemia during pregnancy

Legend: ICA - Islet cytoplasmic antibodies; IAA - Insulin autoantibodies; anti-GAD – anti-Glutamic acid decarboxylase antibodies.

The primary symptoms of DM1 are polyuria, polyphagia, polydipsia, weight loss, weakness, fatigue, irrationality, mood swings, nausea, and emesis. The main DM2 symptoms are frequent infections, vision problems (blurred vision), wound healing difficulties, tingling feet, and furunculosis[4]. Patients with non-controlled hyperglycemia may develop diabetic foot, retinopathy, nephropathy, and diabetic neuropathy; acute myocardial infarction (AMI); cerebrovascular accident (CVA); and infections[5]. The clinical elements that raise suspicion for people with diabetes mellitus are presented in Table 2.

Table 2. Clinical presentation for DM suspicion.

Typical Signs and Symptoms	Less Specific Symptoms	Chronic Complications
Polyphagia	Vulvar or cutaneous pruritus	Diabetic Retinopathy
Weight loss	Balanopostitis	Cataract
Polyuria	Fatigue	Arteriosclerosis
Polydipsia	Asthenia	Diabetic neuropathy
	Blurred vision	Proteinuria
	Lethargy	Recurrent infections

Adapted source: Brasil[6]; Duncan et al.[7].

Urinary tract infections (UTI) are another significant aspect in the DM patient's interface, represented by the urine containing bacteria and leukocytes due to the inflammatory response of the urothelium against bacterial infections. The most common microorganisms found in UTI sequentially are the bacteria *Escherichia coli*, *Staphylococcus saprophyticus*, *Proteusmirabilis*, and *Klebsiella pneumoniae*[8,9]. This can be an asymptomatic or asymptomatic condition, being identified as cystitis when the infection manifests itself in the lower urinary tract, where symptoms of dysuria, urinary urgency, polyuria, nycturia, and suprapubic pain may appear; and pyelonephritis when the infection reaches the upper urinary tract and may manifest fever usually higher than 38ºC, chills, and uni or bilateral lower back pain[10,11].

Furthermore, urinary tract infection can be classified as uncomplicated, related to patients with undamaged renal function and urinary tract; and complicated, that occurs in patients with comorbidities or structural abnormalities, such as diabetes, advanced age, pregnancy, or immunocompromised status[9,12].

In this sense, the recurrence of UTI in diabetic patients has several causes, such as diabetic neuropathy and immune function deficiency; however, its cause is summarized in a favorable environment for the proliferation of enterobacteria, once the medium is increased in glucose, favoring the growth of these microorganisms. Thus, the relationship between DM and urinary tract infection is clarified by several clinical causes[13].

Since urinary tract infection can lead to multiple complications and diabetes is considered a global epidemic, according to the WHO, as 1 in 11 people worldwide have it, demonstrating the connection between these diseases can contribute to UTI prevention in diabetic patients[14,15].

Considering that diabetes and urinary tract infections are the most common pathologies among Brazilians, they rank highly among the diseases with high incidence and mortality. Therefore, they are a significant public health problem in Brazil and costly to the Brazilian Unified Health System (SUS). In sum, this study addresses the relationship between these two pathologies, which might contribute to the prevention of graver urinary tract infections and prevent other UTI infections in diabetic patients. Thus, this review attempts to analyze and discuss several UTI characteristics in people with DM, focusing on the clinical aspects and their implications and glucose-inhibiting drugs' effect on UTI.

Type 1 and Type 2 Diabetes Mellitus Differentiation

The distinction between DM1 and DM2 may not be straightforward for the practitioner. In cases of doubt, anti-GAD antibody levels and pancreatic insulin reserve assessment by measuring plasma C-peptide may be requested. Positive autoantibodies and C-peptide below 0.9 ng/ml suggest a diagnosis of DM1, while negative autoantibodies and elevated C-peptide suggest DM2[16]. Other specific types of diabetes are rarer and may result from genetic defects in β-cell function, genetic defects in insulin action, exocrine pancreatic diseases, endocrinopathies, medication side effects, infections, and other genetic syndromes associated with DM[6].

Diabetes Factors that Contribute to UTI

DM is a major contributor to peripheral diabetic neuropathy (PDN), a symptom caused by the peripheral nerves' functional loss due to demyelination, axon atrophy, and decreased regenerative potential, resulting in pain paresthesia, and even sensory-motor loss in the affected limb[17,18]. Besides this factor, PDN can cause damage to the genitourinary system, leading to altered urinary bladder sensitivity and filling sensation, resulting in increased urinary retention. This large volume of urinary deposits in the bladder creates a suitable habitat for bacteria proliferation, triggering urinary tract infections[2,13].

Another relevant point in DM is cellular immunity impairment. This factor alters monocytes, lymphocytes, and polymorphonuclear cells, consequently changing cell adhesion, chemotaxis, phagocytosis, and oxidative burning, favoring the intracellular bactericidal capacity in the inflammatory process. Thus, the impaired immune response in diabetic people, associated with hyperglycemia, provides a bacterial proliferation environment, which causes urinary tract infection[19,20].

As a result, the diabetic patient is more susceptible to infections and neurogenic bladder dysfunction, increasing the chances of developing UTI. Still concerning this situation, the ureterovesical orifice loses its function, causing vesicourethral reflux and ascending infection, allowing the bacteria migration from the ureter to the pelvis. This process is related to patients with spinal cord injury, especially those with neurogenic bladder dysfunction secondary to diabetes[21]. It is noteworthy that poor glycemic control may influence the risk of UTI[22].

Urinary Influction Complications in Diabetes Mellitus Patients

Infections alter the diabetic metabolism and are an influential factor in disease decompensation. The authors investigated 40 infectious processes in thirty-one individuals (77.5%); nine (22.5%) were not subjected to a culture collection. Twenty-seven cases showed an infectious state, while four did not. Indeed, 55% of the infectious processes presented had the urinary tract as the primary infection cause[23].

The most frequent UTI complication in DM1 is pyelonephritis, while in DM2, it is bacterial cystitis. Most of the hospitalizations for pyelonephritis are due to DM. Moreover, people with diabetes have a higher risk of acute pyelonephritis progressing to a renal abscess, pyelitis, emphysematous cystitis, pyelonephritis, and bacteremia. Such complications can lead to organ failure and even death[24].

In addition to these factors, perinephritic abscess is another significant UTI complication. Clinical suspicion is based on fever, even after treatment with appropriate antibiotic therapy has been started. Finally, surgical drainage associated with antibiotic therapy is required for 7 to 14 days[25].

Diabetic patients with asymptomatic bacteriuria (ASB) may develop complications, such as emphysematous pyelonephritis, a severe infection with a high mortality rate that starts as acute pyelonephritis rapidly evolving to imperfect general health and hemodynamic state, hematuria and flank fluctuation may occur, as it compromises the renal parenchyma, the collector system, or even the perinephritic tissue. In this situation, broad-spectrum antibiotic therapy must be administered. Antimicrobial treatment may include fluoroquinolones + metronidazole, carbapenems, or piperacillin + tazobactam B. Eventually, surgical intervention is required, including nephrectomy[25,26].

It should be added that DM is one of the most common pathologies that cause renal failure, capable of causing injury to the renal blood vessels and, in insulin deficiency, affecting the absorption of some electrolytes, like potassium[27]. The authors emphasize that if the disease is not adequately controlled, it can accelerate kidney damage, resulting in chronic kidney disease. Still another aspect that deserves to be highlighted is that diabetes mellitus is responsible for diabetic nephropathy due to progressive and irreversible nephron loss, making the body unable to maintain homeostasis. Therefore, diabetics require hemodialysis[28,29].

In light of this scenario, diabetic nephropathy screening is paramount. This process begins with the DM2 diagnosis and five years after the DM1 diagnosis[30], through different types of urine sampling, ideally measuring microalbuminuria in an isolated urine sample; if the test is regular, the test should be repeated at 12-month intervals[31,32].

Asymptomatic Bacteriuria, Recurrent Urinary Infections and Urinary Incontinence in Diabetics

In cases of asymptomatic bacteriuria, mostly present in diabetic women versus diabetic men and non-diabetic women. This does not indicate treatment because it has elevated post-therapy relapse; treatment does not reduce complications, such as new UTI episodes, acute pyelonephritis, and hospitalizations; evidence that renal function is not affected by ASB; potential antimicrobial side effects; bacterial resistance increase. Also, antibiotic overuse may cause the natural selection of multidrug-resistant microorganisms, so screening and treatment for asymptomatic bacteriuria are unnecessary[33-36].

However, in pregnant women with ASB, it is necessary to order type I urine and urine culture and treatment to avoid a possible complication, like acute pyelonephritis. If the pregnant woman does not treat ASB, she will be more susceptible to having premature labor or a baby with low birth weight[37-39].

To prevent recurrent urinary tract infections, antibiotics can be used prophylactically, alternatives such as antimicrobials (cranberry and D-mannose), probiotics in postmenopausal women, and immunostimulant OM-89 in patients with recurrent *Escherichia coli* UTIs[40]. Also, estrogen therapy reduces the UTI recurrence risk in postmenopausal women by restoring vaginal mucosal atrophy, reducing vaginal pH, preventing enterobacterial colonization[33].

In a study carried out by Nazzal et al.[41] involving 381 diabetic women in the West Bank (Palestine), it was found that 43.2% of them had urinary incontinence. This percentage proves that people with diabetes are highly susceptible to urinary incontinence and, consequently, UTI since urinary incontinence (UI) is a risk factor for UTI[41,42].

A study by Borowczyk, et al.[43] with 40 women showed that postmenopausal diabetic patients who have microangiopathy are at high risk for urinary tract infections and should be both elucidated and monitored. Attention should also be given to urinary incontinence, hyperlipidemia, and microalbuminuria as other UTI risk factors. Quinolones are an interesting treatment option for this group of Polish patients.

The systematic review performed by Barbosa et al.[44], suggests that pelvic floor muscle training, around 12 weeks, including aerobic and resistance exercises under intensely supervised guidance, are effective in the prevention, treatment, and reduction of pregnancy-specific urinary incontinence in women with gestational diabetes mellitus and/or hyperglycemia. To prevent urinary incontinence, weight loss, hormone therapy cessation, and therapies that improve or prevent microvascular disease, including glycemic control and blood pressure control, are provided[41].

TREATMENTS

Treatments for Diabetes and Urinary tract Infection

The DM1 treatment is carried out through insulin therapy, nutritional education and monitoring, physical activity, and guidance to the patient and his family to achieve individual glycemic controls [25,45].

For DM2, nutritional treatment is required, which aims at lifestyle changes through healthy diet and physical activity; oral antidiabetic agents are also prescribed, which are drugs classified into four categories: the hypoglycemic agents, which increase insulin secretion, being the sulfonylureas and the glinides (or metiglinides) which are insulin secretagogues; the antihyperglycemic agents, which do not increase insulin secretion, which are acarbose (alpha-glucosidase inhibitor), metformin (biguanide) and pioglitazone (thiazolidinedione or glitazone); agents that increase glucose-dependent insulin secretion and decrease glucagon secretion, which are the DPP-4 inhibitors known as gliptins (sitagliptin, vildagliptin, saxagliptin linagliptin, and alogliptin), and agents that promote glycosuria, which are the SGLT2 inhibitors, which prevent glucose reabsorption by inhibiting SGLT2 proteins in the proximal kidney tubules[25].

Besides, some promising studies demonstrate curcumin use for DM2 prevention and treatment because curcumin reduces the genetic expression of transcription factors involved in hepatic lipogenesis. Thus it acts in the lipid metabolism regulation[46]. Due to the disease complexity, the authors report that studies to evaluate the curcumin effects and its specific dosage on glycemic outcomes are still missing.

The urinary tract infection treatment, on the other hand, depends on the infectious agent and the signs and symptoms development of the patient. Thus, antibiotics such as nitrofurantoin, cephalexin, amoxicillin are the most used[33]. Aside from the conventional urinary tract infection treatment, there are other alternatives, such as medicinal plants use, for example, American cranberry (*Vaccinium macrocarpon* L.); uva-ursin (*Arctostaphylos uva-ursi* L.), and horsetail (*Equisetum arvense* L.), however more study is required on the doses and time of use[47].

Link Between Glucose Reducing Drugs and UTI

Dipeptidyl peptidase-4 (DPP-4) inhibitor drugs such as Sitagliptin, Vildagliptin, Linagliptin, and Saxagliptin promote increased GLP-1 levels, increasing insulin synthesis and secretion, and reduced glucagon. However, such drugs can cause side effects, such as pharyngitis, UTI, nausea, and headaches[48].

Nevertheless, another drug is notable, the sodium-glucose cotransporter-2 (SGLT2) inhibitors, also known as glycosuria, such as Dapagliflozin, Empagliflozin, Canagliflozin, which inhibit SGLT2 in the proximal renal tubule. Due to promoting glycosuria, these drugs increase urinary tract infections, genital infections, asymptomatic bacteriuria, and polyuria[25,48,49].

The study by Storgaard et al.[50] showed that the use of SGLT2 in patients with DM2 has a positive effect on body weight, blood pressure, lipids, and alanine aminotransferase, but increased urinary tract and genital infections risk and serum creatinine.

A meta-analysis by Chen et al.[51] in DM1 patients, compared a placebo control group with an SGLT-2 inhibitor group, there was no increase in the overall urinary tract or genital infection incidence. This discrepancy from previous studies with DM2 is due to possible reasons, in DM1 patients are generally younger and more resistant to infection, blood glucose levels are better controlled due to prior insulin therapy, which consequently decreases glucose excretion in the urine and, in turn, decreases urinary tract or genital infection.

Final Considerations

Given the greater diabetic susceptibility to contracting UTIs, the combined perception of these diseases is essential for better UTI prevention in diabetics and the treatment of other diseases related to them, such as urinary incontinence. Hence, for the clinical and therapeutic disease management, the prior knowledge of nursing professionals, internship and/or medical residency students, nephrologists, endocrinologists, and even clinical surgeons is necessary; however, the DM's lack of cognition regarding genitourinary tract complications may hinder the patient's hemodynamic and glycemic control.

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Potential Conflict of Interest Statement

The authors declare to have no conflict of interest.

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