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INCIDENCE OF URINARY TRACT INFECTION IN PATIENTS WITH SODIUM GLUCOSE CO-TRANSPORTER (SGLT-2) INHIBITORS

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ABSTRACT:
Urinary tract infections (UTIs) are a common concern among patients with diabetes mellitus who are treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors, a class of hypoglycaemic medications. This systematic review and meta-analysis aimed to assess the incidence of UTIs in patients receiving SGLT2 inhibitors compared to other antidiabetic treatments or a placebo. A comprehensive literature search was conducted in major scientific databases, including PubMed, Embase, and Cochrane Library. Studies that reported the incidence of UTIs in adult patients with diabetes treated with SGLT2 inhibitors were included. The primary outcome measure was the incidence rate of UTIs, and secondary outcomes included the severity of UTIs and the association of UTIs with specific SGLT2 inhibitors. The pooled data revealed a higher overall incidence rate of UTIs in patients treated with SGLT2 inhibitors when compared to those on other antidiabetic therapies or placebo. Analysis based on specific SGLT2 inhibitors demonstrated varying degrees of UTI risk. Furthermore, the severity of UTIs in patients receiving SGLT2 inhibitors was found to be similar to those receiving alternative treatments or placebo. However, there was evidence of a higher frequency of genitourinary infections, particularly in females treated with SGLT2 inhibitors. The findings of this systematic review and meta-analysis highlight the increased risk of UTIs associated with SGLT2 inhibitor use in patients with diabetes. While SGLT2 inhibitors have shown significant benefits in glycaemic control, improving renal function and cardiovascular outcomes, physicians should be aware of this potential side effect and consider proper monitoring and preventive measures for patients at higher risk of developing UTIs. Future research may further explore the underlying mechanisms contributing to UTI risk with SGLT2 inhibitors and investigate strategies to alleviate this adverse effect.

KEYWORDS:
Urinary tract infections (UTI), Sodium glucose co-transporter (SGLT-2) inhibitors, Placebo, Genital infections, Type -2 diabetes mellitus, Chronic kidney disease, Bacteriuria, Hypoglycaemia, Heart failure, Meta analysis.

INTRODUCTION:
UTI is a highly prevalent disease caused by various etiological agents, affecting approximately 250 million people annually and leading to the death of around 150 million individuals worldwide. The condition is more commonly observed in women (40%-50%) compared to men (5%). Preventing UTIs is crucial as they have been associated with various adverse outcomes, including renal scarring, low birth weight, fetal growth restrictions, neonatal UTIs, premature labor, miscarriage, hypertension, preeclampsia, septic shock, malformation, anorectal malformation, and an increased incidence of fetal mortality. The most commonly implicated bacterial species in UTIs include E. coli, Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa, and Proteus mirabilis. Diabetic females are more prone to UTIs compared to males due to their anatomical structure, such as a shorter urethra, the absence of prostatic secretion, and contamination of the urinary tract with faecal flora from the perineal area. Complicated UTIs especially affect patients with abnormal genitourinary tracts. UTIs are also common among individuals with various chronic conditions, including diabetes, stroke, arthritis, obesity, alcohol use disorder, hypertension, HIV, liver cirrhosis, Hepatitis C, long-term care residents, immunocompromised individuals, pregnant women, those with a history of current catheterization, spinal cord dysfunction, and certain cancers [1,2,13]. SGLT2 inhibitors induce hypoglycaemia by blocking SGLT2, a high-capacity, low-affinity transporter found in the early segment of the proximal convoluted renal tubule. Normally, SGLT2 is responsible for reabsorbing 90% of the glucose filtered at the glomerulus, while the remaining glucose is transported back into the systemic circulation through SGLT1, located in the distal segment of the proximal convoluted tubule. By inhibiting SGLT2, these inhibitors cause glycosuria and reduce blood glucose levels. Approximately 70-80g of glucose is excreted per day due to this inhibition. It is important to note that while SGLT2 inhibitors reduce renal glucose reabsorptive capacity by up to 50%, physiological changes occurring with respect to their administration limit the extent of this reduction [3,7,11,12,17]. The most frequently administered SGLT2 inhibitors are canagliflozin, dapagliflozin, and empagliflozin. The SGLT2 transporter is

responsible for reabsorption of more than 90% of renal glucose from the urine filtered by renal glomeruli [4]. Somehow unexpectedly, SGLT2 inhibitors were found to be potentially useful in the treatment of heart failure [5]. Furthermore, research conducted on patients with chronic kidney disease revealed that SGLT2 inhibitors decreased the risk of renal function decline or end-stage kidney disease, irrespective of the presence of diabetes. These beneficial qualities have led to a growing prescription of SGLT2 inhibitors not only for patients with type 2 diabetes mellitus but also for those with cardiovascular and renal conditions. Intriguingly, SGLT2 inhibitors have also demonstrated efficacy in reducing body weight in obese patients without type 2 diabetes [6,15,16]. While SGLT2 inhibitors are generally well-tolerated, there have been reports of higher rates of genital and urinary tract infections. The increased occurrence of genital infections in diabetic patients treated with SGLT2 inhibitors can be attributed to the increased urinary glucose concentrations, which can facilitate fungal growth on the surface of genital mucous membranes. As a result, the risk of genital infections in patients taking SGLT2 inhibitors for conditions other than type 2 diabetes may differ compared to patients with type 2 diabetes [4,13,14]. Urinary tract infections most commonly occur due to a combination of factors. These infections are often found in the urinary tract, primarily due to immune and nervous system defects associated with hyperglycaemia and the presence of a glucose-rich environment (glycosuria) in the urinary tract. This environment promotes the growth of pathogens and strengthens bacterial resistance, making individuals more susceptible to urinary tract infections [7]. Due to their mechanism of action, which is not dependent on beta-cell function (insulin), SGLT2 inhibitors can be utilized at any stage of the disease progression, offering potential advantages such as reduced glycated haemoglobin levels, decreased fasting and postprandial glucose levels, weight loss, lowered blood pressure, and prevention of micro and macrovascular diabetes complications. These benefits contribute to an improved quality of life for patients. However, it is essential to note that in some of the studies that demonstrate the efficacy of SGLT2 inhibitors, instances of genito-urinary infections have been observed in users. This effect is associated with glycosuria induced by SGLT2 inhibitors [8,9,10].

OBJECTIVE:

The aim of this review is to evaluate the risk of urinary tract infections in patients taking SGLT2 inhibitors.

METHODS:

For this analysis, data was pooled from all randomized controlled, blinded Phase I to III clinical trials of sglt2 inhibitors administered to diabetic or non-diabetic patients. Phase I to III clinical trials of 8 days to 104 weeks' duration [9]. Types of studies - randomized controlled trials (RCTs) evaluating the side effects of SGLT2 inhibitors, administered to diabetic or non-diabetic patients [4].

Types of interventions administered to patients on treatment with SGLT2 inhibitors or placebo were included in the present review. A systematic computerized search was performed using the following databases: PubMed (Public MEDLINE - Medical Literature Analysis and Retrieval System Online - US National Library of Medicine National Institutes of Health), SciELO (Scientific Electronic Library Online) and Cochrane Library [4,8].

Clinical trails were included and analysed in the review. In these the following drugs used were: Dapagliflozin, Canagliflozin, Empagliflozin, and Tofogliflozin. The profiles of the patients analysed in the studies were those with DM2, using or not oral antidiabetic drugs or insulin, with or without associated comorbidities and of both genders [8].

RESULTS:

In different subgroups, the incidence of UTI was examined based on the patient's use of SGLT2i either as monotherapy or in combination therapy, considering specific comorbidities within each sample, as well as the specific SGLT2i drug used. Both monotherapy and combination therapy with SGLT2i were associated with higher odds of developing UTI compared to the placebo, with the study samples consisting of obese patients. Among the patients using SGLT2i, some were using it in combination with insulin or Metformin. When insulin and Metformin were used together, there was no significant difference in the chance of developing UTI compared to the placebo.

When the studies were analysed together statistically, they revealed an increased chance of UTI with the use of SGLT2i compared to placebo. This increased risk was also observed in patients with established cardiovascular disease or risk factors for this condition, and these characteristics were present in three of the studies. Additionally, one study specifically looked at the risk of UTI in patients with microalbuminuria using SGLT2i.Looking at individual SGLT2i drugs, Dapagliflozin, Canagliflozin, and Tofogliflozin showed an increased chance of UTI, irrespective of the dose taken. However, Empagliflozin did not demonstrate an increased chance of UTI compared to the placebo in most studies. There was an exception, where one article included in the review indicated that Empagliflozin at a 50mg dose showed an increased chance of developing UTI. Interestingly, the same study also found an increased chance of UTI when the drug was used at a lower dose [8].

In non-diabetic patients, the use of SGLT2 inhibitors compared to a placebo showed a statistically significant difference in the odds of urinary tract infections. The resulting adjusted odds ratio was 1.30, indicating a higher likelihood of developing UTIs with SGLT2 inhibitors. When comparing non-diabetic and diabetic patients taking SGLT2 inhibitors for heart failure or chronic kidney disease in four studies, there was no statistically significant difference in the odds ratio for urinary tract infections. However, in the same four studies, when comparing diabetic and non-diabetic patients taking a placebo for the same conditions, a statistically significant odds ratio for urinary tract infections was found [4]. The prevalence of UTI in dapagliflozin was less compared to Empagliflozin. The prevalence of UTI in males and females is higher with empagliflozin when compared to dapagliflozin [17].

DISCUSION:

The relationship between elevated urinary glucose levels and the risk of urinary tract and genital infections remains largely unexplored. While diabetes is widely recognized as a significant risk factor for urinary tract infections, the potential contribution of high urine glucose concentrations to the development of such infections has not been conclusively established [4]. Treatment with SGLT2 inhibitors of patients with type 2 diabetes was associated with a small increase in incidence of urinary tract infections, with no increase in serious or upper urinary tract infections. The incidence of uti in patients with sglt2 inhibitors was

more than 30% compared to those who have used non sglt2 inhibitors [22]. The patients on SGLT2 inhibitors had a significantly higher risk of developing ASBU in our study. The association between SGLT2 inhibitors and UTI has been established, and the reason is the mechanism of action of these drugs, to inhibit renal glucose uptake and lead to pharmacologically-induced glycosuria which leads to increased risk for UTI. However, we found no study that correlated the use of SGLT2 inhibitors with ASBU. The finding indicates that SGLT2 inhibitors need to be investigated in more detail regarding their interaction with the host microbiome[7].

The simultaneous presence of these various risk factors in a diabetic patient will undoubtedly hold significant clinical implications. Diabetic women with inadequate glycaemic control, longer diabetic duration, a history of UTIs, along with proteinuria and excessive antibiotic use, will face a higher risk of developing subsequent UTIs. It is crucial to consider these risk factors when managing such patients to ensure comprehensive care. For instance, clinicians should refrain from prescribing SGLT2 inhibitors to this specific patient population, as it could further elevate the risk of UTIs.

The discussion above emphasizes the necessity for more extensive studies and cohorts to thoroughly evaluate the proposed risk factors and explore how different population characteristics might influence the occurrence of UTIs. While routine screening for UTIs is not recommended due to its limited benefits, once the risk factors are established through studies like ours, it may aid in identifying diabetic individuals at a higher risk of developing UTIs [10,17].

Diabetic patients experience a higher incidence of UTI compared to non-diabetic patients and also exhibit increased disease severity. Among diabetic women, bacterial cystitis, asymptomatic bacteriuria, and symptomatic UTI with associated complications occur more frequently than in non-diabetic women, with an estimated fourfold higher risk. One possible explanation for this heightened risk in diabetics is related to the physiopathology of the condition, where elevated levels of glucose in the urine can encourage bacterial growth. Furthermore, prolonged diabetes leading to restricted peripheral blood circulation can result in abnormalities in the defense system, increasing the likelihood of infections and the seriousness of the condition. Consequently, there has been significant research exploring the correlation between glycosuria induced by SGLT2 inhibitors and infectious processes in the genitourinary tract [8].

While diabetes itself seems to increase the risk of uti, the studies we discovered suggest that the associated risk following sglt2 inhibitor (sglt2i) exposure is minimal. UTIs linked to sglt2 inhibitors are primarily described as mild to moderate in intensity: Mild utis are characterized by symptoms that are easily tolerated, causing minimal discomfort and not significantly interfering with everyday activities. Moderate utis cause enough discomfort to interfere with normal activity. It's noteworthy that severe utis, which lead to extreme distress and significant impairment of functioning or incapacitation, appear to be rare in association with sglt2 inhibitors. Moreover, the reported severe events or events leading to hospital admission were observed in only 0.1–0.4 percent of patients in clinical trials. Kidney infections and sepsis were classified as "rare" occurrences. Notably, utis associated with sglt2 inhibitors typically respond well to standard treatment and are rarely a cause for discontinuation of the medication [11].

CONCLUSION:

The incidence of urinary tract infections (UTIs) in patients treated with SGLT2 inhibitors is significantly higher compared to those receiving other antidiabetic therapies or placebo. This conclusion is drawn based on the findings of the systematic review and meta-analysis conducted on diverse population of patients with diabetes. SGLT2 inhibitors have been recognized for their efficacy in glycaemic control and cardiovascular outcomes, making them a valuable treatment option for diabetes management. However, the increased incidence of UTIs is an important consideration when prescribing these medications to patients. The meta-analysis revealed that the overall risk of developing UTIs was greater in patients receiving SGLT2 inhibitors, emphasizing the need for healthcare providers to be cautious in monitoring for UTIs in this patient population. Additionally, subgroup analysis identified varying degrees of UTI risk associated with specific SGLT2 inhibitors, indicating that individual drugs within the class may have different effects on UTI incidence. Despite the higher risk of UTIs, the severity of UTIs in patients treated with SGLT2 inhibitors was found to be comparable to those on alternative treatments or placebo. Nevertheless, there was evidence of an increased frequency of genitourinary infections, particularly in female patients. In conclusion, while SGLT2 inhibitors offer several benefits in the management of diabetes, the incidence of UTIs represents a potential adverse effect that clinicians should be mindful of when prescribing these medications. Patients initiating SGLT2 inhibitor therapy should be informed about the risk of UTIs and monitored regularly for any signs or symptoms of urinary tract infections. Proactive measures to prevent UTIs, such as patient education, appropriate hygiene practices, and early detection, should be implemented to reduce the impact of this side effect and ensure the overall safety and effectiveness of SGLT2 inhibitor treatment in patients with diabetes. Further research and clinical investigations may be necessary to gain a deeper understanding of the underlying mechanisms behind the increased UTI risk and identify strategies to minimize its occurrence.

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