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Research Article

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Comparative Analysis of Fournier's Gangrene Risk between Canagliflozin and Dapagliflozin: A Molecular and Clinical Investigation

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Abstract

Fournier's gangrene, a rare but severe complication associated with sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy, has raised concerns regarding its differential risk across distinct SGLT2 inhibitors. This case study review aims to understand the specific molecular mechanisms and clinical characteristics underlying the varying propensity of two commonly prescribed SGLT2 inhibitors, canagliflozin and dapagliflozin, to precipitate Fournier's gangrene in patients with type 2 diabetes mellitus. Utilizing a comprehensive research strategy, this investigation will describe the distinct pharmacokinetic and pharmacodynamic properties of canagliflozin and dapagliflozin to analyze their differential effects on glucose metabolism, osmotic diuresis, and microbial ecology within the perineal region. In vitro experimentation will focus on how each SGLT2 inhibitor modulates immune cell function, tissue integrity, and bacterial proliferation, shedding light on the unique molecular pathways contributing to Fournier's gangrene development. By conducting a comparison between canagliflozin and dapagliflozin, this paper aims to provide nuanced insights into the differential risk profiles of SGLT2 inhibitors regarding Fournier's gangrene development. Ultimately, these findings may inform clinical decision-making, guide patient risk stratification, and facilitate the development of safer antidiabetic therapies for individuals with type 2 diabetes mellitus.

Introduction

Fournier's gangrene (FG) is a rare but life-threatening bacterial infection, increasingly associated with sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy. This severe condition affects the genital, perineal, and perianal regions, characterized by rapid tissue necrosis caused by polymicrobial infections. Immediate medical intervention, including the surgical removal of necrotized tissue and administration of antibiotics, is crucial for patient survival. FG predominantly occurs in individuals with pre-existing health conditions such as diabetes, immunosuppression, and chronic alcohol abuse. Notably, 25-50% of FG patients have an alcohol use disorder, and 20-70% are diabetic [1]. The rapid progression of FG requires early diagnosis and treatment to improve survival rates and minimize complications [2].

The incidence of FG is about 1.6 cases per 100,000 males, with the rate in females remaining unclear [3]. The condition's rapid progression leads to a mortality rate of approximately 40%, but delays in diagnosis and treatment, compounded by multiple comorbidities, can increase this rate to 88%. However, prompt surgical intervention has been shown to reduce mortality by approximately 50% [4]. Factors such as age, lifestyle, and the duration of diabetes significantly influence FG risk. Older adults face higher risks due to reduced immune function and comorbidities like diabetes. Additionally, lifestyle factors such as smoking, alcohol use, and obesity exacerbate these risks. Smoking impairs vascular function and immune response, alcohol weakens the immune system and damages tissues, and obesity is linked to chronic inflammation and metabolic dysregulation. Long-standing diabetes further compounds these risks through cumulative vascular and nerve damage, impaired wound healing, and increased susceptibility to severe infections, underscoring the need for comprehensive management strategies [5].

Patients on SGLT2 inhibitors, used to manage type 2 diabetes mellitus (T2DM) by preventing glucose reabsorption in the kidneys, are at higher risk of developing FG. These inhibitors also offer benefits like reducing heart failure risk and slowing kidney disease progression in diabetic patients [6]. While the exact mechanism by which SGLT2 inhibitors contribute to FG is not fully understood, increased glucose levels in the urine may create a favorable environment for bacterial growth, thereby increasing infection risk [7]. Common SGLT2 inhibitors include canagliflozin and dapagliflozin. The rising use of these inhibitors, from 3.8% to 11.9% among T2DM patients between 2015 and 2019, highlights the importance of understanding the associated risks, including potential increases in FG incidence [8].

This review aims to understand the molecular mechanisms and clinical characteristics contributing to the different tendencies of canagliflozin and dapagliflozin to precipitate FG in patients with T2DM. It encompasses a detailed examination of pharmacokinetics, pharmacodynamics, immune modulation, microbial ecology, and clinical implications of these drugs. These findings aim to enhance the clinical decision-making, support patient risk stratification, and inform the development of safer antidiabetic therapies for T2DM patients.

Discussion

Pathophysiology of Fournier's Gangrene

FG, a rare life-threatening variant of necrotizing fasciitis, affects the deep and superficial tissues of the perineal, anal, scrotal, and genital regions [4]. This condition predominantly impacts adult males, though females can also be affected [9]. FG is characterized by rapid tissue destruction, sepsis, and a high mortality rate of up to 40% [4]. The disease rapidly spreads along fascial planes, causing severe inflammation and infection in adjacent soft tissues. This process results in blood vessel thrombosis, leading to ischemia and tissue necrosis of the surrounding tissue and fascia [4]. Due to its quick spread into the Dartos, Colles, and Scarpa's fascias, the abdominal wall may become infected early in the disease course [4]. However, FG can be overlooked or misdiagnosed in its early stages due to minimal skin symptoms and clinical presentations overlapping with other conditions like cellulitis.

Microbial Ecology in the Perineal Region

FG's rapid progression, high mortality rates, and polymicrobial infection necessitate prompt surgical intervention and aggressive medical management. The polymicrobial nature of FG involves a synergistic combination of aerobic and anaerobic bacteria. Aerobic bacteria initiate the infection, producing toxins that damage tissues and reduce oxygen tension, creating a favorable environment for anaerobes. Anaerobes then exacerbate tissue destruction and gas production, leading to more extensive necrosis and systemic complications. The symbiotic relationship between these bacterial groups amplifies the severity of the infection and complicates treatment efforts.

Commonly isolated pathogens include gram-positive bacteria such as Group A *Streptococci* and *Staphylococcus aureus*, and gram-negative bacteria like *E. coli* and *Pseudomonas aeruginosa* [4]. Other notable pathogens include *Bacteroides fragilis*, *Klebsiella*, *Corynebacteria*, *Enterobacteriaceae*, *Actinomyces*, and *Clostridium* species [10]. These bacteria collaborate synergistically, leading to rapid tissue necrosis and systemic toxicity. Their entry points into the area may be urinary, bowel, or dermal sources. Understanding microbial ecology in the perineal region and the immune system's role in FG is crucial for effective management and improving patient outcomes.

The mechanisms of bacterial invasion and synergy in tissue destruction in FG involve complex interactions between bacterial species, facilitating tissue invasion and destruction. Bacterial introduction into the subcutaneous tissues can occur through surgical manipulation, traumatic insult, localized skin breakdown, or urinary and other infectious perineal processes [10]. Following an initial insult, bacterial synergy leads to the production of tissue-destructive enzymes, collagenases, and endotoxins, causing obliterative endarteritis with subcutaneous vessels developing micro-thromboses [4]. Aerobic bacteria, such as *E. coli*, produce toxins and enzymes that degrade tissues and create an environment conducive to anaerobic growth, like *Bacteroides* species. Anaerobes produce gas and further tissue destruction, contributing to FG's characteristic crepitus. This bacterial infection accelerates infection progression, leading to extensive tissue necrosis and systemic involvement [4]. Early identification and prompt treatment are crucial to prevent severe conditions from developing.

Bacterial toxins and enzymes play pivotal roles in FG progression. Metalloproteases, proteases, hemolysins, and leukocidins contribute to cell lysis and immune evasion [11]. Enzymes such as hyaluronidase and collagenase degrade extracellular matrices, facilitating infection spread. Lipopolysaccharides can trigger severe inflammatory responses. Systemic toxin release can lead to sepsis and multi-organ failure. Gallois et al. described a fatal necrotizing fasciitis case caused by a necrotic toxin-producing *E. coli* strain belonging to phylogenetic group C possessing multiple virulence factors [12]. These virulence genes may encode adhesins, invasins, siderophores, proteins, and other toxins, resulting in fatal clinical outcomes. Understanding these molecular mechanisms is essential for developing targeted therapies to improve patient outcomes.

Role of the Immune System in FG

Patients with diabetes mellitus (DM) are more susceptible to FG due to increased bacterial infection susceptibility, impaired immune response, delayed healing times, and microbiome alterations. Diabetic patients have higher numbers *Escherichia*, *Prevotella*, and *Lactobacillus* species in their gut microbiome [13]. Research shows bacteria commonly affect the urinary tract, respiratory tract, skin, and soft tissues in diabetic patients [14]. Increased glucose levels in diabetic patients provide a nutrient-rich environment that promotes pathogen growth. Diabetic patients are also vulnerable to skin conditions such as intertrigo and ulcers. Complications at any of these sites of infection entry can lead to FG's rapid development. DM is present in an estimated 20-70% of FG patients, with an increased FG incidence associated with SGLT2 inhibitor use [14]. Careful monitoring and management of diabetic patients are crucial to preventing FG onset and progression.

Perineal hygiene and local skin conditions significantly impact microbial colonization and FG progression. Poor hygiene and conditions like moisture, warmth, and occlusion promote microbial colonization, increasing FG risk [4]. These factors create an environment favoring pathogenic bacterial growth and polymicrobial infections. Maintaining proper hygiene can prevent skin breakdown and pathogen introduction. Conditions like candidiasis, delayed wound healing, incontinence dermatitis, and irritation in intertriginous areas, especially with DM, increase infection risk [15]. Proper perineal hygiene and effective local skin condition management are vital in reducing FG risk.

The immune response to FG is due to the rapid spread of inflammatory and infectious processes in soft tissue. Systemic complications in immunocompromised or diabetic patients include acute renal failure, acute respiratory distress syndrome, cardiac arrhythmias, heart failure, multiple organ failure, and bacteremia [4]. FG complications seen in DM patients occur at a rate of 36-56% due to small vessel disease, defective neuropathy, and immunosuppression [16]. Elbeddini et al. discussed a T2DM patient developing FG from dapagliflozin, an SGLT2 inhibitor associated with an increased urogenital

infection risk [17]. Uncontrolled DM at FG onset, with an average HbA1c of 9.5%, was observed in a retrospective study of 26 diabetic FG patients [18]. FG is particularly critical in diabetic patients, necessitating prompt diagnosis and urgent clinical management for favorable outcomes and reduced mortality.

Comparative Analysis

Understanding the pharmacokinetic and pharmacodynamic differences between dapagliflozin and canagliflozin is essential for evaluating their impacts on infection risk, including severe conditions such as FG. Key factors in this comparison include oral absorption and hepatic metabolism, which influence the drugs' bioavailability and systemic effects. Notably, dapagliflozin and canagliflozin have distinct renal excretion profiles that significantly affect glucose homeostasis and the potential for glucose-rich environments conducive to bacterial growth [19]. Additionally, their pharmacodynamic properties, such as diuretic effects and fluid balance, play crucial roles in patient outcomes.

Beyond infection risks, this analysis explores the broader benefits and risks of these medications in comparison to other SGLT2 inhibitors, with a focus on cardiovascular health and other organ systems. Tolerability and potential medication interactions are critical, as they impact the real-world effectiveness and safety of dapagliflozin and canagliflozin. These differences are vital for clinicians to make informed prescribing decisions, especially for patients at higher risk of infections. The pharmacokinetic profiles, including absorption, metabolism, and excretion, provide insights into the safety and efficacy of these drugs. Additionally, their effects on fluid and electrolyte balance can influence patient comfort and compliance, potentially leading to dehydration, reduced tissue perfusion, orthostatic hypotension, and fall risks [20,21]. Comparative studies on cardiovascular outcomes have yielded varied results, underscoring the importance of personalized treatment plans tailored to individual patient profiles.

Canagliflozin

Mechanism of Action, Pharmacokinetics, and Pharma codynamics

Canagliflozin, a widely prescribed SGLT2 inhibitor for managing T2DM, lowers blood glucose levels by inhibiting the reabsorption of glucose in the proximal convoluted tubule, facilitating its excretion through urine. When taken orally, canagliflozin demonstrates a 65% bioavailability, allowing for rapid absorption into the bloodstream and peak effects within 30-120 minutes [21,22]. After exerting its effects on the kidneys, canagliflozin is metabolized in the liver and excreted through urine and feces. Understanding these pharmacokinetics is critical, particularly regarding potential interactions with other medications metabolized by hepatic enzymes. Beyond its glucose-lowering effects, canagliflozin significantly impacts fluid and electrolyte balance, potentially leading to dehydration and reduced perfusion of peripheral tissues [23]. These changes can increase susceptibility to infections, including severe conditions like FG.

The effects of canagliflozin on renal function and electrolyte balance are particularly noteworthy. By inhibiting SGLT2, canagliflozin increases glucose and sodium excretion, causing measurable changes in electrolyte homeostasis. The natriuretic effect is most pronounced early in treatment and may transiently resolve [19]. However, the long-term impact on sodium levels is not well established. Prolonged use of canagliflozin is linked to side effects such as urinary tract infections (UTIs) and genital mycotic infections, attributed to the glucose-rich environment promoting bacterial and fungal growth. This established association raises concerns about the potential for severe infections like FG, especially in high-risk patients. Experimental data suggests that canagliflozin may enhance growth rates of pathogenic bacteria in the perineal region, complicating its infection risk profile, with one study finding that SGLT2 inhibitors were associated with nearly a three-fold increase in genital infections [24]. Another study involving T2DM patients controlled with metformin found no significant increase in asymptomatic bacteriuria or UTIs in the canagliflozin group compared to placebo, indicating a potential drug interaction that warrants further investigation [25].

Immune Modulation and Infection Risk

Canagliflozin's impact on immune cell function introduces additional complexities to its therapeutic profile. As an SGLT2 inhibitor, canagliflozin can alter neutrophil function and cytokine production, thereby affecting the immune response. It has been shown to significantly inhibit the production and release of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1, although its effects on serum neutrophil levels are not well studied [26]. These immunomodulatory effects can impair the body's ability to combat infections effectively, potentially leading to severe conditions such as FG.

By suppressing key inflammatory mediators like TNF-α and IL-6, canagliflozin may dampen the inflammatory response, delaying pathogen recognition and clearance. This suppression could compromise the activation and recruitment of immune cells to infection sites, creating an environment conducive to bacterial growth and dissemination, thus increasing the risk of severe infections. Moreover, canagliflozin's impact on immune function could pose broader challenges for patients with existing immunocompromised conditions. Understanding these interactions is essential, particularly when considering concomitant medications that affect immune function. Careful patient selection and monitoring are crucial to mitigate the potential risks associated with canagliflozin therapy.

Further research is needed to explore the mechanisms by which canagliflozin influences FG incidence. Although current research indicates that canagliflozin and metformin do not have clinically significant interactions, the potential consequences of other antidiabetic medications, such as insulin, warrant further investigation [27]. These combinations could exacerbate side effects or modify drug efficacy. Long-term safety data emphasize the need for regular monitoring of renal function and electrolyte levels in patients undergoing canagliflozin therapy, highlighting the importance of personalized treatment plans that address the specific needs and risks of each patient.

Canagliflozin's immunomodulatory effects extend beyond infection risk, posing potential challenges in managing inflammatory conditions. Canagliflozin administration has been observed to reduce levels of TNF receptor 1, IL-6, matrix metalloproteinase 7, and fibronectin 1, indicating a potential reversal of inflammatory processes [28]. For patients with chronic inflammatory diseases, this suppression of cytokine production could interfere with the efficacy of existing anti-inflammatory therapies, necessitating adjustments in treatment

regimens to balance glycemic control with the risk of exacerbating underlying conditions. Additionally, these immunosuppressive effects may necessitate closer monitoring and more frequent evaluations to ensure that inflammatory conditions remain controlled while using canagliflozin.

Moreover, alterations in immune cell function could affect wound healing, a critical consideration for diabetic patients prone to ulcers and other slow-healing wounds. Clinicians must be vigilant in monitoring signs of impaired healing and consider alternative diabetes treatments if complications arise. The immunosuppressive potential of canagliflozin also has implications for patients undergoing immunotherapy for conditions like cancer, where robust immune activity is essential for therapeutic efficacy. This underscores the need for a multidisciplinary approach in managing patients on canagliflozin, involving endocrinologists, immunologists, and other specialists to ensure comprehensive care.

Dapagliflozin

Mechanism of Action, Pharmacokinetics, and Pharmaco dynamics

Dapagliflozin, another SGLT2 inhibitor, shares the mechanism of action with canagliflozin but displays distinct pharmacokinetic and pharmacodynamic properties that affect its safety and efficacy profile. Dapagliflozin is absorbed orally and undergoes extensive hepatic metabolism primarily by the CYP3A4 enzyme before being excreted predominantly through the kidneys [29]. Its higher bioavailability of 78% compared to canagliflozin's 65% suggests differences in absorption rates and systemic exposure [21]. This metabolic pathway implies that hepatic or renal impairment in patients could significantly alter the drug's pharmacokinetics, requiring careful dose adjustments and vigilant monitoring.

Dapagliflozin is approved for a maximum dose of 10 mg, whereas canagliflozin's maximum approved dose is 300 mg, reflecting their differing safety and efficacy profiles [22]. At the maximum recommended doses, canagliflozin has been shown to have stronger effects on increasing glucose excretion and lowering the renal glucose threshold while maintaining low rates of adverse events [30,31]. These differences in dosage and bioavailability suggest that canagliflozin might create a more glucose-rich urinary environment, potentially increasing the risk of FG. By promoting glucose excretion in the urine, dapagliflozin lowers plasma glucose levels and induces osmotic diuresis. This diuretic effect, similar to canagliflozin, can result in changes in fluid and electrolyte balance, potentially contributing to dehydration and reduced tissue perfusion. Additionally, the higher bioavailability of dapagliflozin indicates it is more readily absorbed into the bloodstream, influencing the overall risk profile and systemic exposure.

Dapagliflozin has demonstrated protective effects on cardiovascular health, distinguishing it from some other SGLT2 inhibitors. Clinical trials have highlighted its ability to reduce the risk of heart failure and cardiovascular death in patients with T2DM, making it a preferred choice for those with existing cardiovascular conditions [20]. However, these cardiovascular benefits must be carefully balanced against potential risks, such as severe infections. The immunomodulatory effects of dapagliflozin, while beneficial for cardiovascular health, could potentially compromise the body's ability to fight infections effectively. Dapagliflozin's role in reducing arterial stiffness and lowering blood pressure adds to its cardiovascular protective profile, but these same effects can lead to decreased perfusion in peripheral tissues. This decreased perfusion, especially in combination with dehydration, might exacerbate the risk of tissue necrosis.

The impact of dapagliflozin on renal function requires regular monitoring, particularly in patients with pre-existing kidney conditions. Renal impairment not only affects drug clearance but also heightens the risk of adverse renal outcomes, necessitating a delicate balance in managing these patients. Impaired renal function can alter the drug's excretion, leading to higher systemic levels and increased risk of side effects. Additionally, both dapagliflozin and canagliflozin's effects on electrolyte balance and fluid status must be monitored to prevent complications such as hyponatremia or hyperkalemia, which can further compromise patient health and increase susceptibility to infections. The diuretic effect of dapagliflozin can lead to significant fluid shifts, potentially causing orthostatic hypotension and increasing fall risk in elderly patients. Close monitoring and individualized treatment plans are essential to mitigate these risks and ensure optimal therapeutic outcomes for patients on dapagliflozin.

Immune Modulation and Infection Risk

Comparative studies have shown that while dapagliflozin and canagliflozin have similar effects on glycemia, their impacts on tissue health differ significantly. Londzin et al. demonstrated that dapagliflozin exhibits distinct effects on tissue health in rat models compared to canagliflozin, suggesting that although these drugs share a primary action on glucose levels, their broader physiological impacts may vary greatly [32]. This variation can significantly influence their overall risk-benefit profile in clinical use. Maintaining healthy tissues is vital for mitigating infection risk; therefore, drugs that negatively impact tissue integrity could increase susceptibility to FG. Additionally, tissue health is crucial for wound healing and recovery from infections, underscoring the importance of selecting the appropriate drug for each patient. These differences in tissue health impacts may reflect underlying variations in the drugs' pharmacokinetics and pharmacodynamics.

The modulation of immune responses by dapagliflozin has also been an area of active research, particularly in the context of infection risk. Dapagliflozin has been shown to reduce the production of pro-inflammatory cytokines in human endothelial and immune cells, indicating an anti-inflammatory mechanism of action [33]. Further experimental evidence by Saenkham et al. demonstrated that dapagliflozin-induced hyperglycosuria promotes bacterial colonization in the urinary tract and facilitates systemic spread to organs such as the spleen and liver in murine models [34]. This hyperglycosuria, characterized by increased glucose excretion in urine, creates a nutrient-rich environment that supports bacterial growth, thereby increasing the risk of infections. The relationship between hyperglycosuria and infection risk highlights the importance of balancing glucose-lowering benefits with potential adverse effects.

Dapagliflozin's specific impact on microbial ecology and immune responses in the perineal region appears to differ from canagliflozin, suggesting a nuanced interplay between the drug and host microbial dynamics. Wu et al. demonstrated that dapagliflozin affects the gut microbiome differently compared to canagliflozin in rat models of diabetic kidney disease [35]. While the study focused on the broader implications of SGLT2 inhibitors on the gut microbiome, it suggests that these drugs

have specific differential effects on microbial ecology. Patients on dapagliflozin may be at increased risk for infections due to the drug's tendency to enhance bacterial growth in glucose-rich environments.

Molecular Mechanisms of SGLT2 Inhibitor-Induced FG

Effects on Glucose Metabolism and Microbial Ecology

SGLT2 inhibitors function by targeting the proximal tubule of the nephron, resulting in increased urinary glucose excretion. This reduction in serum glucose levels is therapeutically beneficial for patients with T2DM. In such patients, the use of SGLT2 inhibitors can cause even greater levels of urinary glucose due to their elevated serum glucose load and the upregulation of SGLT2 transporters in diabetic kidneys [36]. Both dapagliflozin and canagliflozin reduce serum glucose levels through renal excretion, but their exact effects on glucose excretion, serum electrolyte changes, and other physiological parameters may differ. A single 100 mg dose of dapagliflozin results in a median 24-hour urinary glucose excretion of 80 grams in diabetic patients, compared to 60 grams in non-diabetic patients [36]. This discrepancy underscores the potential for SGLT2 inhibitors to create an environment conducive to microbial growth, especially in diabetic patients. Although urinary glucose excretion is expected to slightly decrease over time with continuous SGLT2 inhibitor use, the extent and variability depend on the specific inhibitor used [36]. Further research is needed to assess how urinary glucose excretion changes over time, how it varies between different SGLT2 inhibitors, and its impact on infection risk.

An increase in urinary glucose can create a favorable environment for bacteria and other pathogens, potentially increasing infection risk in patients taking SGLT2 inhibitors. However, there is no strong consensus on whether SGLT2 inhibitors are correlated with an increased risk of UTIs. A systematic review and meta-analysis found no increased risk of UTIs in patients taking SGLT2 inhibitors compared to a control group [37]. In contrast, another study reported a 3.7-fold higher risk of developing a UTI in patients taking an SGLT2 inhibitor [38]. These conflicting results may be due to patient-specific factors such as genitourinary anatomy, baseline infection risk, type of SGLT2 inhibitor used, and medication dosage. Despite the inconsistent association between SGLT2 inhibitor use and UTI occurrence, the potential for increased genital infection risk remains. Bacterial contamination due to anatomical proximity and changes in genital pH and flora can increase susceptibility to infection.

A stronger consensus exists on the increased risk of genital infections with SGLT2 inhibitor use. Data from a United Kingdom primary care database showed that genital infections were more common in patients treated with SGLT2 inhibitors compared to DPP4 inhibitors (8.1% vs. 1.8%) [39]. DPP4 inhibitors enhance incretin levels, leading to increased insulin and decreased glucagon, thereby improving serum glucose control without affecting urinary glucose excretion. This difference likely contributes to the lower incidence of genital infections in patients using DPP4 inhibitors. Two significant risk factors associated with genital infection were female sex and history of prior infection [39]. These findings highlight the role of patient-specific factors in infection risk and suggest potential synergistic effects with SGLT2 inhibitor use. The choice of SGLT2 inhibitor also influences the risk of genital infections. A double-blind study found that 546 patients using dapagliflozin reported genital infections, with no correlation between infection rates and dapagliflozin dosage [36]. Similarly, patients using canagliflozin also reported increased genital infection symptoms [38]. These results indicate that even a slight increase in urine glucose can significantly alter the genital microbial environment, warranting further investigation into how different SGLT2 inhibitors and their dosages affect infection risk.

Impact on Tissue Integrity

SGLT2 inhibitors increase urinary glucose excretion, creating an osmotic gradient that enhances water excretion into the urine. This osmotic diuretic effect results in increased urine volume and frequency, along with changes in electrolyte homeostasis. The skin, particularly the stratum corneum, natural moisturizing factors, and hyaluronic acid within the dermis, plays a crucial role in maintaining the body's electrolyte balance and water reserves, thereby regulating hydration and sodium retention. Consequently, any alteration in these factors can have significant implications for overall skin health and function.

Proper skin hydration is essential for cell proliferation, enzyme activity, and immune cell migration, all of which are critical for tissue infection response and healing. Studies have not observed significant reductions in tissue water content with SGLT2 inhibitors. For instance, a study with dapagliflozin reported no difference in tissue water content after six weeks of treatment but found a significant reduction in skin sodium content [40]. Another study using electrical capacitance and conductance as indicators of skin water content found no significant differences in patients treated with ipragliflozin for 14 days [41]. Similarly, empagliflozin showed a statistically significant decrease in skin sodium content at one and three months without affecting muscle sodium content [42]. These changes in osmotic balance may impact the microbial flora of the skin and affect collagen synthesis and remodeling, which are crucial for tissue healing.

While reducing sodium levels is beneficial for lowering blood pressure, providing cardioprotective effects, and promoting renal protection, further changes in skin sodium content can compromise barrier integrity, cellular functioning, and inflammatory responses. Research has shown that in response to bacterial infection, sodium accumulates in the skin, creating a hypertonic microenvironment [43]. This sodium increase enhances macrophage activation and antimicrobial activity [43,44]. These findings underscore the complex and context-dependent roles of sodium in various physiological processes, emphasizing the need for careful management of sodium levels to optimize both systemic and local tissue health.

Modulation of Immune Cell Function

SGLT2 inhibitors have been shown to increase the phosphorylation of AMPK and enhance the activity of the AMPK pathway [45]. AMPK activation, triggered by a high AMP/ATP ratio indicating low cellular energy levels, inhibits NF-kB and mTOR while activating SIRT1. This cascade collectively reduces oxidative stress, pro-inflammatory pathways, apoptosis, and mitochondrial dysfunction [45]. While these effects are beneficial for visceral organs, they may reduce pro-inflammatory markers in the skin, potentially lowering microbial infectivity thresholds and compromising the skin's role as a first line of defense. For instance, AMPK activation enhances neutrophil chemotaxis and prevents inhibition by bacterial lipopolysaccharide exposure, thereby promoting a rapid immune response to minimize tissue infection and damage

[46]. However, changes in skin pH and osmolarity can negate these benefits. Moreover, AMPK activation also boosts macrophage and neutrophil phagocytic abilities through improved efferocytosis [47]. The effects of these pathways on sodium skin concentrations warrant further investigation, as SGLT2 inhibitors might bolster immune defense by strengthening immune responses.

Furthermore, SGLT2 inhibitors suppress NLRP3 inflammasome activation [45]. The NLRP3 inflammasome detects pathogen-associated and damage-associated molecular patterns, initiating pro-inflammatory responses. Studies in mouse models treated with SGLT2 inhibitors demonstrated suppression of the NLRP3 inflammasome in heart and kidney tissues, resulting in decreased IL-1 release [48]. While this suppression benefits organ function, it may contribute to higher infection rates in the skin due to reduced pro-inflammatory responses. Additionally, dapagliflozin prevents ROS-NLRP3 inflammasome activation, protecting against steatosis, inflammation, and liver injury [48]. However, diminished ROS-NLRP3 inflammasome activity lowers the skin's innate immune response, increasing susceptibility to infections. Despite the cardiovascular advantages, reduced NLRP3 inflammasome activity may impair bacterial clearance and pro-inflammatory cytokine activation, heightening infection risk.

Additional studies on dapagliflozin and canagliflozin have revealed their impacts on cytokine proliferation and immune cell response. In a mouse model of the inherited metabolic disorder GSDIb, dapagliflozin improved neutrophil function by reducing 1,5-AG6P accumulation, leading to enhanced neutrophil numbers, maturation, phagocytic activity, migratory capacity, and reduced apoptosis [49]. These positive effects on neutrophil function might mitigate microbial infection in the skin, though further research is necessary to determine if all SGLT2 inhibitors exert similar effects. Faridvand et al. found that dapagliflozin decreased ROS, IL-6, and TNF-α levels while increasing SIRT1, PGC-1α, and p-AMPK in human umbilical vein endothelial cells [50]. This modulation of inflammatory and oxidative stress pathways could enhance the skin's immune response and barrier function.

Similarly, Abd El-Fattah et al. reported that dapagliflozin reduced MCP-1, IL-1β, IL-18, and TNF-α levels while increasing p-AMPK in rat lung tissue [51] This reduction in pro-inflammatory cytokines and inflammasome activity could strengthen the skin's resilience to infections by reducing inflammation-induced damage and promoting a robust immune defense. Research also shows that canagliflozin reduces Iba1, IL-6, and macrophage accumulation in skeletal muscle of male mice [52]. Lower IL-6 levels may attenuate the inflammatory response, potentially limiting immune cell recruitment to infection sites and altering the local immune environment. Another study found that canagliflozin lowered median serum IL-6 by 22% and increased median serum TNF-α by 7% [47]. While these anti-inflammatory effects of SGLT2 inhibitors are advantageous for cardiovascular and renal health, they might explain the increased incidence of genital infections in patients using these medications.

Implications for Clinical Practice

Guidelines for Risk Stratification

To enhance patient safety, especially regarding the risk of developing FG in those using SGLT2 inhibitors, it is crucial to tailor treatment plans based on individual risk profiles. Risk stratification tools are essential for this personalized approach, incorporating patient characteristics and specifics of SGLT2 inhibitor usage. By analyzing factors such as comorbid conditions, history of infections, and demographic information, these tools can identify patients at higher risk for FG. For example, individuals with diabetes who have a history of frequent UTIs, immunosuppression, or other complications are at increased risk and require more intensive monitoring and personalized treatment plans [4,5]. This comprehensive and individualized approach ensures that patient care addresses specific risks associated with SGLT2 inhibitors.

Implementing data-driven recommendations involves developing algorithms that stratify patients by risk level. When integrated into electronic health records (EHRs), these algorithms provide real-time risk assessments and automated alerts for healthcare providers, ensuring timely care for high-risk patients. Embedding these tools in EHRs allows clinicians to receive prompts for early intervention and monitoring protocols, critical for preventing the progression of FG. Such integration not only enhances patient outcomes through proactive management but also standardizes care processes across different healthcare settings, leading to improved consistency in patient care and reducing the likelihood of oversight in high-risk cases.

Training healthcare providers on the use of risk assessment tools is crucial for their effective implementation. Educational programs should focus on interpreting risk scores and integrating these assessments into clinical decision-making processes. Additionally, case studies demonstrating successful risk management can serve as practical examples for clinicians. For instance, a case study detailing how a patient with diabetes and frequent UTIs was managed with an adjusted dose of an SGLT2 inhibitor and regular screenings, ultimately preventing the onset of FG [2]. These real-world examples underscore the importance of integrating risk stratification into routine clinical practice, thereby reinforcing the value of personalized medicine.

Moreover, continuous updates and improvements in these tools based on new research findings are necessary. Regularly revisiting and refining algorithms ensure they remain accurate and effective in predicting risk, adapting to new data and evolving clinical understandings. This iterative process is vital for maintaining high standards of patient care and effectively managing the risks associated with SGLT2 inhibitors [4]. These updates ensure that risk stratification tools evolve alongside advancements in medical research and clinical practice, maintaining their relevance and efficacy in a rapidly changing healthcare landscape.

Clinical Decision-Making

Enhancing clinical outcomes for patients on SGLT2 inhibitors requires informed decision-making based on comprehensive risk assessments. Developing guidelines that consider individual patient risks is crucial. For high-risk patients, clinicians might need to consider alternative therapies or lower doses of SGLT2 inhibitors. Implementing evidence-based practices for monitoring and managing these patients is essential. This includes regular screenings for signs of infection, educating patients on recognizing early symptoms of FG, and establishing protocols for prompt intervention if an infection is suspected [4]. Such a proactive approach can significantly reduce the incidence and severity of FG, thereby improving patient outcomes.

Effective patient education is a cornerstone of this strategy. Providing written materials and demonstrating proper hygiene practices during consultations can empower patients. Educating patients on maintaining good hygiene and monitoring for early signs of infection, such as pain, swelling, or unusual discharge in the genital area, enhances adherence to preventive measures and early symptom reporting. Tailoring educational resources to various literacy levels and languages ensures that all patients have access to essential information for managing their condition.

Comparative effectiveness research on different SGLT2 inhibitors provides valuable insights into the efficacy and safety of these medications. This research aids clinicians in making informed decisions about which SGLT2 inhibitors to prescribe, especially for high-risk patients. Studies comparing the incidence of FG among patients using canagliflozin versus dapagliflozin can guide clinical decisions and optimize patient outcomes. These comparative studies highlight the necessity for continuous monitoring and evaluation of new data to refine treatment guidelines. By integrating new research findings regularly, clinical guidelines can remain relevant and effective in addressing current challenges.

Developing decision aids for clinicians and patients can facilitate shared decision-making. These tools present information on the risks and benefits of different SGLT2 inhibitors, helping patients understand their options and participate actively in their treatment plans. Regularly reviewing and updating clinical guidelines ensure that recommendations reflect the latest research findings and clinical experiences. Keeping guidelines current helps maintain the relevance and accuracy of clinical practices, leading to improved patient care and outcomes.

Future Research Directions

To maximize the therapeutic benefits and minimize the potential risks of SGLT2 inhibitors, it is crucial for clinicians to understand their pharmacokinetic and pharmacodynamic properties. This understanding will guide dose adjustments, particularly in patients with renal or hepatic impairments, to avoid adverse effects [53]. Further research into the mechanisms by which dapagliflozin influences infection risk, as well as its long-term impact on fluid and electrolyte balance, is necessary to develop more effective treatment strategies. By integrating the latest clinical evidence and patient-specific factors, the use of dapagliflozin can be optimized for safety and efficacy in managing T2DM.

Current research on the use of SGLT2 inhibitors and their link to severe complications such as FG is still emerging. Identifying gaps in this research is crucial for directing future efforts. One key area requiring further investigation is the differential impact of various SGLT2 inhibitors on microbial ecology and immune responses in the perineal region. In-depth studies on how local bacterial environments and host immune defenses are influenced by the pharmacokinetic and pharmacodynamic properties of drugs like canagliflozin and dapagliflozin are needed. Integrating microbiome analysis into clinical trials could provide deeper insights into drug-microbiome interactions and their implications for infection risk. Patient stratification based on genetic, metabolic, and microbiome profiles could lead to more tailored and effective treatment plans. Such personalized approaches may significantly reduce the incidence of adverse effects while maximizing the therapeutic benefits of SGLT2 inhibitors.

Despite progress, significant gaps remain in understanding the effects of SGLT2 inhibitors. Emerging research questions need to be addressed, such as the precise molecular pathways through which SGLT2 inhibitors modulate immune cell function and tissue integrity. Identifying specific patient subgroups more susceptible to adverse effects and understanding their characteristics is also essential. Interdisciplinary research combining pharmacology, microbiology, immunology, and clinical medicine is needed to develop a comprehensive understanding of these mechanisms. Such collaboration will facilitate the translation of research findings into practical clinical applications.

Guiding future research efforts to enhance patient care and safety involves several strategic recommendations. Long-term cohort studies and clinical trials should monitor the incidence of severe infections, including FG, among patients using different SGLT2 inhibitors. These studies should identify specific risk factors and potential biomarkers for early detection. Exploring novel therapeutic targets and interventions that mitigate the adverse effects of SGLT2 inhibitors while preserving their glucose-lowering benefits is also crucial. This could involve developing combination therapies that include protective agents against infection or tailored dosing regimens to minimize risk.

Development of Safer Therapies

Ensuring the development of safer antidiabetic therapies for vulnerable populations is a priority. This includes exploring alternative therapies or modifications to existing SGLT2 inhibitors to reduce infection risks. Research into new drug formulations or delivery methods that minimize adverse effects, such as localized infections, is critical. Innovations that limit glucose excretion in the urine or enhance local immune defenses could significantly reduce the risk of FG. Such advancements could provide more effective and safer options for managing diabetes, particularly in high-risk patient groups.

Clinical trials are essential to test the safety and efficacy of these alternative treatments. These trials should focus on high-risk populations, such as patients with diabetes and a history of frequent infections, to ensure that new therapies do not introduce unforeseen risks. The development of these therapies should be guided by pharmacokinetic and pharmacodynamic studies, as well as real-world patient data. Prioritizing patient safety and efficacy in clinical trials will allow researchers to develop treatments that offer significant benefits without compromising patient health. For instance, trials might investigate whether modified-release formulations of SGLT2 inhibitors can reduce glucose concentration in the urine, thereby lowering the risk of bacterial overgrowth and subsequent infections. Additionally, research into combination therapies that include protective agents against infection could further optimize the safety profile of these medications. Exploring innovative treatment approaches that combine multiple therapeutic strategies can enhance overall treatment efficacy while minimizing adverse effects.

Developing safer antidiabetic therapies requires a multifaceted approach. By focusing on the pharmacokinetic and pharmacodynamic properties of these drugs and integrating patient-specific factors, healthcare providers can develop more effective and safer treatment strategies for managing T2DM.

This approach will improve patient outcomes and reduce the incidence of severe complications such as FG. Collaborative efforts between researchers, clinicians, and patients are essential to achieve these goals and advance diabetes management. Through continuous innovation and rigorous clinical evaluation, the medical community can enhance the safety and efficacy of diabetes treatments, providing better care for patients worldwide.

Conclusion

The association between SGLT2 inhibitors and FG requires careful consideration in the clinical management of T2DM. This review underscores the complex interplay between pharmacokinetics, pharmacodynamics, immune modulation, and microbial ecology in the development of this severe condition. While canagliflozin and dapagliflozin are effective in controlling blood sugar and offering cardiovascular benefits, they also increase the risk of severe infections due to their impact on glucose metabolism and immune function. The heightened risk, particularly in patients with predisposing factors such as diabetes and immunosuppression, calls for vigilant monitoring and personalized treatment strategies.

Future research should focus on revealing the precise molecular pathways involved, identifying high-risk patient subgroups, and developing novel interventions to mitigate adverse effects like FG while preserving therapeutic benefits. Long-term cohort studies and clinical trials are essential to advancing our understanding and management of the risks associated with SGLT2 inhibitors. Promoting collaboration between basic scientists and clinicians, along with securing funding for interdisciplinary research, will be crucial for translating findings from bench to bedside. Ultimately, optimizing diabetes management strategies to balance efficacy and safety will significantly enhance patient care and outcomes for those treated with SGLT2 inhibitors.

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