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The impact of sodium-glucose cotransporter-2 inhibitors on the incidence, therapy, and outcomes of fournier gangrene: insights from a systematic review of case reports

Yufi Aulia Azmi[1], Firas F. Alkaff[2,3], Kevin Muliawan Soetanto[4], Soetojo Wirjopranoto[5], Maarten J. Postma[1,2,6,7,8†] and Abdul Khairul Rizki Purba[1,2*†]

Abstract

Background The clinical characteristics, therapy, and outcome of Fournier Gangrene (FG) in patients using sodium-glucose cotransporter-2 inhibitors (SGLT2i) were examined in this systematic review.

Methods Without a publication year restriction, we searched PubMed, ScienceDirect, and Cochrane. Additionally, we manually searched bibliographies using the terms "Fournier's gangrene" and "SGLT2 inhibitors." The requirements for inclusion were the English language case reports with specific patient data and FG patients with diabetes who were using SGLT2 medication. The risk of bias was analyzed utilizing the Joanna Briggs Institute checklists.

Results A total of 78 studies were identified, and 14 of them were included in this review. The duration of SGLT2i use varied from 6 months to 6 years. The patients' age varied from 34 to 72 years, with 10 studies including male participants only and patients with obesity. All studies have discontinued SGLT2i and replaced them with other anti-diabetic drugs. Therapy options included perianal ring block, insulin, rigid sigmoidoscopy, aggressive debridement, antibiotics, fluid resuscitation, incision, drainage, surgery, hyperbaric oxygen therapy, plastic surgery, and fasciocutaneous flaps. Seven studies reported patients discharged in the range of 9–51 days.

Conclusions The incidence of FG following SGLT2i use is rare. Therapy was performed by replacing SGLT2i with other anti-diabetic drugs. The patient's outcome improved after treatment.

Keywords Fournier's gangrene, SGLT2 inhibitors, Clinical characteristics, Systematic review

†Maarten J. Postma and Abdul Khairul Rizki Purba contributed equally as the last author.

*Correspondence:
Abdul Khairul Rizki Purba
khairul_purba@fk.unair.ac.id
[1] Department of Health Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Division of Pharmacology and Therapy, Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia
[3] Division of Nephrology, Department of Internal Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[4] Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[5] Department of Urology, Faculty of Medicine Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[6] Institute of Science in Healthy Ageing & Healthcare (SHARE), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[7] Department of Pharmacy, Unit of Pharmacotherapy, Epidemiology and Economics (PTE2), University of Groningen, Groningen, The Netherlands
[8] Department of Economics, Econometrics and Finance, Faculty of Economics & Business, University of Groningen, Groningen, The Netherlands

Background

Fournier Gangrene (FG) is an uncommon serious infection affecting the perineal and genital areas and is characterized by severe complications and a high mortality rate [1]. It exhibits gender disparity, with males being disproportionately afflicted at a ratio of 10:1. The annual prevalence increases to 1.6 cases per 100,000 males, and mortality rates range from 18 to 88%. Immunocompromised individuals with diabetes, obesity, or cancer are more vulnerable to FG [2].

The use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) is associated with the risk of FG, whereas one of the therapies for patients with diabetes is the use of SGLT2i. The European Society of Cardiology guidelines assigned a 1A recommendation for SGLT2i for heart failure patients regardless of diabetes status, which has been incorporated globally [3]. These drugs potentially contribute to glucose accumulation in the urine [4]. A meta-analysis found no risk of FG in patients on SGLT2i therapy, but the sample size was small. This indicates that more data is needed regarding SGLT2i and FG so that more accurate research is needed regarding the possibility of this relationship [5]. A study reported 10 cases showing the time to first therapy, ranging from 1 month to 6 years for the occurrence of adverse reactions. FG caused by SGLT2i, although the incidence is low, can be rapidly progressive and severe [6]. This risk raises a newly identified safety concern in patients on SGLT2i therapy. Prescribing physicians should be aware of the risk of FG and try to detect cases early [7].

The characteristics of FG patients taking SGLT2i are unknown. These characteristics are related to the risk of progression and therapy selection for patients. The association of predisposing factors may have contributed to the development of FG in this case and although the benefits of SGLT2i outweigh the risks, serious adverse events need to be reported [8].

The therapy of choice in patients with SGLT2i and FG cases is still questionable. There are differences in prescribing decisions for this agent, considering the benefits of other therapy [9]. If a patient taking an SGLT2i is suspected of having FG, it is recommended that the drug be immediately stopped and active therapy should be initiated to ensure clinical safety. Patients are advised to start combination therapy with broad-spectrum antibacterial drugs and surgical debridement. If the patient has diabetic ketoacidosis, insulin injections and aggressive fluid resuscitation are also required [6]. There may be differences in decision making that may provide therapy.

Better outcomes are found in multidisciplinary care so that the survival rate of FG continues to increase. However, multiple debridements often cause extensive skin damage. Therefore, clinicians still need to continue to explore better diagnosis, therapy, and care methods for FG [10]. In this systematic case review, we discuss FG's clinical characteristics, management, and outcomes in patients taking SGLT2i. The impact of this paper suggests that certain patient characteristics, such as the history of SGLT2i use and other demographic factors associated with increased risk of FG, should be considered so that prevention can be carried out in the hospital. The selection of suitable therapy can be adjusted, so that it can improve the patient's condition and prevent poor prognosis. In addition, this review explores the management of FG and diabetes following SGLT2i therapy discontinuation. The current condition of the patient after FG occurs causes changes in the therapy that the patient will experience to prevent a poor prognosis.

Methods

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to provide accuracy and reliability in the reporting process [6].

Eligibility

A systematic search for case reports and case series of FG after SGLT2i therapy was performed. FG is defined as a fulminant form of infective necrotizing fasciitis of the perineal, genital, or perianal regions [11]. There was no publication limitation. Only studies with full-text articles and English language were included. Non-human subjects were excluded. All duplicates were removed before screening the titles and abstracts.

Search strategy and selection studies

A systematic search was carried out using the PubMed, Science Direct, and Cochrane databases on June 13, 2023. The search strategy included the keywords "Fournier's gangrene" and "SGLT2 inhibitors." Due to the limited number of studies regarding patients with SGLT2i therapy who experience FG, additional relevant manual searches ('snowballing', i.e. checking reference lists to find additional studies) or 'grey literature', i.e. unpublished studies, were performed. The article titles and abstracts for eligible studies were independently scrutinized for full-text review.

Articles extraction

Relevant articles were independently screened for full-text review and data extraction. The extracted data included author and year of publication, country, age,

gender, drug name, drug initiation, hemoglobin A1C (HbA1C) levels, body mass index (BMI), presenting signs and symptoms, medical history, complications, management, and follow-up results.

Quality assessment

The risk of bias in the selected studies was evaluated independently by three authors using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series [12, 13]. This checklist evaluates the methodological quality of case reports based on specific criteria. The results of the bias assessment are presented as a checklist to indicate the presence or absence of potential bias instead of an accumulated score [12].

Statistical analysis

Because of the rarity of FG cases associated with SGLT2i therapy, the extracted data were analyzed descriptively using quantitative methods. Similar findings, such as clinical presentation, type of SGLT2i, and comorbidities, were grouped to evaluate their frequency.

Results

The search obtained 78 records, two of which were identical. After scrutinizing the titles and abstracts, 67 articles were eliminated, and 14 studies were incorporated into the systematic review following an in-depth examination of the full texts. The PRISMA flow diagram (Fig. 1) illustrates the selection process and the reasons for exclusion.

Quality assessment

All of the selected case reports were evaluated using the JBI checklist for case reports (Table 1). Although there is no definition of how to define the low risk of bias from the JBI checklist manual, the risk of bias in all case reports included in the review can be considered low since all criteria from the JBI checklist were fulfilled in each case report [12].

Study characteristics

This systematic review included 14 case reports (Table 1) [14–27]. The case reports were published between 2016 and 2022. Five cases were reported in America [14, 15,

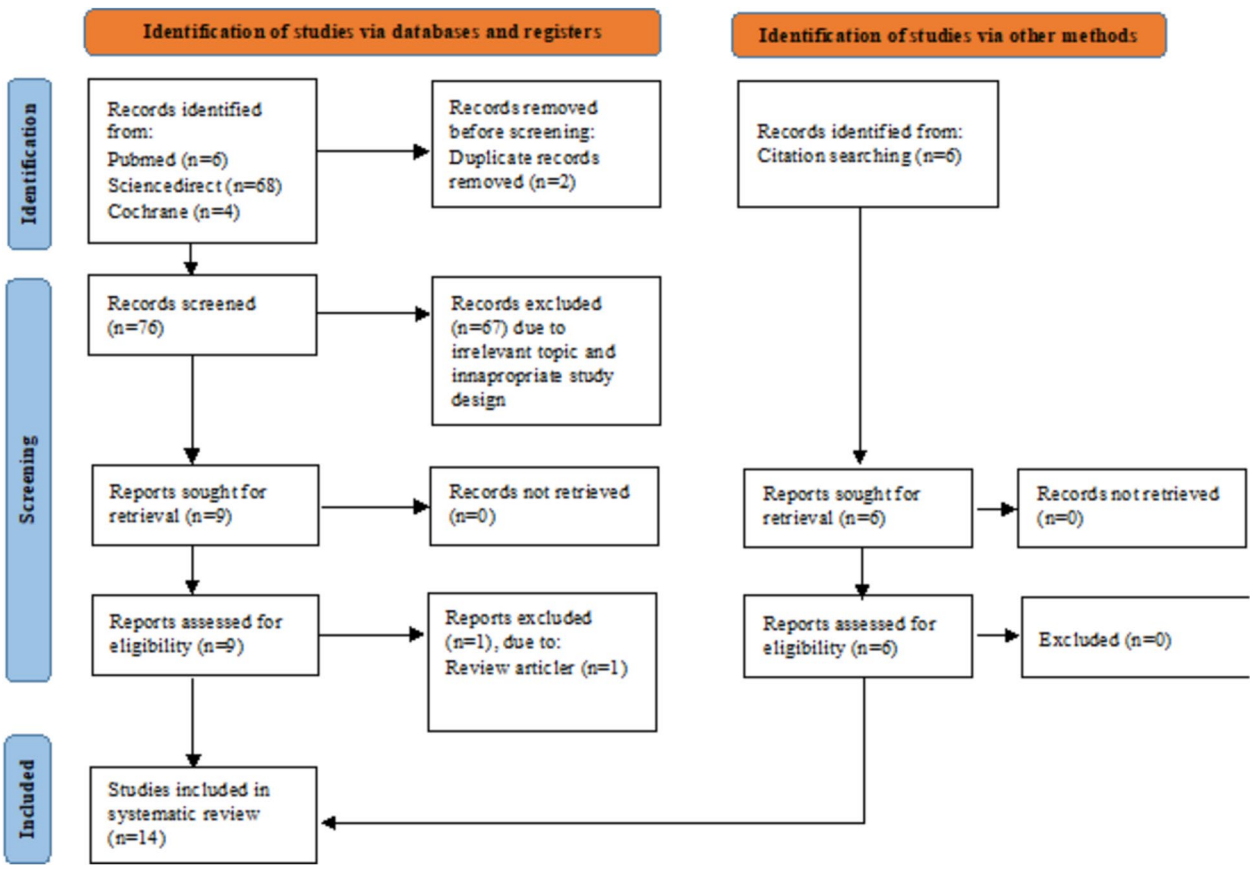

Fig. 1 PRISMA flow diagram

Table 1 Article quality assessment using Joanna Briggs Institute checklist

Author	Were the patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Jahir et al. [14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vargo et al. [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kumar &Costello [16]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Onder et al. [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Elshimy et al. [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Elbeddini et al. [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Elbeddini et al. [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kasbawala & Stamatiades [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ellegardz and Prytz [22]	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Vadi and Ismail [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nagano et al. [24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rodler et al. [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cecilia-Chi & Lim-Tio [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Omer et al. [27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

18–20] and 4 cases in Europe [21, 22, 25, 27], 3 cases in Asia [17, 23, 24], and 2 cases in Australia [16, 26].

Clinical characteristics

Clinical characteristics are presented in Table 2 in Appendix. The age of patients ranged from 34 to 72 years, with a median of 57 years. We found 10 articles describing cases in men; 8 studies reported patients with obesity, with a BMI exceeding 30 kg/m^2; 5 studies reported hypertension; 3 patients were smokers and 1 was a former smoker. Common symptoms include pain, swelling, and redness in the genital area and groin. [14–16, 24]. One study reported painless discomfort for several days. After physical examination, a broad perineal abscess with 5 cm of necrotic tissue is a significant finding. [20]. In 4 cases, the patient may come with a toxic appearance accompanied by a fever. It is important to emphasize that our systematic review included 4 cases with systemic symptoms [14, 22, 25, 27]. Among these symptoms, pain and swelling of the scrotum are the most common complaints. HbA1C level was between 6.50% and 13.20%

History of SGLT2i medication

All cases confirmed the presence of FG and had a history of use of SGLT2i. The duration of SGLT2i therapy varies widely, ranging from 6 months to 6 years. Only 2 studies did not mention the duration of drug consumption [14, 15]. Currently, 3 different drugs in the SGLT2i class have been approved for sale on the market, namely Dapagliflozin, Empagliflozin, and Canagliflozin. The use of Dapagliflozin was reported in 7 cases [15, 17, 20, 22, 25–27], Empagliflozin in 5 cases [15, 16, 18, 23, 24] and Canagliflozin in 2 cases [19, 21]. Three cases used only SGLT2i, and the rest were in combination with other antidiabetic drugs.

Complication

Complications associated with FG indicate sepsis observed in 2 cases. Other cases are peripheral neuropathy, Hashimoto's hypothyroidism, horseshoe abscess and posterior communication of bilateral ischiorectal fossa, diabetic ketoacidosis, delirium, and derailed diabetes mellitus.

Management

Regarding disease management, all studies (14 studies) have discontinued certain SGLT2i and replaced them with other therapies. Two studies reported the resumption of therapy [24, 25], and 2 studies reported permanent discontinuation of SGLT2i therapy [22, 27]. The other 10 cases in their report only indicated drug discontinuation and did not report permanent or reintroduction of the drug. The therapies include aggressive debridement, antibiotics, fluid resuscitation, incisions, drainage, or insulin, rigid sigmoidoscopy, perianal ring block, surgery, hyperbaric oxygen therapy, plastic surgery, and faciocular flap. It should be noted that not all studies included in this review had complications [14, 18–21] (Table 3 in Appendix).

Outcome

The results of the therapy showed improvement. Seven cases reported patients discharged in the range of 9–51 days after receiving antibiotics and glucose control [15–17, 20–24, 26]. Three other cases reported progress in patient stability and wound healing [14]. A total of 4 cases did not report the results of the follow-up cases [18, 19, 25, 27].

Discussion

In this systematic review, we evaluated 14 case reports from various databases without setting a time limit, with details of 10 men and 4 women. Our findings showed that patients with FG caused by SGLT2i were aged between 32 and 72 years; however, it is important to note that there is an increasing risk of FG with increasing age [28]. Furthermore, our results are consistent with existing systematic reviews, which show that men are at higher risk of developing FG compared to women [2]. We identified ten case reports involving males, and a small number involving females. The most common risk factor identified in our systematic review was obesity, which was observed in nine cases. Existing systematic studies also highlight obesity as a significant risk factor, ranking second only to diabetes. Risk factors associated with FG can compromise the immune system, making it difficult to detect and treat infections. This results in bacterial growth and synergistic activity between aerobic and anaerobic bacteria. These molecules contribute to tissue damage and the spread of infection. The combined effects of platelet aggregation caused by aerobic bacteria, complement fixation caused by heparinase, and collagenase produced by anaerobic bacteria can result in microvascular thrombosis and skin necrosis. This may affect the management of FG patients undergoing SGLT2i therapy. Furthermore, impaired phagocytic activity in necrotic tissue may further facilitate the spread of infection [11].

The duration of SGLT2i prescriptions varies significantly, ranging from as little as ten days to as long as six years. In general, studies have shown that the average

duration of SGLT2i use resulting in FG is approximately nine months, although there is considerable variation, with some cases lasting as little as five days and others lasting as long as 49 months [4]. There were 542 cases of FG identified in the FDA Adverse Event Reporting System (FAERS) database in patients receiving SGLT2i. Among all SGLT2 inhibitor therapies, empagliflozin was associated with the highest number of FG reports (232 in total), while empagliflozin plus metformin had the strongest association with FG events. Three new cases of FG caused by ertugliflozin were identified in 2019 [29].

In therapy, the selection of suitable therapy can be adjusted, so that it can improve the patient's condition and prevent sepsis. The use of therapy varies in the handling of FG cases in patients with SGLT2i. Management of FG requires urgent and aggressive intervention, including debridement of necrotic tissue and administration of broad-spectrum antibiotics. The Infectious Disease Society of America recommends empiric antimicrobial therapy that covers aerobic and anaerobic bacteria and includes methicillin-resistant Staphylococcus aureus (MRSA) [30]. Empirical antimicrobial therapy should consist of vancomycin or linezolid for MRSA combined with piperacillin-tazobactam, a carbapenem, or ceftriaxone, and metronidazole for broad-spectrum therapy. For cases of suspected streptococcal species, the use of penicillin combined with clindamycin is recommended [31]. Based on previous studies, sepsis contributed to the highest mortality rate associated with FG, reaching 76% (95% CI 63%–86%), followed by multiple organ failure at 66% (95% CI 37%–87%) [32]. Delayed diagnosis is often an underlying factor in the high mortality rate associated with sepsis [33]. Sepsis is the most common and most fatal complication observed. Sepsis is a possible complication of Fournier's gangrene, a rare but life-threatening infection that can occur in patients taking SGLT2i. If FG is suspected, discontinue the SGLT2i and immediately begin therapy with antibiotics and surgical wound cleansing [34]. Another study found sepsis to also be the most common complication of FG for SGLT2i users [7].

Most cases showed that the wounds healed gradually and improved after 31 days. Another study housed at the FDA identified 55 unique cases of FG in patients receiving SGLT2i between March 1, 2013, and January 31, 2019. All patients underwent surgical debridement and were critically ill. Three patients died [7]. Despite recent improvements in FG therapy, the mortality rate appears to have remained unchanged at 20% to 30%, according to earlier research. The prognosis is directly correlated with the time it takes to detect FG and the amount of time that passes before surgical debridement [10].

The association of predisposing factors may have contributed to the development of FG in this case, and although the benefits of SGLT2i outweigh the risks, serious adverse events need to be reported voluntarily to promptly intervene, verify association, and minimize the risk of bias [8]. With multidisciplinary cooperation and the improvement of medical level and postoperative nursing levels, the survival rate of FG continues to increase. However, multiple debridements often cause large-area skin damage, therefore, clinicians still need to continue to explore better diagnosis, therapy, and care methods for FG. Multidisciplinary collaborative diagnosis and therapy are essential in the management of FG [10]. Artificial intelligence systems are gaining significant attention in the healthcare domain as they have a significant impact. Artificial intelligence systems can improve healthcare institutions and help doctors make informed decisions [35].

Limitation

The findings from this systematic review cannot be generalized because it is a case report. This systematic review was limited in scope as it primarily focused on case reports with a small sample size without any randomized controlled trials. The inclusion of only a few cases may be attributed to the rarity of the disease, thus preventing us from conducting formal statistical analyses. Diabetes is not the only condition that makes FG worse.

Conclusion

The incidence of FG following SGLT2i use is rare. Therapy was performed by replacing SGLT2i with other anti-diabetic drugs. The patient's outcome improved after treatment. Most cases show that the wound heals gradually and improves after 31 days. Sepsis is the most common and fatal complication ever observed. Future studies with larger sample sizes must clarify the relationship between SGLT2i and FG in diabetes patients. This can be achieved by conducting large-scale multicenter pharmacovigilance studies, with participating centers in developed and developing countries. Additionally, the severity of FG and its impact (i.e. mortality) should also be assessed to gain more insight into the magnitude of the FG burden after SGLT2i.

Appendix

Table 2 Demographics, HbA1C, BMI, and comorbidities of patients in the included studies

Author	Year of publication	Country	Age	Gender	HbA1C	BMI	Comorbidities of significant medical history
Jahir et al. [14]	2022	USA	58 years	Female	7.30%	48.3	Obesity, Hypertension, Kidney Failure, Hypoalbuminemia
Vargo et al. [15]	2021	USA	64 years	Male	NA	N/A	Atrial fibrillation, CAD, Post-aortic valve replacement
Kumar &Costello [16]	2017	Australia	41 years	Male	11.50%	38	Obesity, Smoker
Onder et al. [17]	2019	Turkey	64 years	Male	7.40%	33	Obesity, Ex-smoker
Elshimy et al. [18]	2019	USA	54 years	Male	N/A	62.76	Obesity
Elbeddini et al. [19]	2019	Canada	72 years	Male	7.50%	N/A	Prostate cancer, Hemorrhoids
Elbeddini et al. [20]	2020	Canada	71 years	Female	11.70%	N/A	Hypertension, Kidney Failure, Obesity
Kasbawala & Stamatiades [21]	2019	Netherlands	37 years	Female	9.80%	45.8	Obesity, GERD, Depression, Intellectual Disability
Ellegardz and Prytz [22]	2020	Sweden	52 years	Female	NA	42	Obesity, Hypertension, Asthma, Hepatitis B, Smoking, Thyroid cancer
Vadi and Ismail [23]	2020	India	56 years	Male	13.20%	N/A	Hypertension, CAD
Nagano et al. [24]	2019	Japan	34 years	Male	6.50%	28	None
Rodler et al. [25]	2019	Germany	39 years	Male	10%	49	Smoker, Obesity
Cecilia-Chi & Lim-Tio [26]	2016	Australia	67 years	Male	10.80%	N/A	Obesity
Omer et al. [27]	2018	UK	60 years	Male	9.1%	N/A	Dyslipidemia, Obesity, Hypertension

Table 3 Drug use, drug initiation, presenting signs and symptoms, complications, management, and follow-up results

Author	SGLT inhibitors and other drugs	Drug initiation	Sign and symptoms	Complications	Management	Follow-up results
Jahir et al. [14]	Empagliflozin	NA	Severe pain, redness, and swelling in the right upper thigh and perineum for the past week. A review of the system was remarkable for a severely tender, indurated, erythematous, possible abscess-like lesion in the right upper thigh and pelvis, which was associated with fever and chills. Patient appeared toxic, with significantly tender, warm, erythematous, indurated crepitation on the perineum and area on the medial aspect of the right thigh with mild malodorous vaginal discharge	Septic	1. Intravenous fluid according to sepsis protocol (30 ml/kg) 2. Broadspectrum antibiotics, including vancomycin, meropenem, and clindamycin 3. Emergency exploration surgery with washout and application of a vacuum dressing in the right thigh 4. Empagliflozin was discontinued and started on a basal-bolus insulin regimen	In 3 days the total WBC count downtrend from 11.3
Vargo et al. [15]	Dapaglifozin, metformin	NA	Enlarging, painful left hemiscrotum over the previous few years. Physical examination was consistent with a large left hydrocele and scrotal ultrasound confirmed the diagnosis	None	1. Hydrolectomy 2. SGLT2 inhibitors were stopped	The patient was discharged from the hospital on postoperative day nine on intravenous antibiotics, and he ultimately underwent complex scrotoplasty two months after discharge
Kumar &Costello [16]	Empaglifozin, Metformin	14 months	Scrotal Pain and Swelling. Grossly swollen and indurated scrotum with tender spermatic cord, epididymis, and testicles. Bilateral inguinal lymphadenopathy	N/A	1. Discontinued empaglifozin and smoking 2. Basal-bolus insulin regimen 3. Exploration, washout, and application of a vacuum dressing 4. Sin grafting to his perineum 5. Initial antibiotic management included intravenous amoxicillin, gentamicin, and vancomycin which was changed to intravenous meropenem for a total 14-day course	Discharged after day 15 on oral antibiotics

Author	SGLT inhibitors and other drugs	Drug initiation	Sign and symptoms	Complications	Management	Follow-up results
Onder et al. [17]	Dapaglifozin, premixed insulin twice a day, vildagliptin, and metformin	6 Months	Scrotal pain, swelling, and redness that had progressed over a period of 3 days	N/A	1. Discontinued dapagliflozin, 2. Started basal-bolus insulin regimen, debridement 3. Empirical intravenous antibiotics (ceftriaxone 1 g, twice a day, and metronidazole 500 mg, three times a day), 4. Plastic surgery for reconstruction of defective tissues and a fasciocutaneous flap to cover the perianal scrotal and penile regions	Discharged after 4 weeks course of intravenous antibiotics
Elshimy et al. [18]	Empagliflozin, glipizide, metformin, linagliptin	10 days	Perineal examination revealed a grossly swollen and indurated right scrotum with tender spermatic cord, epididymis, and testicles	Peripheral neuropathy, Hashimoto's hypothyroidism	Stopped all oral medications in the hospital and two surgical interventions with hyperbaric oxygen therapy	N/A
Elbeddini et al. [19]	Canafligozin	Six years	Rectal pain. The patient presented to the ED for the third time 2 days after his previous visit with abdominal pain rated 8/10 and significant nausea. He reported explosive diarrhea which persisted throughout the first 5 days of his admission	Horseshoe abscess and posterior communication of bilateral ischiorectal fossa	1. Aggressive debridement 2. Intravenous antibiotic 3. Oral antibiotics, 4. Discontinued canagliflozin 5. Home medications: metformin, sitagliptin, and insulin glargine	N/A
Elbeddini et al. [20]	Dapagliflozin, glimepiride, and linagliptin	Five years taking dapagliflozin	Patient came to the hospital after a fall in the bathroom, patient didn't feel pain but just discomfort for a few days. There was an extensive abscess was observed in the perianal area with 5 cm of necrotic tissue and foul-smelling discharge	N/A	1. Intravenous antibiotic using vancomycin, intravenous piperacillin–tazobactam, and intravenous clindamycin 2. Patient got debridement, rigid sigmoidoscopy, and perianal ring block 3. Insulin glargine 10 U with breakfast then insulin aspart three times daily on a low–moderate sliding scale 4. Dapagliflozin was discontinued	After 14 days of hospitalization, the patient was discharged with controlled blood glucose under insulin administration and a clean and odorless wound
Kasbawala & Stamatiades [21]	Canaglifozin, metformin, and sitagliptin	One month	After 1 month she complained of pain in the left gluteal region associated with dysuria and therapy with trimethoprim/sulfamethoxazole for a presumed urinary tract infection was initiated	Diabetic Ketoacidosis	1. Fluid resuscitation with initial bolus normal saline 0.9% 2. Intravenous empirically of antibiotic 3. IV clindamycin, and vancomycin, debridement 4. Incision and drainage 5. DKA was treated with only subcutaneous insulin 6. Patient using insulin glargine 18 U and discontinued canagliflozin and sitagliptin-metformin	On 28 days the patient was DKA resolved and medically stable condition with a urinary catheter, vacuum dressing, and colonostomy in place at a short-term rehabilitation facility
Ellegardz and Prytz [22]	Dapaglifozin, insulin	1.5 years using dapaglifozin	Three days of fever and increased swelling and pain in the gluteal region. An abscess, the size of a tennis ball, 5 cm from the anus on the left side of the gluteal region. It was indurated, inflamed, and warm with pus discharge from a minor opening. The right side of the gluteal region was unaffected	NA	1. Intravenous fluid 2. Broadspectrum antibiotics (4 g piperacillin with 0.5 g tazobactam) 3. Intravenous cortisone were rapidly initiated 4. The patient underwent surgical exploration three times 5. Dapaglifozin was discontinued permanently	The patient was discharged on day 18. Two months later, the healing process was still ongoing, and the wound was tended to by home health care daily. Five months later, the wounds were fully healed with new skin covering the area
Vadi and Ismail [23]	Empaglifozin, Vildagliptin	2 years	Testicular swelling and localized pain for 10 days. There was discoloration and edema of the external genitalia	NA	1. Intravenous antibiotics (meropenem), 2. Intravenous fluids, short-acting insulin, 3. Surgical debridement 4. Empagliflozin and vildagliptin were discontinued	The wound had healed well with blood glucose levels under control
Nagano et al. [24]	Empaglifozin, glibenclamide, sitagliptine	5 months	Pain and swelling in the perineum. Skin redness, induration, swelling, and tenderness were observed in the perineum, scrotum, and left inguinal region	None	1. Surgical incision, debridement 2. Postoperatively, the medications for T2DM were discontinued 3. Drainage. Intravenous antibiotics (meropenem and clindamycin which was changed to vancomycin after MRSA was cultured) 4. Sitagliptin restarted 9 days after surgery 5. Metformin started 21 days after surgery 6. Insulin initiated according to a sliding scale	The patient's wounds healed gradually. He was discharged from the hospital 41 days after surgery and continued his therapy for T2DM

Author	SGLT inhibitors and other drugs	Drug initiation	Sign and symptoms	Complications	Management	Follow-up results
Rodler et al. [25]	Dapaglifozin, Metformin, Sitagliptin	4 years	Fever (1 week), swelling, and pain in groin and testicles with pus discharge. Swelling in the right groin, intense smell	delirium and derailed diabetes mellitus	1. Removal of necrotic tissue and further debridement procedures 2. Intravenous antimicrobials (gentamicin and piperacillin–tazobactam) started in ED was changed to linezolid, meropenem, and nystatin; 3. Linezolid stopped and meropenem and nystatin changed to fluconazole) 4. Dapagliflozin discontinued 5. Basal-bolus insulin from admission to day 19 6. Metformin and sitagliptin restarted on day 23 of admission	NA
Cecilia-Chi & Lim-Tio [26]	Dapagliflozin	3 weeks	5 days of increasing scrotal pain and swelling. Scrotal swelling, tenderness, and erythema tracking down the perineum	NA	1. Surgical debridement and broadspectrum antibiotics 2. Dapagliflozin was ceased and basal-bolus insulin commenced	Discharged after 51 hospital days
Omer et al. [27]	Dapaglifozine, Metformin, Glicazide, insulin, exanetide, and pioglitazone	2 years	Painful and red between his scrotum and anus. High-grade fever and fatigue	Septic	1. Intravenous flucloxacillin, ciprofloxacin and metronidazole 2. Debridement 3. Dapagliflozin was withheld and not restarted	NA

Abbreviations

BMI	Body Mass Index
FG	Fournier Gangrene
JBI	Joanna Briggs Institute
MRSA	Methicillin-Resistant Staphylococcus aureus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
SGLT2i	Sodium-Glucose Cotransporter-2 inhibitors
UTI	Urinary Tract Infection

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Authors' contributions
Yufi A Azmi: Project development, data collection, manuscript writing. Firas F Alkaff: Data analysis, manuscript writing. Soetojo Wirjopranoto: Data collection, manuscript editing. Kevin Muliawan Soetanto: Data analysis, manuscript editing. Maarten J Postma: Project development, manuscript editing. AKR Purba: Project development, manuscript editing.

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Data availability
All data generated or analyzed during this study are included in this published. article (and its supplementary information files).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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