ORIGINAL RESEARCH

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Fournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors

A Review of Spontaneous Postmarketing Cases

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Background: Use of sodium–glucose cotransporter-2 (SGLT2) inhibitors has been associated with Fournier gangrene (FG), a rare urologic emergency characterized by necrotizing infection of the external genitalia, perineum, and perianal region.

Objective: To describe and compare reported cases of FG in diabetic adults receiving treatment with SGLT2 inhibitors or other antiglycemic agents.

Design: Descriptive case series.

Setting: U.S. Food and Drug Administration (FDA) Adverse Event Reporting System and published case reports.

Patients: Adults receiving SGLT2 inhibitors or other antiglycemic agents.

Measurements: Clinical and laboratory data.

Results: The FDA identified 55 unique cases of FG in patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019. The patients ranged in age from 33 to 87 years; 39 were men, and 16 were women. Time to onset after initiation of SGLT2-inhibitor therapy ranged from 5 days to 49 months. All patients had surgical debridement and were severely ill. Reported complications included diabetic ketoacidosis (n = 8), sepsis or septic shock (n = 9), and acute kidney injury (n = 4). Eight patients had fecal diversion surgery, 2 patients developed necrotizing fasciitis of a lower extremity that required amputation, and 1 patient required a lower-extremity bypass procedure because of gangrenous toes. Three patients died. For comparison, the FDA identified 19 FG cases associated with other antiglycemic agents between 1984 and 31 January 2019: metformin (n = 8), insulin glargine (n = 6), short-acting insulin (n = 2), sitagliptin plus metformin (n = 2), and dulaglutide (n = 1). These patients ranged in age from 42 to 79 years; 12 were men, and 7 were women. Two patients died.

Limitation: Inability to establish causality or incidence, variable quality of reports, possible underreporting, and confounding by indication.

Conclusion: FG is a newly identified safety concern in patients receiving SGLT2 inhibitors. Physicians prescribing these agents should be aware of this possible complication and have a high index of suspicion to recognize it in its early stages.

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Fournier gangrene (FG) was named for Jean Alfred Fournier, a French dermatologist and venereologist who, in 1883, described a perineal disease of acute onset and rapid progression in previously healthy young men (1). This condition, also known as necrotizing fasciitis of the perineum, is a urologic emergency. It is characterized by a rapidly progressive necrotizing infection of the external genitalia, perineum, and perianal region requiring broad-spectrum antibiotics and immediate surgical intervention. Although the initial description from the 1800s described FG as idiopathic and occurring in males, knowledge surrounding this disease has evolved. More recent publications have reported FG in both men and women, as well as a cause for 75% to 95% of cases, including cutaneous, anorectal, and urogenital infections (2, 3).

Reported risk factors include alcoholism, HIV infection, and use of cytotoxic drugs (4, 5). Diabetes is a comorbid condition in 32% to 66% of cases (5, 6). Although many of the associated comorbid risk factors are common diseases, FG is rare, with an overall incidence of 1.6 in 100 000 males and a peak incidence of 3.3 in 100 000 men aged 50 to 79 years (7). Moreover, fewer than 0.02% hospitalizations are for FG. Why FG develops in only a small minority of patients with comorbid risk factors is not understood.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors improve glycemic control by inhibiting reabsorption of filtered glucose in the proximal tubules of the kidney, which increases urinary glucose excretion (8). Moreover, the U.S. Food and Drug Administration (FDA) approved 2 SGLT2 inhibitors (empagliflozin and canagliflozin) to reduce the risk for major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. The most common adverse reactions identified with SGLT2 inhibitors in clinical trials were genital mycotic and urinary tract infections (9–12). Urosepsis, pyelonephritis, ketoacidosis, and acute kidney injury also were identified as adverse events after these agents were approved. In addition, the FDA issued warnings that canagliflozin is associated with an increased risk for lower-limb amputation (9, 13, 14) and that the SGLT2 inhibitor class is associated with FG (15).

The purpose of this review is to describe and compare reported cases of FG in diabetic adults receiving SGLT2 inhibitors versus other antiglycemic agents.

Methods

The FDA Adverse Event Reporting System (FAERS) database contains reports of adverse drug events vol-

untarily submitted by health care providers, patients, drug manufacturers, and others (16, 17). To identify FG cases reported in patients receiving SGLT2 inhibitors, we searched FAERS using the following preferred terms from Medical Dictionary for Regulatory Activities (MedDRA), version 20.1: *necrotizing fasciitis, necrotizing fasciitis fungal, necrotizing fasciitis staphylococcal, necrotizing fasciitis streptococcal, necrotizing soft tissue infection, fasciitis, fascial infection, perineal abscess, perineal necrosis, perineal infection, perineal cellulitis, perineal operation, scrotal abscess, scrotal gangrene, vulval abscess, and vulval cellulitis*. The term *Fournier's gangrene* was previously a MedDRA lower-level term under the preferred term *necrotizing fasciitis*; however, it recently was upgraded to a preferred term in MedDRA, version 21.1.

We included all reports of FG submitted to FAERS between 1 March 2013 (the date of U.S. canagliflozin approval) and 31 January 2019 in which the patient was receiving an FDA-approved SGLT2 inhibitor at the time of the FG diagnosis and the following criteria were met: The patient had a necrotizing infection of the perineum (vulva/vagina or scrotum or buttocks) and surgical debridement in response to the infection. Reports were excluded if they did not specifically mention whether the perineal infection was necrotizing or if no surgical intervention occurred. Duplicate reports, reports with insufficient information, and reports with an alternative cause of FG also were excluded.

We searched the databases of PubMed, Google Scholar, EMBASE (Elsevier), and EBSCOhost (EBSCO Information Services) from 1 March 2013 to 31 January 2019 to identify case series, case reports, and epidemiologic studies reporting on FG and SGLT2-inhibitor therapy. Search terms included *SGLT2 inhibitor with necrotizing fasciitis*, *genital infection*, and *Fournier's gangrene*.

To identify cases of FG in diabetic patients receiving agents other than SGLT2 inhibitors, we searched FAERS and the literature between 1984 (the year of U.S. glipizide approval) and 2019. We used the same criteria and terms from the SGLT2 inhibitor search to identify reports of FG with other standard-of-care antiglycemic agents across several drug classes: short- and long-acting insulins, sulfonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists.

Statistical Analysis

Cases were compiled in Excel, version 14 (Microsoft), to produce descriptive (aggregate) attributes of the case series. No tests of statistical significance were planned or performed.

Role of the Funding Source

This study was not funded.

RESULTS

The FAERS search for FG with SGLT2 inhibitors retrieved 183 reports. Of these, 128 were excluded for 1 or more of the following reasons: duplicate report (n = 21); case did not meet the case definition (n = 8); perineal infection (abscess or cellulitis) without documented necrotizing fasciitis (n = 21); FG mentioned in the case narrative without documentation of surgery (n = 41); necrotizing fasciitis, site not specified (n = 13); necrotizing fasciitis of perineum with sepsis but without documentation of surgery (n = 1); nonnecrotizing fasciitis (n = 1); and necrotizing fasciitis elsewhere on the body (n = 22). In total, 55 cases meeting the inclusion criteria were found in FAERS. The medical literature searches identified 4 case reports, all of which had been reported to FAERS (18–21).

The **Table** shows the characteristics of the 55 cases of FG in patients receiving SGLT2 inhibitors. They were a median age of 56 years (range, 33 to 87 years); 39 were men, and 16 were women. Forty-one cases occurred in the United States. The average time to event from initiation of SGLT2-inhibitor therapy was 9 months (range, 5 days to 49 months). Cases involved every drug in the SGLT2 inhibitor class marketed in the United States except ertugliflozin. At least 31 patients were receiving another antiglycemic agent in addition to the SGLT2 inhibitor. In 3 cases, the SGLT2 inhibitor was the only antiglycemic drug used; for 21 cases, concurrent medications were not reported.

All patients were severely ill with FG and were hospitalized. As required by our case definition, they all had surgical debridement. Although the number of surgeries was not consistently reported, at least 25 patients needed more than 1 procedure, including 1 patient with a reported 17 trips to the operating room. Eight patients underwent a procedure for fecal diversion; at least 4 patients had skin grafting.

The clinical course for some patients was complicated by diabetic ketoacidosis (n = 8), sepsis or septic shock (n = 9), or acute kidney injury (n = 4); some patients may have had more than 1 complication. Necrotizing fasciitis of a lower extremity developed in 2 patients during their hospitalization for FG and required amputation. Another patient required a lower-extremity bypass procedure for gangrenous toes. Three patients died. Duration of acute hospitalization for the surviving patients ranged from 5 to 51 days. The SGLT2 inhibitor was discontinued in at least 22 of the 52 surviving patients.

The FAERS search for FG with other standard antiglycemic drug classes reported between 1984 (the year of U.S. glipizide approval) and 31 January 2019 retrieved 97 reports. Of these, 75 were excluded for 1 or more of the following reasons: duplicate report (n = 29); necrotizing fasciitis elsewhere on the body (n = 18); genital or perineal infection (abscess or cellulitis) without documented necrotizing fasciitis (n = 10); FG mentioned in the case narrative without documentation of surgery (n = 8); necrotizing fasciitis, site not specified (n = 5); nonnecrotizing fasciitis (n = 4); and osteonecrosis of the jaw (n = 1). Twenty-two cases met the case definition for FG; in 3 of these cases, patients also were receiving an SGLT2 inhibitor and were included in the SGLT2 inhibitor case series. The remaining 19 FG cases reported during the 35-year period were associated

Table. Characteristics of Cases of Fournier Gangrene in Patients Receiving an SGLT2 Inhibitor, From FAERS, 1 March 2013 to 31 January 2019 (*n* = 55)*

Characteristic	Value
Diabetes type	
Type 2 diabetes mellitus	22
Not specified	8
Not reported	25
SGLT2 inhibitor	
Canagliflozin	21
Dapagliflozin	16
Empagliflozin	18
Concurrent antiglycemics†	
Biguanides	20
Insulins	13
Sulfonylureas	8
Glucagon-like peptide-1 agonists	5
Thiazolidinediones	4
Dipeptidyl peptidase-4 inhibitors	1
α-Glucosidase	1
None	3
Not reported	21
Time to onset‡	
Median	4.5 mo
Range	5 d–49 mo
SGLT2 inhibitor discontinued	
Yes	22
No	1
Not reported	29
Serious outcome§	
Hospitalization (initial or prolonged)‖	53
Life-threatening	23
Disability	5
Death¶	3
Complications†	
Diabetic ketoacidosis	8
Acute kidney injury	4
Sepsis, septic shock	9
Admission to intensive care unit	10
Fecal diversion	8
Lower-extremity amputation	2
Lower-extremity bypass for gangrenous toes	1
Myocardial infarction	1
Potential precipitating factors†**	
Urinary tract infection	2
Perineal hygiene difficulty	1
Recurrent genital fungal infection (self-treated)	1
Colostomy reversal (5 mo prior)	1
Concurrent colon cancer diagnosis	1

FAERS = U.S. Food and Drug Administration Adverse Event Reporting System; SGLT2 = sodium–glucose cotransporter-2.
* Values are numbers of cases unless otherwise noted.
† A case may report >1 antiglycemic, complication, or precipitating factor.
‡ Reported for 28 cases.
§ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), and disability; cases may report >1 regulatory outcome. A report may be coded with >1 serious outcome.
‖ Two cases were not coded with hospitalization, but hospitalization was reported in the narrative.
¶ Not reported as a regulatory outcome but was reported in the case narrative.
** Reported for 6 cases.

with the following antiglycemic agents: metformin (*n* = 8), insulin glargine (*n* = 6), short-acting insulin (*n* = 2), sitagliptin plus metformin (*n* = 2), and dulaglutide (*n* = 1). These 19 cases occurred in 12 men and 7 women, with ages ranging from 42 to 79 years. Seventeen patients were hospitalized, and 2 died. Fourteen cases occurred in the United States and 5 in other countries (Mexico, *n* = 2; Argentina, *n* = 1; Great Britain, *n* = 1; and Japan, *n* = 1). Searches of the medical literature identified no published cases that specifically associated other antiglycemic agents with FG.

DISCUSSION

We identified 55 FG cases among patients receiving SGLT2 inhibitors during the 6 years since canagliflozin received U.S. marketing approval in March 2013. Cases of FG were reported with all FDA-approved SGLT2 inhibitors except ertugliflozin; the absence of cases with ertugliflozin may be the result of its limited time on the market (U.S. approval, December 2017) (12). We found only 19 FG cases in 35 years among patients receiving other classes of antiglycemic agents. If FG were associated only with diabetes mellitus and not SGLT2 inhibitors, we would expect far more cases reported with the other antiglycemic agents, considering the 35-year timeframe and the large number of agents.

Data from this analysis include information provided in the 2018 FDA warning regarding FG and SGLT2 inhibitors (15). Since the warning was published, additional reports of FG in patients using SGLT2 inhibitors, as well as other antiglycemic agents, have been submitted to the FDA. This influx of reports may have been prompted by growing awareness of the safety issue (22). The upsurge in FG reports also might represent a rising incidence of this disorder in diabetic patients due to the overall increased prevalence of diabetes (23), combined with the use of SGLT2 inhibitors. In addition, confounding by indication is possible, because SGLT2 inhibitors may be used more often than comparator diabetes drugs for patients with hypertension and cardiovascular disease.

Previous studies describing FG implicated diabetes as a major risk factor (5, 6). Although diabetes is common (24), FG is very rare, with an overall incidence of 1.6 in 100 000 males and a peak incidence of 3.3 in 100 000 men aged 50 to 79 years (7). Why FG develops in only a small minority of patients with diabetes is not understood. Because organisms must somehow enter host tissue, one element in FG's development may be an inciting event. Postcoital trauma, urinary tract infection, genital piercing, prosthetic penile implant, and rectal foreign body all have been implicated as precipitating factors (25). Still, most patients with diabetes have sexual intercourse or may have a urinary tract infection at some point, yet very few ever develop FG. Thus, even with a known risk factor and an inciting event, FG remains rare, accounting for less than 0.02% of annual hospitalizations in the United States (7).

To support the hypothesis that we had identified a true FG safety signal with SGLT2 inhibitors, rather than cases of FG in patients with diabetes, we considered examining epidemiologic databases to compare risk for FG according to antiglycemic agent. Preliminary analysis, however, showed that the very small number of FG cases with both SGLT2 inhibitors and comparators would furnish insufficient data to provide meaningful statistical comparisons. We also considered comparing FG reporting rates or ratios. These measures may be useful in generating hypotheses of potential safety issues; however, in the case of FG, the number of cases again was too small for a meaningful comparison.

We noted wide variability in time to FG from initiation of SGLT2-inhibitor therapy (5 days to 49 months). Variation in time to diagnosis might be explained by fluctuating glycemic control, microvascular complications, or an inciting event associated with SGLT2 inhibitors (such as urinary tract infection, mycotic infection, or skin or mucosal breakdown due to pruritus [9–12]). Some of these events may not occur immediately after therapy begins or may be unpredictable. For example, 1 patient with a 7-day latency was diagnosed with a urinary tract infection—a potential inciting event early in SGLT2-inhibitor treatment. Glycosuria is expected with such treatment and is associated with an increased risk for urinary tract and urogenital infections (26, 27). In addition, because the perineum already is colonized with organisms from the gastrointestinal tract, the enriched environment provided by glycosuria-enhanced growth of urogenital flora may provide the ideal milieu for FG. Although urinary tract infection is a known risk factor for FG, only 2 reports in our case series specifically mention it in patients in whom FG ultimately developed. Whether urinary tract infection was an important inciting event in the remaining cases is unclear, and the true mechanism by which SGLT2 inhibitors create the ideal environment for FG is not known.

Microvascular complications, which may take longer to develop, might explain the longer time to onset in some patients. The endothelial damage and microthrombosis that occur in the small subcutaneous arterioles of patients with FG are similar in some ways to the endothelial dysfunction that manifests in patients with diabetes and contribute to microvascular complications, such as limb amputations. Although limb amputations in patients with type 2 diabetes mellitus have been decreasing considerably during the past few decades (28), a higher incidence of lower-limb amputations in patients receiving canagliflozin was reported from clinical trials of diabetic patients with a history of cardiovascular disease (29, 30). In our case series, while hospitalized 2 patients with FG required amputation of a lower extremity and a third had lower-extremity bypass because of gangrenous toes. The precise mechanism for these findings is not known, and whether these observations are the result of a shared underlying mechanism also is unknown (28, 30, 31).

Length of hospitalization for acute inpatient care ranged from 5 to 51 days. Disposition at discharge was mentioned for only 6 patients, all of whom required continued care in a rehabilitation facility. Because of the limitations typical of spontaneous postmarket reports (32), follow-up information after the time of reporting usually is not available. However, we suspect that almost no patient could return home immediately and that total inpatient time was much longer. Disfigurement and morbidity associated with surgical debridement of the perineum, which in some cases was extensive, should not be underestimated. All patients probably required subacute rehabilitation and possibly additional surgical intervention with skin grafting, colostomy reversal, or other therapy. In an article assessing quality of life in patients who survived FG, the authors reported that physical and psychological problems persisted long after the initial hospitalizations and that patients' overall quality of life was diminished (33).

This work has several weaknesses and strengths. Data in FAERS are acquired through spontaneous reporting from health care providers and patients. The information cannot establish incidence and is limited by underreporting of events and variable quality of reported data. In addition to the cases included in our series, we found 41 unique FAERS reports that mentioned FG in the case narrative. Because FG is a specialized diagnosis, its specific mention is likely to indicate true disease. However, these 41 reports lacked a documented surgical procedure (as was required by our case definition) and were excluded from our case series. We suspect that our numbers underestimate the true burden of FG with SGLT2 inhibitors. Another possibility is that health care providers may have considered FG to be an event related to a disease (such as diabetes) rather than to a drug. Of importance, in the absence of a control group, causality cannot be established and such issues as confounding by indication cannot be excluded. Despite these weaknesses, in the postmarket setting, spontaneous reporting may be the only way to learn about very rare drug-related adverse events.

Mortality among diabetic patients with FG is higher than among those with other comorbid conditions (36% vs. 0% in 1 published series) (34). The single most important factor in preventing death in patients with diabetes is early recognition and surgical intervention (7, 33, 34), with tissue sampling for culture (35). In the event of sepsis, blood cultures also should be obtained with the goal of definitively identifying a microbe. Health care providers who prescribe SGLT2 inhibitors to their patients with diabetes should be alerted to and educated about the signs and symptoms of FG, given the substantial morbidity and mortality associated with this life-threatening and potentially devastating disease. Six patients in our series had more than 1 encounter with a provider before receiving a diagnosis of FG, indicating that the provider may not have recognized the diagnosis because of its nonspecific symptoms. Systemic symptoms, such as fatigue, fever, and malaise, may be variable and nonspecific. Local symptoms may include tenderness, erythema, and swelling.

Pain that seems out of proportion to findings on physical examination is a strong clinical indicator of necrotizing fasciitis (36–38) and may be the most important diagnostic clue. A high index of suspicion therefore is necessary to identify FG in its early stages to prevent or minimize the potential for both morbidity and mortality in patients using SGLT2 inhibitors.

Permanent disfigurement, prolonged hospitalization, disability, and complications from sepsis all may be seen in patients with FG. In our case series, all patients were hospitalized, some required several surgeries, some had complications, and 3 died. Serious complications and death are likely if FG is not recognized immediately and surgical intervention is not carried out within the first few hours of diagnosis. Awareness of the association between FG and SGLT2 inhibitor use may be an important factor in an informed prescriber–patient discussion regarding appropriate diabetes therapy. Although the risk for FG is low, serious infection should be considered and weighed against the benefits of SGLT2-inhibitor therapy.

From U.S. Food and Drug Administration, Silver Spring, Maryland (S.J.B., C.C., C.C., C.K., W.H.C.)

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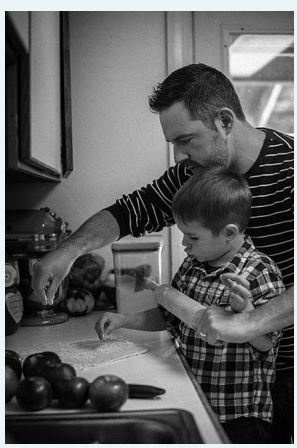
***ANNALS* PERSONAE PRIZE**

Congratulations to Kristen Renneker, winner of the 2018 *Annals* Personae prize. Ms. Renneker's photograph was published on the cover of the 6 February 2018 issue (vol. 168, no. 3) and is reprinted below.



For more information on the *Annals* Personae prize and to view a list of past winners, go to www.annals.org/aim/pages/personae-photography.

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