

Bittersweet: Fournier's Gangrene and SGLT2 Inhibitors

Coralea Kappel^{1,2}, Jean-Michel Guay³

¹Department of Medicine, McMaster University, Hamilton, Ontario, Canada

²Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

³Department of Medicine, The Montfort Hospital, University of Ottawa, Ontario, Canada

ABSTRACT

Type 2 diabetes mellitus is a chronic metabolic disorder associated with a high risk of adverse outcomes, notably cardiovascular disease, with an increased risk of death. There is a growing armamentarium of therapies with Health Canada approved cardiovascular benefit, including two from the sodium-glucose co-transporter 2 (SGLT2) inhibitors class, namely canagliflozin and empagliflozin. Despite their many advantages, the Food and Drug Administration (FDA) issued a black box warning for associated necrotizing fasciitis of the perineum in diabetes treated with SGLT2 inhibitors. This case report highlights a case of Fournier's gangrene (FG) in a male with type 2 diabetes treated with empagliflozin.

RÉSUMÉ

Le diabète du type 2 est une maladie métabolique chronique associée avec nombreuses atteintes défavorables, notamment les maladies cardiovasculaires avec un risque accru de mortalité. Il existe nombreuses thérapies offrant des avantages cardiovasculaires, dont deux provenant de la classe des inhibiteurs du sodium-glucose cotransporteur 2 (SGLT2). En dépit de leurs nombreux avantages, l'Agence américaine des produits alimentaires et médicaments a émis une alerte sur le risque de fasciite nécrosante périnéale avec l'utilisation des inhibiteur SGLT2. Cette étude de cas met en évidence un cas de gangrène de Fournier (FG) chez un homme avec le diabète traité avec l'empagliflozine.

A 49-year-old male, with well-controlled diabetes, presented to the emergency department with progressive pain over his buttock and perineal region that rapidly progressed over the course of four days. This started as a small pustule that ruptured spontaneously. The erythema progressed very quickly along with pain felt as pressure. His presentation was associated with fever, general malaise, decreased oral intake and one day of loose stools. Two days prior, he had been seen at an after-hours clinic and was prescribed a course of cephalexin for presumed balanitis.

His medical history included type 2 diabetes mellitus, with an HbA1C of 7.1% six months prior, hypertension, dyslipidemia, and erectile dysfunction (using a penile pump device for several years). He was being followed by the diabetes clinic with a regimen consisting of insulin glargine 70 units, empagliflozin 10 mg, sitagliptin 100 mg, and metformin 1000 mg b.i.d. Empagliflozin was started a year prior at which time the long-acting insulin was decreased by 30 units. Socially, he was a lifelong smoker with a 40-pack year history, a non-drinker, and denied the use of illicit drugs.

On review of systems, the patient did not endorse any dyspnea, cough, chest pain, abdominal pain, or urinary symptoms.

On examination, he was found to have an oral temperature of 36.6°C, a pulse of 100 beats per minute, blood pressure of 91/56 mm Hg, respiratory rate of 16 breaths per minutes, and an oxygen saturation of 100% on room air. The physical examination was notable for erythema of the perineal region bilaterally, which was more prominent on the right side. There were areas of induration and crepitus with exudate noted near the anus. The area was very tender to palpation and extended beyond the outlined erythematous skin.

Initial laboratory values were notable for leukocytosis, with a white blood cell count of 20.3 x 10⁹/L and a neutrophil and monocytic shift, a normal hemoglobin of 162 x 10¹² g/L, a baseline elevation of creatinine at 146 mmol/L, a urea of 9.0 mmol/L, and a normal lactate of 1.8 mmol/L. The bicarbonate was slightly elevated at 29.3 mmol/L, sodium was 133 mmol/L, potassium was 4.1 mmol/L, and random glucose was 13.7 mmol/L. A CT scan was requested and revealed evidence of Fournier's gangrene (FG) (Figure 1).

An urgent surgical early debridement was performed on the same day of presentation and diagnosis was confirmed through tissue sampling. On day 1, the patient was started on piperacillin-tazobactam, clindamycin, and vancomycin, and was admitted to the intensive care unit for close monitoring.

Keywords: SGLT2 inhibitors, Fournier's Syndrome, pharmacotherapy, medication adverse effects, urology

CASE REPORT

The right buttock pus microbiology revealed a growth of mixed anaerobic flora, including heavy growth of *Bacteroides ovatus*, and no aerobic growth.

On day 5, a laparoscopic diverting loop colostomy was performed due to the proximity of the debridement to the anus. The penile prosthesis was not involved and was left in situ. The patient was discharged home on day 15 and was seen by plastic surgery approximately 2 weeks later, who devised a plan to continue using the vacuum-assisted closure (VAC) device for wound management.

DISCUSSION

Sodium-glucose cotransporter 2 inhibitors are a class of oral anti-glycemic agents introduced in 2013 after the re-discovery of a French chemist's experiments on a compound

isolated from the root bark of an apple tree called phloridzin (1). This class of drug acts by inhibiting glucose reabsorption in the proximal renal tubule (2). They are reliable and effective given their insulin-independent mechanism that promotes urinary glucose excretion without increasing the risk of hypoglycemia. Additional benefits comprise of a 2 to 3 kg weight loss, a reduction in systolic and diastolic blood pressure of approximately 5 and 2 mmHg respectively, an alteration in lipid profiles including a reduction in triglycerides and an increase in HDL cholesterol, as well as a reduction of albuminuria by 30 to 40% (2). Recent trials have also demonstrated cardiovascular benefit with regards to certain SGLT2 inhibitors which is of great benefit given the two to fourfold increase risk of cardiovascular disease in patients with diabetes (3). Notably, the EMPA-REG and CANVAS trials showed a significant reduction in the primary endpoint of mortality associated cardiovascular events (MACE) and heart failure with empagliflozin and canagliflozin, respectively (4,5). DECLARE-TIMI58 revealed a reduction in heart failure hospitalizations with dapagliflozin in both secondary and primary prevention (6). The long-term effects of ertugliflozin on cardiovascular outcomes are currently being assessed in the VERTIS-CV trial (7).

However, in August 2018, the FDA issued a black box warning linking SGLT2 inhibitor therapy to FG and have since identified 55 unique cases of FG in patients on an SGLT2 inhibitor (39 men and 16 women of various ages) reported between March 2013 and January 2019 (8,9). In contrast, only 6 cases of FG (all men) were reported for all other anti-hyperglycemic drug

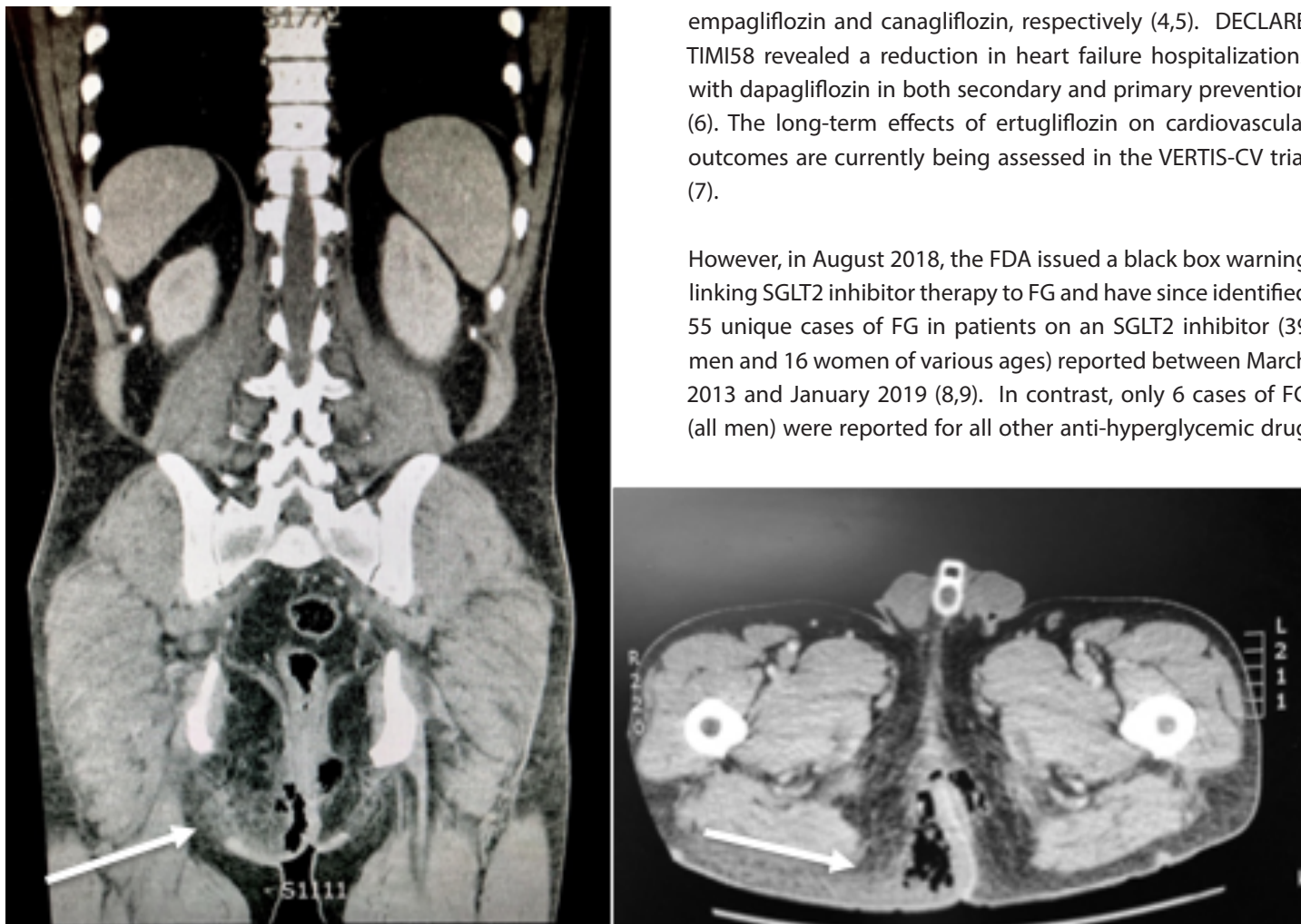


Figure 1. A coronal (left) and transverse (right) view of the CT abdo-pelvis reveals a large amount of gas (white arrows) within the subcutaneous tissue of the right gluteal fold and right buttock. This extends inferiorly and anteriorly to cross the midline of the perineum and involve the left gluteal fold. There is some involvement of the ischio-rectal fossa on the right side. No significant fluid collection is noted. Imaging confirms a diagnosis of Fournier's gangrene.

classes over 30 years (8). FG is a severe and rare polymicrobial infection resulting in necrosis of the perineal and genital fascia (10). Diagnosis of FG is an emergency with a high morbidity and high mortality of 20 to 40% thus, requiring early recognition, immediate treatment with early debridement, and broad-spectrum antibiotics (10).

Meta-analysis of randomized control trials (RCT) confirm an increase in the risk of genital infections with SGLT2 inhibitors versus other anti-hyperglycemic medication classes (11, 12). SGLT2 inhibitors inhibit the absorption of glucose from the proximal tubule of the kidney. This pharmacologically-induced glycosuria is thought to promote the growth of commensal genital microorganisms in addition to the gastrointestinal tract organisms that already colonize the perineum (9,13). Because organisms must enter the host tissue, one proposed mechanism is additional patient risk factors that would predispose patients when initiated on an SGLT2 inhibitor. For example, postcoital trauma, genital piercing, prosthetic penile implants, and rectal foreign bodies have all been implicated as precipitating factors (14). This was the case for our patient due to his history of a prosthetic penile implant. As compared to the 55 cases reported, this patient presented 12 months from the initiation of the SGLT2 inhibitor compared to the mean of 9 months (range of 5 days to 49 months). The majority of reported cases had concurrent anti-hyperglycemic use, similar to the patient in this case report. Although there are several proposed mechanisms, the definite pathophysiology by which SGLT2 inhibitors promote the ideal environment for FG remains unknown at this time (9). All SGLT2 inhibitors were associated with cases of FG except ertugliflozin, likely due to its limited time on the market.

CONCLUSION

Upon reflection of this case, this patient unfortunately developed FG despite adequate control of his diabetes. Several factors predisposed this patient to FG including diabetes mellitus, smoking, and a prior operative procedure or trauma in the perineum area. Some studies report that the rate of infection after penile prosthesis implantation in diabetic patient is six times greater than in non-diabetic patients (15). We believe that given the longevity of the prosthetic penile implant, and his well-controlled diabetes mellitus, the culprit of the development of FG in our patient was likely due to the SGLT2 inhibitor. In patients with predisposing factors, such as in this case, it may be better to avoid this class of medication all-together and use an agent from an alternative

anti-hyperglycemic class with similar cardiovascular benefit, if indicated. This is an important consideration moving forward to prevent predisposing patients to the risk of FG, a severe infection with high morbidity and mortality.

REFERENCES

1. Petersen C. Analyse des phloridzins. *Ann Acad Sci Fr.* 1835;15:178.
2. Hsia DS, Grove O, Cefalu WT. An Update on SGLT2 Inhibitors for the Treatment of Diabetes Mellitus. *Curr Opin Endocrinol Diabetes Obes.* 2017;24(1):73–79.
3. Heerspink HJ, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation.* 2016;134:752–772.
4. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117–2128.
5. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:644–657.
6. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the dapagliflozin effect on cardiovascular events (DECLARE)-TIMI 58 trial. *Am Heart J.* 2018;200:83–9.
7. Cannon CP, McGuire DK, Pratley R, et al. Design and baseline characteristics of the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am. Heart J.* 2018;206:11–23.
8. U.S. Food and Drug Administration [internet]. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes; 2018 Aug 29 [cited 2019 March 24]. Available from at www.fda.gov/Drugs/DrugSafety/ucm617360.htm.
9. Bersoff-Matcha SJ, Chamberlain C, Cao C, et al. Fournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. *Ann Intern Med.* 2019;170:764–769.
10. Sorensen MD, Krieger JN, Rivara FP, et al. Fournier's Gangrene: population based epidemiology and outcomes. *J Urol.* 2009;181:2120-6.
11. Storgaard H, Gluud LL, Bennett C, et al. Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *PLoS ONE* 2016;11:e0166125.
12. Zhang XL, Zhu QQ, Chen YH, et al. Cardiovascular Safety, Long-Term Noncardiovascular Safety, and Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis With Trial Sequential Analysis. *J. Am. Heart Assoc.* 2018;7.
13. Geerlings S, Fonseca V, Castro-Diaz D, et al. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. *Diabetes Res Clin Pract.* 2014;103:373–381.
14. Thwaini A, Khan A, Malik A, et al. Fournier's gangrene and its emergency management. *Postgrad Med J.* 2006;82:516-9.
15. Erikoglu M, Tavli S, Turk S. Fournier's gangrene after renal transplantation. *Nephrology Dialysis Transplantation.* 2005;20(2):449–450.