Case Report

Empagliflozin Use and Fournier’s Gangrene: Case Report and Systematic Literature Review

Mario Antunes 1,2, Antonio Cabrera de León 3, Damiano Pizzol 4,\*, Amir Hussein Abubacar Seni 5, Mike Trott 6, Anne Marie Carrie 7, Petre Cristian Ilie 7, Nicola Veronese 8 and Lee Smith 6

|  |
| --- |
| **Citation:** Antunes, M.; de León, A.; Pizzol, D.; Seni, A.H.A.; Trott, M.; Carrie, A.M.; Ilie, P.C.; Veronese, N.; Smith, L. Empagliflozin Use and Fournier’s Gangrene: Case Report and Systematic Literature Review. *Surgeries* **2021**, *2*, x. https://doi.org/10.3390/xxxxx  Received: date  Accepted: date  Published: date  **Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.    **Copyright:** © 2021 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/). |

1 Department of Surgery, Central Hospital of Beira, Beira, Mozambique

2 Faculty of Science and Health, Catholic University of Mozambique, Beira, Mozambique

3 Preventive Medicine and Public Health, Universidad de La Laguna, Santa Cruz de Tenerife, Spain

4 Italian Agency for Development Cooperation-Khartoum, Sudan

5 Department of Pediatrics, Central Hospital of Beira, Beira, Mozambique

6 The Cambridge Centre for Sport & Exercise Sciences, Anglia Ruskin University, Cambridge, UK

7 Research and Innovation Department, The Queen Elizabeth Hospital Foundation Trust, King’s Lynn, UK

8 Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy

**\*** Correspondence: Damiano Pizzol, MD, PhD, Italian Agency for Development Cooperation, 33 Street,   
Amarat, Khartoum, Sudan, Mobile (+39) 3668731237 e-mail: damianopizzol8@gmail.com

**Abstract: Background:** Fournier’s gangrene (FG) is a rare necrotising soft tissue infection localised in the genital areas with possible dramatic outcomes. Recently, sodium glucose co-transporter-2 (SGLT2) inhibitors were identified as a risk factor. **Methods**: We present a case report of a 57 years female patient with type 2 diabetes mellitus (T2DM) in treatment with empagliflozin which led to the development of FG. Moreover, we performed a systematic review assessing the association between empagliflozin use and FG. **Results**: The female patient with 15-years treated diabetes presented a massive FB after 6 months from starting empagliflozin. Over the period of two months she was successfully treated in a low income setting. The systematic review included two studies with a total of 9915 participants. Although no participant had FG, there was an increase rate of urinary and genital infection in patients treated with empagliflozin compared to those treated with other antidiabetics or placebo. **Conclusions:** FG should be considered as a possible complication in patients using SGLT2. Patients should be educated to report early signs of genital infection and healthy behaviours as well as a balanced diet should be promoted to aid in prevention of FG**.**

**Keywords:** empagliflozin; sodium-glucose transporter 2 inhibitors; SGLT2-inhibitors; Fournier’s gangrene; diabetes

1. Introduction

Fournier’s gangrene (FG) is a rare necrotising soft tissue infection localised in the perineal, perianal, and genital areas [1]. The pathophysiologic mechanism of FG assumes the existence of an initial outbreak of the infection, in the genitourinary tract, which spreads rapidly causing multi-organ dysfunction, septic shock, and also death [2]. The infection is usually polymicrobial and the most frequent infective agents include Escherichia coli, Klebsiella pneumonia, Bacteroides fragilis, and Staphylococcus aureus [3]. The multiple infections, acting in synergy, allows the rapid spread and, thus leads to tissue necrosis [3]. Immunodeficiency, diabetes, liver or kidney failure, cancer, obesity, smoking and alcoholism are recognised as risk factors due to their ability in creating a favorable micro-environment and promoting the extension of the infection [4]. The clinical presentation may vary according to time to presentation of the disease, the degree of infection extension, and comorbidities [5]. The most frequent symptoms are perianal or genital pain, redness, swelling, and skin necrosis, followed by gangrenous changes [5]. Clinical findings are used to carry out a diagnosis which then may be confirmed by laboratory tests or imaging mainly that is predominantly used for atypical presentation [5]. The management of FG treatment, depending on the severity of presentation, includes broad spectrum antibiotics, hemodynamic resuscitation and aggressive surgical debridement [5]. There is a growing body of literature on the risk of sodium glucose co-transporter-2 (SGLT2) inhibitors in promoting the process of necrotising fasciitis and FG [6]. SGLT2 inhibitors are used in the treatment of type 2 diabetes mellitus (T2DM), and act by increasing the excretion of glucose through the urine and include: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin [6]. However, the literature regarding SGLT2 inhibitors and FG is limited. Given this background, we present here a case report of a patient with FG and T2DM in treatment with empagliflozin and perform a systematic review assessing the association between empagliflozin use and FG.

2. Materials and Methods

2.1. Search Strategy

We searched four electronic databases–Medline, Cinhal, PsychInfo and Embase–targeting reports published up to the 17th of October 2020. The following search strategy was used: (“Empagliflozin” OR “sodium-glucose cotransporter-2 inhibitor” OR “SGLT2-inhibitors” OR “SGLT2-inhibitors” [Mesh term] AND “Fournier’s gangrene” OR “Fournier’s putrefaction” OR “Gangrene of the perineum” OR “Necrotizing Fasciitis” OR “Perineal Necrotizing Fasciitis”)

References of identified articles were then hand searched as well as proceedings of relevant conferences to identify eligible studies not identified in the original search.

Two investigators (MA, DP) independently carried out the literature search, assessment of inclusion and exclusion criteria, data extraction and quality assessment. Any discrepancies between the two reviewers were resolved through discussion with a third senior author (LS). No language restrictions were implemented.

2.2. Type of Studies, Inclusion and Exclusion Criteria

Following the PICOS (participants, intervention, controls, outcomes, study design) criteria, we included studies assessing:

P: People with diabetes treated with empagliflozin

I: empagliflozin treatment

C: people with diabetes using other treatment

O: Number/prevalence of FG

S: Observational (case-control, cross-sectional) and randomised controlled trials.

All retrospective or prospective studies evaluating the association between empagliflozin use and Fournier’s gangrene were included. We excluded studies that did not meet the inclusion criteria.

3. Results

The electronic search yielded 49 studies that were assessed for inclusion in the review. Of those, 11 were potentially eligible and full text reviews were carried out (Supplementary Figure 1).

*Excluded studies*

Amongst the relevant studies, 9 failed to meet the inclusion criteria and were excluded from this review mainly due to no specific data on empagliflozin use. Two studies were excluded because samples were composed of FG patients only.

*Included studies*

The two studies included a total of 9915 participants. One was conducted in Japan and one was a multi-country study. Both were randomised controlled trials and in one case the controls were patients undergoing others treatments and in the other using placebo.

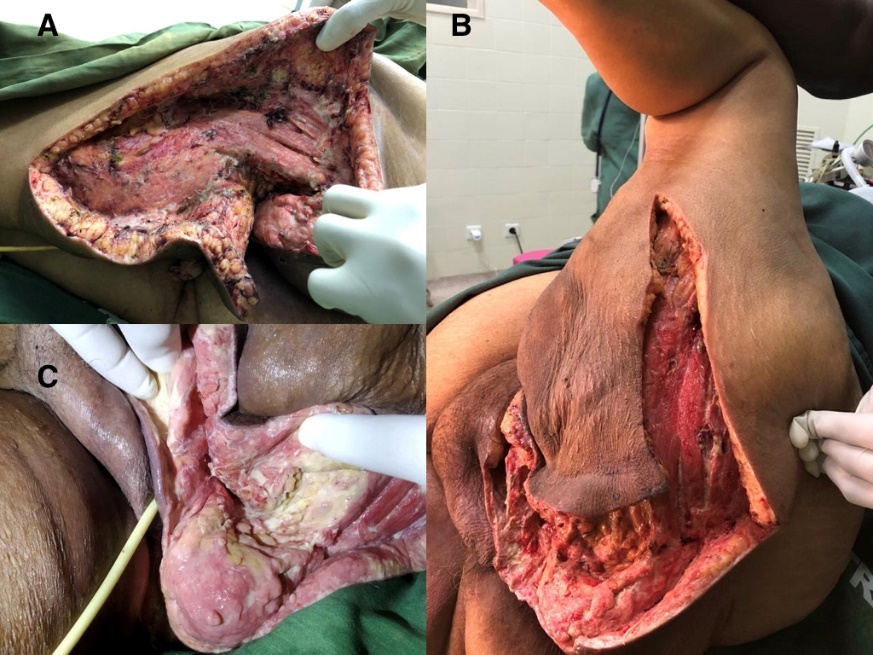
3.1. Main Outcomes

One study including 2895 patients showed a similar incidence of adverse events in patients using empagliflozin compared to those using linagliptin or the combination of two. Empagliflozin mono-therapy was associated with a higher percentage of genital infection (5.1%) compared to those receiving empagliflozin/linagliptin (3.0%) and those receiving linagliptin mono-therapy (1.9%). No cases of FG, diabetic ketoacidosis, pemphigoid or other relevant adverse events occurred in all groups [7].  
The second study including 7020 patients was focused mainly on cardiovascular outcomes and showed that empagliflozin was associated with a lower rate of the primary composite cardiovascular outcome as well as small reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood pressure. Moreover, small increases in LDL and HDL cholesterol were observed. However, there was no reported change in heart rate. The proportion of patients who experienced adverse events in the two groups was similar. Moreover, a similar proportion of patients between the groups was observed in relation to hypoglycaemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events consistent with volume depletion. In patients using empagliflozin a higher percentage of genital infection was reported but no FG [8].

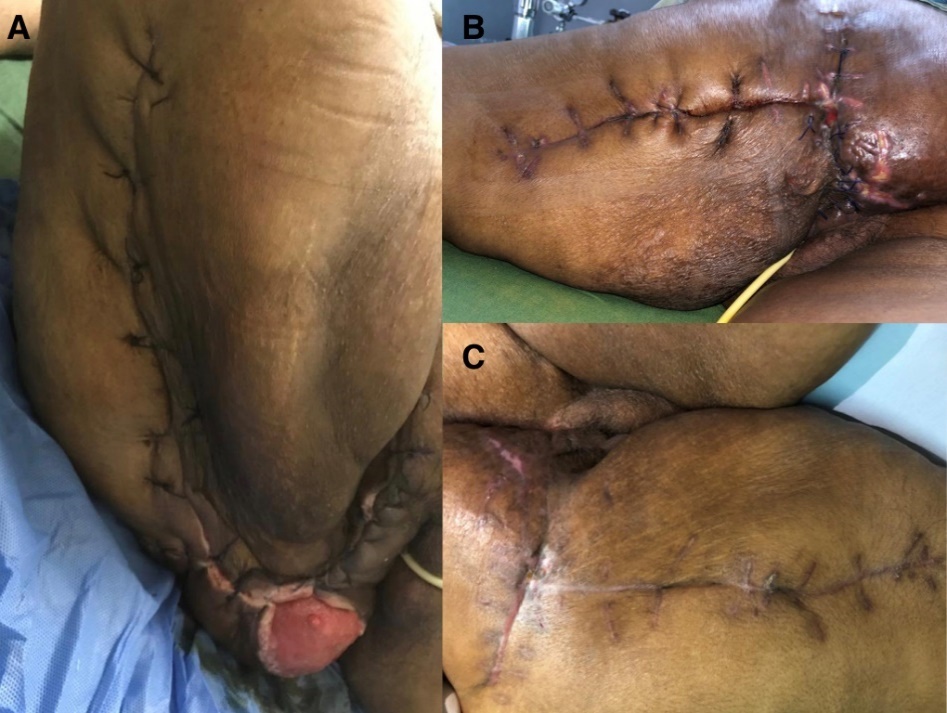
3.2. Case Report

A 57-year old obese (BMI = 38.5Kg/m2) female was referred to a hospital in Beira, Mozambique, with a 3-weeks history of increasing pain, fever, erythema and swelling of the left gluteus and thigh that evolved in fistula with egress of purulent material. The patient was being treated with basal long acting Insulin (Lantus), short acting insulin, SGLT2 inhibitors (Empagliflozin, Jardiance), Amlodipine/Valsartan (Exforge) and Atorvastatin. The patient was diagnosed with diabetes in 2004 but the empagliflozin was added to the patient’s diabetes therapy 6 months prior to the occurrence of the above mentioned symptoms. The patient had no diabetes complications and was without history of genital or urinary infections. She was HIV negative, had a past history of smoking but not of alcohol intake.

On admission, other than complaints in relation to the above-mentioned symptoms, she presented with anemia (Red cell 3.88 × 106/ul and HB 7.3 d/dL), blood pressure 150/80 mmHg, and a respiratory rate of 19 breaths per min. A preliminary surgical exploration was performed with a surgical incision from the border of the ulcer in which it was determined that the wound extended inferiorly from the buttocks, including perineal area, up to the distal third of the posterior thigh and superior-laterally in the direction of the iliac crest and purulent material drained (Figure 1A). The day after, a second surgical treatment was performed with the drainage of a substantial amount of dark grey purulent material, the performance of necrosectomy with deep toilette of the wound and the insertion of Penrose drainage (Figure 1B). The patient underwent five additional interventions to achieve adequate necrosectomy and starting from the sixth day (Figure 1C) only wound dressing without surgical intervention was performed.



**Figure 1.** Clinical presentation of a massive Fournier’s gangrene after preliminary exploration (**A**), after 1 day of treatment (**B**) and after 6 days (**C**).

A systemic multi-drug antibiotic therapy was started and regular cleaning was performed. After two weeks (Figure 2A) the wound showed a healthy pink reddish aspect, freely bleeding, without necrotic tissue and then the gradual approximation of the borders by suturing was started. In the following days, approximation of the borders was performed excising and suturing in order to provide adequate adhesion of the tissues. After 39 days the patient was discharged (Figure 2B) and the control after 30 days from discharge confirmed the successful healing (Figure 2C).

**Figure 2.** Clinical presentation of a massive Fournier’s gangrene after 15 days of management (**A**), after 39 days (**B**) and after 2 months (**C**).

Considering the case history of this patient, the presentation of the ulcer and associated symptoms, as well as the successful treatment, it was concluded that this patient was suffering from FG associated empagliflozin use.

4. Discussion

SGLT2 inhibitors are used in the treatment of T2DM and act by inhibiting the reabsorption of glucose in the proximal convoluted tubule, facilitating its excretion in urine [6]. Empagliflozin has been approved by the Food and Drug Administration (FDA) in 2014 and, like other SGLT2 inhibitors, it is associated with high rates of genital infections, urinary tract infections, and lower limb amputations [7,8]. FG is an aggressive infection that rapidly spreads affecting the tissue surrounding the muscles, nerves, fat, and blood vessels of the perineum and can ultimately lead to death of the patient. Although it is a rare disease, FDA documented, from May 2013 to May 2018, 12 case reports of FG in T2DM patients treated with SGLT2 inhibitors [6]. Later, another search performed through the Adverse Event Reporting System database detected 55 cases [9]. Although the number of cases may seem relatively low, it is significant when compared with the 19 cases of FG associated with other antitidiabetic agents reported from 1984 to 2019 [9].

We reported a case of a massive FG in a low-income setting in a T2DM patient treated with empagliflozin. Next, we performed a systematic review on this specific SGLT2 inhibitor. Although, among the known risk factors for FG, only diabetes and obesity were listed, we suspected FG due to the clinical presentation and after revision of the patient’s medication including empagliflozin. The lesion severity in the present case was determined mainly by the “time to care” due to the low access to care, typical of low-income settings. Despite the late stage presentation and the limited resources, the management of this case was successful although it required a long-time admission and it absorbed limited human and economic resources.

This is not the first case reported as others have been documented in recent years especially in industrialised countries [10–13]. However, we present here the first systematic review on this topic. Unfortunately, we identified only two studies eligible for the review with no possibility of in-depth analysis. However, interestingly, in both studies, involving almost ten thousand patients, an increase rate of genital infection in patients treated with empagliflozin compared to those treated with other antidiabetics or placebo, was observed. These findings support, at least, the role of empagliflozin as a facilitator agent for infection. Although, so far, pathophysiologic mechanisms are not clear, the increased urinary glucose concentration induced by empagliflozin and other SGLT2 inhibitors, provides a favourable growth environment for urinary and genital infections that represent a first step to the development of fasciitis gangrene. Despite the weakness due to the lack of data, this work has important clinical implication and allows one to set some important points. Firstly, if gangrene is confirmed or even suspected, treatment with SGLT2 inhibitors should be immediately stopped. Simultaneously, the treatment for gangrene has to be started immediately and, depending on the clinical presentation, it may include antibiotics and surgical debridement. Moreover, considering that urogenital infection or perineal abscess necrotising fasciitis may precede, it is crucial to educate patients before prescribing this pharmaceutical class. It is particularly important especially in low income countries where the hygienic conditions often represent an additional risk factor, the access to healthcare is limited, the health system is usually weak and patients arrive with late stage diseases.

In conclusion, although more consistent data is needed for conclusive indications, health workers should consider FG as a possible complication in patients using SGLT2. Patients should be educated to report any early signs of genital infection and healthy behaviours as well as a balanced diet should be promoted to aid in prevention of FG.

**Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1.

**Author Contributions:** Conceptualisation, M.A. and D.P.; Methodology, A.C.L. and N.V; Data Curation, N.V and A.M.C.; Writing—Original Draft Preparation, M.A., A.H.A. and M.T.; Writing—Review & Editing, A.M.C. and P.C.I; Supervision, L.S and A.C.L.

**Funding:** none to declare.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Written informed consent has been obtained from the patient to publish this paper.

**Conflicts of Interest:** The authors declare no conflict of interest.

References

1. Hakkarainen TW, Kopari NM, Pham TN, Evans HL. Necrotizing soft tissue infections: review and current concepts in treatment, systems of care, and outcomes. Curr Probl Surg. 2014 Aug;51(8) 344-62.
2. Gadler T, Huey S, Hunt K. Recognizing Fournier’s Gangrene in the Emergency Department. Adv Emerg Nurs J. 2019 Jan/Mar;41(1):33-38.
3. Tang LM, Su YJ, Lai YC. The evaluation of microbiology and prognosis of fournier’s gangrene in past five years. Springerplus. 2015 Jan 13;4(1):14.
4. Chernyadyev SA, Ufimtseva MA, Vishnevskaya IF, Bochkarev YM, Ushakov AA, Beresneva TA, Galimzyanov FV, Khodakov VV. Fournier’s Gangrene: Literature Review and Clinical Cases. Urol Int. 2018;101(1):91-97.
5. Montrief T, Long B, Koyfman A, Auerbach J. Fournier Gangrene: A Review for Emergency Clinicians. J Emerg Med. 2019 Oct;57(4):488-500.
6. Aschenbrenner DS. Risk of Rare, Serious Genital Infection from some Diabetes Drugs. Am J Nurs. 2018 Dec;118(12):23.
7. Watada H, Yamauchi T, Yamamoto F, Taniguchi A, Yarush L, Heilmann C, Yasui A. Safety and tolerability of empagliflozin and linagliptin combination therapy in patients with type 2 diabetes mellitus: a pooled analysis of data from five randomized, controlled clinical trials. Expert Opin Drug Saf. 2020 Sep;19(9):1193-1202.
8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28.
9. Berso -Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier gangrene associated with sodium-glucose cotrans- porter-2 inhibitors. Ann Intern Med. 2019;170:764–9.
10. Nagano Y, Yakame NK, Aoki H, Yamakawa T, Kondo NI. Fournier’s Gangrene in a Patient with Type 2 Diabetes Mellitus Treated with Empagliflozin: A Case Report. Drug Saf Case Rep. 2019 Oct 18;6(1):11.
11. Ramachandra Pai RP, Kangath RV. Bilateral gangrene of fingers in a patient on empagliflozin: First case report. World J Diabetes. 2019 Feb 15;10(2):133-136.
12. Kumar S, Costello AJ, Colman PG. Fournier’s gangrene in a man on empagliflozin for treatment of Type 2 diabetes. Diabet Med. 2017 Nov;34(11):1646-1648.
13. Elshimy G, Correa R, Alsayed M, Jyothinagaram S. Early Presentation of a Rare Complication of Sodium-Glucose Cotransporter-2 Inhibitors 10 Days After Initiation: Case Report and Literature Review. Cureus. 2019 Jul 19;11(7):e5173.

