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Case Report

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

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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-year-old 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 FG 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 increased 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 the prevention of FG.

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

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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, allow the rapid spread and thus lead to tissue necrosis [3]. Immunodeficiency, diabetes, liver or kidney failure, cancer, obesity, smoking and alcoholism are recognised as risk factors due to their ability to create a favourable micro-environment and promote 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 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 17 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 (M.A., D.P.) 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 (L.S.). 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 FG 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 S1).

Excluded Studies

Amongst the relevant studies, nine 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 other 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 the 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 = 38.5 kg/m^2) female was referred to a hospital in Beira, Mozambique, with a 3-week history of increasing pain, fever, erythema and swelling of the left gluteus and thigh that evolved in a 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 anaemia (red cell 3.88 $\times$ 10^6/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 the perineal area, up to the distal third of the posterior thigh and superior-laterally in the direction of the iliac crest, and purulent material was 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. 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).

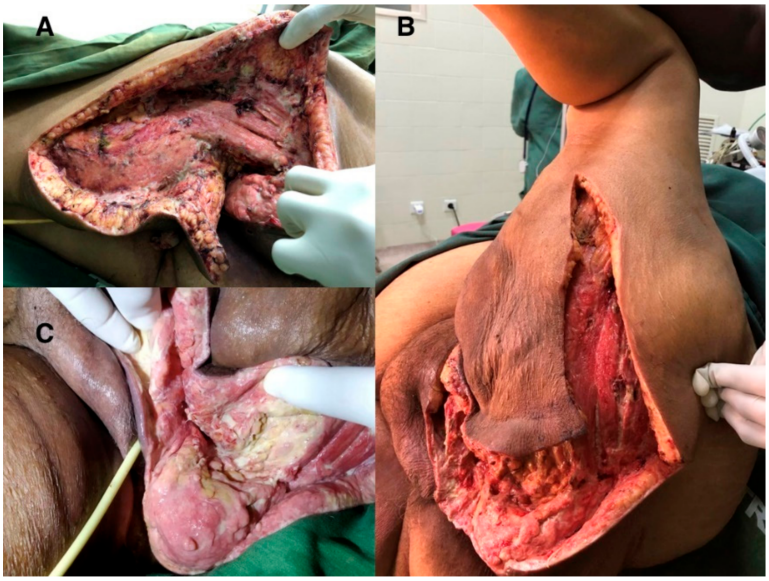

Figure 1. Clinical presentation of a massive Fournier's gangrene after preliminary exploration (**A**), after 1 day of treatment (**B**) and after 6 days (**C**).

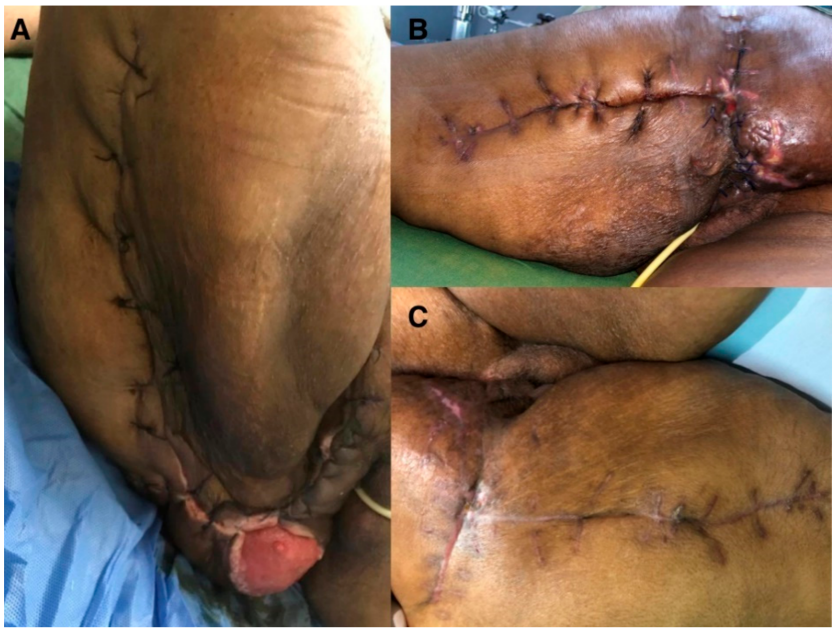

Figure 2. Clinical presentation of a massive Fournier's gangrene after 15 days of management (**A**), after 39 days (**B**) and after 2 months (**C**).

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 was 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 spreads rapidly, affecting the tissue surrounding the muscles, nerves, fat, and blood vessels of the

perineum, and can ultimately lead to the death of the patient. Although it is a rare disease, the 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 antidiabetic 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 increased 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 are 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 the prevention of FG.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/surgeries2020018/s1.

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