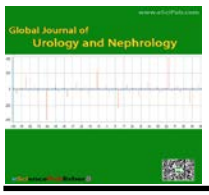
Case Report **GJUN (2019) 2:13**



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Two Options the sweetest among them is bitter: Fournier-gangrene associated with sodium-glucose co-transporter 2-inhibitors

Awad Magbri, MD, FACP, Mariam El-Magbri, BSC, MPH, Kamran Suljuki, PharmD, MBA, Shaukat Rashid, MD.

Regency Vascular Access, Toledo, OH

ABSTRACT

The authors discuss a case of sodium-glucose co-transporter 2 inhibitor associated with Fournier-gangrene in a patient with type-2 diabetes millets. The patient had extensive surgical intervention and skin graft but succumbed to her disease.

Keywords: Fournier's gangrene, diabetes, perineum infection, sodium-glucose cotransporter-2 inhibitors, glycosuria.

The authors have no financial closure

***Correspondence to Author:**
Awad Magbri, MD, FACP
Regency Vascular Access, Toledo, OH

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Case History

The patient is 63-year female with a 12-year history of type-2 diabetes mellitus on metformin, atherosclerotic coronary heart disease, hypertension, and hyperlipidemia. Her diabetes had been fairly control on metformin with normal kidney function. However, in the past 2-years her diabetes was out of control with HbA1C ranging from 8-10.5%. She was started on empagliflozin (sodium-glucose co-transporter 2-inhibitor, SGLT-2 Inhibitor) to control her diabetes and modify the risks of coronary artery disease. In the interims she had several episodes of urinary tract and genital mycotic infections resulted in Fournier-gangrene of the perineum necessitating a total of 5-surgical interventions including debridement and skin grafts. She eventually succumbed to her disease after 13-months of starting SGLT-2 inhibitor.

Case discussion

Fournier-gangrene (FG) was named after a French dermatologist, Jean Alfred Fournier (1883) who described a perineal infection of acute onset with rapid progressive course in relatively? healthy young man (1). This condition was also known as necrotizing fasciitis of the perineum. The disease is manifested as rapid progressive necrotizing fasciitis of the external genitalia, perineum, and perianal region requiring broad-spectrum antibiotics and emergent surgical intervention. Fournier-gangrene is reported with alcoholism, HIV infection, and the use of cytotoxic drugs (2,3). Fournier-gangrene is reported in both men and women. It is implicated in 75% to 95% of cases including cutaneous, anorectal, and urogenital infections (4,5). Diabetes remains a major risk factor in FG accounting for 32% to 66% of cases (3,6).

Despite the association of FG with diabetes and other risk factors it remains a rare disease with an overall incidence of 1.6 in 100,000 males and a peak incidence of 3.3 in 100,000 men aged 50-79-years (7). Fournier-gangrene accounts for < 0.02% of patients hospitalized with perineal infections. The reason for such a low incidence of FG is not well understood.

Sodium-glucose cotransporter-2 inhibitors improve glycemic control by inhibiting glucose absorption in the proximal tubules of the kidney and thereby increase glucose disposal in the urine (8). The food and drug administration (FDA) approved SGLT-2 inhibitors to reduce the risk for major adverse cardiovascular disease in adults with type-2 DM. The most common adverse reactions identified with SGLT-2 inhibitors in major clinical trials were genital mycotic and urinary tract infections including urosepsis, pyelonephritis, and ketoacidosis with normal or near normal blood glucose as well as acute kidney injury (9-12). In addition, the FDA issued a warning that canagliflozin (SGLT-2 inhibitor) carries an increased risk for lower limb ischemia and amputation (9,13,14).

Fournier-gangrene is added to the adverse effects of SGLT-2 inhibitors which was identified in patients receiving SGLT-2 inhibitors (15). Study by Bersoff-Matcha et al (16) in 55 cases of FG over 6-years since canagliflozin was approved by the FDA in March 2013 demonstrated the association of SGLT-2 inhibitors with FG. Cases of FG were reported with all SGLT-2 inhibitors except ertugliflozin; which was recently approved by the FDA in December 2017 (12). Data from the FDA in 2018 warning about FG and SGLT-2 inhibitors were published (15) and showed the surge in reporting FG in association with the use of SGLT-2 inhibitors. This may be due to growing awareness of the safety of SGLIT-2 inhibitors or the increased prevalence of diabetes combined with the increased use of SGLT-2 inhibitors in patients with hypertension and cardiovascular diseases (17,18).

Diabetes was implicated as a major risk factor for FG in previous studies (3,6). Although diabetes is common (20), 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 50-79-years (7). Why FG develops in only a small minority of patients with diabetes is not well

known. Postcoital trauma, urinary tract infection, genital piercing, prosthetic penile implants, and rectal foreign bodies might explain the precipitating factors (20). Bersoff-Matcha et al have observed a wide variety in time between the initiation of SGLT-2 inhibitors and the development of FG (5-days to 49-months), (16). This time variation in the development of FG after SGLT-2 inhibitors can be explained by fluctuating glycemic control, time to develop microvascular complications, or an inciting event associated with SGLT-2 inhibitor use (9-12).

Glycosuria is an expected finding in SGLT-2 inhibitor treatment and is associated with an increased risk of urinary tract and urogenital infection (21,22). Because the perineum is already colonized by bacteria from the gastrointestinal tract, the addition of glycosuria provides enriched environment for growth of urogenital flora which facilitate the development of FG. The endothelial damage and the micro thrombosis that occur in the small subcutaneous vessels in patients with FG are akin to the endothelial dysfunction in diabetic patients that contributes to microvascular complications such as limb ischemia and amputation (23). In clinical trials a higher risk of limb amputation in patients treated with canagliflozin have been reported (24,25).

The tendency of longer hospitalization for acute care in patients with FG (5-51-days), compounded with continued care in a rehabilitation facility, added to the disfigurement and morbidity associated with surgical debridement of the perineum should not be under-estimated (26,27).

Mortality among diabetic patients with FG is higher than those with other comorbid conditions (36% vs 0%) in one published series (28). Early recognition and surgical intervention can be mitigating factors to curb the high mortality and morbidity in these patients (7,27,28). Health care providers who prescribe SGLT-2 inhibitors in patients with diabetes should be educated about the signs and symptoms of FG. Pain out of proportion to the clinical findings on physical examination is a strong clinical indicator for necrotizing fasciitis and should prompted the clinician for quick and decisive action to prevent or mitigate the development of FG (29-31).

Back to our patient, the benefits of improving diabetes and mitigating risk factors of cardiovascular diseases by using SGLT-2 inhibitors should be weighed against the small but real possibility of permanent disfigurement, prolonged hospitalization, disability, and sepsis associated with FG. The choice between two options the sweetest among them is bitter sometimes leaves us squandering for rationalizing remedy with unattended consequences.

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