

Online-Only Supplemental Material

Search terms

The following search terms have been used to mine the FAERS, as describe in the main manuscript.

SGLT2i: "canagliflozin" OR "dapagliflozin" OR "empagliflozin" OR "metformin and canagliflozin" OR "linagliptin and empagliflozin" OR "metformin and empagliflozin" OR "ipragliflozin" OR "ertugliflozin" OR "metformin and dapagliflozin".

ATC10 class + insulin: "sitagliptin" OR "metformin and sitagliptin" OR "linagliptin" OR "saxagliptin" OR "vildagliptin" OR "metformin and vildagliptin" OR "alogliptin" OR "metformin and saxagliptin" OR "metformin and linagliptin" OR "metformin and alogliptin" OR "pioglitazone and alogliptin" OR "evogliptin" OR "gemigliptin" OR "phenformin" OR "metformin" OR "metformin and rosiglitazone" OR "metformin and pioglitazone" OR "metformin and repaglinide" OR "metformin and acarbose" OR "metformin and sulfonylureas" OR "glibenclamide" OR "chlorpropamide" OR "tolbutamide" OR "glibornuride" OR "tolazamide" OR "carbutamide" OR "glipizide" OR "metformin and sulfonylureas" OR "gliquidone" OR "gliclazide" OR "glisoxepide" OR "glimepiride" OR "glimepiride and rosiglitazone" OR "glimepiride and pioglitazone" OR "acetoexamide" OR "glymidine" OR "acarbose" OR "metformin and acarbose" OR "miglitol" OR "voglibose" OR "troglitazone" OR "rosiglitazone" OR "metformin and rosiglitazone" OR "glimepiride and rosiglitazone" OR "pioglitazone" OR "metformin and pioglitazone" OR "glimepiride and pioglitazone" OR "pioglitazone and alogliptin" OR "exenatide" OR "liraglutide" OR "lixisenatide" OR "albiglutide" OR "dulaglutide" OR "semaglutide" OR "guar gum" OR "repaglinide" OR "metformin and repaglinide" OR "nateglinide" OR "pramlintide" OR "benfluorex" OR "mitiglinide" OR "tolrestat" OR "insulins and analogues" OR "insulins and analogues for injection, long-acting" OR "insulins and analogues for injection, fast-acting" OR "insulins and analogues for injection, intermediate- or long-acting combined with fast-acting" OR "insulins and analogues for injection, intermediate-acting" OR "insulin glargine" OR "insulin (human)" OR "insulins and analogues for inhalation" OR "insulin lispro" OR "insulin aspart" OR "insulin detemir" OR "insulin glulisine" OR "insulin (beef)" OR "insulin degludec" OR "insulin (pork)" OR "insulin degludec and insulin aspart" OR "insulin degludec and liraglutide".

Diabetes indication: "glucose metabolism disorders (incl diabetes mellitus)" OR "diabetes mellitus (incl subtypes)" OR "diabetes mellitus" OR "type 2 diabetes mellitus" OR "diabetes mellitus non-insulin-dependent" OR "type 1 diabetes mellitus" OR "carbohydrate tolerance analyses (incl diabetes)" OR "insulin-requiring type 2 diabetes mellitus" OR "diabetes mellitus insulin-dependent" OR "gestational diabetes" OR "insulin-requiring type ii diabetes mellitus" OR "diabetes mellitus inadequate control" OR "diabetes mellitus management" OR "diabetes" OR "type ii diabetes mellitus" OR "diabetes prophylaxis" OR "latent autoimmune

diabetes in adults" OR "insulin resistant diabetes" OR "type i diabetes mellitus" OR "cystic fibrosis related diabetes" OR "type 3 diabetes mellitus" OR "pancreatogenous diabetes" OR "diabetes mellitus malnutrition-related" OR "diabetes mellitus" OR "fulminant type 1 diabetes mellitus" OR "insulin-dependent diabetes mellitus" OR "non-insulin-dependent diabetes mellitus" OR "diabetes complicating pregnancy" OR "type ii diabetes" OR "monogenic diabetes" OR "prediabetes" OR "diabetes mellitus nos" OR "pre-diabetes" OR "acquired lipoatrophic diabetes" OR "borderline diabetes" OR "diabetes mellitus loss of control" OR "diabetes mellitus poor control" OR "diabetes mellitus without mention of complication" OR "diabetes steroid-induced" OR "diabetes with renal manifestations".

Fournier's gangrene: "fournier's gangrene" OR "scrotal gangrene" OR "scrotal abscess" OR "perineal abscess" OR "perineal cellulitis" OR "perineal infection" OR "necrotising fasciitis" OR "necrotising fasciitis streptococcal" OR "necrotising fasciitis staphylococcal" OR "gangrenous balanitis" OR "vulval cellulitis" OR "cellulitis of male external genital organ".

Strict Fournier's gangrene definition: "fournier's gangrene" OR "necrotising fasciitis" OR "necrotising fasciitis streptococcal" OR "necrotising fasciitis staphylococcal" OR "scrotal abscess" OR "scrotal gangrene".

Amputations: "amputation" OR "limb amputation" OR "leg amputation" OR "foot amputation" OR "finger amputation" OR "toe amputation" OR "arm amputation" OR "hand amputation".

Psoriasis: "psoriasis" OR "pustular psoriasis" OR "guttate psoriasis" OR "erythrodermic psoriasis" OR "nail psoriasis" OR "parapsoriasis" OR "plaque psoriasis" OR "psoriasis vulgaris" OR "psoriasis area severity index" OR "rebound psoriasis".

Table S1

Individual reports of SGLT2i-associated Fournier's gangrene and other severe genital adverse events.

See file "*Table_S1.xlsx*".

Table S2. Causality assessment of Fournier's gangrene (FG) based on Bradford Hill criteria.

Criterion	Findings
Strength of the association	This is the first disproportionality analysis comparing reports of FG among antidiabetics. Although PRR is not a measure of risk, the strength of the PRR suggests a strong signal (the impact of unmeasurable confounders is likely to be negligible)
Consistency	Results of disproportionality approaches were consistent across various analyses, accounting for potential biases.
Coherence	Case reports and descriptive case series have been recently published suggesting a potential association. No concern of FG emerged from clinical trials, which are however underpowered to identify rare AEs
Specificity	Although several patient- and disease-related risk factors have been described, the occurrence of FG appears a specific safety issue with SGLT2i. The strategy for case selection is both sensitive and specific to identify actual FG cases vs serious infection (exploitation of multiple strategies, and the use of narratives)
Biological gradient	The variable quality of reports (missing data) does not allow to identify potential dose- or duration-response relationships
Temporal relationship	Wide variability in time to FG onset does not allow to easily predict the occurrence of these events and establish a clear temporal relationship
Biological plausibility and experiment	Although there are no formal basic studies, the underlying microvascular complications (e.g., endothelial damage and thrombosis) together with the recognized increased risk of genital/urinary/cutaneous infections with SGLT2i represent a plausible mechanistic basis that may increase patients' susceptibility to FG occurrence
Analogy	The association of SGLT2i with amputations (documented from pharmacovigilance analyses and clinical trials) is comparable in terms of reporting frequency, and a partially shared underlying mechanism can be theorized

PRR: proportional reporting ratio; AEs: adverse events; SGLT2i: sodium glucose cotransporter-2 inhibitors.

Figure S1. Strategies to identify FG cases associated with SGLT2i or other glucose lowering medications.

A) Starting from a search on FDABLE, after excluding AEs unrelated to the genital area, reports were filtered with information retrieved from the FDA public dashboard and from the freedom of information (FOI). B) Starting from a query on AERSMine from 2013q1 to 2014q3, we refined the search by including only reports for glucose lowering medication (GLM, drugs of the ATC10 class and insulin), with the diabetes indication, and refined the definition of Fournier's gangrene (FG).

