Sodium-glucose co-transporter-2 inhibitors (SGLT2i) treatment and risk of osteomyelitis: a pharmacovigilance study of the FAERS database

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Abstract

Abstract Aim: we sought to estimate the association between hypoglycemic medications especially sodium-glucose co-transporter-2 inhibitors (SGLT2i) and osteomyelitis based on the FDA adverse event reporting system (FAERS). Methods: Publicly available FAERS data were analyzed using reporting odd ratio (ROR) method and Bayesian confidence propagation neural network (BCPNN) method. The developing trend of ROR were revealed by series of calculation based on accumulating dataset quarter by quarter. Results: Ketoacidosis, infections, peripheral ischemia, renal impairment, inflammation including osteomyelitis might more likely to occur among SGLT2i users, especially canagliflozin. Osteomyelitis and cellulitis are AEs unique to canagliflozin. Among 2,888 osteomyelitis-related reports referring to glucose lowering medications, 2,333 cases were associated with SGLT2i, mostly with canagliflozin counting 2,283 which generated an ROR value of 360.89 and a lower limit of information component (IC025) of 7.79. No BCPNN-positive signal could be generated for drugs other than insulin, canagliflozin or drug groups excluding canagliflozin. Reports referring to insulin could generate BCPNN-positive signals during the entire timespan from 2004 to 2021, while BCPNN-positive signal emerged since second quarter (Q2) of 2017, four years since the approval of SGLT2i in Q2 of 2013, for canagliflozin and drug groups containing canagliflozin. Conclusion: This data mining revealed that strong association between canagliflozin treatment and developing osteomyelitis which might be a precursor to lower extremity amputation. Further study with updated data is needed to better characterize the risk of osteomyelitis associated with SGLT2i.

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Association between SGLT2i and osteomyelitis risk

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What is already known about this subject:

- Several clinical trials have indicated that the use of canagliflozin, a new class of oral antidiabetic drugs that inhibit sodium-glucose cotransporter 2, increases the risk of lower extremity amputation.
- Diabetes is also a risk of lower extremity amputation.
- FDA had withdrawn its black box warning amputation risk on canagliflozin, but this risk still exists.

What this study adds:

- To investigate adverse events (AEs) of various hypoglycemic drugs using data mining procedure based on FDA adverse event reporting system (FAERS).
- To discuss what makes sodium-glucose co-transporter-2 inhibitors (SGLT2i) so special, especially for canagliflozin.
- To screen out AEs that might be used as warnings of immanent lower extremity amputation.

Abstract

Aim: we sought to estimate the association between hypoglycemic medications especially sodium-glucose co-transporter-2 inhibitors (SGLT2i) and osteomyelitis based on the FDA adverse event reporting system (FAERS).

Methods: Publicly available FAERS data were analyzed using reporting odd ratio (ROR) method and Bayesian confidence propagation neural network (BCPNN) method. The developing trend of ROR were revealed by series of calculation based on accumulating dataset quarter by quarter.

Results: Ketoacidosis, infections, peripheral ischemia, renal impairment, inflammation including osteomyelitis might more likely to occur among SGLT2i users, especially canagliflozin. Osteomyelitis and cellulitis are AEs unique to canagliflozin. Among 2,888 osteomyelitis-related reports referring to glucose lowering medications, 2,333 cases were associated with SGLT2i, mostly with canagliflozin counting 2,283 which generated an ROR value of 360.89 and a lower limit of information component (IC025) of 7.79. No BCPNN-positive signal could be generated for drugs other than insulin, canagliflozin or drug groups excluding canagliflozin. Reports referring to insulin could generate BCPNN-positive signals during the entire timespan from 2004 to 2021, while BCPNN-positive signal emerged since second quarter (Q2) of 2017, four years since the approval of SGLT2i in Q2 of 2013, for canagliflozin and drug groups containing canagliflozin.

Conclusion: This data mining revealed that strong association between canagliflozin treatment and developing osteomyelitis which might be a precursor to lower extremity amputation. Further study with updated data is needed to better characterize the risk of osteomyelitis associated with SGLT2i.

Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a class of oral hypoglycemic agents that spell their glucose lowering effect by lowering the renal threshold for glucose reabsorption in the proximal renal tubule, causing glycosuria, increasing renal excretion of glucose. In patients with type 2 diabetes (T2D), SGLT2i are effective in controlling glycaemia, blood pressure, and body weight [1]. Since approval of canagliflozin in 2013, these drugs have been reported to demonstrate protective effect on renal and cardiovascular disease (CVD) [2-4], such as preventing hospitalization for heart failure (HF) in patients with T2D with or without a prior history of HF or cardiovascular disease at baseline [5], or significantly improving outcomes for patients with HF and reduced ejection fraction , 42–50% of whom had T2D [6].

However, in 2017, the US Food and Drug Administration (FDA) issued a Drug Safety Communication regarding a boxed warning about foot and leg amputations with the use of canagliflozin, and removed it in 2020 reconsidering its additional benefits [7, 8]. The amputation risk with canagliflozin remains and is still described in the Warnings and Precautions section of the prescribing information. Health care professionals and patients should continue to recognize the importance of preventative foot care and monitor for new pain, tenderness, sores, ulcers, and infections in the legs and feet. Risk factors that may predispose patients to the need for amputation should be considered when choosing antidiabetic medicines [8]. This warning was based on the evidence from two clinical trials. The Canagliflozin Cardiovascular Assessment Study (CANVAS) program used data from two trials and showed that there was a statistically significantly higher risk of amputation with canagliflozin than with placebo (6.3 vs. 3.4 participants with amputations per 1,000 patient-years) [9, 10]. A retrospective cohort study has raised concerns in relation to increased risk of lower extremities amputation with canagliflozin and it remains unclear whether and to what extent this side effect could also occur with other SGLT2i, in which risk of osteomyelitis was also mentioned about [11].

To the best of our knowledge there is no assessment of association between hypoglycemic drugs and AEs, which might be precursors to lower extremity amputation, especially osteomyelitis, based on real world data. Osteomyelitis is an inflammatory bone disease that is caused by an infecting microorganism and leads to progressive bone destruction and loss [12, 13], which complicates approximately 10-20% of foot ulcers in individuals with diabetes attending specialist clinics [14], although a frequency of as high as 68% has been reported in one study [15, 16]. This complication greatly increases the risk of a lower-extremity amputation [17, 18]. Although, both the CANVAS and Canagliflozin Cardiovascular Assessment Study–Renal (CANVAS-R) suggested an increased risk for lower limb amputations, they underestimated the importance of osteomyelitis, since its treatment might greatly reduce the risk of amputation. In this study, based on the US Food and Drug Administration Adverse Event Reporting System (FAERS), we investigated the association between treatment of hypoglycemic drugs and adverse events (AEs) referred, as well as association between diabetes and AEs. Drug-AEs which could generated stronger signals than the pair of the same AEs and diabetes, especially osteonecrosis-related AEs, could be used as warning for prognosis of lower extremity amputation.

Methods

Publicly available FAERS data since January 1 2004 to September 30, 2021 was downloaded from FDA website as raw data. Hypoglycemic medications were mapped to the anatomic therapeutic classification (ATC) as A10 class. "Osteomyelitis" was defined as all of the adverse events (AEs) containing the key word "osteomyelitis", which were determined by the Standardized MedDRA Query (SMQ, version 23.0)

terminology [19]. Dataset of "Diabetes" was composed by all reports in FAERS with indication containing the key word "diabetes".

Criteria of exclusion (**Figure 1**) were applied: each potential case was subjected to data cleaning procedure to make sure the removal of reports which were officially deleted by FDA authority, duplicated, missing caseid and date, or with inaccurate data for gender and age, and then was filtered with the targeted drug as the primary suspected (PS) drug. All the reports containing A10 medications other than the targeted one were removed, to minimize the possibility of interfering effects.

Data mining procedure using reporting odd ratio (ROR) method [21, 22] was introduced to investigate the disproportionality in reporting ratio caused by interested drug-AE pairs compared with random drug-AE pair, which were then tandem with Bayesian confidence propagation neural network (BCPNN) method introduced by Bate A et al. in 1998 [23], deducing linkage between the target drug and event by a prior possibility. The association between "diabetes" and AEs was also investigated. Drug-AE pairs which could generated stronger signals than the same AEs paired and diabetes were screened out and demonstrated with a heatmap. Osteomyelitis was picked as the major precursor to lower extremity amputation.

All the drugs and drug groups mentioned above were subjected to descriptive analysis for demographics, including gender, age category, annual report counts, occupation of the reporter, role of the targeted drug, and outcomes. Since hypoglycemic medications may sometimes be used by non-diabetic individuals or purpose [24, 25], meanwhile a considerable proportion of reports presents no specific indications or missing information, all interested drugs or drug groups were performed in duplicates with or without filtering diabetes as indication (**Figure 1**). Reports referring to competing interfering such as drugs known for causing osteomyelitis, including zoledronic acid, alendronate sodium were cast out, as well as reports listing osteology conditions as indications and adverse events (AE), since osteomyelitis may occurs preferentially in patients with diabetic ulcers, lower extremity amputation, metatarsal excision [17]. Because that osteomyelitis might occur preferentially in patients with known infection [18], we excluded reports containing competing indications and AEs which are typically reported preferentially among users of SGLT2i, in order to minimize the bias due to dilution or competition [26, 27], such as diabetic foot [28], infection [29], especially for genital infection, genitourinary tract infections (GUTI), urinary tract infection, diabetic ketoacidosis (DKA), and Fournier's gangrene (FG), as well as reports that listing all the anti-biotics or becaplermin [30]. Furthermore, the using of insulin and its analogs (A10A) is typically considered a proxy of disease severity or advanced disease stage [26, 27], we category reports referring to A10A as a control group. In addition**,** the gender bias of the osteomyelitis reports was also put to the investigation. Reports referring to testosterone and estrogen were extract and underwent the same cleansing procedure described above.

The developing trend of ROR on quarterly basis was investigated. We designed a procedure to mimic the accumulation of FAERS data in real world by adding up every quarter of data into the dataset. Series of quarterly ROR (q-ROR) value was generated for interested drug (drug group)-osteomyelitis pairs. Chi-square tests (Chi2 tests) were induced to compare the changing tendencies of q-ROR of given pairs, as well as tendencies prior to and since SGLT2i were approved by FDA, to eliminate the interfering effect cause by comorbidities or concomitants.

Data process were conducted with R Studio 4.1.2 (RStudio), using logistic regression model. For ROR, a signal was determined as count of drug-AE pair (a) larger than 3, plus the value of the ROR higher than 1, as well as lower limit of the 95% confidence interval (95%CI) exceeding 1. For BCPNN, a signal was defined as the value of lower limit of information component (IC_{025}) exceeding 0, which to be specific, IC_{025} value between 0 and 1.5 was defined as a weak signal, while IC_{025} between 1.5 and 3 was considered as a medium signal, and $IC_{025} > 3$ was considered as a strong signal.

Results

As shown in **Figure 2 and supplement table 1** , comparing with the risk factor "diabetes", most of A10 drugs demonstrated curative effects for patients with diabetes, while sglt2i might increase risk of ketoacidosis (IC_{025} of diabetes: 3.57 **vs.**IC_{025} of empagliflozin: 6.99), lower limb extremity amputation such as toe amputation (IC_{025} of diabetes: 3.38 **vs.** IC_{025} of canagliflozin: 5.35), gangrene such as Fournier's gangrene (IC_{025} of diabetes: 3.75 **vs.** IC_{025} of empagliflozin: 6.76), infection such as urinary tract infection (IC_{025} of diabetes: 0.10 **vs.** IC_{025} of canagliflozin: 1.84), ulcer such as skin ulcer (IC_{025} of diabetes: 0.79**vs.** IC_{025} of canagliflozin: 2.42), peripheral ischemia (IC_{025} of diabetes: 0.39 **vs.**IC_{025} of canagliflozin: 2.23), kidney injury such as acute kidney injury (IC_{025} of diabetes: 1.56**vs.** IC_{025} of dapagliflozin: 2.27), various inflammation including osteomyelitis, fasciitis and cellulitis, especially for the case of canagliflozin. osteomyelitis (IC_{025} of diabetes: 1.80 **vs.**IC_{025} of canagliflozin: 4.17) and cellulitis (IC_{025} of diabetes: 0.56 **vs.**IC_{025} of canagliflozin: 2.16) were AEs unique to canagliflozin.

The FAERS database is composed by a total 14,073,327 AE reports from January 1 2004 to up to September 30, 2021. Following the data cleanse procedure described above, there are 2,888 osteomyelitis-related reports referring to hypoglycemic drugs (A10), among which 2,333 cases are associated with SGLT2i, mostly contributed by canagliflozin counting 2,283 (**Table 1**). Among reports referring to both canagliflozin and osteomyelitis, 73.50% of patients are male, while the gross gender ratio for each category of A10 drugs is relatively balanced. Among all osteomyelitis-related patients treated with canagliflozin, 59.22% are 30 to 49-year-old, as well as 23.74% patients aged 18 to 29-year-old, 14.76% patients aged 50 to 64-year-old, which added up 97.72% patients aged from 18 to 64-year-old, comparing to 79.07% cases are categorized in the same age group for A10 treated patients. For reports exposure to canagliflozin, 99.82% of which classed the targeted drug as primary suspect drug (PS). The most common reporting source is from consumers, counting 91.90% for canagliflozin-related case associated with osteomyelitis, on the contrary, for all reports referring to A10 drugs about 50% of are filed by consumers**.**

All interested drugs-osteomyelitis pair were subjected to disproportional analysis and BCPNN in duplicates with filtering for the diabetes indication, and results are demonstrated in **Figure 3** . As demonstrated in **Figure 3** , a total of 1,451 counts of osteomyelitis related AEs are generated out of total 1,438 reports listing canagliflozin, and the ROR value is 360.89 (95% CI 340.58-382.41) coupled with IC_{025} value as 7.79. Detailed to each osteomyelitis-related AE individually, canagliflozin-osteomyelitis pair counted 1,214, generated ROR as 315.60 (95% CI 296.51-335.93) and IC_{025} as 7.62, canagliflozin-osteomyelitis acute pair counted 157, ROR as 1391.14 (95% CI 1134.55-1705.76) and IC_{025} as 6.48, canagliflozin-osteomyelitis chronic pair counted 72, ROR as 716.11 (95% CI 546.95-937.60) and IC_{025} as 5.03. All above signals are classed as strong signals. For canagliflozin-staphylococcal osteomyelitis pair, although a high ROR value was generated as 168.49 (95% CI 81.87-346.74), but coupled with IC_{025} as -1.21, and therefore cast out as a negative signal by BCPNN, as false positive. For osteomyelitis associated with empagliflozin, ROR value is 2.72 (95% CI 1.22-6.06) and IC_{025} as -0.19 (**Figure 3**), while other SGLT2i as well as other hypoglycemic drugs (A10) except for insulin and its analogs (A10A) did not generate any valid ROR. Non-canagliflozin SGLT2i as a group could generate ROR as 1.99 (95%CI 0.95-4.17) and IC_{025} as -0.33, while other hypoglycemic drug groups including biguanides, DPP4, GLP1, TZD did not generate any valid ROR signal. Among all reports referring to osteomyelitis, 405 cases referring to insulin and its analogs and generated ROR as 1.32 (95% CI 1.08-1.62) and IC_{025} as 0.09, which could be considered as a weak signal, 484 cases referring to non-insulin hypoglycemic drugs (A10B) other than SGLT2i and could not generated valid ROR as 0.28 and IC_{025} as -2.25, which meant no signal. Taking gender as filter, there is significant difference in the ROR of osteomyelitis associated with canagliflozin between males (ROR 453.79, 95% CI 424.51–485.10, IC_{025} as 7.96) and females (ROR 190.38, 95% CI 171.07–211.87, IC_{025} as 6.69). For insulin-osteomyelitis pair, only male generates a weak signal (ROR 2.00, 95% CI 1.53-2.63, IC_{025} as 0.57).

To demonstrate the changing patter of q-ROR (**Supplement Table 2**& **Figure 4**), natural logarithm value of ROR (Ln ROR) was used as vertical coordinates, and plotted against quarters of year as horizontal coordinates. As shown in **Figure 4** , although reporting counts of canagliflozin-osteomyelitis pair diminishes

considerably with filtering diabetes as indication comparing to without doing so, the curve of canagliflozin is almost overlapped with curve of canagliflozin (wo, without). When A10 drugs excluding SGLT2i and insulin were investigated as drug group, all the q-ROR value are below the threshold of ROR value as 1 (Ln ROR as 0), while the Ln ROR-time curve of insulin (insulin and its analogs as a group, A10A) remains a generally horizontal line, with ROR value consistently within range from 1 to 2 (Ln ROR range from 0 to 1), since the second quarter (Q2) of 2013. As shown in **Supplement Table 2** , during 18 years from January 1 2004 to up to September 30, 2021, q-ROR value of insulin is always above the recognition threshold of 1 and fluctuates consistently around a median as 1.57 (mean 1.71 ± 0.44), and valid ROR could be identified since Q3 of 2004. The curve of canagliflozin and SGLT2i starts to generate valid ROR signal, since as early as 2017 Q4, while for any drug group including SGLT2i, first valid ROR emerges since 2018 Q1. For any drug group excluding canagliflozin, such as non-canagliflozin A10 and non-SGLT2i A10, no valid ROR signal is ever generated (**Supplement Table 2**).

Chi2 tests were then applied to investigate correlation between the series of q-ROR, using a null hypothesis claiming the prevalence of any two-given series of q-ROR was the same. Among all series, canagliflozin, canagliflozin (wo), and SGLT2i, share the same pattern, although the scales of ROR were considerably different. Changing pattern of canagliflozin and SGLT2i demonstrates differences from insulin ($p = 0.00$) and other hypoglycemic drugs or drug groups (**Supplement Table 3**). Another Chi-square test was introduced to determine the prevalence of q-ROR of A10-osteomyelitis pair before and after the approval of SGLT2i during the same span of time, which is from Q2 of 2004 to Q4 of 2012 as serial A and from Q2 of 2013 to Q3 of 2021 as serial B and a p value of 0.00924 was generated, and the null hypothesis was rejected.

Discussion

As shown in **Figure 2** , ketoacidosis, various infection, peripheral ischemia, renal impairment, inflammation including osteomyelitis might more likely to occur among SGLT2i users, especially canagliflozin. Our findings suggested that SGLT2i increased the risk of these issues, or was less effective on them. SGLT2i treatment for patients who suffered from ketoacidosis, cardiovascular issues, renal problem and inflammation was therefore not recommended. Osteomyelitis and cellulitis are AEs unique to canagliflozin. Since osteomyelitis is considered to greatly increases the risk of a lower-extremity amputation [17, 18], our findings indicated that exposure to canagliflozin could notably increase the risk of developing osteomyelitis while other A10 drugs could reduce such a risk. On the other hand, these events could be monitored as warning prior to lower limb extreme amputation.

Most osteomyelitis-related cases were referred to canagliflozin, indicated that there might be a strong correlation between SGLT2i exposure, especially canagliflozin, and developing osteomyelitis according to FAERS data. In this study, ROR and BCPNN method were applied to investigate association between hypoglycemic drugs and osteomyelitis. Signals with high value of ROR were detected for canagliflozin-osteomyelitis pairs, as well as any drug group containing canagliflozin. Since the value of ROR did not directly indicate the significance of a signal, all positive signals were validated by BCPNN method, strong signals were generated canagliflozin or any drug groups containing canagliflozin associated with osteomyelitis, while weak signal was generated for insulin (A10A-osteomyelitis pair), and no signal was ever generated for other A10 drugs or drug groups excluding canagliflozin as well as insulin. Therefore, these findings indicated that association between canagliflozin treatment and osteomyelitis was quite convincing. Weak signal generated by insulin-osteomyelitis pair, might be explained by the insulin exposure as well as morbidity of diabetes since insulin treatment indicating a proxy of disease severity or disease advanced stage [26, 27], but the morbidity of diabetes might neither be a sufficient condition nor necessary condition for a patient with diabetes to develop osteomyelitis. Case number of targeted drugs presented notable differences with or without filtering diabetes as indication, and IC_{025} of canagliflozin-osteomyelitis pairs with the filtering was lower than without it, which could lead to the conclusion that casting out cases without a specific indication as diabetes resulted in dwindling the intensity of BCPNN signal.

Among patients developed osteomyelitis, 73.50% of whom are male, while the gross gender ratio for each category of drugs is relatively more balanced (**Table 1**). Further disproportional analysis using gender as filtering was applied and results suggested that there was significant difference in the ROR of canagliflozin-osteomyelitis pairs between two genders. Since the cleansing procedure according to including/excluding criteria mention above had excluded all reports with infection know as competing indication and reaction [29], the gender ratio as well as differences of ROR and IC_{025} value between male and females was possibly due to sex differences, negative correlation might existed between glycosylated hemoglobin (HbA1c) and serum testosterone levels [31]. As displayed by insulin-osteomyelitis pair, only the dataset of male patients could generate a valid ROR and a weak signal of BCPNN, these findings support the hypothesis that male patient might more likely to develop osteomyelitis. When exposure to SGT2i, and canagliflozin were the major factor for causing disproportionality, dataset of male could generate ROR value three times larger than female. When the signals were validated by BCPNN method, both genders generated strong signals (IC_{025} 7.96 for male vs. IC_{025} 6.69 for female), which indicated that for reports of each gender, however their difference in ROR, canagliflozin presented a strong correlation with developing osteomyelitis.

A new approach so-called quarterly ROR (q-ROR) was introduced to demonstrate the ROR developing pattern, and the series of q-ROR generated by different drugs or drug groups was subjected to Chi-square tests to determine their correlations statistically. Canagliflozin (wo), canagliflozin, SGLT2i and A10 demonstrates no prevalence difference although there might be gap in the scale of ROR value (**Supplement Table 2** & **Figure 4**) and supported the speculation mentioned above that the disproportionality of osteomyelitis-related reports was generated by canagliflozin. For hypoglycemic drugs other than canagliflozin and drug groups excluding SGLT2i, no positive signal was ever generated. These findings strongly indicated that developing pattern of these drugs or drug groups were synchronised by the presents canagliflozin.

In pharmacovigilance study, disproportionality emerges when a specific adverse event is associated with a given drug [32-34]. In this study, we tried this approach called q-ROR to utilize the FAERS data quarterly, and mimicked accumulation of reports to the database in real world. Starting from a setting date, slice of data was added to dataset in chronologically order on quarterly basis and a ROR value from the setting date up to that quarter was calculated. A serial of RORs was generated for any given interested drug (drug group)-AE pair. Finally, value of q-ROR achieved equilibrium approached its theoretically true value. For those lately approved drugs with limited reports but analogs of which had been long approved, the q-ROR curve might be used to predict its association with interested AE according to their precursors or as a drug group, such as ertugliflozin, luseogliflozin, remogliflozin and other new SGLT2i fail to generate any positive signal. The q-ROR value of the insulin-osteomyelitis is always above the recognition threshold and fluctuate consistently around 1.5 and positive signal could be identified since Q1 of 2005, while series of q-ROR referring to any drug group excluding canagliflozin and insulin went beneath the thread hold of 1, since 2005. Coupled with the dramatic increasing reports of canagliflozin related osteomyelitis in FAERS (25 cases in 2017 vs. 1,402 cases in 2018) (**Table 1**), the q-ROR pattern of canagliflozin bounds from 3.24 in Q4 of 2017 to 79.54 in Q4 of 2018 (**Supplement Table 2**).This finding indicated that, q-ROR could be used to monitor drug-induced ADRs unknown to premarketing trials as pharmacovigilance, when a dramatic rise in ROR value was spotted for given drug-AE pairs, and needed to be further vilified by BCPNN method.

Diabetes was a competing risk factor of developing osteomyelitis, which occurs in approximately 10-20% of patients with diabetes-related foot ulcers [17], and osteomyelitis of the lower extremity is a commonly encountered problem in patients with diabetes [35]. In this study, such a data pack in FAERS was equivalent to considering all hypoglycemic drugs as a drug group and filtering with diabetes as indication which generated a signal considered to be caused by both the treatment and the morbidity. And this data pack was also examined by quarterly ROR method (q-ROR). Chi2 test was induced to comparing q-ROR value prior to and since canagliflozin was approved in Q1 of 2013, and a p value of $0.00924 < 0.05$ indicated that ROR developing pattern experienced a significant change, which probably due to the exposure to SGLT2i, especially canagliflozin, since before the approval of SGLT2i, ROR serial of drug-event pair generated no positive signal and the indication was confined as diabetes mellitus.

Although previous publication suggested that osteomyelitis of the lower extremity is a commonly encountered problem in patients with diabetes [35] and occurred in approximately 10-20% of patients with diabetes-related foot ulcers [17]. According to our findings, q-ROR series of drug groups excluding canagliflozin and insulin generates no positive signal (**Supplement Table 2** & **Figure 4**). q-ROR serial of insulin presented all its value of q-ROR ranging 1.71 ± 0.44, with median as 1.57, as well as ranging 1.53 ± 0.25, with median as 1.45, since Q2 of 2013, when canagliflozin was approved as the first of SGLT2i, which indicated that the morbidity of diabetes mellitus, even at a proxy of disease severity or disease advanced stage [26, 27] might not be consider as a significant interfering factor for drug-associated osteomyelitis based on FAERS, otherwise all drug groups filtering diabetes as indication should consequently generate ROR signals above 1. And therefore, it strengthened the results of Chi2 test between q-ROR series, that was, canagliflozin exposure might be the predominant cause of developing osteomyelitis for patients with or without filtering diabetes as indication, based on FAERS database. On the contrary, other widely used SGLT2i, such as dapagliflozin and empagliflozin might not associated with developing osteomyelitis, and for those lately approval SGLT2i which had not accumulated enough ADR reports for disproportional analysis yet, predictions could be made base on the q-ROR pattern as pharmacovigilance.

There are certain limitations might undermine this study. Spontaneous reporting systems including FEARS were exposed to the biases inherent to pharmacovigilance studies. To the best of our knowledge, in 2018, Chang, H.Y., et al. [11] had mentioned about risk of osteomyelitis when discussing about the association between SGLT2i treatment and lower extremity amputation among patients with T2D, and osteomyelitis of the lower extremity is a commonly encountered problem in patients with diabetes [35] and occurs in approximately 10-20% of patients with diabetes-related foot ulcers [17]. These publications coincidently match with a gush of osteomyelitis related ADR reports and a surge in ROR for canagliflozin-osteomyelitis pair.

In conclusion, based on FAERS data, diabetes is a predominant risk for lower extremity amputation, and most antidiabetic drugs demonstrated curative affects on this prognosis, while SGLT2i was less effective on this issue. Ketoacidosis, infections, peripheral ischemia, renal impairment, inflammation might more likely to occur among SGLT2i users, especially canagliflozin. Osteomyelitis and cellulitis are AEs unique to canagliflozin, and therefore intensively discussed. ROR, IC_{025} as well as q-ROR tendency of canagliflozin-osteomyelitis pair were significantly different from those generated by insulin-osteomyelitis pair, and there was no positive signal for hypoglycemic drugs other than canagliflozin and insulin. Our findings strongly indicated that canagliflozin treatment increasing the risk of developing osteomyelitis from the very early stage, prior to the advanced stage when insulin was prescribed. It is worth investigating whether SGLT2i can result in developing osteomyelitis also in patients without diabetes, and association between osteomyelitis and the lately approved SGLT2i, whenever there are enough reports. Further studies are needed to characterize a better understanding the association between SGLT2i treatment and risk of osteomyelitis.

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Author contribution: Xiao-Yan Qiu and Ming-Kang Zhong designed the study; Ming-Ming Yan, Hui Zhao conducted the study; Zi-Ran Li and Qian Zhang contributed to the formation of figures and Jun-Wei Chow contributed to improve the analytical method. Ming-Ming Yan and Hui Zhao contributed equally to the manuscript. Xiao-Yan Qiu and Ming-Kang Zhong are co-corresponding authors. Xiao-Yan Qiu is the lead

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References

1. Zaccardi F, Webb D, Htike Z, Youssef D, Khunti K, Davies M. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes, obesity & metabolism 2016; 18: 783-94.

2. Zelniker T, Wiviott S, Raz I, Im K, Goodrich E, Bonaca M, Mosenzon O, Kato E, Cahn A, Furtado R, Bhatt D, Leiter L, McGuire D, Wilding J, Sabatine M. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet (London, England) 2019; 393: 31-39.

3. Perkovic V, Jardine M, Neal B, Bompoint S, Heerspink H, Charytan D, Edwards R, Agarwal R, Bakris G, Bull S, Cannon C, Capuano G, Chu P, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler D, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner B, Mahaffey K. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England journal of medicine 2019; 380: 2295-306.

4. Bauersachs J, de Boer R, Lindenfeld J, Bozkurt B. The year in cardiovascular medicine 2021: heart failure and cardiomyopathies. European heart journal 2022; 43: 367-76.

5. Mahaffey K, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Fabbrini E, Sun T, Li Q, Desai M, Matthews D. Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018; 137: 323-34.

6. Mahaffey K, Jardine M, Bompoint S, Cannon C, Neal B, Heerspink H, Charytan D, Edwards R, Agarwal R, Bakris G, Bull S, Capuano G, de Zeeuw D, Greene T, Levin A, Pollock C, Sun T, Wheeler D, Yavin Y, Zhang H, Zinman B, Rosenthal N, Brenner B, Perkovic V. Canagliflozin and Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus and Chronic Kidney Disease in Primary and Secondary Cardiovascular Prevention Groups. Circulation 2019; 140: 739-50.

7. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). In, 2017.

8. FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine

canagliflozin (Invokana, Invokamet, Invokamet XR). In.

9. Fulcher G, Matthews D, Perkovic V, de Zeeuw D, Mahaffey K, Mathieu C, Woo V, Wysham C, Capuano G, Desai M, Shaw W, Vercruysse F, Meininger G, Neal B. Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes. Diabetes, obesity & metabolism 2016; 18: 82-91.

10. Neal B, Perkovic V, de Zeeuw D, Mahaffey K, Fulcher G, Ways K, Desai M, Shaw W, Capuano G, Alba M, Jiang J, Vercruysse F, Meininger G, Matthews D. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes care 2015; 38: 403-11.

11. Chang HY, Singh S, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes. JAMA Intern Med 2018; 178: 1190-98.

12. Kavanagh N, Ryan E, Widaa A, Sexton G, Fennell J, O'Rourke S, Cahill K, Kearney C, O'Brien F, Kerrigan S. Staphylococcal Osteomyelitis: Disease Progression, Treatment Challenges, and Future Directions. Clinical microbiology reviews 2018; 31.

13. Prokesch BC, TeKippe M, Kim J, Raj P, TeKippe EM, Greenberg DE. Primary osteomyelitis caused by hypervirulent Klebsiella pneumoniae. The Lancet Infectious Diseases 2016; 16: e190-e95.

14. Shone A, Burnside J, Chipchase S, Game F, Jeffcoate W. Probing the validity of the probe-to-bone test in the diagnosis of osteomyelitis of the foot in diabetes. Diabetes care 2006; 29: 945.

15. Schwegler B, Stumpe K, Weishaupt D, Strobel K, Spinas G, von Schulthess G, Hodler J, Böni T, Donath M. Unsuspected osteomyelitis is frequent in persistent diabetic foot ulcer and better diagnosed by MRI than by 18F-FDG PET or 99mTc-MOAB. Journal of internal medicine 2008; 263: 99-106.

16. Newman L, Waller J, Palestro C, Schwartz M, Klein M, Hermann G, Harrington E, Harrington M, Roman S, Stagnaro-Green A. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. JAMA 1991; 266: 1246-51.

17. Game F. Management of osteomyelitis of the foot in diabetes mellitus. Nat Rev Endocrinol 2010; 6: 43-7.

18. Lavery L, Armstrong D, Wunderlich R, Mohler M, Wendel C, Lipsky B. Risk factors for foot infections in individuals with diabetes. Diabetes care 2006; 29: 1288-93.

19. Katsuhara Y, Ikeda S. Correlations Between SGLT-2 Inhibitors and Acute Renal Failure by Signal Detection Using FAERS: Stratified Analysis for Reporting Country and Concomitant Drugs. Clin Drug Investig 2021; 41: 235-43.

20. Raschi E, Poluzzi E, Salvo F, Pariente A, De Ponti F, Marchesini G, Moretti U. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: What a clinician should know on disproportionality analysis of spontaneous reporting systems. Nutrition, metabolism, and cardiovascular diseases : NMCD 2018; 28: 533-42.

21. Min J, Osborne V, Kowalski A, Prosperi M. Reported Adverse Events with Painkillers: Data Mining of the US Food and Drug Administration Adverse Events Reporting System. Drug safety 2018; 41: 313-20.

22. Moreland-Head LN, Coons JC, Seybert AL, Gray MP, Kane-Gill SL. Use of Disproportionality Analysis to Identify Previously Unknown Drug-Associated Causes of Cardiac Arrhythmias Using the Food and Drug Administration Adverse Event Reporting System (FAERS) Database. J Cardiovasc Pharmacol Ther 2021; 26: 341-48.

23. Bate A, Lindquist M, Edwards I, Olsson S, Orre R, Lansner A, De Freitas R. A Bayesian neural network method for adverse drug reaction signal generation. European journal of clinical pharmacology 1998; 54: 315-21.

24. Zhu J, Yu X, Zheng Y, Li J, Wang Y, Lin Y, He Z, Zhao W, Chen C, Qiu K, Wu J. Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map. The Lancet Diabetes & Endocrinology 2020; 8: 192-205.

25. Bonora B, Raschi E, Avogaro A, Fadini G. SGLT-2 inhibitors and atrial fibrillation in the Food and Drug Administration adverse event reporting system. Cardiovascular diabetology 2021; 20: 39.

26. Pasquel F, Lansang M, Dhatariya K, Umpierrez G. Management of diabetes and hyperglycaemia in the hospital. The lancet Diabetes & endocrinology 2021; 9: 174-88.

27. Davies M, D'Alessio D, Fradkin J, Kernan W, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler D, Buse J. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018; 61: 2461-98.

28. Ramsey S, Newton K, Blough D, McCulloch D, Sandhu N, Reiber G, Wagner E. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes care 1999; 22: 382-7.

29. Eckman M, Greenfield S, Mackey W, Wong J, Kaplan S, Sullivan L, Dukes K, Pauker S. Foot infections in diabetic patients. Decision and cost-effectiveness analyses. JAMA 1995; 273: 712-20.

30. Kobayashi H, Fujita R, Hiratsuka S, Shimizu T, Sato D, Hamano H, Iwasaki N, Takahata M. Differential effects of anti-RANKL monoclonal antibody and zoledronic acid on necrotic bone in a murine model of Staphylococcus aureus-induced osteomyelitis. Journal of orthopaedic research : official publication of the Orthopaedic Research Society 2022; 40: 614-23.

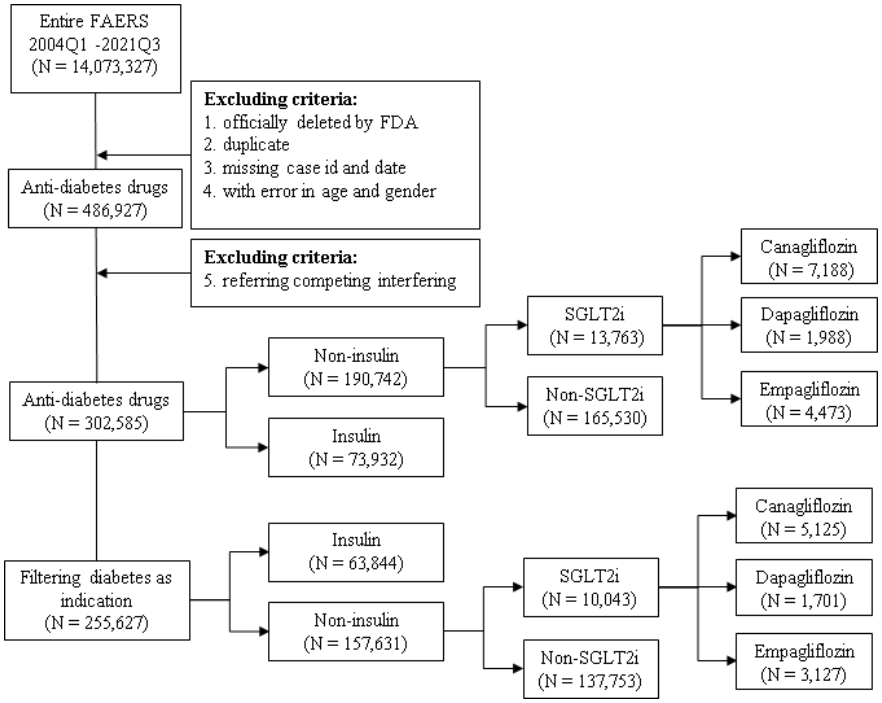
31. Zhang L, Wang Y, Zhao J, Li Y, Chen H. Sex Differences in Osteomyelitis of the Foot in Persons With Diabetes Mellitus: A Meta-Analysis. Wound management & prevention 2021; 67: 19-25.

32. Almenoff J, Pattishall E, Gibbs T, DuMouchel W, Evans S, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clinical pharmacology and therapeutics 2007; 82: 157-66.

33. Ang PS, Chen Z, Chan CL, Tai BC. Data mining spontaneous adverse drug event reports for safety signals in Singapore - a comparison of three different disproportionality measures. Expert Opin Drug Saf 2016; 15: 583-90.

34. Hou Y, Ye X, Wu G, Cheng G, Du X, He J. A comparison of disproportionality analysis methods in national adverse drug reaction databases of China. Expert Opin Drug Saf 2014; 13: 853-7.

35. Butalia S, Palda V, Sargeant R, Detsky A, Mourad O. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA 2008; 299: 806-13.



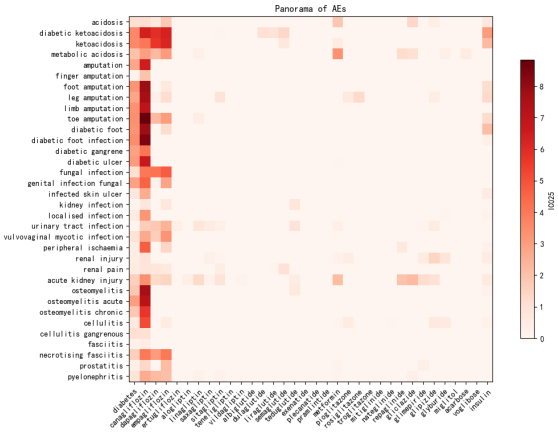


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Table 1 Demographic of reports.docx available at https://authorea.com/users/521230/articles/594254-sodium-glucose-co-transporter-2-inhibitors-sglt2i-treatment-and-risk-of-osteomyelitis-a-pharmacovigilance-study-of-the-faers-database

	Canagliflozin (a/b)	Comparators (c/d)	ROR	95% CI	IC_{025}
Osteomyelitis Total	1,451 /13,998	8,871 /30,885,119	360.89	(340.58–382.41)	7.79
Osteomyelitis	1,214 /14,235	8,346 /30,885,644	315.60	(296.51–335.93)	7.62
Osteomyelitis acute	157 /15,292	228 /30,893,762	1391.14	(1134.55–1705.76)	6.48
Osteomyelitis chronic	72 /15,377	202 /30,893,788	716.11	(546.95–937.60)	5.03
Staphylococcal osteomyelitis	8 /15,441	95 /30,893,895	168.49	(81.87–346.74)	−1.21
	Dapagliflozin (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	1 /4,111	8,999 /29,351,010	0.79	(0.11–5.63)	−2.91
	Empagliflozin (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	6 /7,122	9,907 /31,994,224	2.72	(1.22–6.06)	−0.19
	Non-Canagliflozin SGLT2i (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	7 /11,369	9,906 /31,989,977	1.99	(0.95–4.17)	−0.33
	SGLT2i (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis Total	1,461 /25,423	9,230 /31,975,145	199.08	(188.14–210.66)	7.11
Osteomyelitis	1,224 /25,660	8,689 /31,975,686	175.54	(165.14–186.60)	6.95
Osteomyelitis acute	157 /26,727	233 /31,984,142	806.36	(658.39–987.58)	6.43
Osteomyelitis chronic	72 /26,812	211 /31,984,164	407.06	(311.43–532.05)	5.11
Staphylococcal osteomyelitis	8 /26,876	97 /31,984,278	98.15	(47.72–201.86)	−0.30
	Biguanide (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	5 /46,518	14,356 /42,872,910	0.32	(0.13–0.77)	−2.68
	DPP4 (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	2 /16,690	13,362 /40,300,327	0.36	(0.09–1.45)	−2.93
	GLP1 (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	7 /92,476	13,904 /41,505,130	0.23	(0.11–0.47)	−3.03
	Non-SGLT2i & Non-Insulin (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis	40 /423,310	14,321 /42,496,118	0.28	(0.21–0.38)	−2.25
	Non-Insulin (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis Total	1,616 /477,478	13,903 /42,440,792	10.33	(9.81–10.88)	3.14
Osteomyelitis	1,370 /477,724	12,991 /42,441,704	9.37	(8.86–9.91)	3.01
Osteomyelitis acute	163 /478,931	314 /42,454,381	46.02	(38.08–55.60)	4.45
Osteomyelitis chronic	75 /479,019	432 /42,454,263	15.39	(12.04–19.66)	3.15
Staphylococcal osteomyelitis	8 /479,086	166 /42,454,529	4.27	(2.10–8.68)	0.42
	Insulin (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis Total	92 /192,932	15,427 /42,725,338	1.32	(1.08–1.62)	0.09
Osteomyelitis	89 /192,935	14,272 /42,726,493	1.38	(1.12–1.70)	0.15
Osteomyelitis chronic	1 /193,023	506 /42,740,259	0.44	(0.06–3.11)	−3.16
Osteomyelitis acute	1 /193,023	476 /42,740,289	0.47	(0.07–3.31)	−3.13
Staphylococcal osteomyelitis	1 /193,023	173 /42,740,592	1.28	(0.18–9.14)	−2.91
	All glucose lowering drugs (a/b)	**Comparators (c/d)**	**ROR**	**95% CI**	**IC_{025}**
Osteomyelitis Total	1,787 /799,790	13,732 /42,118,480	6.85	(6.52–7.20)	2.55
Osteomyelitis	1,532 /800,045	12,829 /42,119,383	6.29	(5.96–6.63)	2.44
Osteomyelitis acute	168 /801,409	309 /42,131,903	28.58	(23.69–34.49)	3.85
Osteomyelitis chronic	77 /801,500	430 /42,131,782	9.41	(7.39–12.00)	2.55
Staphylococcal osteomyelitis	10 /801,567	164 /42,132,048	3.21	(1.69–6.07)	0.37