Clinical risk factors predicting genital fungal infections with sodium-glucose cotransporter 2 inhibitor treatment: the ABCD nationwide dapagliflozin audit.

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Abstract

Introduction

Treatment of type 2 diabetes with sodium-glucose cotransporter 2 (SGLT2) inhibitors may result in genital fungal infections. We investigated possible risk factors for developing such infections among patients treated with the SGLT2 inhibitor dapagliflozin.

Methods

The Association of British Clinical Diabetologists (ABCD) collected data on patients treated with dapagliflozin in routine clinical practice from 59 diabetes centres. We assessed possible associations of patient’s age, diabetes duration, body mass index, glycated haemoglobin, renal function, patient sex, ethnicity and prior genital fungal infection, urinary tract infection, urinary incontinence or nocturia, with the occurrence of ≥1 genital fungal infection within 26 weeks of treatment.

Results

1049 out of 1116 patients (476 women, 573 men) were analysed. Baseline characteristics were, mean±SD, age 56.7±10.2 years, BMI 35.5±6.9 kg/m² and HbA₁c 9.4±1.5%. Only patient sex (13.2% women vs 3.3% men) and prior history of genital fungal infection (21.6% vs 7.3%) were found to be associated with occurrence of genital fungal infections after dapagliflozin treatment, adjusted OR 4.22 [95%CI 2.48,7.19], \( P < 0.001 \) and adjusted OR 2.41 [95% CI 1.04,5.57], \( P = 0.039 \), respectively.

Conclusion

Women and patients with previous genital fungal infections had higher risks of developing genital fungal infections with dapagliflozin treatment.
**Introduction**

Type 2 diabetes is characterised by several pathophysiological disruptions including defects in insulin secretion by the pancreas, increased hepatic glucose output and increased insulin resistance in the muscle. It is also now recognised that an adaptive increase in glucose reabsorption in the kidney tubules, mediated by sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2), limits glucosuria and contributes to glucose dysregulation in type 2 diabetes. SGLT2, being higher in capacity and lower in affinity than SGLT1, has become a viable target for pharmacotherapy [1].

Initially available SGLT2 inhibitors include dapagliflozin, canagliflozin and empagliflozin. Among other effects, treatment with SGLT2 inhibitors results in increased glucosuria and natriuresis, and leads to improvements in glycaemia, body weight and blood pressure among patients with type 2 diabetes [1,2]. A recent trial utilising empagliflozin has also demonstrated treatment-led reduction in hospitalisation for heart failure and cardiovascular deaths among patients with type 2 diabetes with high cardiovascular risk [3]. SGLT2 inhibitors are recommended as an option for second or third line therapy in addition to metformin by a joint position statement by the American Diabetes Association and European Association for the Study of Diabetes [4].

Adverse events associated with SGLT2 inhibitor treatment include genital fungal infections, urinary tract infection, volume-related events (hypotension, syncope or dehydration), hypoglycaemia and rarely, ketoacidosis [5-7]. Of these, genital fungal infections appear to be the most prevalent and consistent finding among various trials involving SGLT2 inhibitors. Diabetes patients are at an increased risk of genital fungal infections compared with non-diabetes patients [8]. By inducing glucosuria, treatment with SGLT2 inhibitors likely increases this risk further [9]. Manifestations include vulvo-vaginal infections in female patients and balanitis or balanoposthitis in male patients. Typically, trials of SGLT2 inhibitors have shown genital fungal infections to be more common among women, occur early after treatment initiation (within 24 weeks), and are usually not severe enough to warrant treatment discontinuation [9,10].

The Association of British Clinical Diabetologists (ABCD) is the diabetes specialist society in the UK. ABCD has been conducting nationwide audits of new diabetes
therapies once they become available for use in routine clinical practice, including thus far audits on the glucagon-like peptide-1 receptor agonists exenatide twice daily, liraglutide and exenatide once weekly, as well as on dapagliflozin, canagliflozin and insulin degludec. These audits hoped to accelerate learning of the new therapies and extend surveillance of adverse events in a real-world setting. All the audits bear similar designs including nationwide solicitation but voluntary participation of diabetes centres, collection of data of patients on certain diabetes treatments based on routine treatment decisions and clinical justification of their use, and utilisation of purposed-built audit software to collect pre-specified audit queries. We utilised data from the current ABCD dapagliflozin audit in an attempt to identify clinical predictors for developing genital fungal infections among patients treated with dapagliflozin.

Methods

Subjects

ABCD invited diabetes centres in hospitals and primary care across UK to submit de-identified data of patients routinely treated with dapagliflozin 10mg daily. A few diabetes centres from Hong Kong, Brazil and Australia were also invited to participate as “proof of concept” that a larger scale international audit database can be achieved. Between October 2014 and September 2016, 59 diabetes centres enrolled and submitted varying degrees of data depending on date of participation, the frequency of patients’ health visits and duration of dapagliflozin treatment that had taken place.

Data requested included patients’ age, sex, ethnicity as well as pre- and post-dapagliflozin treatment information including diabetes treatments, glycated haemoglobin (HbA1c), body weight, body mass index (BMI), systolic and diastolic blood pressure, lipid parameters, alanine transaminotransferase and creatinine, whenever these data were available. We accepted laboratory results from individual participating centres. Contributors were asked to identify prior history of genital fungal infections and urinary tract infections within the previous one year, urinary incontinence, nocturia, as well as to report these events or any-other adverse events after treatment.
The audit received data on 1116 patients with at least one follow-up visit after dapagliflozin was initiated. Sixty-four patients with less than 12 weeks data contribution or follow-up, this not being due to discontinuation of dapagliflozin within 12 weeks of initiation, were excluded. Three patients were excluded due to previous SGLT2 inhibitor use. Data on the remaining 1049 patients were analysed.

**Outcome and risk variables**

Patients were divided into those who developed ≥1 genital fungal infection within 26 weeks of treatment and those who did not. We included genital fungal infection proven by microbiology or clinical examination or when there were suggestive symptoms such as pruritus or redness in the genital area. We then assessed possible associations of patient’s age, duration of diabetes, BMI, HbA1c, estimated glomerular filtration rate (eGFR), sex, ethnicity, previous genital fungal infection, previous urinary tract infection, previous urinary incontinence and previous nocturia with the development of genital fungal infections. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

**Statistical analyses**

Univariate associations were tested using Student’s t-test and Chi-Square analysis for continuous and categorical variables, respectively. Fisher’s exact test was used for categorical variables when the number of events was less than five. Variables with statistically significant association in univariate analyses (P < 0.05) were entered into a binary logistic regression analysis. Analyses were performed combining female and male patients together and then separately to exclude sex-specific interactions. Statistical analyses were performed using Minitab® Release 14 (Minitab Ltd, Coventry, UK).

**Results**

The overall proportion of patients reporting ≥1 treatment emergent genital fungal infections was 82/1049 (7.8%). The majority (95.1%) of the reports of genital fungal
infection occurred in the first follow-up visit, which occurred at a median of 18 [interquartile range 13-26] weeks after starting dapagliflozin. 109 (10.4%) patients discontinued dapagliflozin permanently within 26 weeks, 25 (2.4%) due to issues with genital fungal infections.

Baseline characteristics of patients (476 women and 573 men) and possible association with subsequent genital fungal infections are shown in Table 1 and 2. Genital fungal infections were more common among women (13.2%) compared with men (3.3%) (difference $P < 0.001$). Patients reporting a history of genital fungal infections were also more likely to have infection after dapagliflozin treatment compared with patients who did not report such a history (21.6% vs 7.3%, $P = 0.007$). Women with prior history of genital fungal infection were at the greatest risk with 27.6% of these patients developing treatment-emergent genital fungal infections. No other variables were found to be associated with the occurrence of genital fungal infections, either analysed among the entire cohort or by the sexes separately. In a simple two-variable logistic regression, the likelihood for developing genital fungal infections for female sex and previous genital fungal infections were, adjusted odds ratio and 95% confidence interval, OR 4.22 [95%CI 2.48,7.19], $P < 0.001$ and OR 2.41 [95%CI 1.04,5.57], $P = 0.039$, respectively.

**Discussion**

Our study, utilising “real-life” clinical data, identified patient sex and prior history of genital fungal infection to be the only risk factors for developing genital fungal infections with dapagliflozin treatment. Only a small proportion of patients discontinued dapagliflozin due to such infections.

Results from our study are similar to clinical trial data of SGLT2 inhibitors. In a pooled analysis of clinical trials utilising dapagliflozin 10mg, the incidence of genital fungal infection was 9.7% among women and 4.2% in men. The incidence of genital fungal infection among patients with a history of genital infections was 25.0% [9]. In a pooled analysis of trials utilising canagliflozin 100mg and 300mg, the incidence of genital fungal infections were 10.4% and 11.4% in women and 4.2% and 3.7% in men, respectively. Women with a previous history of vulvovaginitis had a higher
incidence of treatment emergent genital fungal infection (29.0%) in the same analysis. Treatment discontinuation due to genital fungal infection occurred in 0.9% and 0.5% of the canagliflozin 100mg and 300mg groups, respectively [10]. In a large cardiovascular outcome study of empagliflozin, pooled events for the 10mg and 25mg dose showed the incidence of genital fungal infection to be 10.0% in women and 5.0% in men [3].

We did not identify other risk factors for developing genital fungal infection with dapagliflozin treatment to help with treatment decisions in the clinical setting. Baseline HbA1c was not a risk factor, a similar finding noted by Johnsson et al [9] and Nyirjesy et al [10]. In contrast, Nyirjesy et al has reported more frequent genital fungal infection among women with younger age or higher BMI (but not among men) [10]. A low incidence of vulvovaginal infections (<5%) was observed in a study of canagliflozin treatment among Japanese patients with type 2 diabetes [11] but we did not find a lower incidence of infections in our Asian cohort. A low incidence of genital fungal infections was also observed in type 2 diabetes patients with moderate renal impairment treated with canagliflozin [12], possibly due to attenuated effects of urinary glucose excretion in patients with reduced renal function. We did not find an effect of renal function on developing genital fungal infection in our study. However, only 5.3% of patients with calculated eGFR in our study had eGFR below 60 ml/min/1.73m^2. Dapagliflozin is not licensed for patients with eGFR below 60 ml/min/1.73m^2 [13].

Our study suggests that women with a history of genital fungal infections should be counselled closely with regards to the risks of genital infection with dapagliflozin treatment. Nonetheless, the risks of treatment should be weighed against the beneficial metabolic profile associated with treatment. When starting SGLT2 inhibitor treatment, patients may need to be told to look out for the specific symptoms of genital fungal infections. A management plan if genital infections occur should also be considered, be it to self-treat with topical or oral antifungal therapy, or to seek medical review. Recurrent genital infections should prompt consideration of an alternative diabetes treatment.

The strength of our study includes having a large number of participating centres with different ethnic groups studied and having pre-specified queries on genital
fungal infection and urinary symptoms before and after treatment. The limitations include the possibility of under-reporting of events due to patient drop-outs or poor recall of events. The number of patients with previous urinary tract infections or urinary incontinence was also very small so we may not have detected a significant interaction with the occurrence of genital fungal infection.

Conclusion

Women and patients with previous genital fungal infections are at higher risk of developing genital fungal infections with dapagliflozin treatment. A history of genital fungal infection should be routinely obtained when considering SGLT2 inhibitor treatment, and women should be given closer consideration both in terms of the decision to start treatment and for monitoring of adverse events.

Conflicts of interest

DSM and KAA have worked as consultants on the ‘Expert on Demand Programme’ for AstraZeneca, providing education and advice on the use of dapagliflozin. SCB has received honoraria, research funding and attended advisory boards funded by Astra Zeneca. KYT, MY, DJB, TAC, LLC, AMR, KAA, REJR have no conflicts of interest to declare.

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Acknowledgment

We like to thank all ABCD Nationwide Dapagliflozin Audit contributors for sending data to the audit.
REFERENCES


Appendix

**ABCD nationwide dapagliflozin audit – initial setup, maintenance and nationwide analysis:** Ryder REJ, Adamson K, Bailey CJ, Walton C, Thong KY, Sen Gupta P, Cull ML, Yadagiri M. Statistician: Blann A

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Wales

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Table 1 - Baseline characteristics (continuous variables) and their association with genital fungal infections among patients treated with dapagliflozin

<table>
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<tr>
<th></th>
<th>n</th>
<th>≥1 Genital fungal infection</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1049</td>
<td>56 ± 11</td>
<td>57 ± 10</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>1048</td>
<td>11 ± 6</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>HbA1c (%; mmol/mol)</td>
<td>1045</td>
<td>9.2 ± 1.5; 77 ± 16</td>
<td>9.4 ± 1.5; 79 ± 16</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1023</td>
<td>34.0 ± 7.4</td>
<td>35.4 ± 6.9</td>
</tr>
<tr>
<td>eGFR* (ml/min/1.73m²)</td>
<td>932</td>
<td>92 ± 18</td>
<td>90 ± 18</td>
</tr>
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</table>

Variables are shown as mean ± SD

eGFR; estimated glomerular filtration rate, calculated by the CKD-EPI equation.
Table 2 - Baseline characteristics (categorical variables) and their association with genital fungal infections among 1049 patients treated with dapagliflozin

<table>
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<th>≥1 Genital fungal infection</th>
<th>P value</th>
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<td>No</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>63 (13.2)</td>
<td>413 (86.8)</td>
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<tr>
<td>Male</td>
<td>19 (3.3)</td>
<td>554 (96.7)</td>
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<tr>
<td>Ethnicity (n=947)</td>
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<tr>
<td>Caucasian</td>
<td>51 (7.1)</td>
<td>671 (92.9)</td>
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<td>Asian</td>
<td>20 (10.8)</td>
<td>166 (89.2)</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>3 (10.7)</td>
<td>25 (89.3)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (9.1)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>Previous genital fungal infection &lt;1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (21.6)</td>
<td>29 (78.4)</td>
</tr>
<tr>
<td>No</td>
<td>74 (7.3)</td>
<td>938 (92.7)</td>
</tr>
<tr>
<td>Previous urinary tract infection &lt;1 year</td>
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<tr>
<td>Yes</td>
<td>2 (9.5)</td>
<td>19 (90.5)</td>
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<td>No</td>
<td>80 (7.8)</td>
<td>948 (92.2)</td>
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<td>History of urinary incontinence</td>
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<td>Yes</td>
<td>2 (15.4)</td>
<td>11 (84.6)</td>
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<td>No</td>
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<td>956 (92.3)</td>
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<td>History of nocturia</td>
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<td>Yes</td>
<td>11 (13.6)</td>
<td>70 (86.4)</td>
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<td>No</td>
<td>71 (7.3)</td>
<td>897 (92.7)</td>
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Variables are shown as n (%)