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Research Article

Genital Infection Risk Profile in Post-menopausal Women with Type 2 Diabetes Mellitus on Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

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Abstract

Background: patients with type 2 diabetes mellitus (T2DM) often discontinue Sodium-Glucose Cotransporter-2-inhibitors (SGLT2-Is) despite high efficacy and safety due to genital infection (GI).

Aim of the study: to assess real-life GI risk profile in post-menopausal T2DM patients educated on strict hygiene-based prevention practices (SHBPPs) due to their intrinsic GI susceptibility.

Methods: 721 post-menopausal T2DM patients willing to follow SHBPPs were randomly assigned to three different SGLT2-Is (intervention group, IG, n=318) or other drugs (control group, CG, n=403) for three- months. Before and after treatment, they underwent routine lab tests and completed a specific questionnaire.

Results: GIs more often occurred (9.6 %; $p < 0.001$) among IG women non-adhering to SHBPPs (41.5%) vs. the 2.9% of adhering ones. Conversely CG women had superimposable GI rates (2.7% vs. 3.1%, respectively, p n.s.) whether or not adhering to SHBPPs (51.4% vs. 49.6%, respectively, p n.s.). The typical profile of women on SGLT2-Is at higher risk for GIs included (i) poor adherence to SHBPPs, (ii) older age, (iii) higher BMI, (iv) poor glucose control as witnessed by high HbA1c levels, and (v) antihypertensive drug utilization.

Conclusion: physicians should consider the importance of strict hygiene control in their post-menopausal T2DM patients undergoing SGLT2-I treatment and thus utilize better-focused education strategies in that specific subgroup to prevent or rehabilitate from repeated GIs.

Keywords: Type 2 Diabetes; SGLT2-Inhibitors; Genital Infections; Menopause; Prevention; Rehabilitation

Key Points

- In daily clinical practice, GIs seem to complicate SGLT2-I-treatment in postmenopausal women with T2DM more often than reported in large clinical trials;
- In our series, despite being repeatedly informed about their vast clinical relevance, most of them disregard best hygiene prevention practice recommendations;
- GIs are more frequent among those who fail to adhere to those recommendations;
- Older age, higher BMI and HbA1c levels, and antihypertensive agent utilization are most often associated with GIs in women disregarding best hygiene prevention/rehabilitation practice recommendations.

Introduction

Sodium glucose co-transporter-2 inhibitors (SGLT2-I), also called gliflozins, represent the newest class of anti-hyperglycemic agents [1] whose effects depend on the ability to dramatically reduce the threshold for maximum glucose tubular resorption rate in patients with type 2 diabetes mellitus (T2DM), with consequently enhanced glycosuria [2]. According to several meta-analyses of randomized controlled trials (RCTs), they can reduce glycated haemoglobin (HbA1c) levels, fasting plasma glucose, body weight, and blood pressure without increasing the risk for hypoglycemic events [3,4]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved canagliflozin, dapagliflozin, and empagliflozin for clinical use in patients with T2DM [5-10]. Quite recently ertugliflozin also entered the list, while other three molecules from the same group, including ipragliflozin, luseogliflozin, and tofogliflozin, were approved in Japan [11-13].

By proving effective and safe in terms of glucose and weight control and of cardio-vascular and renal protection, the whole drug class achieved a first-line position among treatment options, especially for complicated T2DM [14,15].

Due to elevated urinary glucose output, T2DM increases the risk for urinary tract infections (UTIs) and non-sexually transmitted genital infections (GIs) [15]. Massive glycosuria might, indeed, already cause commensal genital microorganism overgrowth in people with T2DM [16] and is likely to increase the risk for GIs and UTIs when further aggravated by SGLT2-Is [17]. Based on such considerations, in December 2015, the FDA warned that SGLT2-Is might result in severe UTIs [18].

Some systematic reviews and meta-analyses examined this issue [3,4,19,20]. One of them, including 77 randomized controlled trials (RCTs) enrolling 50,820 participants and having a 44 to 7,028 sample size range, suggested a higher genital infection risk in those treated with SGLT2-Is than in controls (1,521/24,017 [6.33%] vs. 216/12,552 [1.72%]; RR 3.30, 95% confidence interval (CI) 2.74 to 3.99; $p < 0.01$) with a preference for women, especially post-menopausal ones (the F:M ratio being 2: 1), in the absence of any significant differences in UTI rate (2,526/29,086 [8.68%] vs. 1,278/14,940 [8.55%]; risk ratio (RR) 1.05, 95% CI 0.98 to 1.12; p n.s.) [21]. However, despite being similar, the overall GI rate seemed to differ a bit among SGLT2-I molecules.

Several factors may favor UTIs in women, mainly including fungal or bacterial contamination, having almost undistinguishable clinical features, and sometimes involving vulvar structures as well [22]. Vulvovaginal candidiasis (VVC) represents a genital infection caused by the *Candida* species (i.e., *C. Albicans*, or, less frequently, other yeasts), coming with specific symptoms [23], and classified as the second most frequent cause of vaginitis after bacterial vaginosis (BV) occurring in sexually active women [24]. In greater detail, *Candida* species are commensals in the vaginal tract of 10%-20% of healthy women and cause no clinical symptoms [25] with a higher colonization prevalence (33.3%) in specific population groups, such as women with T2DM [26]. Conversely, BV reflects the overgrowth of certain bacteria disturbing the average balance existing with other ones in the vagina. It is the most common vaginal condition in women aged 15-44 [23,27]. To date, the why some women get it is unknown. However, BV is widely accepted to be less common in post-menopausal than in fertile age women, and its main risk factors are regular sexual activity - especially having sex with several partners - and vaginal irrigation [23].

Symptoms of GIs in women are: (i) abnormal white or gray vaginal discharge, (ii) often foul-smelling vaginal discharge (fish-like odor in BV), (iii) vaginal pain, itching, or burning, (iv) dysuria, (v) dyspareunia.

Based on available data, we designed this real-life observational study to verify whether, upon initiation of SGLT2-I therapy, a careful education strategy might help lower GI rates in post-menopausal women with T2DM, i.e., a population group particularly prone to GIs [21] and to assess the real-life GI risk profile of newly SGLT2-I-treated post-menopausal women with type 2 diabetes mellitus (T2DM) eventually poorly adhering to best hygiene prevention practice despite being carefully educated to do so.

Methods

The present study was carried out by a network of 5 identically organized outpatient diabetes care units (DCUs) previously documented to attain the same performance levels and to come from a single institution, called Nefrocenter Network in Southern Italy, a private consortium supported by the National Health System in association with Naples University "Luigi Vanvitelli" for several clinical aspects, including the ethics committee, a single electronic database and participation in the so-called AMD Annals Initiative [28].

Once approved by the Ethics Committee of the "Luigi Vanvitelli" Naples University, Italy (protocol n. 19/1287, Oct. 11, 2019), the study was conducted in conformance with good clinical practice standards, led according to the Declaration of Helsinki 1975 and subsequent amendments.

When meeting the inclusion/exclusion criteria listed below, all T2DM post-menopausal women consecutively referring to the abovementioned DCUs entered the study. Based on 2020 American Diabetes Association (ADA 2020) recommendations and the Italian Drug Authorizing Agency (AIFA) [29], individually tailored doses

of SGLT-2Is were given as such or added to other oral antihyperglycemic agents [OHAs] or insulin. The molecules of choice (i.e., empagliflozin, dapagliflozin, or canagliflozin)) were randomly assigned according to an algorithm meant to distribute them among participants evenly. During the enrollment period, 721 subjects consecutively entering our clinical database met the inclusion/exclusion criteria listed below: 318 entered the SGLT2-I intervention group (IG), the remaining 403 women on other oral or injectable antihyperglycemic agents (OHAs) served as the control group (CG). All signed the informed consent to the study protocol.

Inclusion criteria

- T2DM
- post-menopausal state (no menstrual cycles for at least the last 12 months)
- 55 to 75 years of age
- no symptoms or lab-assessed signs of urogenital infection for at least the last 6 months
- informed consent
- normal urine lab test results.

Exclusion criteria

- eGFR $\leq$60 ml/min/1.73 m^2
- Urinary incontinence
- Previous hysterectomy or pelvic surgery
- Severe liver disease
- Chronic corticosteroid treatment
- Recurrent urogenital infections
- Routinely use of panty liners
- Prolapsed uterus, vagina, or rectum
- Previous necrotizing perineal fasciitis (Fournier's gangrene).

T2DM diagnosis was made or confirmed by each participating DCU according to ADA Standards of Medical Care in Diabetes 2020 criteria [30]. The International Classification of Diseases, Clinical Modification (ICD-10) served as a basis to define T2DM diagnosis and comorbidities or diabetes-related/unrelated complications [31].

After signing an informed consent to the study at enrollment, all subjects underwent careful anamnestic investigations with particular reference to GI symptoms and signs, physical examinations, and lab tests including microalbuminuria and urine culture for bacteria and fungi to prevent women with asymptomatic infections from being included in the study. Individual participant characteristics were obtained from the only diabetes-related electronic medical database shared by all participating DCUs.

Patients from IG took the SGLT2-I pill with one or two glasses of water at the same time of day, while those from the CG followed their previously prescribed non-SGLT2-I-based treatment schedule. All patients were instructed to pay special attention to eventually occurring GI symptoms during the follow-up while strictly following the GI prevention recommendations (GIPR) issued by the Gender Medicine Study Group of the Associazione Medici Diabetologi (AMD) [32] (Table A supplementary material).

The prevention decalogue

The first prevention tool against genital infections in people with diabetes is represented by achieving and maintaining optimal metabolic control.
1. Wash the intimate area properly. Proper cleansing must be carried out by passing from the vagina to the anus and not vice versa, to avoid infecting the vaginal area with harmful germs present in the anal area. It is good to wash them once a day and always after each sexual intercourse and after defecation. Avoid too aggressive soaps which can alter the correct balance of bacterial flora, and do not abuse intimate deodorants and vaginal irrigation, the latter to be used only on gynecologist advice. Water and bicarbonate are also good, in the presence of vulvar itching.
2. Avoid excessively tight and adherent clothing (trousers, briefs, bodysuits): the continuous garment rubbing against genitals can promote irritation easily turning into infections.
3. Limit the use of panty liners, which create a warm-humid environment ideal for germ overgrowth; change tampons, especially internal ones, quite often upon menstruation.
4. Wear underwear made of natural fabrics, preferably cotton: synthetic fibers, in fact, prevent normal skin transpiration and create a warm-humid environment, which favors germ proliferation.
5. Always use condoms for casual sex.
6. Follow a varied and balanced diet, rich in fiber to promote intestinal transit and avoid dairy products and sugary drinks as much as possible.
7. Use only your own personal towel, even with your family. In public restrooms, use a toilet seat cover or protect the toilet seat with toilet paper. Do not sit on the edge of any pool.
8. Do not neglect even mild symptoms, such as burning, itching and foul-smelling discharge: consult your doctor, as vaginal infections, when diagnosed and treated early enough, recover more easily.
9. IUD-user must undergo periodic checks and, at the slightest disturbance, consult the gynecologist.
10. DO NOT SELF-MEDICATE!

Table A: (Supplementary Material) Recommendations for the prevention of GI infections in women with diabetes:

Manicardi V, Napoli A, Li Volsi P., *et al*. Recommendations for the prevention of uro-genital infections in women with diabetes: The decalogue of prevention. AMD Gender Medicine Study Group (Associazione Medici Diabetologi) 2016.

https://aemmedi.it/wp-content/uploads/2016/09/Prevenzione_Inf_gen_donna.pdf

For the study, we specifically prepared the Female Genital Infection Symptoms Questionnaire (FGISQ) based on GIPR recommendations and checked for appropriate question comprehension and answer concordance as described below by previously administering it to 40 post-menopausal women with T2DM three times at five-day intervals. Answer concordance was 97%. Based on a specific nurses' inquiry and help request rate by patients completing the test, question comprehension was 98%. FGISQ consisted of sections A and B (Figure 1/A and 1/B). In greater detail, we changed question n.5 from Section A by considering that some women had kept sexually active, and question n.8 to assess the intensity of eventually occurring GI -symptoms. We also refrained from formulating any question related to recommendation n.9 as useless (all were post-menopausal, indeed).

Adherence evaluation relied on a score arbitrarily defined according to the first six answers to FGISQ Section A as follows: (i) 0 - 1 = 0 points; (ii) 2 = 1 point; (iii) 3 - 4 = 2 points (questions 7 and 8 were not taken into consideration because not all patients kept on regular sexual activity). Following this method, hygiene prevention

FEMALE GENITAL INFECTION PREVENTION QUESTIONNAIRE Part A (FGISQ-A)

The following questions address your treatment regimen and, in particular, your adherence rate to the recommendations on the prevention of vaginal and vulvo-vaginal infections during treatment with an SGLT2-I drug.

Please answer each question by circling a number on each scale or crossing out an answer box.

1. Did you remember to follow best personal hygiene practice from Recommendations, point 1?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(about 50%)	(80%)	(80 to 100%)	(100%)

2. Did you use undergarments suggested by Recommendations, point 2 ?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(about 50%)	(80%)	(80 to 100%)	(100%)

3. Did you avoid panty liners as suggested by Recommendations, point 3?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(about 50%)	(80%)	(80 to 100%)	(100%)

4. Did you use the underware as suggested by Recommendations, point 4?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(about 50%)	(80%)	(80 to 100%)	(100%)

5. Did you adhere to diet as suggested in Recommendations, point 6?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(about 50%)	(80%)	(80 to 100%)	(100%)

6. Did you follow the best hygiene prevention practice suggested by Recommendations, point 7?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(about 50%)	(80%)	(80 to 100%)	(100%)

(Version approved on October 11, 2019 by the Ethics Committee of Campania University "Luigi Vanvitelli", Prot. N. 19/1287).

See text for arbitrarily adopted scoring method.

Figure 1A: Female Genital Infection Symptoms Questionnaire. Part A (FGISQ-A) is addressed to the general prevention recommendations of genital infections in women, taken from the recommendations (reference n 28, and Table A, supplementary material), only 6 of which have been transformed into general questions. Part B (FGISQ-B), investigating genital infection symptoms and sexual habits, is unscored and resumes GIPR questions 5 and 8 (see supplementary material).

FEMALE GENITAL INFECTION SYMPTOMS QUESTIONNAIRE Part B (FGISQ-B)

1. Have you kept sexually active after menopause onset? (if your answer is no, then skip question n. 2)

NO |__| YES |__|

2. Have you used condoms during intercourses, as suggested in Recommendations, point 5?

|0|	|1|	|2|	|3|	|4|
(never)	(sometimes)	(often)	(quite often)	(consistently)
(0%)	(around 50%)	(80%)	(80 to 100%)	(100%)

3. Did you experience vaginal/yulvo-vaginal discomfort after starting SGLT2-I treatment?

NO |__| YES |__|

In the case you answered yes, you please mark with an "x" experienced symptoms

	SYMPTOMS	NO	YES
1	abnormal white or gray vaginal discharge		
2	foul-smelling vaginal discharge		
3	pain		
4	itching		
5	burning		
6	dysuria *(frequent, difficult and painful urination)*		
7	dyspareunia *(painful sexual intercourse)*		

4. Please describe the intensity of experienced vaginal/yulvo-vaginal discomfort symptoms, if so any:

- **|__| very mild and transient**
- **|__| mild**
- **|__| intense and persistent**
- **|__| very aggressive**

5. Did you self-medicate when experiencing vaginal/yulvo-vaginal discomfort?

NO |__| YES |__|

6. Did you withdraw SGLT2-Is when experiencing vaginal/yulvo-vaginal discomfort?

NO |__| YES |__|

Version approved on October 11, 2019 by the Ethics Committee of Campania University "Luigi Vanvitelli", Prot. N. 19/1287

Figure 1B: Part B (FGISQ-B), investigating genital infection symptoms and sexual habits, is unscored and resumes GIPR questions 5 and 8.

practice-adherent patients (APs) scored 6 to 12; non-adherent patients (NAPs) scored 0 to 5. Possible GI symptoms were evaluated from FGISQ section B. Both FGISQ and physical examination were repeated after three months along with lab tests for serum transaminase, γ-GT, alkaline phosphatase and bilirubin assays, blood cell count, microalbuminuria, and urine culture.

Statistical analysis

Based on previous data pointing to a GI prevalence of 3-6% [16,17], a sample size of 190 subjects per group was calculated to estimate the expected proportions with 8.5% absolute precision and 95% confidence [33]. However, although 220 subjects would have been enough, we went beyond by enrolling 318 subjects in the IG and 403 in the CG to compensate for any unexpectedly high drop-out rate.

We reported patient characteristics as mean ± standard deviation (SD) for continuous variables or number/percentages for categorical variables. We used the SAS Program (Release 9.4, SAS Institute, Cary, NC, USA) to examine variables associated with adherence to GI prevention recommendations by parametric and non-parametric tests as needed (i.e., repeated measures analysis of variance integrated by a two-tailed paired Student's t-test with 95% CI, and Mann–Whitney's U test, Pearson's tests, respectively), and to analyze associations among categorical variables by the $\chi 2$ test with Yates correction or Fisher Exact test. AP and NAP rates entered the Poisson regression models and were expressed as RRs within 95% confidence intervals (95% CI). A $p < 0.05$ was accepted as the least level of statistical significance.

Results

Table 1 summarizes the clinical characteristics, treatment details, and diabetes complications of participants. Numbers and % of subjects treated with each SGLT2-I are reported at the bottom of the table.

Intervention Group (n. 318)		Control Group (n. 403)
Clinical Characteristics		
Age (years) mean ± SD	66.4 ± 8.2	65.3 ± 8.5
Median	65	64
Range	55 – 75	52-75
< 65 years n. (%)	154 (48.5)	199 (49.4)
> 65 years n. (%)	164 (51.7)	204 (50.6)
Diabetes duration (years)	9.5 ± 5.4	9.7 ± 5.8
Smokers n (%)	67 (21)	89 (22)
BMI (Kg/m^2)	29.7 ± 2.6	29.5 ± 2.6
HbA1c (%)	7.5 ± 1.2	7.6 ± 1.0
Total cholesterol (mg/dl)	207.5 ± 18.9	209.0±16.7
HDL cholesterol (mg/dl)	42.4 ± 3.4	41.5 ± 4.6
LDL cholesterol (mg/dl)	106.2 ± 11.7	102.8 ± 15.6
Triglycerides (mg/dl)	168.2 ± 40.8	171.5 ± 37.6
Creatinine (mg/dl)	0.9 ± 0.5	0.9 ± 0.4
eGFR (ml/min/1.73m^2)	90.3 ± 10.4	91.7 ± 10.8
ALT (IU/L)	22.4 ± 11.7	21.2 ± 10.2
AST (IU/L)	25.3 ± 9.8	24.8 ± 8.7
Total Bilirubin (mg/dl)	0.7 ± 0.4	0.8 ± 0.3
ALP (IU/L)	25.8 ± 12.5	28.7 ± 9.4
γ-GT mg/dl)	20.2 ± 9.7	21.4 ± 8.8
Red Blood cell count (10^6/µl)	4.5 ± 0.9	4.6 ± 0.8
White blood cell count (10^3/µl)	5.7 ± 0.8	5.5 ± 0.7
Hb (g/dl)	13.5 ± 1.1	13.8 ± 0.9
Haematocrit (%)	39.4 ± 4.2	38.6 ± 4.7
Platelet count (10^3/µl)	246 ± 3.5	251 ± 4.1
Diabetes Treatment %		
SGLT2-I alone	0.5	-
SGLT2-I + Metformin	27.8	30.5
SGLT2-I + Pioglitazone	0.5	1.0
SGLT2-I + sulphonilureas/ glinides	21.3	22.5
SGLT2-I + GLP1-RA	9.4	11.8
SGLT2-I + Insulin	18.6	20.9
SGLT2-I + other associations*	13.5	13.3
Diabetes complications %		
Cardio/cerebrovascular	18.9	19.5
Lower Limb	18.9	17.3
Retinopathy	31.2	37.35
Microalbuminuria	42.1	48.2
Sensory-Motor Neuropathy	24.1	25.7
Autonomic Neuropathy	32.5	34.2
Lipohypertrophy due to insulin injections	43.3	41.3
Diabetes associated treatments %		
Antihypertensive drugs	57.5	55.9
Lipid-lowering agents	47.8	45.7
Antiplatelet agents or anticoagulants	41.2	44.3
Diuretics	18.9	19.5
SGLT2-I treatment %		
Empagliflozin	32.7	-
Dapagliflozin	33.4	-
Canagliflozin	33.3	-

Table 1: Clinical and treatment characteristics, and diabetes complications of enrolled subjects, as divided into IG and CG. No significant differences between groups were apparent.

* combination of more than 2 hypoglycemic agents (the most frequent association was with insulin and metformin).

All patients completed the study by invariably taking prescribed drugs every day. No changes exceeding 5% occurred in general biochemistry between baseline and follow-up. No group reported either GI symptoms or severe adverse effects throughout the study.

Urine culture allowed to detect high Colony Forming Unit (CFU) levels of yeast (*Candida* Albicans) in 68 e 55 subjects (IG and CG, respectively), of *E. coli* in only 2 and 4, respectively, and of both microorganisms in 17 and 22 cases, respectively. Clinically non-relevant CFU levels were found for yeast in 7 and 10 more women, respectively, and for bacteria in 7 and 11, respectively, in the absence of any GI symptoms. As for adherence to GI prevention recommendations, we observed 186 NAPs and 132 APs (58.5% vs. 41.5%, respectively; $p < 0.01$) in the IG and 50.4% vs. 49.6%, respectively (p ns) in the CG.

No one from NAPs was adherent to recommendation n. five on condom utilization (FGISQ-B, figure B). 140 (44.0%) in the IG and 151 (37.5%) in the CG were sexually active (p n.s.). However, while being almost equally frequent among APs and NAPs (36.7% vs. 38.5%, respectively) in the CG, sexually active women were 71.4% among APs and 24.5% among NAPs in the IG with a clear-cut age difference (< 65-year-old and > 65-year-old, respectively). Despite being significantly more frequent in younger women, sexual activity did not correlate with GI rate.

Table 2 reports the main clinical and laboratory results of the IG and the CG at the end of the follow-up. Opposite to what was observed in the IG, no differences were apparent between NAPs and APs in the CG, whose parameters were superimposable to those of APs from the IG except for regular sexual activity, being present in 37.5% of CG subjects and 44.0% of IG subjects ($p < 0.05$).

	Intervention Group (n.318)			**Control Group (n.403)**		
	Adherent subjects (n. 132)	**Non-Adherent Subjects (n. 186)**	**p**	**Adherent subjects (n. 200)**	**Non-Adherent Subjects (n. 203)**	**p**
Age (years) mean ± SD	61.4 ± 3.6	71.6 ± 6.6	< 0.005	65.2 ± 7.2	65.7 ± 6.3	n.s.
Median	59	68	< 0.005	59	58	n.s.
Range	55 - 66	65 - 75	-	54 - 68	55 - 68	n.s.
< 65 years %	47.1	52.9	<0.002	49.6	48.9	n.s.
≥ 65 years %	34.2	65.8	< 0.002	50.4	51.4	n.s.
Diabetes duration (years)	6 ± 5	10 ± 5	n.s.	9.5 ± 6.4	9.3 ± 5.2	n.s.
Smokers n (%)	22 (51.2)	21 (49.8)	n.s.	21.5	22.7	n.s.
BMI (Kg/m^2)	27.2 ± 2.0	32.6 ± 2.1	<0.05	29.3 ± 7.2	29.7 ± 5.8	n.s.
HbA1c (%)	6.7 ± 0.7	8.0 ± 09	< 0.05	7.5 ± 0.6	7.6 ± 0.8	n.s.
Total cholesterol (mg/dl)	192.5 ± 9.7	226.5 ± 8.9	<0.05	202.2 ± 9.6	208.5 ± 8.8	n.s.
HDL cholesterol (mg/dl)	43.1 ± 3.6	43.8 ± 4.2	n.s.	40.8 ± 5.5	41.9 ± 4.9	n.s.
LDL cholesterol (mg/dl)	105.5 ± 9.7	109.3 ± 11.4	n.s.	100.8 ± 11.3	101.5 ± 10.2	n.s.
Triglycerides (mg/dl)	142 ± 32.2	188 ± 27.6	< 0.02	105.3 ± 15.6	107.4 ± 14.3	n.s.
Creatinine (mg/dl)	0.9 ± 0.5	0.9 ± 0.8	n.s.	0.9 ± 0.3	1.0 ± 0.4	n.s.
eGFR ($ml/min/1.73m^2$)	89.5 ± 8.8	91.7 ± 9.2	n.s.	88.6 ± 10.6	91.4 ± 11.8	n.s.
ALT (IU/L)	31.6 ± 8.4	33.6 ± 9.5	n.s.	33.3 ± 6.4	36.7 ± 5.5	n.s.
AST (IU/L)	28.4 ± 5.3	31.2 ± 5.4	n.s.	26.3 ± 7.2	28.2 ± 8.6	n.s.
Total Bilirubin (mg/dl)	0.8 ± 0.3	0.8 ± 0.2	n.s.	0.9 ± 0.2	0.8 ± 0.3	n.s.
ALP (IU/L)	28.3 ± 12.5	29.2 ± 13.6	n.s.	27.7 ± 3.7	29.4 ± 3.3	n.s.
γ-GT mg/dl)	20.5 ± 8.7	19.8 ± 9.7	n.s.	20.4 ± 3.7	21.6 ± 4.8	n.s.
Red Blood cell ($10^3/\mu l$)	4.3 ± 0.7	4.5 ± 0.6	n.s.	4.4 ± 0.8	4.4 ± 0.5	n.s.
White blood cell ($10^6/\mu l$)	6.0 ± 0.6	6.5 ± 0.8	n.s.	6.0 ± 0.6	6.1 ± 0.5	n.s.
Hb (g/dl)	13.3 ± 1.0	13.5 ± 1.1	n.s.	13.7 ± 0.9	13.4 ± 0.9	n.s.
Hematocrit (%)	41.3 ± 3.5	41.7 ± 5.8	n.s.	38.8 ± 2.5	39.6 ± 2.8	n.s.
Platelet count ($10^3/\mu l$)	244.0 ± 3.3	244.2 ± 3.1	n.s.	247.8 ± 3.3	251.7 ± 4.1	n.s.
Cardio-Vascular Complications %	28.7	30.2	n.s	31.2	30.7	n.s.
Microalbuminuria %	43.9	56.1	< 0.02	45.4	46.8	n.s.
Retinopathy %	33.3	46.7	<0.05	37.5	36.8	n.s.
Sensory Motor Neuropathy %	26.3	29.2	n.s.	28.2	27.6	n.s.

Autonomic Neuropathy %	34.4	35.6	n.s.	35.5	33.7	n.s.
Antihypertensive Drugs n (%)	38.6	61.4	< 0.002	55.3	54.1	n.s.
Lipid-lowering gents %	48.6	51.4	n.s.	47.6	48.3	n.s.
antiplatelet agents or anticoagulants %	44.9	49.1	n.s.	48.5	47.9	n.s.
Diuretics %	48.8	51.2	n.s.			n.s.
Genital Infections %	3.0	9.6	< 0.002	2.8	3.1	n.s.
Regular sexual activity %	71.4	24.6	<0.001	36.7	38.5	n.s.

Table 2: Overall and compared clinical and lab parameters from Adherent and Non-Adherent Subjects. Significance stated by the Mann–Whitney U test and Pearson chi-square test, as appropriate.

In the IG, the significance of observed differences between APs and NAPs, showing that NAPs, besides being 186 (58.5%) vs. 132 (41.5%) of APs ($p < 0.05$), were older (71.6 ± 6.6 vs. 61.4 ± 3.6 years of age; $p < 0.05$), and had higher BMI (32.6 ± 2.1 vs. 27.2 ± 2.0; $p < 0.05$) and HbA1c levels (8.0 ± 09 vs. 6.7 ± 0.7; $p < 0.05$). Diabetes duration and smoking habits were superimposable between groups, as biochemical parameters were too, except for higher triglycerides in NAPs than in APs (188 ± 27.6 vs. 142 ± 32.2; $p < 0.02$).

Among diabetes complications, only retinopathy (46.7% vs. 33.3%, respectively, $p < 0.05$) and microalbuminuria (56.1% vs. 43.9%, respectively, $p < 0.02$) were more frequent in NAPs. Among drugs, only antihypertensives were more common in NAPs (61.4%, vs. 38.6%, $p < 0.002$].

In NAPs, GIs were over three times more frequent too (9.6% vs. 2.9%, $p < 0.002$), yet sexual activity was less often maintained (24.6% vs. 71.4%, $p < 0.001$).

As seen from table 3, based on univariate analysis, NAPs were similar to APs in terms of diabetes durations, smoking habits, general biochemical parameters except for triglycerides, treatment with lipid-lowering/antiplatelet agents, anticoagulants or diuretics, and complications (including cardio-vasculopathy, autonomic or peripheral neuropathy). However, statistically significant associations were apparent at multivariate analysis ($p < 0.05$ to < 0.01) for NAP qualification with age, BMI, HbA1c, antihypertensive drug utilization, and genital infections.

	Univarate logistic regression		**Multivariate logistic regression**	
	Unadjusted Odds Ratio (95% CI)	**Significance**	**Adjusted Odds Ratio (95% CI)**	**Significance**
Age (years) mean ± SD	4.3 (1.30 - 9.10)	0.002	7.3 (1.88 - 22.67)	0.05
BMI (Kg/m^2)	2.9 (1.72 - 7.11)	0.005	3.2 (1.13 - 8.14)	0.05
HbA1c (%)	3.7 (1.55 - 6.57)	0.002	5.5 (2.88 - 7.45)	0.02
Triglycerides (mg/dl)	1.9 (0.72 - 5.21)	0.157	Dropped (0.25)*	-
Genital Infections n (%)	2.8 (2.1 - 2.9)	0.001	1.1 (1.0 - 3.3)	0.01
Regular sexual activity n (%)	2.2 (1.45 - 4.75)	0.001	Dropped (0.37)*	-
Microalbuminuria n (%)	1.6 (1.00 - 2.65)	0.049	Dropped (0.31)*	-
Retinopathy n (%)	1.6 (1.00 - 2.65)	0.116	Dropped (0.51)*	-
Antihypertensive Drugs n %)	3.7 (1.55 - 6.71)	0.002	6.4 (3.13 - 10.78)	0.02

Table 3: Unadjusted and adjusted odds ratios of variables associated with adherence to GI prevention practice recommendations in the Intervention Group.

*sequentially dropped during the final model attainment process due to loss of significance.

Finally, as also seen in table 1, single SGLT-2I displayed an almost superimposable NAP/AP distribution (62 NAPs and 44 APs out of 104 empagliflozin users; 64 NAPs and 48 APs out of 108 dapagliflozin users; 60 NAPs and 40 APs among 106 canagliflozin users).

Discussion

SGLT2-I treatment is acknowledged as effective and safe in T2DM, free from hypoglycemic risks, and protects against cardiovascular and renal complications [14,34,35]. However, it associates with a low GI risk, yet more prominent than observed with other OHAs, pending mostly on women [16,17,21], especially postmenopausal ones [36], and occasionally causing drug discontinuation. Based on that, we designed this real-life study in association with a careful GI prevention strategy based on strict adherence to general and personal hygiene practice recommendations, despite marked glycosuria.

Collected data clearly showed that many participants failed to adhere to those recommendations despite being individually and carefully instructed and educated to do so since the very beginning, as required by their postmenopausal and T2DM condition [21]. Indeed, age-related and hormone-dependent vulvovaginal changes notoriously represent potential risk factors for GIs [23], further aggravated by glycosuria's enhancing effect on bacterial/fungal growth [16,36]. Such a phenomenon easily explains the higher GI rate observed in our series than the one reported in RCTs meant to SGLT-2I effectiveness evaluation [16,25]. Different GI rates could also depend on the fact that our study's primary outcome required a specific and systematic search for GI symptoms and signs. On the opposite, despite including regular reports concerning adverse effects, RCTs mainly looked at efficacy and safety parameters [36-39]. Moreover, the GI occurrence rate in the CG, which reflects the one reported in the general T2DM populations so far [20,21], supports this consideration.

The inability to show any correlation between condom-less sexual activity ad GI rate in our series is no wonder. Indeed, condoms are an effective barrier against GIs. That is why, independently of regular partner attendance or occasional intercourses, the North American Menopause Society suggests their daily life utilization, emphasizing fertile age women living in the developing countries [40-42]. Indeed, our participants were neither from developing countries nor suffering from disadvantaged socioeconomic conditions [43,44]. GI rates are high in developing countries despite little or no access to expensive drugs like SGLT2-Is and widespread old, low-cost OHA utilization. Such a phenomenon might depend on epidemiology, patient phenotypes, cultural conditions and socioeconomic status, and the practice of ritual mutilation, which at present appears particularly widespread in Africa. However, apropos of that, we have to point out that rural populations essentially differ from urbanized ones in those countries and the latter, despite sticking to the western lifestyle and being wealthy enough to afford a costly SGLT2-I treatment, mostly maintain their original uses and customs all the time. Unfortunately, although we cannot provide any supporting data for such a statement, the differences mentioned earlier might influence the relationship between GIs and SGLT2-I utilization shortly within those subpopulations, making our study clinically interesting for low-income countries, too [45-47].

Finally, we consider it clinically reassuring that all three gliflozins shared the same GI rates and caused no severe discontinuation-requiring symptoms, as well as that symptomatic culture-confirmed cases healed smoothly and recovered promptly after topic antimycotic/antibacterial treatment.

Limitations

The results of our study rely on a series of T2DM women characterized by their post-menopausal condition. Despite making the study population non-representative of all T2DM women, this choice was driven by the need to explore GI prevalence in a subset known to be more susceptible to GIs due to local post-menopausal changes.

Another limitation is the short follow-up duration. However, as the literature reports GIs to occur within the first few SGLT2-I treatment weeks, if so ever, three months seem to be enough to explore their overall prevalence.

Conclusion

In conclusion, by observing differences between APs and NAPs in newly SGLT-2I-treated post-menopausal women, a high GI risk profile comes out, specifically characterized by (i) little or no adherence to prevention recommendations, (ii) older age, (iii) higher BMI, (iv) poor glucose control as witnessed by elevated HbA1c levels, and (v) antihypertensive drug utilization.

Based on those risk factors, physicians may intensify education strategies to have patients with such characteristics engaged in improving appropriate hygiene recommendation adherence and thus effectively preventing or getting rehabilitated against GIs, instead of displaying high discontinuation rates.

Education would be of great help, especially for older post-menopausal women trying to attain better overall clinical outcomes through SGLT2-Is.

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Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions

SG, and FS designed the study and wrote the paper. GG, TDC, shared and approved the study protocol, enrolled patients, critically assessed the results, and approved the final text. All members of the Study Group contributed to the critical reading of the paper and approved the final version.

Compliance with Ethical Standards

Ours was a spontaneous, unconditioned study organized and authorized by the Ethics Committee of the Campania University "Luigi Vanvitelli", Naples, Italy, (protocol n. 19/1287 del 11.10.2019).

Ethical Standard

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, as subsequent amendments.

Human and Animal Rights

All followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (both institutional and national), and in accordance with usual clinical practice.

Informed Consent

Written informed consent was obtained from all participants before enrollment.

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Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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