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RESEARCH ARTICLE

DO SODIUM GLUCOSE CO-TRANSPORTER-2 (SGLT-2) INHIBITORS AFFECT LOWER URINARY TRACT, SLEEP AND QUALITY OF LIFE IN PEOPLE WITH TYPE 2 DIABETES?

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ABSTRACT

Purpose: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are primarily preferred in patients with type 2 diabetes. The purpose of this paper was to elucidate the effects of SGLT-2 inhibitor use on patients' voiding habits, sleep, and quality of life**.**
Methods: Our study involved patients with type 2 diabetes who had an SGLT2 inhibitor added to their current treatment. The frequency of day-night urination, lower urinary tract symptoms, sleep and quality of life were assessed both prior to initiation of the treatment and during subsequent 1st and 3rd months.
Results: The study included 38 women and 34 men. At the third month after SGLT-2 inhibitor had been added, there was a significant decrease in HbA1c, triglyceride and microalbumin levels ($p<0.05$). There was no increase in voiding frequency (day/night) and there was no difference in the evaluation of lower urinary tract symptoms, but voiding volumes increased in uroflowmetry. When the short form-36 (SF-36) scale was examined, there was a significant improvement in physical function, one of the sub-parameters ($p = 0.01$). The factor affecting this most, was the improvement in HbA1c.
Conclusion: This paper suggests that SGLT-2 inhibitors don't increase voiding frequency and don't cause an increase in lower urinary tract symptoms.

Key Words: Sodium-glucose cotrasporter-2 inhibitor, lower urinary tract symptoms, nocturia, quality of life, type 2 diabetes.

INTRODUCTION

It is well established that the prevalence of type 2 diabetes is swiftly rising in both developed and developing nations, largely attributed to rapidly evolving lifestyles. Type 2 diabetes mellitus is widely recognised as the most common form of diabetes, accounting for over 90% of cases. (1). Patients with type 2 diabetes typically do not need insulin in the first

years after diagnosis and a considerable proportion may not require it during their lifetime. Many patients can be protected from the effects of hyperglycemia by diet, adequate physical activity, and oral antidiabetics (OAD). Sodium-glucose co-transporter 2 inhibitors (SGLT 2I), one of the oral antidiabetics, targets SGLT-2. SGLT-2 helps reabsorb 90% of filtered glucose in the proximal tubule of the kidney. SGLT 2 inhibitors contribute to the renal excretion of glucose and the reduction of elevated blood glucose in type 2 diabetic patients. Its main advantages are weight loss, low risk of hypoglycemia, and mild lowering effect on blood pressure (2). Studies showed that it slows the progression of kidney damage in diabetics with chronic kidney disease. Using SGLT2 inhibitors in patients with heart failure or those at high risk of heart failure can decrease the likelihood of hospitalization due to heart failure (3,4).

With the use of SGLT 2 inhibitors, an increase in urinary tract and genital infections due to glucosuria and dehydration due to diuresis can be observed (2). An increase in the frequency and amount of urine and an increase in nighttime urinary frequency (nocturia) may be expected in patients using the drug due to its diuretic activity. When the literature was examined, few studies investigated urinary complaints and evaluated the quality of life and sleep related to these complaints (5,6). Complaints such as urinary incontinence, frequent urination and nocturia are expected in diabetic patients. It remains unclear how taking a SGLT-2 inhibitor affects these patients' symptoms, sleep, and quality of life.

The objective of this study was to examine the impact of SGLT-2 inhibitor therapy on the day-night voiding habits of patients and to determine whether these changes have any effect on their quality of life and sleep.

MATERIALS AND METHODS

Study protocol

Ethical approval for the study was obtained from the Non-Interventional Research Ethics Committee of Dokuz Eylul University (Date: 22.02.2023, Decision No: 2023/025-20). Among the type 2 diabetic patients who applied to the endocrinology outpatient clinic for routine check-ups and examination in 2021-2022, male and female patients over the age of 18 who had an SGLT-2 inhibitor added to their treatment were included in the study. Patient files were scanned retrospectively, demographic data, laboratory data, weight changes, day and night urination frequency, urinary incontinence and the effects of these conditions on sleep and quality of life were investigated before treatment and in the 1st and 3rd months of treatment. Patients who reported any urinary symptoms were assessed with uroflowmetry and re-evaluated in the first and third month of treatment at the urology outpatient clinic. Type 1 DM, presence of active urinary tract infection (proven by urine culture), presence of genital infection, history of major surgery on the urinary system, active disease affecting the urinary system, presence of active cancer, patients with any diagnosed sleep problems, who used SGLT before and cases in which the inhibitor was stopped for any reason were not included in the study.

Laboratory Investigations

As part of routine check-ups, serum creatinine, GFR, hemoglobin A1c (HbA1c), triglyceride, LDL cholesterol, and urinary microalbumin values were recorded. Among the evaluated parameters, creatinine, LDL cholesterol, triglyceride, spot urine microalbumin, and creatinine were examined using the spectrophotometric method with a Beckman Coulter AU5800 biochemistry analyzer. GFR was calculated with the CKD-EPI GFR formula. HbA1c was studied using the HPLC method with a Tosoh G8 HPLC analyzer.

Uroflowmetry was performed using the Oruflow device with serial number ORF20210528-04 branded as 'Oruba' for patients with voiding problems and evaluated in the urology department.

Questionnaires

Lower urinary tract symptoms were evaluated with questionnaires (ICIQ-FLUTS/ MLUTS). Daytime sleepiness was examined with the Epworth sleepiness scale and quality of life with Quality of Life Scale-Short Form-36 (SF-36) scale. The effect of nocturia on the quality of life was determined by the NQOL scale. All parameters were evaluated at baseline, and in the first and third months of treatment.

Male lower urinary tract symptoms questionnaire (MLUTS) was applied to males, while FLUTS, which is a questionnaire about female lower urinary system symptoms, was completed by women. The first 5 questions on MLUTS inquire about voiding-related symptoms (V score), the next 6 questions ask about incontinence-related symptoms (I score), the next two questions ask daytime urination frequency (F score)

and nocturnal urination frequency (N score). Among the FLUTS scale components, the 'F score' relates to filling symptoms, the 'V score' asks voiding symptoms, and the 'I' score refers to incontinence symptoms. Uğurlucan and colleagues studied the reliability and validity of the Turkish version of the FLUTS scale in 2020 (7). Similarly, the reliability and validity of the Turkish version of the MLUTS scale were scrutinized by Mertoğlu et al. in 2016 (8).

The SF-36 was administered at the start of treatment as well as at the 1-month and 3-month treatment milestones. The reliability and validity of its Turkish version were established by Koçyiğit and colleagues in 1999 (9). The SF-36 scale is a self-assessment tool that evaluates eight sub-dimensions of health through 36 items. These items assess physical function, social functionality, role difficulties (physical and emotional), mental health, vitality, pain, and general evaluation of health. The form evaluates health on a scale of zero to 100, with a higher score indicating better health. The form provides an evaluation between zero and 100, and a higher score indicates a better level of health.

The NQOL about the effect of nocturnal urination (nocturia) on quality of life consists of 13 questions. The questionnaire was developed and validated by Abraham et al. (10). In the form, the questions are rated between 0 and 4, and the score is obtained by summing all the ratings. As the score increases, it indicates that the quality of life is badly affected by nocturia.

The Epworth sleepiness scale helps detect increased daytime sleepiness. Reliability and validity of the Turkish version was examined by İzci et al. in 2008 (11). It consists of 8 questions. The questions are scored as 0, 1, 2 or 3. While 0-5 points are defined as normal, 11 points and above indicate excessive daytime sleepiness.

Statistical Analysis

The statistical analyses were achieved with the SPSS software package, version 29. The normality of the distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as by assessing skewness and kurtosis to check for distribution symmetry. For variables following a normal distribution, the mean and standard deviation (SD) are reported, whereas those not conforming to the normal distribution are described using the median and interquartile range (IQR). The analysis of categorical variables was executed using the Chi-square and Fisher's exact tests. Comparisons of measurements at different time points were made using the Wilcoxon signed-rank test and the paired samples t-test. Operating a two-tailed test, a p-value below 0.05 was deemed to indicate statistical significance.

RESULTS

Baseline characteristics

Our study evaluated data from 82 patients. Four patients were removed from the study because they had undergone urinary surgery, while six more were excluded due to incomplete data. This study encompassed 72 participants in total, comprising 38 women and 34 men. The average age among these participants was 59.63 ± 8.19 years, and the mean duration of diabetes across the group was 10.28 ± 7.61 years. Among the patients, the most frequently observed comorbid conditions were hypertension (84.7%), hyperlipidemia (81.9%), and coronary artery disease (40.3%). When the antidiabetic treatments are examined, the most common oral treatments were metformin (88.9%) and DPP-4 (38.9%) inhibitors. While 8.3% of the patients were using basal insulin, 27.8% were using intensive insulin.

SGLT-2 inhibitor therapy was discontinued due to recurrent urinary -genital infections in 9 of 72 patients. During follow-up, documented urinary infections were detected in 8 (11%) patients and genital infections in 3 (4.2%) patients.

Metabolic control

Significant weight loss was observed in patients at the routine visit in the 3rd month of the treatment ($p < 0.001$). There was a significant decrease in HbA1c, triglyceride level and microalbuminuria ($p<0.001$, $p=0.005$, $p=0.003$, respectively), while there was a significant increase in hematocrit values ($p < 0.001$). The change in other laboratory tests was not statistically significant, LDL decreased slightly, and there was no significant change in creatinine ($p>0.05$). The metabolic values and the change in body weight of the patients in the 3rd month of treatment are summarized in Table 1.

Urine flow parameters - voiding frequency - infection

Patients with urinary complaints at the beginning of the treatment were evaluated in the urology

Table 1. Metabolic control before and after treatment

	0 month	3rd month	p
Body weight	87.07±16.17	82.85±15.58	**<0.001***
HbA1c	8.15 (7.22-9.70)	7.50 (6.70-8.15)	**<0.001****
TG	146 (98-215)	135 (101.75-173.50)	**0.005****
LDL	98 (78-140)	96.20 (81.75-127.80)	0.700**
MAU	16.50 (9-52.50)	14 (6-44)	**0.003****
Creatinine	0.79 (0.66-0.94)	0.79 (0.66-0.96)	0.210**
GFR	96 (79.50-104.25)	95 (80-102)	0.200**
Hct	39.90 (37.4-42.75)	41.80 (39.02-44.57)	**<0.001****

Data are given as [median (25-75%)]. Data are given as mean ± standard deviation. *Paired samples T test. **Wilcoxon signed-rank test. **Abbreviations:** HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; TG, triglycerides; MAU, microalbumin; GFR, glomerular filtration rate; Hct, hematocrit.

Table 2. Comparison of uroflowmeter- urine flow parameters and day/night voiding frequency

	0 month (n=61)	3rd month (n=44)	p*
Qmax (ml/sn)	15 (11-24.30)	18.50(14.6- 22)	0.090
Mean Velocity (mL/sn)	8.40 (4.95-15.4)	10 (7-14.60)	0.210
Voiding volume (ml)	209.0(178.5-381.0)	274.0 (205.5- 484.5)	**0.028***
PVR (ml)	40 (17.50-63.0)	35 (25-52.50)	0.960
Daytime urination frequency	6.79 ± 2.04 6 (6-7.75)	6.78 ± 2.10 6 (6-8)	0.957
Nighttime urination frequency	1.83 ± 1.06 2 (1-3)	1.77 ± 1.09 2 (1-3)	0.655

Data are given as [median (25-75%)], data are given as mean ± standard deviation. *Wilcoxon signed-rank test
Abbreviations: PVR: post voiding residue, Qmax: maximum flow rate

department and routine uroflowmetry measurements were examined. Urinary maximum flow rate, mean velocity and voiding volume increased at the 3rd month follow-ups. (Results with a voiding volume of 150 ml and above were evaluated.) The increase was statistically significant ($p<0.05$) when the voiding volume before treatment was compared with the voiding volume in the 3rd month. The post voiding residue (PVR) decreased (not statistically significant). The frequency of daytime and nighttime voiding was evaluated using a voiding diary at the beginning and end of the 3-month treatment period. No significant changes were observed in the frequency of daytime and nighttime voiding before and after treatment ($p>0.05$). Tables 2 shows uroflowmeter voiding dynamics and voiding frequencies according to voiding diaries.

The incidence of urinary tract infections was significantly higher in women than in men ($p<0.01$). All 8 patients with urinary infections were women. All 3 patients with genital infections were female too (Table 3).

Questionnaires

The NQOL was completed by patients at the start of treatment, as well as in the first and third months of treatment. No significant change was found for patients when the initiation of treatment was compared with the 1st month and 3rd months.

The Epworth sleepiness scale detects increased daytime sleepiness, with a score of 11 and above indicating excessive daytime sleepiness. When the Epworth score was compared at 1 month and 3 months with the initiation of treatment (0-1st month; 0-3rd month; 1st-3rd months), no significant change was found ($p>0.05$).

MLUTs was completed by men, while women completed the FLUTS questionnaires. When the 1st month and 3rd month of treatment are compared in male patients, the frequency of daily voiding (MLUTS F score) increased ($p<0.05$). There was no significant

Table 3. Infection prevalence in men and women

	Urinary Infection		
Gender	**No** **n (%)**	**Yes** **n (%)**	***p***
Female	30 (78.9)	8 (21.1)	**.006***
Male	34 (100.0)	0 (0.0)	
	Genital infection		***p***
Gender	**No** **n (%)**	**Yes** **n (%)**	
Female	35 (92.1)	3 (7.9)	.242*
Male	34 (100.0)	0 (0.0)	

*Fisher exact test

Table 4. Epworth sleepiness scale, NQOL, MLUTS in men, FLUTS in women scores and month-by-month comparisons

	0 month	1st month	3rd month	*p* (0-3 m.)	*p* (1-3 m.)
Epworth	6 (2-10)	7 (2.75-13.25)	6 (3-10)	0.921	0.636
NQOL	10 (2-19)	7 (3-15.25)	10 (3-19)	0.557	0.082
MLUTS V	4 (2-9)	4 (2-7)	4 (2-8)	0.989	0.752
MLUTS I	2 (1-4)	1 (0-3)	2 (1-3)	0.059	0.546
MLUTS F	0.5 (0-1)	0 (0-1)	1 (0-1)	0.448	**0.046***
MLUTS N	2 (1-2)	2 (1-3)	2 (1-2.75)	1.000	0.414
FLUTS F	4 (2-6)	4 (3-6)	3.5 (2-7)	0.602	0.444
FLUTS V	1 (0-2)	2 (0-6)	0 (0-2)	0.642	0.072
FLUTS I	2 (1-6)	5 (0-7)	3.5 (1-7.25)	0.193	0.294

Data are shown as n (%) and [median (25-75%)]. *Wilcoxon signed-rank test.
Abbreviations: NQOL: Effect of nocturia on quality of life, MLUTS: Male lower urinary tract symptoms, FLUTS: Female lower urinary tract symptoms. MLUTS V: Voiding related symptoms, MLUTS I : Incontinence, MLUTS F : Daytime urination frequency, MLUTS N: Nocturnal urination frequency, FLUTS F : Filling symptoms, FLUTS V: Voiding related symptoms, FLUTS I: Incontinence, m: months

Table 5. Comparison of SF-36 symptom scores

SF-36	p=0-1 month	p=0-3 month	p=1-3 month
Physical function	0.204	0.203	**0.010***
Physical-role difficulties	0.485	0.799	0.161
Emotional-role difficulty	0.054	0.304	0.298
Energy	0.392	0.841	0.238
Mental health	0.914	0.239	0.851
Social function	0.288	0.924	0.583
Pain	0.359	0.096	0.129
General Health	0.773	0.244	0.345

*Wilcoxon signed rank test. **Abbreviations:** SF 36: Quality of life scale-short form.

change in lower urinary system symptom scores in female patients. In Table 4, month-by-month comparisons of NQOL, Epworth sleepiness scale and MLUTS-FLUTS scores are presented.

Evaluation of Life Quality

Patients completed the SF-36 questionnaire at the start of treatment, as well as in the first and third months. In our cases, physical function increased significantly in the 1st and 3rd month comparisons. No significant changes were detected for other sub-parameters. Table 5 shows the SF-36 symptom scores.

When multivariate linear regression analysis was performed, the parameter that most affected the significant change in SF-36- physical function was the decline in HbA1c.

If men and women are examined separately, there was an improvement in the mental health of women in the 3rd month of the treatment based on SF-36 mental health scores (p=0.03). HbA1c and body weight decreased significantly in both men and woman.

When patients with a history of coronary artery disease are examined (n=29), HbA1c decreased significantly in this group and the group without coronary artery disease. There was significant weight reduction in both groups consistent with the whole group. According to the SF-36 scale, the group with coronary artery disease showed a significant improvement in physical function.

DISCUSSION

SGLT-2 inhibitors have been included in the treatment of diabetes in recent years. These drugs, which inhibit glucose reabsorption in the kidney proximal tubules and act as a glucosuric, are importance for their contribution to metabolic control, as well as their diuretic effect, providing weight loss, a reduction in blood pressure, and playing an active role in cardiovascular protection (12). An increase in the frequency and amount of urine and an increase in nocturia can be expected in patients using SGLT-2 inhibitors. Nocturia, which is one of the lower urinary tract symptoms, is described as waking from sleep to urinate at least once during the night. It causes sleep disturbances and decreased sleep quality and is related to an increased risk of loss of balance and falling, especially in the elderly group. Currently, diabetic and elderly patient groups may have lower

urinary system complaints. When the literature is examined, there are various studies evaluating urinary complaints (pollakiuria, nocturia, incontinence, urinary infection, etc.) associated with SGLT-2 inhibitors (5,13,14). There are few publications in the literature regarding the impact of SGLT-2 inhibitors on quality of life and sleep. (6,15).

Adding SGLT-2 inhibitors to the current treatment did not increase the frequency of nocturia in our study. In parallel with our data, no significant changes were detected in the quality-of-life score and daytime sleepiness score related to nocturia. Significant decreases in HbA1c, triglyceride, spot urine microalbuminuria levels and body weight were identified. The health-Related Quality of Life - Physical Function score demonstrated significant improvement, with HbA1c being the most contributing parameter.

When the literature is examined, a study conducted in Japan in 2018 (5) recruited 55 patients. Their symptoms were recorded before treatment and one month after adding SGLT-2 inhibitors. The frequency of daytime voiding increased significantly after SGLT-2 treatment, and the frequency of nocturia did not change. In our study, similar to the results of this study, the daytime voiding frequency score increased significantly only in male patients when the 1st and 3rd months of treatment are compared ($p<0.05$). When all participants are evaluated, there was no significant change in the frequency of voiding both during the day and at night.

In a case series published in Italy in 2018, data for 50 diabetic male patients were reviewed retrospectively (12). After starting SGLT-2 inhibitor therapy, pollakiuria and nocturia were the most common lower urinary tract symptoms. Pollakiuria was statistically more frequent in the patient group without autonomic neuropathy than in the group with autonomic neuropathy. In addition, pollakiuria was stated to be the earliest finding after starting an SGLT-2 inhibitor. This study only evaluated male patients.

In our study, the urine maximum flow rate, mean velocity and voiding volume increased in uroflowmetry examinations of the patients (urinary volumes of 150 ml and above were evaluated). The increase in voiding volume was statistically significant ($p<0.05$). When voiding diaries were examined, no increase was observed in the frequency of daytime and nighttime voiding, and no significant change was observed in the quality-of-life scores due to nocturia. There was no significant change in Epworth scores measuring daytime sleepiness, either (increased score represents increased daytime sleepiness). Our study is the first to evaluate the urinary flow dynamics of patients using uroflowmetry.

In 2021, a study evaluated the impact of SGLT-2 inhibitors on patients' quality of life, sleep quality, and anxiety levels. The study compared patients who received SGLT-2 inhibitor therapy in addition to other OADs with a group that only received other OADs and a healthy control group. After 3 months of treatment, the SGLT-2 group experienced a significant decrease in HbA1c and body mass index (BMI). However, the group receiving SGLT-2 inhibitors had a significantly higher frequency of genital-urinary tract infection, daytime voiding, nocturia, and incontinence. The SGLT-2 group showed a statistically significant improvement in the sub-parameters of the SF-36 quality of life scale, including physical function, pain, general health perception, emotional role difficulty, energy, and mental health perception scores. Energy and general health perception, which are sub-parameters of SF-36, and BMI had negative correlations. On the sleep scale, there was no difference between the groups (6).

Similar to the aforementioned study, a significant improvement in metabolic parameters and a significant decrease in body weight were found in our study. There was significant improvement in the SF36 score-physical function component (1st-3rd month comparison). The improvement in the SF-36 score was correlated with the decrease in HbA1c. In our study, contrary to the aforementioned study, there was no increase in the frequency of daytime and nighttime voiding, and there was no change in the daytime sleepiness scores of patients.

Individuals with diabetes generally experience a lower quality of life compared to those without chronic illnesses. However, managing blood glucose levels can improve the quality of life for those with type 2 diabetes (16). Few studies have evaluated the impact of SGLT-2 inhibitors on the quality of life of individuals with type 2 diabetes. In these studies, the effects of SGLT-2 inhibitors were found for weight loss, improvement in glycemic control and improvement in health-related quality of life scores (HR-QOL) with low incidence of hypoglycemia (6,15). In our study, quality of life scores were negatively correlated with HbA1c, which supports the literature. In addition to studies in the literature, there was a significant improvement in SF-36 physical function score in patients with coronary artery disease. This is an important finding

showing that the well-being of these patients increased. Another interesting finding is the improvement in the perception of SF-36 mental health in women.

During follow-up, after SGLT-2 inhibitor treatment, the drug was discontinued in 5 patients due to recurrent genital-urinary infections. Urinary infections were more common than genital infections. The frequency of documented urinary infections in women was significantly higher than in men ($p<0.01$). Upon examination of previous studies, a meta-analysis of 56 randomized controlled studies revealed that SGLT-2 inhibitors significantly increased the risk of genital infections. However, no clear effect on urinary tract infections was observed (17).

Our study included more participants than other published studies, but lacking a control group is limiting the inability of the patients to properly record the amount of fluid taken and urine excreted while keeping a voiding diary is another limitation of our study. This study is the first to evaluate the urinary flow dynamics of patients using uroflowmetry.

Consequently, in this real-life study, SGLT-2 inhibitors improved quality of life by improving glycemic control. Although the amount of urine increases, it does not significantly change the frequency of urination (day or night). With SGLT-2 inhibitor treatment, no significant change was found in lower urinary tract symptoms and there was no change in daytime sleepiness or effect of nocturia on quality of life. But care should be taken in terms of genitourinary infections.

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