ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

ORIGINAL ARTICLE
Endocrinol Res Pract. 2025;29(1):22-29

An Investigation of Long-Term Changes in Biometric and Biochemical Parameters in a Retrospective Cohort Using Uninterrupted SGLT-2 Inhibitor Therapy

ABSTRACT

Objective: The study aims to examine the long-term effects of sodium-glucose Co-transporter 2 (SGLT-2) inhibitor therapy on biometric and biochemical parameters in patients with type 2 diabetes mellitus.

Methods: We investigated 473 patients between November 2019 and October 2020. After patients with interrupted medication, taking medications for obesity, and not attending follow-up visits were excluded, 94 patients formed the study group. Patients were observed before the initiation of SGLT-2 inhibitors and continued to be followed for up to 156 weeks.

Results: Significant decreases in body weight and body mass index (BMI) observed in the short term (Week 12) continued to plateau in the medium term (Weeks 52 and 104). However, in the long term (156th week), body weight and BMI were statistically reduced compared to week 12th. The favorable change observed in the patients' lipid profiles, hepatic enzymes, and serum uric acid levels in the short term was replaced by a plateau in the medium and long term.

Conclusion: The beneficial effects observed in the short term with SGLT-2 inhibitors may differ in the long term. Accordingly, weight loss increases significantly again at Week 156, but biochemical parameters such as lipid profiles, hepatic enzymes, and uric acid levels continued to plateau.

Keywords: Body weights and measures, biomarkers, diabetes mellitus, sodium-glucose transporter 2 inhibitors, time

Introduction

Sodium-glucose Co-transporter 2 (SGLT-2) inhibitors increase urinary glucose excretion by inhibiting glucose and sodium reabsorption in the renal proximal tubule independently of insulin secretion.[1] Studies have shown that SGLT-2 inhibitors have favorable and desirable effects on glycemic control, lipid profile, and cardio-renovascular outcomes of patients with type 2 diabetes.[2-5] In addition, current guidelines position SGLT-2 inhibitors among the drug groups to be prioritized in the management of patients with type 2 diabetes who have difficulty with weight control.[6]

It is known that reduced insulin demand, reduced adipose tissue inflammation, effective caloric deficit through glucose excretion, and water loss through osmotic diuresis lead to weight loss in patients with SGLT-2 inhibition.[7-9] The fact that SGLT-2 inhibitors cause 70-90 g/day of urinary glucose excretion results in 300 kcal/day of energy loss and 400 mL/day of fluid loss due to osmotic diuresis.[10,11] With continuous SGLT-2 inhibition, patients are theoretically expected to lose 10 kg/year of body weight due to daily caloric restriction and osmotic diuresis.[11] Contrary to general expectations, the EMPAREG-OUTCOME, DECLARE-TIMI, and CANVAS studies, which are among the largest studies in the literature on this topic, observed a weight loss of 2-3 kg/year with SGLT-2 inhibitor treatment.[3,4,12] Again, in the meta-analysis by Liu et al, a 2.47 kg/year weight loss was observed with SGLT-2 inhibitor treatment.[13]

In addition, it is understood that different studies have evaluated the weight losses that occur with SGLT-2 inhibition at different durations of use.[3,4,12,13] As understood from these studies, the decrease in body weight is significant in the first 12-26 weeks of SGLT-2 inhibitor treatment. This decrease continues minimally after the 26th week.[14] Some other studies

Emre Vuraloglu[1]
Merve Alyamac Yasar[2]
Esra Borazan[1]
Altug Kut[1]
Ayse Yavuz Derman[3]
Özlem Turhan İyidir[4]

[1]*Department of Family Medicine, Başkent University School of Medicine, Ankara, Türkiye*
[2]*Department of Family Medicine, Mamak State Hospital, Ankara, Türkiye*
[3]*Department of Biostatistics, Başkent University School of Medicine, Ankara, Türkiye*
[4]*Department of Endocrinology and Metabolism, Başkent University School of Medicine, Ankara, Türkiye*

Corresponding author:
Altug Kut
✉ altugkut@gmail.com

Received: July 3, 2024
Revision Requested: August 22, 2024
Last Revision Received: October 13, 2024
Accepted: October 28, 2024
Publication Date: January 2, 2025

Cite this article as: Vuraloglu E, Alyamac Yasar M, Borazan E, Kut A, Yavuz Derman A, Turhan İyidir Ö. An investigation of long-term changes in biometric and biochemical parameters in a retrospective cohort using uninterrupted SGLT-2 inhibitor therapy. *Endocrinol Res Pract.* 2025;29(1):22-29.

DOI: 10.5152/erp.2025.24509

also claim that the weight loss initially achieved with SGLT-2 inhibitors continues or at least plateaus, even if it slows down.[15-17] In other words, although it is known as a common finding that SGLT-2 inhibitors effectively reduce weight in the short term, there are different results on how SGLT-2 inhibitors affect body weight in the long term.

These conflicting results suggest that new regional studies of real-life data with long-term follow-up investigating the biometric and biochemical effects of long-term SGLT-2 inhibitor use in a cohort not receiving obesity treatment may shed light on the issue. Accordingly, this study, which was a 156-week long-term real-time follow-up at a university hospital, aimed to examine long-term changes in biometric and biochemical parameters in a retrospective Turkish population cohort on continuous SGLT-2 inhibitor therapy.

Materials and Methods

Study Design

This retrospective cohort study was approved by BBaşkent University Medical and Health Sciences Research and Ethics Committee with the project approval date 03/04/2024 and project number KA 24/151. Since the study was retrospective and did not include interventional features, obtaining an informed consent form was not deemed necessary by the ethics committee in terms of compliance with the Personal Data Protection Law in Türkiye. The study group consists of patients diagnosed with type 2 diabetes mellitus (DM) who were registered at the Endocrinology and Metabolic Diseases Outpatient Clinics of Başkent University in the Ankara Hospital between November 1, 2019 and October 31, 2020. We did not randomize patients at recruitment and collected data from all patients who met the study criteria. Only patients who fully met the inclusion criteria and had no missing data were included in the study. We have presented the study flowchart in Figure 1.

In 2017, with the introduction of first dapagliflozin and then empagliflozin, the clinical use of SGLT-2 inhibitors began in Türkiye. At the time of the study, only these 2 active substances were available as SGLT-2 inhibitors in Türkiye. Between November 1, 2019 and October 31, 2020, the total number of applications to Başkent University Endocrinology and Metabolic Diseases Outpatient Clinics with a diagnosis of type 2 diabetes was 8197. After eliminating duplicate records, the remaining number of patients with type 2 diabetes was 4503. Among these patients with type 2 diabetes, 473 who started SGLT-2 inhibitor treatment were the study population.

MAIN POINTS

- The beneficial effects observed in the short term with SGLT-2 inhibitors differ in the long term.
- The significant decrease in weight loss and BMI in the first 12 weeks continues to be noteworthy at Week 156 after a plateau period.
- The significant improvements in the lipid profile seen in the first 12 weeks appear to have been ineffective in the long term.
- After significant improvements in the first 12 weeks, hepatic enzymes and serum uric acid levels continued to plateau in the medium and long term.
- Creatinine levels do not show a significant improvement in the first 12 weeks but improve significantly in the medium and long term compared to pre-drug and Week 12.

We used the electronic medical information system of BBaşkent University Hospital as a data source and compared the biometric and biochemical parameters measured before SGLT-2 inhibitor treatment with the values measured and recorded at Weeks 12, 52, 104, and 156. Throughout this period, the patients remained on SGLT-2 inhibitor treatment without interruption. Since the effects of SGLT-2 inhibitors on biometric and biochemical parameters were analyzed in a time-dependent manner, a control group was not required in the study.

Biometric and Biochemical Parameters

Biometric parameters, waist circumference, body mass index (BMI), and weight of the patients who participated in our study were evaluated before the start of drug use and were repeated by the same researcher using the same measuring instruments for all patients in the study group at each subsequent control.

As biochemical parameters, glycated hemoglobin (HbA1c), fasting blood glucose (FPG), low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), serum uric acid (SUA), creatinine, alanine transaminase (ALT), and gamma -glutamyltransferase (GGT) values were evaluated for all patients in the study group before the start of drug use and at each subsequent control. As all patients in our study group were already diagnosed with type 2 DM, we did not evaluate the changes in HOMA-IR. The researchers did not change or intervene with any parts of the patient file information and gave extreme caution not to cause any collection bias.

Inclusion and Exclusion Criteria

Patients whose drug use was interrupted at any time during the 36 months following the initiation of SGLT-2 inhibitor treatment and who received obesity treatment with glucagon-like peptide-1 receptor agonists during these 36 months, in addition to their current diabetes treatment, were excluded from the study. We also excluded patients who had any change in their current diabetes treatment during this time. Our inclusion criteria were that the patients were older than 18 years of age and that their height, body weight, waist circumference, and laboratory values were measured before starting SGLT-2 inhibitor treatment. The inclusion criteria for the study required that enrolled patients had complete HbA1c, FPG, creatinine, HDL-C, LDL-C, triglyceride, SUA, ALT, and GGT tests. After carefully applying the inclusion and exclusion criteria, 94 patients formed the sample for the study.

Statistical Analyses

Statistical analyses were performed with SPSS version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) and Jamovi version 2.4 programs (The Jamovi project. *jamovi* (Version 2.4) [Computer Software]). The Shapiro–Wilk test was used to analyze the normality of the variables. We used mean, standard deviation, median, and minimum-maximum values for descriptive analyses. Frequency and percentage values of the variables were used when presenting categorical variables. Whether there was a difference between 2 independent groups in terms of quantitative variables was determined by the Student *t*-test when parametric test assumptions were met. When the relationship between 2 quantitative variables was analyzed, Pearson's test was used when the assumptions were met. The correlation coefficient (*r*) was evaluated as demonstrating a very strong correlation between 0.81 and 1.0, a strong correlation between 0.60 and 0.79, a moderate correlation between 0.40 and 0.59, a weak correlation between 0.20

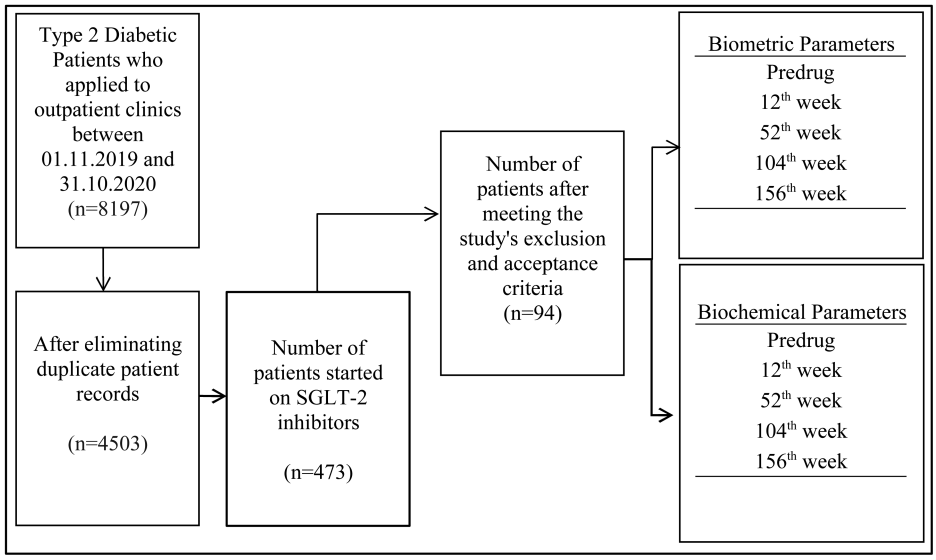

Figure 1. Flowchart of the "An Investigation of Long-Term Changes in Biometric and Biochemical Parameters in a Retrospective Cohort Using Uninterrupted SGLT-2 Inhibitor Therapy" (2024).

and 0.39, and a very weak correlation between 0 and 0.19. The Mixed Effect Model was used to investigate significant differences in terms of repeated measurements. Dunn's Bonferroni test determined differences between groups, and *P*-values below .05 at a 95% CI were considered statistically significant results.

Results

We included 94 patients in the study, and 67.02% of them were female. The mean age of the patients was 62.81 ± 10.72 years. Table 1 presents data on patient demographic variables. The majority of study group patients had hypertension followed by dyslipidemia as a comorbid disease to DM. In addition to SGLT-2, metformin was the most used agent for treating DM during the study period. None of the patients in the study group were treated with GLP-1 agonists since using this agent was an exclusion criterion.

Our study observed a statistically significant weight loss during the first 12 weeks of SGLT-2 inhibitor treatment (Table 2). No statistically significant changes in body weight were observed in the medium to long-term period between Weeks 12 and 104 of continuous drug treatment. However, between Weeks 104 and 156, which we define as the long-term period, we observed that patients started to lose statistically significant weight while on drug treatment. Accordingly, the decrease in BMI was also statistically significant. Table 2 shows these biometric changes in detail.

We calculated the distribution of changes in biochemical parameters by week. Table 3 shows these changes. In general, our study revealed that SGLT-2 inhibitors showed favorable effects on biochemical parameters in the short term, but these effects could not be sustained in the long term. In other words, the favorable effect

Table 1. Distribution of Demographic Data of the Study Group

Age (years)		**Mean ± SD**	**62.81 ± 10.72**
		n	**%**
Gender	Female	63	67.02
	Male	31	32.98
Co-morbidities of diabetes during the study period	Hypertension	74	82.22
	Dyslipidemia	64	71.11
	Thyroid disorders	42	46.66
	Coronary artery disease	14	15.56
	Others	12	12.76
Other diabetes medicines used alongside SGLT-2 treatment during the study period	Metformin	75	79.79
	DPP-4 inh	24	25.53
	İnsuline	23	24.47
	Pioglitazone	20	21.28
	Gliclazide	13	13.83
Number of urinary infections during the study period	None	82	87.23
	1	8	8.51
	2	2	2.13
	3	2	2.13

Table 2. Evaluation of Biometric Values Before Treatment and According to the Weeks of SGLT-2 Treatment

Measurement	Visits	Mean ± SD	P*	Pairwise Comparision**
BMI	Predrug	31.35 ± 5.94	**<.001**	**1>2,3,4,5 2>5**
	12th week	30.77 ± 5.79		
	52th week	30.47 ± 5.45		
	104th week	30.21 ± 5.59		
	156th week	29.92 ± 5.41		
Waist circumference	Predrug	104.84 ± 12.69	**<.001**	**1>2,3,4,5**
	12th week	102.89 ± 12.56		
	52th week	102.24 ± 12.29		
	104th week	102.73 ± 13.07		
	156th week	102.12 ± 13.06		
Body weight	Predrug	84.71 ± 16.90	**<.001**	**1>2,3,4,5 2>5**
	12th week	83.11 ± 16.28		
	52th week	82.18 ± 14.67		
	104th week	81.26 ± 15.40		
	156th week	80.49 ± 15.14		

BMI, body mass index; SD, standard deviation.
*Mixed effect model, 95% CI.
**Dunn's Bonferroni test determined differences between groups.

Table 3. Evaluation of Biochemical Values Before Treatment and According to the Weeks of SGLT-2 Treatment

Biochemical Parameter	Visit	Mean ± SD	P*	Pairwise Comparision**
HbA1c (%)	Predrug	7.37 ± 1.72	**<.001**	**1>2,3,4,5 2>4**
	12th week	6.47 ± 1.05		
	52th week	6.72 ± 1.20		
	104th week	6.81 ± 1.22		
	156th week	6.68 ± 1.26		
FPG (mg/dL)	Predrug	148.38 ± 52.90	**<.001**	**1>2,3,4,5**
	12th week	129.88 ± 38.07		
	52th week	125.72 ± 35.78		
	104th week	128.06 ± 31.15		
	156th week	130.09 ± 46.95		
LDL-c (mg/dL)	Predrug	128.11 ± 37.24	**<.001**	**1>2,3,4,5**
	12th week	118.01 ± 29.85		
	52th week	117.49 ± 33.64		
	104th week	115.19 ± 33.85		
	156th week	109.74 ± 32.48		
Triglyceride (mg/dL)	Predrug	186.26 ± 88.69	**<.001**	**1>2,3,4,5**
	12th week	160.63 ± 68.68		
	52th week	144.58 ± 59.62		
	104th week	141.34 ± 62.73		
	156th week	145.64 ± 67.01		
HDL-c (mg/dL)	Predrug	44.65 ± 12.38	**<.001**	**1>2,3,4,5**
	12th week	47.95 ± 11.56		
	52th week	49.52 ± 11.46		
	104th week	49.31 ± 12.62		
	156th week	48.96 ± 13.77		
Serum uric acid (mg/dL)	Predrug	5.70 ± 1.24	**<.001**	**1>2,3,4,5**
	12th week	5.03 ± 1.14		
	52th week	4.98 ± 1.17		
	104th week	4.96 ± 1.09		
	156th week	4.94 ± 1.19		
Creatinine (mg/dl)	Predrug	0.85 ± 0.15	**<.001**	**1>4,5 2>4,5**
	12th week	0.84 ± 0.15		
	52th week	0.83 ± 0.16		
	104th week	0.82 ± 0.17		
	156th week	0.80 ± 0.17		
ALT (U/L)	Predrug	28.19 ± 17.89	**<.001**	**1>2,3,4,5**
	12th week	22.96 ± 13.77		
	52th week	22.29 ± 10.73		
	104th week	20.57 ± 9.88		
	156th week	20.25 ± 8.45		
GGT (IU/L)	Predrug	31.96 ± 17.72	**<.001**	**1>2,3,4,5**
	12th week	25.85 ± 14.72		
	52th week	24.90 ± 12.36		
	104th week	23.03 ± 12.48		
	156th week	22.75 ± 11.42		

ALT, alanine aminotransferase; BMI, body mass index; FPG, fasting plasma glucose; GGT, gamma glutamyl transferase; HbA1c, glycosylated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.
*Mixed effect model, 95% CI.
**Dunn's Bonferroni test determined differences between groups.

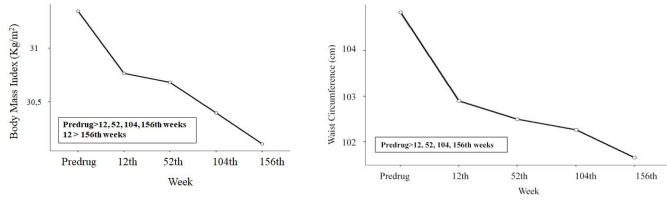

Figure 2. Evaluation of biometric measurements before treatment and according to the weeks of SGLT-2 treatment. Significance according to Dunn's Bonferroni post hoc test.

of SGLT-2 inhibitors on HbA1c levels in the short term could not be sustained in the medium-long term or the long term. In addition, it was observed that LDL-C and triglyceride levels in patients decreased significantly within 12 weeks, defined as the short term after starting treatment. However, this reduction was not statistically maintained in the medium and long term. In addition, although HDL-C increased significantly in the first 12 weeks, this significance was lost in the following weeks. Similarly, although there was a statistically significant decrease in SUA levels and hepatic enzymes in the short 12-week period, this decrease was not maintained in the later stages of the study, and the data plateaued.

The biometric (Figure 2) and biochemical (Figure 3) parameters of the patients measured before the initiation of SGLT-2 inhibitor therapy and the change in the time elapsed under SGLT-2 inhibitor therapy were analyzed by post hoc tests. We presented the statistically significant changes from the obtained results with line graphs. The x-axes of the graphs represent the time before and under drug treatment in weeks, while the y-axes of the graphs examine each biometric or biochemical parameter. The graphs indicate intervals with statistical significance according to Dunn's Bonferroni post hoc test.

In this sense, in the analysis of post hoc tests, the time intervals and *P*-Bonferroni values of statistical significance are given, respectively. Regarding body mass index, there were significant differences between all of the *P* values calculated before the SGLT-2 inhibitor was started and the values measured afterward (Week 12, $P = .026$; Week 52, $P = .007$; Week 104, $P < .001$; Week 156, $P < 0.001$). As an indicator that the decrease in body mass index continued in the long term, the evaluation between Week 12 and Week 156 was found to be significant ($P = .017$). In terms of waist circumference, there were significant differences between all *P* values calculated before and after SGLT-2 inhibitor initiation (Week 12, $P = .003$; Week 52, $P < .001$; Week 104, $P < .001$; Week 156, $P < .001$). No significant difference was found between the measurements after the first 12 weeks.

When we looked at our analyses in terms of HbA1c, there were significant differences between all of the calculated *P* values compared to the values before the SGLT-2 inhibitor was started and the values measured afterward (Week 12, $P < .001$; Week 52, $P < .001$; Week 104, $P < .001$; Week 156, $P < .001$). In addition, it was found that the initial decrease in HbA1c measurements was replaced by a gradually significant increase in the medium-length period between the 12th and 104th week ($P = .049$).

When we analyzed our data in terms of HDL-C, there were significant differences between all of the calculated *P* values compared to the values before the SGLT-2 inhibitor was started and the values measured afterward (Week 12, $P < .001$; Week 52, $P < .001$; Week 104, $P = .002$; Week 156, $P < .001$). The data did not change significantly after the 12th week and statistically plateaued, maintaining the initial elevated values. Regarding LDL-C, there were significant differences

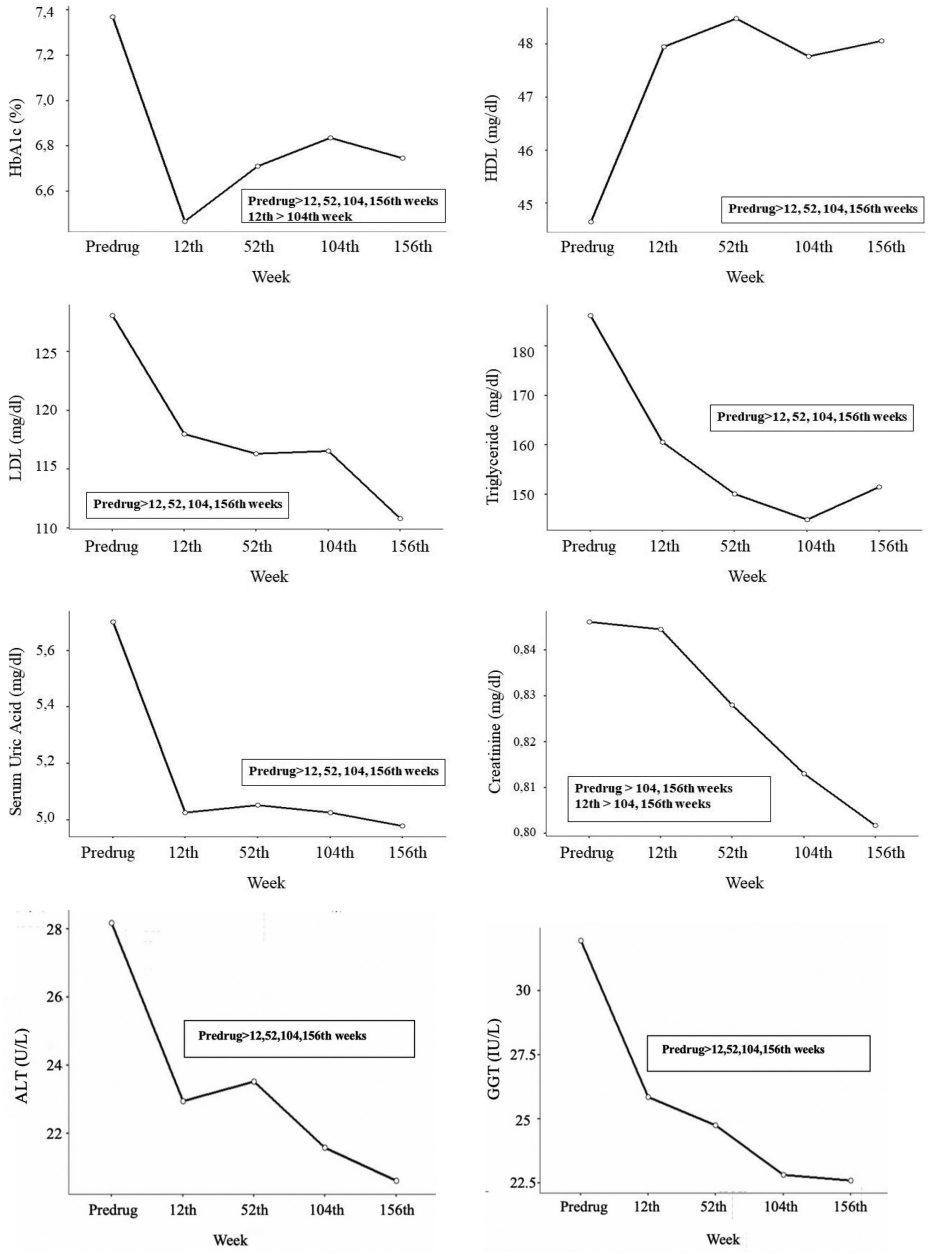

Figure 3. Evaluation of biochemical measurements before treatment and according to the weeks of SGLT-2 treatment. Significance according to Dunn's Bonferroni post hoc test.

between all *P* values calculated before SGLT-2 inhibitor initiation and those measured afterward (Week 12, $P < .001$; Week 52, $P = .002$; Week 104, $P = .008$; Week 156, $P < .001$). The data did not change significantly after the 12th week and statistically plateaued, maintaining the values decreasing at the beginning. In terms of triglycerides, SUA, and ALT, there were significant differences for all three parameters between the calculated *P* values before SGLT-2 inhibitor initiation and the values measured afterward (Week 12, $P < .001$; Week 52, $P < .001$; Week 104, $P < .001$; Week 156, $P < .001$). No significant change was observed in the measured values of any of these 3 parameters after the 12th week.

Regarding creatinine, no significant decreases were observed in the first 104 weeks after the SGLT-2 inhibitor was started. However, creatinine levels began to decrease significantly at the 104th and 156th weeks compared to baseline ($P = .023$, $P < .001$, respectively). In terms of GGT, there were significant differences between all the calculated *P*-values compared to the values before the SGLT-2 inhibitor was started and the values measured afterward (Week 12, $P < .009$; Week 52, $P = .002$; Week 104, $P < .001$; Week 156, $P < .001$). This significant decrease in GGT levels observed in the first 12 weeks did not maintain its significance afterward.

Discussion

The findings of our study indicate that SGLT-2 inhibitors are not only efficacious agents for glycemic regulation but also exert a significant impact on the biometric and biochemical parameters of patients during both the short-term and long-term. Previous studies supported these results and showed that these effects may change

as the duration of treatment with the active substance continues uninterruptedly.[3-5,12]

The cardiorenal protective effects of SGLT-2 inhibitors in patients with type 2 diabetes are well known. For this reason, in current guidelines, SGLT-2 inhibitors are shown as one of the preferred treatment options to reduce the risk of cardiovascular disease and improve renal function in patients with type 2 diabetes.[6] Although the short-term proven favorable effects of SGLT-2 inhibitors on biometric parameters in patients with type 2 diabetes are well known, we have limited information about their long-term effects on biometric parameters in the literature.

In this context, a literature review reveals studies examining patients' body weight changes using SGLT-2 inhibitors and even investigating the differences that occur when this active substance is administered for different periods.[3,4,12-17] In the EMPAREG-OUTCOME[3] and CANVAS[12] studies, which are among the major studies on SGLT-2 inhibitors in the literature, authors observed that patients lost approximately 2 kg in the short term of 12 weeks with SGLT-2 inhibitors and 3 kg in the long term of 156 weeks.[3,12] On the other hand, there is disagreement in the literature about how the weight loss of patients under SGLT-2 inhibitors changes with the duration of treatment. While Monami et al[15] and Bolinder et al[16] claimed that the weight loss of the patients continued as long as they received SGLT-2 inhibitor treatment, Nauck et al[17] reported that the weight loss of the patients under SGLT-2 inhibitor treatment stopped after the 24th week. Based on these different results regarding the long-term use of SGLT-2 inhibitors, researchers such as Polidori et al[18] and Ferrannini et al[19] tried to explain these different results with mathematical models of counter-regulatory mechanisms (increase in appetite, energy balance, change in brain activity in response to food) in their articles, and medical circles generally accepted these views. Perhaps the fact that the patient's weight loss in the first 12 weeks of our study did not continue in the medium-long term can be explained by this mathematical method and counter-regulatory mechanisms. However, ongoing studies on the subject have led to different views, finding that the long-term effect of weight loss with SGLT-2 inhibitors does not persist and stating that other explanations are needed.[20,21] In our study, the significant decrease in weight loss again at Week 156, which is called the long-term, supports that there may be other underlying mechanisms. In other words, it is necessary to look beyond mathematical models and randomized controlled trials to see the effects of SGLT-2 inhibitors on weight in the long term.

In another study, Huang et al[22] reported that the weight loss did not continue after the 12th-16th week of SGLT-2 inhibitor treatment. Since our study reflects real-life data, it will contribute to the issue of long-term weight changes in SGLT-2 treatment, which remains obscure because of different explanations in the literature. In our study, we observed a mean weight loss of 1.6 kg in the 12th week after the start of SGLT-2 inhibitor treatment, which was statistically significant. The weight loss observed in the medium-long period between the 12th and 104th weeks, when the drug treatment continued uninterruptedly, showed statistically insignificant changes. However, we observed that after 156 weeks of drug treatment, which we will define as long-term, patients lost an average of 3.2 kg. In conclusion, although there was a deceleration period between the 12th and 104th weeks, the weight loss between the 12th and 156th weeks under drug treatment and the associated decrease in BMI was statistically significant. In addition, we suggest that independent variables such as GFR, agent, glycemic regulation, etc., do not influence weight loss in patients on drug treatment. In the meta-analysis published by Zaccardi et al[23] observed similar weight loss was observed without any difference between SGLT-2 inhibitors whose active substance differed as empa-dapa-canagliflozin, which was in line with our study.[23] In addition, Kohan et al[24] found that weight loss in patients treated with SGLT-2 inhibitors was independent of the GFR levels of the patients, which also supports our study.[24]

Although we excluded the group of patients who did not have diabetes and received concurrent obesity treatment due to the exclusion criteria in the design of our study, there are also studies in the literature that combine the weight loss effect of SGLT-2 inhibitors with obesity treatment in people without diabetes. Many studies have shown that weight loss is greater when combined with obesity treatment than with SGLT-2 inhibitor treatment alone. The DURATION-8 study,[25] Pereira et al,[26] Lundkvist et al,[27] Bays et al[28] have published large studies on the weight-loss effects of SGLT-2 inhibitors in non-diabetic patients. However, this issue should have been commented on since it was beyond the scope of this study.

In general, the favorable effect of SGLT-2 inhibitor therapy on the lipid profile of patients with type 2 diabetes is well known. Although some studies have shown that SGLT-2 inhibitors modestly increase HDL-C levels compared with placebo, there are also available data showing an increase in LDL-C.[3,23,29] In addition, there are also studies in the literature showing that SGLT-2 inhibitors do not affect the LDL-C levels of patients.[30] Therefore, more studies, such as our study, including real-life data, are needed to prove that improvements in blood lipoproteins are significant following SGLT-2 inhibitor treatment. In our study, it was observed that LDL-C and triglyceride levels of the patients decreased significantly within 12 weeks, which can be defined as a short period after the start of treatment, but this decrease could not be maintained in the long term. In addition, no increase in LDL-C levels was observed in any period of our study. In our study, HDL-C increased significantly within 3 months, which can be defined as a short period after the start of treatment, but this increase also lost its significance in the long term.

SGLT-2 inhibitors decrease urate reabsorption in the proximal tubule via the hexose/urate transporter GLUT9b in the basolateral membrane of proximal renal tubular cells and decrease SUA levels via uricosuria.[31] Chino et al[32] showed that SGLT-2 inhibitors statistically significantly decreased SUA levels in the 12th week after the initiation of treatment. Similarly, in our study, SUA decreased statistically significantly in the 12th week, which is a short period after the initiation of SGLT-2 inhibitor treatment, but the SUA level plateaued under SGLT-2 inhibitor treatment for a long period of 156 weeks after the 12th week. Similar to our study, in the EMPAREG-OUTCOME[3] study, it was observed that there was a significant decrease in SUA levels in the first 12 weeks with SGLT-2 inhibitors, and then SUA levels plateaued during the treatment period. Additionally, in the Insights From a Mediation Analysis of the EMPA-REG OUTCOME[33] study, it was suggested that this change in SUA levels with SGLT-2 inhibitors contributed to the decrease in cardiovascular mortality.

This study has many strengths but also some limitations. Firstly, a strength is that this study has a very well-delimited sample, which allowed us to minimize confounding factors as much as possible.

Including all patients instead of a randomized sample that met the inclusion and exclusion criteria is advantageous. Unfortunately, these constraints led us to a smaller sample size and forced us to use nonparametric tests in conditions where groups were not homogeneously distributed. However, the fact that the patients included in the study were collected from the patient group of a university hospital raises the possibility that this group may be affected by the scope of "high prevalence medicine." Therefore, since the data on the results of the active substances do not include the differences in the provision of primary and secondary health care services, they may be slightly affected by the selection of the patient group. In addition, an increasing number of articles show that the therapeutic effect is increased when SGLT-2 inhibitors are used together with SGLT-1 inhibitors.[34] The fact that active substances such as double-acting luseogliflozin and sotagliflozin are not yet used in Türkiye prevented us from performing a study in which we could observe this effect.

This study showed that the beneficial effect observed with SGLT-2 inhibitors on patients' biometric and biochemical parameters in the short term may differ in the long term. The significant body weight and BMI reduction observed at Week 12 was sustained without augmentation at Weeks 52 and 104. Nevertheless, at the long-term endpoint (Week 156), the body weight and BMI reduction achieved statistical significance compared to Week 12. The favorable change observed in patients' lipid profiles, hepatic enzymes**,** and SUA levels in the short term plateaued in the long term. It is evident that SGLT-2 inhibitors, which are one of the most popular treatments today, require further randomized controlled trials or more long-term studies based on real-life data in order to ascertain their effects on the biometric and biochemical parameters of patients and their cardiorenoprotective effects both in the treatment of diabetes.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: The study was conducted and approved by the Bioethical Commission of the Başkent University, Türkiye (approval no: KA 24/151, date: 03/04/2024).

Informed Consent: Since the study is retrospective, informed consent was not deemed necessary by the ethics committee.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.V., M.A.Y., E.B., A.K., A.Y.D., Ö.T.İ.; Design – E.V., M.A.Y., E.B., A.K., A.Y.D., Ö.T.İ.; Supervision – A.K.; Data Collection and/or Processing – E.V., E.B., M.A.Y.; Analysis and/or Interpretation – A.Y.D.; Literature Search – E.V., E.B.; Writing Manuscript – E.V., M.A.Y., A.K., Ö.T.İ.; Critical Review – E.V., M.A.Y., E.B., A.K., A.Y.D., Ö.T.İ.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This study received no funding.

References

1. DeFronzo RA, Hompesch M, Kasichayanula S, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care*. 2013;36(10):3169-3176. [CrossRef]
2. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *BMJ Open*. 2016;6(2):e009417. [CrossRef]
3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. [CrossRef]
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. [CrossRef]
5. Wanner C. EMPA-REG OUTCOME: the nephrologist's point of view. *Am J Med*. 2017;130(6S):S63-S72. [CrossRef]
6. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in Diabetes-2024 [published correction appears in *Diabetes Care*. 2024;47(7):1238. [CrossRef]. *Diabetes Care*. 2024;47(suppl 1):S158-S178. [CrossRef]
7. Janež A, Fioretto P. SGLT2 inhibitors and the clinical implications of associated weight loss in type 2 diabetes: a narrative review. *Diabetes Ther*. 2021;12(8):2249-2261. [CrossRef]
8. Xu L, Nagata N, Nagashimada M, et al. SGLT2 inhibition by empagliflozin promotes fat utilization and browning and attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. *EBiomedicine*. 2017;20:137-149. [CrossRef]
9. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr*. 2006;83(2):461S-465S. [CrossRef]
10. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30-50% of filtered glucose load in humans. *Diabetes*. 2013;62(10):3324-3328. [CrossRef]
11. Brown E, Rajeev SP, Cuthbertson DJ, Wilding JPH. A review of the mechanism of action, metabolic profile and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors. *Diabetes Obes Metab*. 2019;21(suppl 2):9-18. [CrossRef]
12. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. [CrossRef]
13. Liu XY, Zhang N, Chen R, Zhao JG, Yu P. Efficacy and safety of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2years. *J Diabetes Complications*. 2015;29(8):1295-1303. [CrossRef]
14. Vallianou NG, Geladari E, Kazazis CE. SGLT-2 inhibitors: their pleiotropic properties. *Diabetes Metab Syndr*. 2017;11(4):311-315. [CrossRef]
15. Monami M, Liistro F, Scatena A, Nreu B, Mannucci E. Short and medium-term efficacy of sodium glucose co-transporter-2 (SGLT-2) inhibitors: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2018;20(5):1213-1222. [CrossRef]
16. Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab*. 2014;16(2):159-169. [CrossRef]
17. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care*. 2011;34(9):2015-2022. [CrossRef]
18. Polidori D, Sanghvi A, Seeley RJ, Hall KD. How strongly does appetite counter weight loss? Quantification of the feedback control of human energy intake. *Obesity (Silver Spring)*. 2016;24(11):2289-2295. [CrossRef]
19. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose co-transporter 2 inhibition in type 2 diabetic patients [published correction appears in *J Clin Invest*. 2014;124(4):1868]. *J Clin Invest*. 2014;124(2):499-508. [CrossRef]
20. Sargeant JA, King JA, Yates T, et al. The effects of empagliflozin, dietary energy restriction, or both on appetite-regulatory gut peptides in individuals with type 2 diabetes and overweight or obesity: the SEESAW randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2022;24(8):1509-1521. [CrossRef]
21. Rajeev SP, Roberts CA, Brown E, et al. No evidence of compensatory changes in energy balance, despite reductions in body weight and liver fat, during dapagliflozin treatment in type 2 diabetes mellitus: A

randomized, double-blind, placebo-controlled, cross-over trial (ENERGIZE). *Diabetes Obes Metab*. 2023;25(12):3621-3631. [CrossRef]
22. Huang Y, Jiang Z, Wei Y. Short- and medium-term efficacy of sodium glucose co-transporter 2 (SGLT-2) inhibitors for the treatment of type 1 diabetes: systematic review and meta-analysis. *Endokrynol Pol*. 2020;71(4):325-333. [CrossRef]
23. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab*. 2016;18(8):783-794. [CrossRef]
24. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int*. 2014;85(4):962-971. [CrossRef]
25. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial [published correction appears in *Lancet Diabetes Endocrinol*. 2017;5(12):e8. [CrossRef]. *Lancet Diabetes Endocrinol*. 2016;4(12):1004-1016. [CrossRef]
26. Pereira MJ, Eriksson JW. Emerging role of SGLT-2 inhibitors for the treatment of obesity. *Drugs*. 2019;79(3):219-230. [CrossRef]
27. Lundkvist P, Pereira MJ, Katsogiannos P, Sjöström CD, Johnsson E, Eriksson JW. Dapagliflozin once daily plus exenatide once weekly in obese adults without diabetes: sustained reductions in body weight, glycaemia and blood pressure over 1 year. *Diabetes Obes Metab*. 2017;19(9):1276-1288. [CrossRef]
28. Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. *Obesity (Silver Spring)*. 2014;22(4):1042-1049. [CrossRef]
29. Osto E, Bonacina F, Pirillo A, Norata GD. Neutral effect of SGLT2 inhibitors on lipoprotein metabolism: from clinical evidence to molecular mechanisms. *Pharmacol Res*. 2023;188:106667. [CrossRef]
30. Cesaro A, Acerbo V, Vetrano E, et al. Sodium-glucose co-transporter 2 inhibitors in patients with diabetes and coronary artery disease: translating the benefits of the molecular mechanisms of gliflozins into clinical practice. *Int J Mol Sci*. 2023;24(9):8099. [CrossRef]
31. Chino Y, Samukawa Y, Sakai S, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos*. 2014;35(7):391-404. [CrossRef]
32. Chino Y, Kuwabara M, Hisatome I. Factors influencing change in serum uric acid after administration of the sodium-glucose co-transporter 2 inhibitor luseogliflozin in patients with type 2 diabetes mellitus. *J Clin Pharmacol*. 2022;62(3):366-375. [CrossRef]
33. Inzucchi SE, Zinman B, Fitchett D, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41(2):356-363. [CrossRef]
34. Cheong AJY, Teo YN, Teo YH, et al. SGLT inhibitors on weight and body mass: a meta-analysis of 116 randomized controlled trials. *Obesity (Silver Spring)*. 2022;30(1):117-128. [CrossRef]