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EMPAGLIFLOZIN IS MORE EFFECTIVE IN REDUCING MICROALBUMINURIA AND ALT LEVELS COMPARED WITH DAPAGLIFLOZIN: REAL LIFE EXPERIENCE

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Abstract

Context. Sodium Glucose Co-Transporter-2 inhibitors (SGLT2i) are oral antidiabetic agents that can be used with insulin in the treatment of type 2 diabetes mellitus, known for cardiovascular and renal benefits. Dapagliflozin and empagliflozin are available in Turkey and we aimed to evaluate real-life data of using these two molecules with other oral antidiabetic drugs (OAD) or insulin.

Subjects and methods. 119 patients (59 women, 60 men) files who had started SGLT2i between 2017-2019 were examined retrospectively until 6 months after the treatment change. Patients' weight, body mass index (BMI), insulin doses, fasting blood glucose, HbA1c, lipid profile, spot urine albumin/creatinine ratio, e-GFR values, ALT, AST, uric acid levels were evaluated at baseline, 3 months and 6 months.

Results. 41.2% of patients were using dapagliflozin and 58.8% were using empagliflozin. After 6 months of follow-up, HbA1c decreased from 8.27% to 7.45% ($p<0.001$). Daily total insulin dose decreased from 84.75 to 75.58 U/day in 3 months ($p<0.004$). Weight and BMI decreased significantly at 6 months. ALT, AST decreased significantly in patients using insulin (p 0.001 and 0.007), whereas spot urine microalbumin/creatinine ratio decreased at 3 and 6 months (p 0.005 and 0.020). A significant decrease was also observed in uric acid levels (p: 0.026).

Conclusions. Dapagliflozin and empagliflozin have beneficial effects on decreasing glycemic parameters, weight, transaminases, uric acid and microalbuminuria in the real life environment. We also observed that SGLT2i and insulin combination is as safe and effective as combination with OAD.

Key words: SGLT2 inhibitors, Type 2 diabetes mellitus, HbA1c, Body mass index, Weight loss, Real life experience.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease that can cause serious complications. Prevalence of T2DM increases very rapidly worldwide and in Turkey as well. Turkish Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study (TURDEP I and II) studies showed prevalence of T2DM raised from 7.2% to 13.7% in 12 years (1,2). According to International Diabetes Federation (IDF), Turkey has the highest diabetes rate in Europe (3). In a recent study, Society of Turkish Endocrinology and Metabolic Diseases (TEMD) Study Group reported that only 40.2% of T2DM patients could achieve glycemic goals (4). Diabetes Mellitus guidelines have been revised each year and authors study on new treatment modalities.

Sodium Glucose Co-Transporter-2 inhibitors (SGLT2i) recently approved by FDA (Food and Drug Administration) for treatment of T2DM and afterwards showed effective on glycemic control and cardiovascular complications. SGLT2i decrease serum glucose levels without inducing excessive insulin secretion by increasing urinary glucose excretion via blocking the specific transport system SGLT2. Dapagliflozin and Empagliflozin are available in Turkey whereas Canagliflozin is not. Cardiovascular safety studies of SGLT2i drugs reported that these drugs cause weight loss, lower systolic blood pressure while decreasing HbA1c and prevent diabetic renal involvement, microalbuminuria and heart failure (5-7). Zelniker TA *et al.* (8) notified that SGLT2i drugs are beneficial on patients with established atherosclerotic cardiovascular diseases and on reducing hospitalization for heart failure. They also emphasized these drugs are beneficial on progression of renal disease and microalbuminuria in diabetic patients. Because of these results, not only ADA (American Diabetes Association) 2019 Diabetes Mellitus guideline, but also cardiology and nephrology guidelines recommended SGLT2i as second line therapy in T2DM patients who have atherosclerotic cardiovascular disease, heart failure or

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renal failure just after metformin (9-11). Safety profile of these drugs is generally acceptable where most common side effect is genital mycotic infection.

In Turkey, we have experienced Dapagliflozin and Empagliflozin since 2016 and 2018 respectively. According to our experience, T2DM patients on both all other oral anti-diabetic drugs (OAD) and insulin treatment tolerated SGLT2i very well and used effectively. There are several studies about experience on SGLT2i. Thus, we aimed to see effectiveness and safety of SGLT2i in our patients with T2DM still on OAD and insulin treatment in terms of metabolic and anthropometric parameters.

PATIENTS AND METHODS

This single center retrospective observational study performed in patients with Type 2 Diabetes Mellitus who were admitted to the endocrinology outpatient clinic between January 2017 and June 2019 and whose SGLT-2 inhibitor was started within the indication were selected retrospectively from the files of the computerized data system of our hospital. Marmara University School of Medicine's local ethics committee has approved our study (09.2019.697). A total of 119 type 2 diabetic patients (59 female, 60 male) were included in the study. The patients were retrospectively selected and classified into two groups using insulin or only OAD. All patients were over 18 years old.

The data files of patients were prepared by detailed examination. The presence of hypertension and hyperlipidemia, duration of diabetes and medications used were recorded. Anthropometric data were recorded at examination and data of the fasting plasma glucose (FPG) and HbA1c values measured at our center were recorded and used as glycemic control parameters. Total cholesterol, Low-Density Lipoprotein (LDL) cholesterol, High-Density Lipoprotein (HDL), triglyceride and spot urinary albumin to creatinine ratio (ACR) levels were evaluated. Glomerular filtration rates (GFR) of patients were calculated according to the Modification of Diet and Renal Disease (MDRD) (GFR = 175 X ([Serum creatinine] -1.154) X ([Age] -0.203) X (0.742 women) X (1.212 is black)).

Baseline data, third and sixth months' data of treatment were re-evaluated and recorded.

Statistical Analysis

All the analyses were carried out with statistical package SPSS (Statistical Package for the Social Sciences) v.22.0, which is accessible from our network. Independent sample T-test or Mann Whitney U variance analysis test was used according to assumption of the normal distribution. Numerical data in dependent groups were compared by dependent sample T-test or Wilcoxon test chosen according to normal distribution assumption. Mean (+/-) standard deviation for the continuous variables (such as fasting plasma glucose, weight, lipid profile), and the number (n) and percentage (%) values for categorical variables (sex, etc.) were evaluated. Correlation analyses were assessed with Spearman correlation coefficient. Significance level of p-value less than 0.05 was regarded as statistically significant.

RESULTS

Average age was 56.46 ± 8.31 years and average time since diagnosis was 11.36 ± 6.39 years. The average HbA1c blood concentration was 8.27 ± 1.46 %, average BMI was 35.05 ± 7.29 kg/m^2.

Seventy one patients were on the treatment of insulin and oral antidiabetic (OAD), one patient was using only insulin and fourty seven patients were on oral antidiabetic regimes without insulin. Forty nine patients were prescribed dapagliflozin (41.2%), and seventy patients were prescribed empagliflozin (58.8%). Seventy three of patients (67%) had a history of hypertension, thirty eight patients (31.9%) had coronary artery disease and 100 patients (84.5%) had dyslipidemia. The number of patients with disease duration of 10 years and over was 67 (56.3%). There was not any significant difference between insulin users and non-users. Table 1 shows the baseline characteristics and averages of the parameters investigated in the patients who started SGLT2i and the distributions of these values regarding both insulin users and non-users are also shown in the same table.

Glycemic control and insulin dose reduction

Considering all patients included in the study, after 5.47 ± 1.14 months follow-up, significant HbA1c reductions were observed [8.27 % to 7.45 % ($p<0.001$)] (Table 2), in patients using insulin had a reduction of HbA1c from 8.6% to 7.8% which was accompanied by total daily insulin dose reduction from 84.75 to 78.58 UI/day (p 0.004) in the first three months of treatment (Table 4). However, similar changes were not observed for both parameters in between third and sixth months. Patients using empagliflozin had a significant decrease after three months treatment (p 0.005) but patients using dapagliflozin did not have a significant decrease of total

daily insulin doses in six months treatment (p 0.211). In six months follow-up two patients using dapagliflozin and three patients using empagliflozin (totally five patients) managed to stop taking short acting insulin treatments. Two patients under oral antidiabetic regime as given long-acting insulin treatment managed to end insulin treatment (Tables 5, 6).

Body weight

The average body weight and body mass index significantly decreased in six months' time and the same effect was also seen in the second three months' time. Patients using dapagliflozin managed to continue weight loss and BMI decrease during six months follow-up while patients using empagliflozin had a decrease in weight and BMI in the first three months but could not continue in the second three months follow-up (Tables 2, 4, 6).

Lipid profile

The treatment with SGLT2i did not change the lipid profile (total cholesterol, triglycerides, LDL and HDL levels) in total patients and in insulin user patients' group. However, patients using only oral antidiabetic regimes had a significant decrease of triglycerides in the second period of three months follow-up (p 0.021) but there was not a significant change in triglyceride levels in total six months therapy. Moreover, other lipid parameters did not show any statistically significant change in only oral antidiabetic drug using patients (Table 3).

The addition of SGL2i drugs to antidiabetic therapy caused a significant decrease in ALT and AST levels in six months treatment (respectively p 0.001 and 0.027). This effect to ALT and AST levels was significant when SGLT2i drugs were added to insulin users (respectively p 0.001 and 0.007). However, patients who were not using insulin did not have any significant difference in ALT and AST levels after six months treatment of SGLT-2 inhibitors (respectively p 0.149 and 0.460) (Tables 2-4). Patients who added Dapagliflozin had significant decreases in ALT levels

Table 1. Initial demographic parameters and biochemical results

	All patients	Insulin users	Non-users	P value
n	119	72	47	
Female / Male	59/60	36/36	23/24	1.000
Age (years)	56.46 ± 8.31	56.68 ± 7.81	56.11 ± 9.16	0.502
Diabetes duration (years)	11.36 ± 6.39	12.26 ± 6.67	9.86 ± 5.67	0.056
Coronary artery disease	38 (%31.9)	27 (% 37.5)	11 (% 23.4)	0.114
Hypertension	73 (% 61.3)	47 (%65.2)	26(%55.3)	0.337
Hyperlipidemia	100 (%84.5)	63 (% 87.5)	37 (%78.7)	0.212
Microalbuminuria	34 (% 28.5)	23(%31.9)	11(%23.4)	0.295
Macroalbuminuria	7(% 5.8)	5(%6.9)	2(%4.2)	0.698
Metformin	111 (% 93.2)	65(%90.2)	46(%97.8)	0.145
Dpp-4 inhibitor	72 (%60.5)	38(%52.7)	34(%72.3)	**0.037**
Glp-1 analogue	16 (%13.4)	12(%16.6)	4(%8.5)	0.227
Sulfonylurea	25 (%21)	3(%4.1)	22(%46.8)	**<0.0001**
Thiazolidinedione	3 (%2.5)	2(%2.7)	1(%2.1)	1.000
Glinid	5 (%4.2)	0(% 0.0)	5(%10.6)	**0.008**
Follow-up duration (month)	5.47 ± 1.14	5.40± 1.20	5.60 ± 1.03	0.261
BMI (kg/m^2)	35.05 ± 7.29	36.31 ± 7.41	32.57 ± 6.70	**0.014**
Body weight (kg)	94.38 ± 22.71	98.47 ± 22.70	86.91 ± 21.16	**0.007**
Fasting plasma glucose (mg/dL)	172.57 ± 53.16	181.47 ± 57.90	136.60 ± 30.14	**0.029**
HbA1c (%)	8.27 ± 1.46	8.63 ± 1.63	7.05 ± 0.84	**0.001**
c-peptide (µg/L)	2.89 ± 1.51	2.61 ± 1.42	2.97 ± 1.15	0.029
Insulin (mU/L)	24.61 ± 39.18	26.63 ± 45.57	11.37 ± 7.49	0.957
Total cholesterol (mg/dL)	187.86 ± 40.20	185.74 ± 43.34	195.59 ± 38.74	0.333
LDL cholesterol (mg/dL)	109.70 ± 36.26	109.81 ± 38.81	115.10 ± 35.02	0.665
HDL cholesterol (mg/dL)	43.30 ± 11.85	43.13 ± 12.77	44.53 ± 10.16	0.452
Triglyceride (mg/dL)	184.54 ± 86.67	175.15 ± 78.18	182.35 ± 83.81	0.207
Creatinine (mg/dL)	0.77 ± 0.18	0.77 ± 0.17	0.77 ± 0.20	0.401
e-GFR (mL/dk/1.73m^2)	101.40 ± 23.06	99.86 ± 22.63	103.42 ± 27.40	0.306
Uric acid (µg/L)	5.47 ± 1.49	5.55 ± 1.54	4.81 ±1.44	0.664
Microalbumin/creatinine ratio (mg/g)	75.24 ± 187.28	91.63 ± 216.54	27.70 ± 53.90	0.052
ALT (U/L)	30.96 ± 19.63	30.38 ± 19.72	28.24 ± 17.81	0.501
AST (U/L)	24.20 ± 11.24	24.19 ± 10.80	21.97 ± 7.91	0.745

after six months (p 0.033) and in AST levels after three months (p 0.043). Addition of empagliflozin caused a significant decrease in ALT levels after six months (p 0.016) but did not cause a significant difference in AST levels (p 0.208) (Tables 5, 6).

The changes in microalbumin/creatinine ratio in spot urine

Addition of a SGLT2i to any antidiabetic therapy provided significant decrease in the ratio of microalbumin to creatinine in spot urine both after the three and six months of therapy (respectively p 0.005 and 0.020). There was not a difference between third and sixth months of the treatment (p 0.516) (Table 2). The same effects were seen in insulin user patients at the treatment periods of first three months, second three months and six months (respectively p 0.020, 0.002 and 0,381) (Table 4). However, patients using only oral antidiabetics did not have any significant difference in the ratio of microalbumin to creatinine in spot urine (Table 3).

DISCUSSION

In recent years, SGLT2 inhibitors have been recommended as a form of treatment that should be included in the treatment of type 2 diabetic patients in diabetes, cardiology and also nephrology guidelines

Table 2. Results after SGLT2i addition in all patients

	Basal value (n:119)	3. month (n:119)	6. month (n:98)	P value Baseline *vs.* 3. month	P value Baseline *vs.* 6. month
BMI (kg/m^2)	35.05 ± 7.29	34.52 ± 7.03	34.73 ± 7.57	**<0.001**	**<0.001**
Weight (kg)	94.38 ± 22.71	93.79 ± 22.27	93.21 ± 21.55	**<0.0001**	**<0.001**
Fasting plasma glucose (mg/dL)	172.57 ± 53.16	142.09 ± 41.89	14.86 ± 51.33	**<0.001**	**<0.001**
HbA1c (%)	8.27 ± 1.46	7.55 ± 1.36	7.45 ± 1.24	**<0.001**	**<0.001**
c-peptide (µg/L)	2.89 ± 1.51	2.61 ± 1.26	2.90 ± 1.61	0.548	0.738
Insulin (mU/L)	24.61 ± 39.18	12.66 ± 8.27	17.40 ± 13.28	0.073	0.758
Total cholesterol (mg/dL)	187.86 ± 40.20	186.42 ± 38.84	188.14 ± 41.91	0.875	0.495
LDL cholesterol (mg/dL)	109.70 ± 36.26	107.52 ± 33.02	112.53 ± 52.18	0.735	0.435
HDL cholesterol (mg/dL)	43.30 ± 11.85	43.75 ± 10.93	44.77 ± 12.38	0.570	0.111
Triglyceride (mg/dL)	184.54 ± 86.67	188.66 ± 108.63	173.97 ± 74.63	0.708	0.092
Creatinine (mg/dL)	0.77 ± 0.18	0.81 ± 0.27	0.81 ± 0.29	0.297	0.130
e-GFR (mL/dk/1.73m^2)	101.40 ± 23.06	98.57 ± 26.24	96.99 ± 25.80	0.398	0.307
Uric acid (µg/L)	5.47 ± 1.49	5.18 ±1.56	5.06 ±1.34	**0.001**	**0.026**
Microalbumin/creatinine ratio (mg/g)	75.24 ± 187.28	51.46 ± 105.00	46.20 ± 93.20	**0.005**	**0.020**
ALT (U/L)	30.96 ± 19.63	26.78 ± 15.25	25.87 ± 13.66	**0.003**	**0.001**
AST (U/L)	24.20 ± 11.24	22.01 ± 8.02	21.29 ± 7.56	**0.025**	**0.027**

Table 3. Metabolic effects of SGLT-2 addition in non-insulin using patients

	Basal value (n:47)	3. month (n:47)	6. month (n:41)	P value Baseline *vs.* 3. month	P value Baseline *vs.* 6. month
BMI (kg/m^2)	32.97 ± 6.69	32.57 ± 6.70	31.58 ± 6.21	**0.002**	**0.001**
Weight (kg)	87.65 ± 21.39	86.91 ± 21.16	85.55 ± 19.09	**0.001**	**0.001**
Fasting plasma glucose (mg/dL)	158.93 ± 41.95	136.60 ± 30.14	128.92 ± 27.97	**0.007**	**<0.001**
HbA1c (%)	7.69 ± 0.89	7.05 ± 0.84	6.96 ± 0.65	**<0.001**	**<0.001**
c-peptide (µg/L)	3.41 ± 1.57	2.97 ± 1.15	3.25 ± 1.41	0.110	0.767
Insulin (mU/L)	19.67 ±14.83	11.37 ± 7.49	16.27 ± 11.10	**0.017**	0.600
Total cholesterol (mg/dL)	191.34 ± 34.61	195.59 ± 38.74	194.27 ± 36.95	0.789	0.940
LDL cholesterol (mg/dL)	109.51 ± 31.98	115.10 ± 35.02	113.07 ± 30.69	0.617	0.743
HDL cholesterol (mg/dL)	43.58 ± 10.24	44.53 ± 10.16	45.81 ± 8.65	0.613	0.081
Triglyceride (mg/dL)	200.27 ± 98.23	182.35 ± 83.81	170.28 ± 67.24	0.057	**0.027**
Creatinine (mg/dL)	0.76 ± 0.20	0.77 ± 0.20	0.76 ± 0.19	0.840	0.413
e-GFR (mL/dk/1.73m^2)	103.77 ± 23.76	103.42 ± 27.40	101.08 ± 25.45	0.747	0.307
Uric acid (µg/L)	5.32 ± 1.40	4.81 ±1.44	4.50 ±1.18	**0.012**	**0.021**
Microalbumin/creatinine ratio (mg/g)	51.42 ± 132.89	27.70 ± 53.90	44.24 ± 72.12	0.122	0.482
ALT (U/L)	31.88 ± 19.67	28.24 ± 17.81	28.00 ± 14.21	0.172	0.149
AST (U/L)	24.20 ± 12.04	21.97 ± 7.91	22.29 ± 7.78	0.136	0.966

due to their cardio-renal protective beneficial effects on the heart and kidney, except for glycemic control (9-11). However, there is not enough real-life data about this group of drugs, our clinical experience has recently increased. In this study, we planned to evaluate our own real life data due to the initiation of SGLT-2 inhibitors in a large number of patients added to metformin in type 2 diabetic patients. About 60% of the patients were receiving insulin therapy with metformin, and BMI, fasting plasma glucose and HbA1c levels were significantly higher in this group compared to non-insulin users. Patients on insulin therapy were generally those with a longer duration of diabetes, have lower c-peptide levels, and uncontrolled glycemic control.

When all patients were evaluated, it was observed that there was a statistically significant improvement in weight, BMI, fasting plasma glucose, HbA1c, uric acid levels, AST, ALT and microalbuminuria in the third month after SGLT2i initiation and this improvement continued in the 6th month in terms of all parameters. The same parameters were improved in patients using insulin, whereas

Table 4. Metabolic effects of SGLT-2 addition in insulin using patients

	Basal value	3. month	6. month	P value Baseline *vs.* 3. month	P value Baseline *vs.* 6. month
n	72	72	57		
BMI (kg/m^2)	36.31 ± 7.41	35.58 ± 7.06	36.80 ± 7.75	**<0.001**	**0.001**
Weight (kg)	98.47 ± 22.70	97.55 ± 22.19	98.11 ± 21.84	**<0.001**	**0.001**
Fasting plasma glucose (mg/dL)	181.47 ± 57.90	145.37 ± 47.68	149.38 ± 61.79	**<0.001**	**<0.001**
HbA1c (%)	8.63 ± 1.63	7.87 ± 1.53	7.80 ± 1.44	**<0.001**	**<0.001**
c-peptide (µg/L)	2.61 ± 1.42	2.39 ± 1.31	2.71 ± 1.70	0.733	0.778
Insulin (mU/L)	26.63 ± 45.57	13.53 ± 8.85	18.03 ± 14.52	0.600	0.469
Total cholesterol (mg/dL)	185.74 ± 43.34	180.55 ± 38.07	184.01 ± 44.79	1.000	0.436
LDL cholesterol (mg/dL)	109.81 ± 38.81	102.63 ± 30.98	112.16 ± 63.20	0.420	0.446
HDL cholesterol (mg/dL)	43.13 ± 12.77	43.24 ± 11.45	44.05 ± 14.44	0.825	0.523
Triglyceride (mg/dL)	175.15 ± 78.18	192.74 ± 122.50	176.52 ± 79.85	0.326	0.709
Creatinine (mg/dL)	0.77 ± 0.17	0.83 ± 0.31	0.85 ±0.35	0.137	0.190
e-GFR (mL/dk/1.73m^2)	99.86 ± 22.63	95.39 ± 25.16	94.06 ± 25.88	0.176	0.669
Uric acid (µg/L)	5.55 ± 1.54	5.34 ±1.61	5.31 ±1.35	**0.019**	0.186
Microalbumin/creatinine ratio (mg/g)	91.63 ± 216.54	62.54 ± 120.72	47.57 ± 106.28	**0.020**	**0.002**
ALT (U/L)	30.38 ± 19.72	25.84 ± 13.43	24.32 ± 13.14	**0.009**	**0.001**
AST (U/L)	24.19 ± 10.80	22.04 ± 8.16	20.57 ± 7.38	0.084	**0.007**
Total long acting insulin dose (U/g)	47.74 ± 26.88	46.22 ± 27.06	49.19 ± 26.88	0.205	0.977
Total short acting insulin dose (U/g)	49.96 ± 36.24	46.92 ± 36.35	46.25 ± 33.64	**0.050**	0.104
Total insulin dose (U/g)	84.75 ± 56.74	78.58 ± 56.94	81.41 ± 53.11	**0.004**	0.160

Table 5. Dapagliflozin users

	Baseline value	3. month	6. month	P value Baseline *vs.* 3. month	P value Baseline *vs.* 6. month
n	49	49	42		
BMI (kg/m^2)	35.84 ± 8.28	35.31 ± 7.70	34.84 ± 8.00	**0.001**	**0.001**
Weight (kg)	95.62 ± 21.30	94.30 ± 20.44	91.99 ± 19.79	**<0.001**	**0.001**
Fasting plasma glucose (mg/dL)	182.95 ± 63.67	155.28 ± 49.56	154.20 ± 64.02	**0.002**	**0.003**
HbA1c (%)	8.40 ± 1.54	7.76 ± 1.45	7.62 ± 1.41	**<0.001**	**0.002**
LDL cholesterol (mg/dL)	110.04 ± 33.08	112.63 ± 28.80	118.60 ± 68.89	0.632	0.850
HDL cholesterol (mg/dL)	43.71 ± 12.47	43.95 ± 10.76	45.55 ± 15.38	0.266	0.545
Triglyceride (mg/dL)	185.26 ± 84.05	198.71 ± 110.07	171.72 ± 76.94	0.931	**0.046**
Creatinine (mg/dL)	0.72 ± 0.16	0.79 ± 0.35	0.77 ±0.40	0.942	0.637
e-GFR (mL/dk/1.73m^2)	105.14 ± 22.25	101.18 ± 24.76	103.58 ± 26.76	0.880	0.357
Uric acid (µg/L)	4.84 ± 1.25	4.59 ±1.24	5.14 ±1.55	**0.005**	0.717
Microalbumin/creatinine ratio (mg/g)	65.37 ± 141.82	56.07 ± 97.72	45.84 ± 78.65	**0.557**	**0.713**
ALT (U/L)	29.16 ± 15.55	26.43 ± 14.27	25.00 ± 11.79	0.110	**0.033**
AST (U/L)	24.33 ± 11.90	21.92 ± 8.76	20.39 ± 6.80	**0.043**	0.055
Total short acting insulin dose (U/g)	55.17 ± 41.71	55.44 ± 41.27	60.84 ± 39.95	0.262	0.363
Total insulin dose (U/g)	90.90 ± 60.84	88.64 ± 62.79	97.41 ± 62.82	0.211	0.794

AST, ALT and microalbuminuria values were not significantly decreased in patients who did not use insulin. However, it was observed that triglyceride levels improved in this group, especially in the 6th month.

In the literature, there are many studies showing the positive effects of SGLT2i group on weight, BMI, FPG and HbA1c. Calapkulu *et al.* from Turkey, 6 months dapagliflozin showed that weight, BMI, waist circumference, fasting plasma glucose, postprandial plasma glucose and HbA1c in terms of 3 months and 6 months have been reported to improve significantly (12). In this study, it was shown there was a weight loss of -3.3 kg in the 3rd month and -4.2 kg in the 6th month. Studies have shown that SGLT2i increases glucose excretion in addition to urinary fluid and sodium excretion, leading to calorie loss and weight loss (13). It was shown that 50-75% fat and 15-35% water loss were observed in the body composition change in SGLT2i patients who were followed up for an average of 16 weeks (14-17). According to meta-analysis results of Cai *et al.*, the average weight loss between -1.3-2.24 kg and -1.84-1.93 kg has been shown in patients using Dapagliflozin and Empagliflozin (18). However, the number of patients using insulin was very low in these studies. In our study, although more weight loss was observed with Dapagliflozin in the 6th month, it was found to be low compared to the rates in the literature. The explanation might be that 60% of our patients used insulin with uncontrolled DM.

When the efficacy of SGLT2i on glycemic control was evaluated, it was observed that mean decrease of 30.5 mg/dL and 31.7 mg/dL in FPG and 0.7% and 0.8% in terms of HbA1c at 3 and 6 months. Mean decrease rates of HbA1c were 0.76% and 0.86% for Empagliflozin and 0.64% and 0.78% for Dapagliflozin at the third and sixth month. In the study of Calapkulu *et al.*, Dapagliflozin showed 0.9% change in HbA1c in the 3rd month and 0.79% in the 6th month (12). In a 52-week prospective study of Dapagliflozin 10 mg/day compared to Empagliflozin 25 mg/day by Ku EJ *et al.* in terms of weight, BMI, systolic blood pressure, FPG and HbA1c changes, Empagliflozin was found to be significantly more effective (19). Accordingly, our data seems to be consistent with the literature.

When we evaluated lipid profiles in all patient groups, triglyceride levels decreased numerically after treatment; HDL and LDL levels increased but did not reach significant levels. In patients who did not use insulin, the decrease in triglyceride was significant at 6 months. In the literature, the effects of this group of drugs on lipid panel differ. In a 24-week follow-up study by Cha SA *et al.*, triglyceride and total cholesterol levels decreased numerically in the group receiving SGLT2, but statistical significance was not detected and HDL and LDL levels were significantly increased (20). Basu D and his team also showed that inhibition of SGLT2 in mouse models increased lipoprotein lipase activity, this way reducing postprandial lipemia and accelerating VLDL clearance. The same team also suggested that SGLT2i increased LDL by causing LDL to convert later than circulation (21). In the six months' time observational study of dapagliflozin from Turkey, total cholesterol, triglyceride and LDL levels were significantly decreased but no information has been given about

Table 6. Empagliflozin users

	Basal value	3. month	6. month	P value Baseline *vs.* 3. month	P value Baseline *vs.* 6. month
n	70	70	56		
BMI (kg/m^2)	34.47 ± 6.51	33.89 ± 6.50	34.62 ± 7.25	**<0.001**	**0.005**
Weight (kg)	93.47 ± 23.85	93.85 ± 23.89	94.48 ± 23.55	**<0.001**	**0.004**
Fasting plasma glucose (mg/dL)	165.30 ± 43.38	133.09 ± 33.36	130.48 ± 36.07	**<0.001**	**<0.001**
HbA1c (%)	8.17 ± 1.40	7.41 ± 1.29	7.31 ± 1.10	**<0.001**	**<0.001**
LDL cholesterol (mg/dL)	109.47 ± 38.47	103.88 ± 35.46	107.96 ± 34.77	0.456	0.239
HDL cholesterol (mg/dL)	43.02 ± 11.50	43.61 ± 11.14	44.18 ± 9.65	0.905	0.111
Triglyceride (mg/dL)	184.07 ± 88.98	181.63 ± 107.98	175.67 ± 73.54	0.653	0.492
Creatinine (mg/dL)	0.80 ± 0.19	0.82 ± 0.20	0.84 ±0.19	0.198	**0.033**
e-GFR (mL/dk/1.73m^2)	98.70 ± 23.41	96.80 ± 27.26	92.28 ± 24.25	0.392	0.044
Uric acid (µg/L)	5.86 ± 1.50	5.67 ±1.65	4.99 ±1.11	**0.044**	**0.009**
Microalbumin/creatinine ratio (mg/g)	80.77 ± 209.32	48.46 ± 110.59	46.46 ± 103.51	**0.002**	**0.013**
ALT (U/L)	32.21 ± 22.05	27.00 ± 15.96	26.15 ± 14.95	**0.014**	**0.016**
AST (U/L)	24.10 ± 10.82	22.07 ± 7.58	21.96 ± 8.07	0.177	0.208
Total short acting insulin dose (U/g)	46.54 ± 32.42	41.81 ± 32.72	34.98 ± 22.93	0.134	**0.011**
Total insulin dose (U/g)	80.35 ± 53.94	70.35 ± 52.35	67.84 ± 41.90	**0.005**	0.053

statin use in patients (22). The data in our study were in parallel with other studies in the literature and were found to be a numerical increase in LDL and HDL with a decrease in triglyceride.

In our study, SGLT2i treatment decreased AST and ALT values in all patient groups compared to baseline values. The decrease in ALT levels was higher than in AST levels and this effect was more pronounced in patients receiving insulin. Non-alcoholic hepatosteatosis is frequently observed in patients with type 2 diabetes and transaminase levels are increased, especially in obese diabetics. From this point of view, there are data that SGLT2i treatment decreases the amount of liver fat and reduces transaminase levels. The weight loss effect and the increase in fatty acid oxidation of SGLT2i are shown to be among the mechanisms that reduce liver fat (23-27). Sattar *et al.* reported that this effect was more prominent for ALT and independent of HbA1c (23). In addition, animal studies have shown that SGLT2i drugs have direct positive effects such as insulin resistance and decreased liver damage (28, 29). In a very recent placebo-controlled study, Kahl S *et al.* demonstrated decreased liver fat content in diabetic individuals with Empagliflozin (30-32). In our study, similar to the literature, an improvement was observed in liver enzymes with ALT levels at the forefront.

Because SGLT2i are effective agents over the kidney, their effects on renal function are cared. Although it was feared that it would worsen renal function when it was first used, on the contrary it was found to have a protective effect in time. In our study, when the 6-month data were evaluated, no change was observed in the serum creatinine levels of our patients. Although in the literature it was mentioned about hyperfiltration which will decrease about 1 month after using SGLT2i, GFR values of our patients on 1 month are not available in our study. Despite of there was a numerical decrease in e-GFR during the follow-up period, it did not reach statistical significance and continued within normal limits. In terms of uric acid, a significant decrease in uric acid levels was detected in all patient groups after treatment. For cause SGLT2i also excretes uric acid excretion in urine other than sodium and glucose, this is an expected effect and has been shown in other studies (33-35). Studies have shown that uric acid value increases with increasing BMI. SGLT2i can cause uric acid reduction as it provides weight loss (36, 37).

The most important marker of renal involvement in diabetic patients is microalbuminuria, and renal protective effect of SGLT2i treatment has become increasingly important in recent studies. In our study, the mean values were microalbuminuric in all patient groups and a statistically significant decrease was observed after SGLT2i treatment. However, according to the active substance, this decrease was not significant in dapagliflozin-treated patients, but a statistically significant decrease was observed in patients using empaglifozin. Tang H *et al.* published the results of meta-analysis similar to that of dapagliflozin and renal benefit compared to empagliflozin stated that lower (38). However, according to the results of the DECLARE study of renal outcome, dapagliflozin has been similarly shown to have renal protective activity (39). Therefore, we thought that the results obtained in our study may be related to the smaller number of patients using dapagliflozin. Regarding the renal effects of SGLT2i as a mechanism, it has been suggested that they reduce microalbuminuria by reducing intraglomerular pressure. However, the positive correlation between BMI and microalbuminuria in the correlation analysis in our study suggested that this effect increased with observed weight loss.

Total insulin requirement decreased significantly after 3 months in patients receiving SGLT2i in addition to insulin (-6.17 U/day) in our study. When the sub-group analyses were examined, it was observed that it caused a decrease in short-acting insulin doses especially and no need for short-acting insulin in 4 patients. Data from the literature suggest that SGLT2i treatment reduces the insulin doses, short-acting insulin doses were decreased especially at third months (p 0.050) in our study (40, 41). This has been associated with the effect of treatment, particularly on postprandial glucose. In a very recent study, the earlier the SGLT2i treatment started after metformin, the longer the transition to intensive therapy (42).

Limitations of our study were: a retrospective study, low number of patients, lack of information about blood pressure monitoring and postprandial glucose levels in patients file.

As a result, SGLT2i, which is a new treatment option, can be used effectively in combination with any anti-diabetic drug. In our study, SGLT2i have been shown to have beneficial effects on liver enzymes, uric acid and microalbuminuria in addition to their lowering effects on blood sugar, HbA1c, weight and BMI. Although their effect on lipid levels is not very significant, they may provide some decrease in triglyceride levels. It is an effective and safe option in patients receiving insulin and it has been observed to reduce the need for short-acting insulin. In our study,

in terms of glycemic control and effects on weight, dapagliflozin and empagliflozin were observed to have similar efficacy and the use of empagliflozin was found to be more effective in reducing uric acid level and microalbumiuria, and in terms of positive improvement on ALT.

Conflict of interest

The authors declare that they have no conflict of interest.

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