Original Article

Anthropometric outcomes in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective glycemic control from single center

Murat Calapkulu [a, *], Soner Cander [b], Ozen Oz Gul [b], Canan Ersoy [b]

[a] Dışkapı Yıldırım Beyazıt Training and Research Hospital, Endocrinology and Metabolism, Turkey
[b] Uludag University Medical School, Endocrinology and Metabolism, Turkey

ABSTRACT

Introduction: Dapagliflozin is an antidiabetic drug that has been used as a member of the new antidiabetic drug group that acts by inhibiting SGLT-2 and increasing urinary glucose excretion. With numerous controlled experimental studies of dapagliflozin, evaluation of real-life data after entry into clinical practice is an important condition. In our study, the effects of dapagliflozin on glycemic control and anthropometric measurements were investigated retrospectively.

Methods: A-total of thirty-one type 2 diabetics were enrolled in the study. Data of before dapagliflozin and three and six months of treatment were recorded.

Results: Dapagliflozin reduced HbA1c levels by 0,9% at 3 months and 0,79% at 6 months. Fasting plasma glucose decreased 41,1 mg/dl in the 3rd and 42 mg/dl in the 6th, postprandiyal glucose decreased 86,3 mg/dl in the 3rd and 74,2 mg/dl in the 6th. In the 3rd and 6th, body weights decreased by 3,3 kg and 4,2 kg, BMI decreased by 1,3 kg/m^2 and 1,6 kg/m^2 respectively. Similarly, it was observed that the waist circumference decreased by 1,3 cm at the end of 6th.

Conclusion: Our data show that SGLT-2 inhibitors provide glycemic control with reduce HbA1c levels by 0.8–0.9%, and reduce fasting and postprandial plasma glucose levels without increasing the risk of hypoglycemia and causing weight lose around 5% at the six mounths. SGLT-2 inhibitors were found to be more effective in reduce postprandiyal plasma glucose in patients who did not use insulin and fasting plasma glucose in patients with diabetes mellitus less than 10 years.

© 2018 Published by Elsevier Ltd on behalf of Diabetes India.

1. Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease in which the organism can not adequately use carbohydrates, fat and proteins due to insulin deficiency, defects in tissues affected by insulin, or both [1]. In Europe, the prevalence of diabetes between the 20–79 years is estimated to be 8.8% in 2017, which is expected to be 10.2% in 2045 [2]. While there are 58 million diabetics in Europe in 2017, it is estimated that this figure will increase to 66.7 million by 2045 [2]. In 2014, 9.3% of the entire population in the United States of America was diagnosed with diabetes and the diabetic population reached 29.81 million [3]. TURDEP-I (Türkiye Diyabet,

Hipertansiyon, Obezite ve Endokrinolojik Hastalıklar Prevalans Çalışması) study showed, type 2 DM prevalence of 7.2% according to the results in Turkey between September 1997 and March 1998, while TURDEP-II study conducted between January 2010 and June 2010, this ratio was observed to have reached 13.7% [4,5]. According to the International Diabetes Federation (IDF), there are approximately 425 million people with diabetes in the world, and 12% of their health spending is due to diabetes and related conditions [2]. Four quarters of diabetic patients live in low- and middle-income countries, while two-thirds of the patients live in urban areas [2]. Despite all the precautions in the last 12 years, the prevalence of DM in our country is about 2 times higher.

Type 2 diabetes accounts for about 90–95% of all diabetic patients [3]. Chronic hyperglycemia developed in these patients is associated with the development of microvascular complications such as retinopathy, neuropathy, and nephropathy, which are caused by diabetes [6]. Lifestyle changes such as weight loss,

exercise, and dietary restrictions are included in the initial treatment of Type 2 DM patients. Lifestyle changes are not sufficient in the majority of patients and pharmacotherapy is required [7].

The kidneys increase body glucose by producing glucose through gluconeogenesis and reabsorbing glucose from plasma [8]. SGLT-2 is responsible for 90% of glucose reabsorption in proximal tubules [9]. Inhibition of SGLT-2 reduces glucose reuptake from the kidneys and decreases plasma glucose levels by increasing urinary glucose excretion [10]. Dapagliflozin is the first SGLT-2 inhibitor drug approved in the European Union in 2012 and in the United States in 2014 for use in diabetes [11]. SGLT-2 inhibitors offer a new treatment option independent of insulin action. SGLT-2 inhibitors are especially beneficial in the treatment of overweight or obese diabetic patients because of the weight loss feature. In some studies, increased urinary infections and genital infections have been reported, but the long-term effect of these increases has not been determined.

In this study, changes in anthropometric values and glycemic control parameters were evaluated retrospectively in patients using dapagliflozin. The data were collected by scanning electronic files as single centered real-life study data and the results of patients in the third and sixth months were evaluated. When the literature is reviewed, it is seen that there are few studies on the use of dapagliflozin with real life data. This study aimed to give an idea about the positive and negative effects of the use of dapagliflozin in the treatment of diabetes and to contribute to the literature.

2. Methods

Type 2 DM patients who applied to the Endocrinology outpatient clinic of Uludağ University Medical Faculty between September 2016 and November 2017, or who were hospitalized between the same dates and who used dapagliflozin for the first time, were included in the study. In our study, 78 files were scanned retrospectively. Before the drug was started, the patients who were followed up for the third month and the sixth month after the drug was started, and the assessed data were available, were included in the study.

A total of 31 patients, 22 female and 9 male, were included in the study. The data files of the patients were obtained through detailed examination. The presence of hypertension, the duration of the illness and the medications used were recorded and detailed. Anthropometric evaluation used height, body weight and waist circumference values measured during physical examination of patients. The fasting plasma glucose, postprandial plasma glucose and HbA1c values measured at our center were recorded and used as glycemic control parameters. HbA1c level was measured in Adams A1c HA 8160 device with ion exchanger high performance liquid chromatography (HPLC) principle. BMI was calculated by dividing the meters of the height in kilograms by body weight. The measured values of the patients before using dapagliflozine and the values measured in the third and sixth months were recorded and 0—3 month and 0—6 month changes were calculated.

3. Statistical analysis

All data were transferred to the computer and analyzed for statistical analysis using the application-statistical analysis program of SPSS for Windows, version 23 (IBM Corporation, New York, United States), which accessible from our network. Independent sample T test or Mann Whitney U variance analysis test was used for according to the provision of the normal distribution assumption. To compare numerical data in dependent groups, dependent sample T-test or Wilcoxon test was used according to the provision of the normal distribution assumption. As the descriptive values,

the mean $(+/-$ standard deviation) or median (min-max) according to the distribution of the data for the continuous variables (such as fasting plasma glucose, postprandial plasma glucose, weight), and the number (n) and percentage (%) values for the categorical variables (sex, duration of illness, etc.) were given. The significance level of p value less than 0.05 was regarded as statistically significant.

4. Results

The study included 31 patients, including twenty-two (%71) females and nine males (%29). The average age of the patients was 57,4 in total, 60,2 in males and 56,2 in females. The number of patients under 55 years old was 15 (48%) and the number of patients over 55 years old was 16 (52%). Seventeen of the patients had a history of hypertension while fourteen of the patients had no history of hypertension. The number of patients with a disease duration less than 10 years was 14 (45%), while the number of patients with disease duration of 10 years and over was 17 (%55). A total of eight patients were on treatment of insulin and oral anti-diabetic (OAD), while 23 patients were on OAD combination without insulin. Table 1 shows the baseline characteristics and averages of the parameters investigated in the patients who started dapagliflozin, and the distributions of these values in terms of both men and women are also shown in the same table. In Table 2 and Table 3, three and six-month mean differences were given together with the measured third and sixth month values after the using dapagliflozin. There was a mean reduction 3.3 kg (± 2.5) in weight, 1.3 m (± 1.3) in waist circumference and 1.3 kg/m^2 (± 1) in BMI at the 3rd month. These changes were statistically significant $(p < 0.001)$. The mean fasting plasma glucose level was reduced by 42.1 mg/dl (± 72.1), the mean postprandial plasma glucose level was reduced by 74.2 mg/dL (± 94.4), and the HbA1c average was reduced by % 0,79 $(\pm 1,7)$ at the 6th month. These reductions were statistically significant.

In Table 4, it is shown whether the mean changes in weight, waist circumference and BMI calculated at the third and sixth months after the use of dapagliflozin are influenced by age, gender, disease duration, hypertension history and using insulin.

In Table 5, it is shown whether the mean changes in HbA1c, fasting plasma glucose and postprandial plasma glucose calculated at the third and sixth months after the use of dapagliflozin are influenced by age, gender, disease duration, hypertension history and using insulin.

5. Discussion

SGLT-2 is responsible for 90% of the glucose uptake in proximal tubules [9]. Dapagliflozin inhibits the SGLT-2 molecule, reducing plasma sugar independently of insulin release [10]. Studies with dapagliflozin were in the age range of 60—63 in several studies,

Table 1
Baseline characteristics of the full analysis.

	All patients	Men	Women
Age (years)	57,39 ($\pm 9,2$)	60,2 (± 10)	56,2 ($\pm 8,9$)
Weight (kg)	87,4 ($\pm 17,8$)	93,1 ($\pm 15,6$)	85 ($\pm 18,4$)
BMİ (kg/m^2)	33,2 ($\pm 6,8$)	32 ($\pm 5,4$)	33,7 ($\pm 7,3$)
Waist circumference (cm)	106,4 ($\pm 15,3$)	108,1 ($\pm 10,6$)	105,7 (± 17)
HbA1c (%)	8,5 ($\pm 1,9$)	8,2 (± 2)	8,6 ($\pm 1,9$)
FPG (mg/dl)	192,7 ($\pm 62,6$)	180 ($\pm 43,6$)	198 ($\pm 69,1$)
PPG (mg/dl)	269 ($\pm 79,2$)	238,1 ($\pm 50,9$)	281,7 (± 86)

BMİ:Body mass indeks, FPG:Fasting plasma glucose, PPG:postprandial plasma glucose.

Table 2
Change from baseline at third months in glysemic index and anthropometric measurements.

	0. Month	3. Month	p	0-3 Dif.
Weight (kg)	87,4 (±17,8)	84 (±18,3)	**<0,001**	−3,3 (±2,5)
BMİ (kg/m²)	33,2 (±6,8)	31,9 (±6,9)	**<0,001**	−1,3 (±1)
Waist circumference (cm)	106,4 (±15,3)	105,1 (±15,2)	**<0,001**	−1,3 (±1,3)
HbA1c (%)	8,5 (±1,9)	7,6 (±1)	**0,011**	−0,9(±1,8)
FPG (mg/dl)	192,7 (±62,6)	151,5 (±73,7)	**0,013**	−41,1 (±87,1)
PPG (mg/dl)	269 (±79,2)	182,7 (±44,6)	**<0,001**	−86,3 (±63,1)

BMİ:Body mass indeks, FPG:Fasting plasma glucose, PPG:Postprandial plasma glucose Dif:Difference.

Table 3
Change from baseline at six months in glysemic index and anthropometric measurements.

	0. Month	6. Month	p	0-6 Dif.
Weight (kg)	87,4 (±17,8)	83,1(±18,4)	**<0,001**	−4,2 (±3)
BMİ (kg/m²)	33,2 (±6,8)	31,5 (±7)	**<0,001**	−1,6 (±1,2)
Waist circumference (cm)	106,4 (±15,3)	105 (±15,3)	**<0,001**	−1,3 (±1,4)
HbA1c (%)	8,5 (±1,9)	7,7 (±1)	**0,018**	−0,79 (±1,7)
FPG (mg/dl)	192,7 (±62,6)	150,6 (±3)	**0,003**	−42,1 (±72,1)
PPG (mg/dl)	269 (±79,2)	194,8 (±78,2)	**<0,001**	−74,2 (±94,4)

BMİ:Body mass indeks, FPG:Fasting plasma glucose, PPG:Postprandial plasma glucose Dif:Difference.

Table 4
Third and sixth month changes of anthropometric measurements.

		Weight 0−3 month	Weight 0−6 month	W.C. 0−3 month	W.C. 0−6 month	BMI 0−3 month	BMI 0−6 month
Age	<55	−3,6(±2,6)	−4,2(±2,9)	−1,4(±1,68)	−1,4(±1,7)	−1,6(±1,1)	−1,8(±1,3)
	≥55	−3,06(±2,4)	−4,3(±3,1)	−1,2(±1)	−1,3(±1,1)	−1,08(±0,8)	−1,5(±1,1)
	p	0,53	0,90	0,76	0,96	0,14	0,58
Sex	M	−3(±1,88)	−3,9(±2,4)	−1,6(±1,8)	−1,7(±1,9)	−1,03(±0,6)	−1,3(±0,8)
	F	−3,4(±2,7)	−4,4(±3,2)	−1,1(±1,09)	−1,2(±1,1)	−1,4(±1,1)	−1,8(±1,3)
	p	0,63	0,7	0,37	0,33	0,29	0,26
Duration of type 2 DM (Years)	<10	−2,7(±2,6)	−3,7(±2,9)	−1,1(±1,29)	−1,2(±1,3)	−1(±1,1)	−1,4(±1,1)
	≥10	−3,8 (±2,3)	−4,7(±3)	−1,4(±1,4)	−1,5(±1,5)	−1,6(±0,9)	−1,9(±1,2)
	p	0,21	0,35	0,5	0,5	0,12	0,29
HT	pos	−3,18 (±2,4)	−4,3(±2,7)	−1,1(±1,1)	−1,1(±1,1)	−1,4(±1,09)	−1,8(±1,2)
	neg	−3,5(±2,6)	−4,1(±3,3)	−1,5(±1,6)	−1,6(±1,7)	−1,2(±0,98)	−1,4(±1,2)
	p	0,7	0,8	0,36	0,37	0,73	0,38
Insulin treatment	pos	−2(±1,75)	−3(±2,6)	−0,87(±1,1)	−0,8(±1,4)	−0,8(±0,75)	−1,2(±1)
	neg	−3,8(±2,59)	−4,7(±3)	−1,4(±1,4)	−1,5(±1,4)	−1,5(±1)	−1,8(±1,2)
	p	0,07	0,19	0,28	0,24	0,08	0,20

W.C.: Waist circumference, BMI: Body mass indeks, HT: Hypertension M:Male F:Female pos: positive neg:negative.

Table 5
Third and sixth month changes of glycemic parameters.

		HbA1c 0−3.month	HbA1c 0−6 month	FPG 0−3 month	FPG 0−6 month	PPG 0−3 month	PPG 0−6 month
Age	<55	−0,87(±1,9)	−0,89(±1,3)	−49(±109)	−40(±85,7)	−100(±61)	−81(±85,9)
	≥55	−0,9(±1,86)	−0,69(±2,0)	−33(±61,3)	−43(±59,4)	−73(±63)	−67(±104)
	p	0,93	0,75	0,60	0,92	0,23	0,69
Sex	E	−1,02(±1,8)	−0,9(±1,77)	−50,8(±43)	−46(±37,5)	−60,8(±59)	−72(±78,9)
	K	−0,85(±1,9)	−0,7(±1,77)	−37(±100)	−40(±82,9)	−96,7(±63)	−74(±101)
	p	0,82	0,76	0,69	0,83	0,15	0,95
Duration of type 2 DM (Years)	<10	−1,27(±2,3)	−0,95(±2)	−79,8(±86)	−59(±76,7)	−92(±70)	−68(±107)
	≥10	−0,59(±1,3)	−0,65(±1,5)	−9(±75,9)	−28(±67)	−81,5(±58)	−79(±85,8)
	p	0,31	0,65	**0,02**	0,24	0,65	0,75
HT	pos	−1,1(±2)	−1,05(±1,7)	−39(±108)	−42(±83,9)	−106(±63)	−100(±85)
	neg	−0,6(±1,65)	−0,46(±1,74)	−42,7(±54)	−42(±57,7)	−62(±55)	−42,8(98)
	p	0,47	0,35	0,92	0,99	0,05	0,09
Insulin treatment	pos	−1,8(±2,77)	−1,38(±2,3)	−79(±112)	−40(±103)	−55,8(±65)	−10,3(±86)
	neg	−0,57(±1,3)	−0,58(±1,4)	−28(±75)	−42,8(±60)	−96,9(±60)	−96(±88)
	p	0,25	0,27	0,15	0,93	0,11	**0,02**

HT: Hypertension M:Male F:Female pos: positive neg:negative FPG:Fasting plasma glucose, PPG:Postprandial plasma glucose.

although the age range of the majority was between 50 and 60 [12–19]. The mean age of our study was 57 years and was consistent with the literature. It was observed that the BMI measured before the start of the drug was over 30 kg/m² in most studies. in our study, the initial VKI was 33.2 kg/m², which was consistent with these studies [12,15,17,19]. Dapagliflozin usually start patients who are overweight. This is due to the fact that the drug helps to lose calories by increasing urinary glucose excretion and helps to lose

weight. In our study, the basal waist circumference was 106.4 cm, in a study by Jan Bolinder and colleagues, basal waist circumference was 105.6 cm, similar to ours [15]. In a study by List and et al., an average of 2.5–3.4% weight loss and a 1.6–3.5% decrease in waist circumference were observed after 12 weeks of treatment with dapagliflozin [14]. Similarly, a study by Wilding JP et al. found that patients who used dapagliflozin after 12 weeks lost an average of 4.5 kg [20]. In our study, a mean weight loss of 3.3 kg was detected at the end of the third month and a decrease of 1.3 kg/m^2 was observed in BMI. Also a decrease of 1.3 cm was observed in the waist circumference. It was observed that our findings were compatible with previous studies.

In six placebo-controlled trials, body weight changes which observed at 24th week were significantly higher in patients using dapagliflozin than in placebo [12–14,21–23]. Bolinder and colleagues found that patients who used dapagliflozin had a 1.52 cm decrease in waist circumference compared to placebo at 24th week [15]. In our study, a mean weight loss of 4.2 kg was seen in the patients at the end of the sixth month, while a decrease of about 1.6 kg/m^2 in the BMI and 1.3 cm in the waist circumference were observed. In our study, the changes which observed at the end of the sixth month were similar to previous studies. Results of statistical analyzes revealed that the age, gender, duration of illness, or history of hypertension did not have a significant effect on anthropometric changes. There was no significant difference between the patients who were using insulin and the patients who were not using insulin in terms of anthropometric changes.

Most studies have shown that the use of dapagliflozin reduces HbA1c levels by 0.5–1% on average [24–26]. In the one of them, the study of Lambers Heerspink et al., found a decrease in HbA1c by 0.7% at the end of the third month [24]. In our study, HbA1c value decreased by 0.9% similarly to the literature at the end of the third month. In a study conducted by List and colleagues, a decrease of 10.1 mg/dl in the postprandial plasma glucose and a decrease of 21 mg/dl in the fasting plasma glucose were found at the end of the third month [25]. In a study by Wilding et al., a decrease of 34.4 mg/dl in the postprandial plasma glucose and decrease of 15.4 mg/dl in the fasting plasma glucose were detected [27]. In our study, a decrease of 41.1 mg/dl in fasting plasma glucose was detected at the end of the third month and a decrease of 86.3 mg/dl in the postprandial plasma sugar were detected. In the placebo-controlled seven study, mean HbA1c and fasting plasma glucose reductions were significantly greater than placebo at the end of 24 weeks (p < 0.001). In these studies, range of decrease in the HbA1c levels were between 0.49% and 0.97% and in the fasting plasma glucose were 19 mg/dl and 34 mg/dl [12–14,21–23,28]. In the three studies performed, significant decreases were found in the postprandial plasma glucose at the end of 24 weeks compared to the placebo. (p < 0,001). The reductions in postprandial plasma glucose observed in these studies ranged from 21 mg/dl to 67.5 mg/dl [13,14,23]. As a result of our study, at the end of the sixth month, a decrease of 0.79% in HbA1c, 42,1 mg/dL in the fasting plasma glucose and 74,2 mg/dL in the postprandial plasma glucose was detected according to the baseline and these values were found to be decreased in accordance with the literature. The results of the statistical analysis revealed that hypertension story, age or gender did not have a significant effect on HbA1c, fasting plasma glucose and postprandial glucose changes. In patients who did not use insulin, the decrease in postprandial plasma glucose at the end of the sixth month was significantly higher than in patients who did use insulin (p = 0.02). In addition, the decrease in fasting plasma glucose observed at the end of the third month was significantly higher in the patients with a disease duration of less than 10 years than that in patients with a disease duration of over than 10 years (p = 0.02). This result showed that the effect of dapagliflozin on fasting plasma glucose is more pronounced in the patients with low diabetes duration.

6. Conclusion

In conclusion, dapagliflozin therapy offers a new treatment option independent of insulin action in type 2 DM treatment. Dapagliflozin decreases the fasting plasma glucose, postprandial plasma glucose and HbA1c levels effectively in the six months period and the weight loss during treatment and reduction in waist circumference are useful in the treatment of obese or overweight diabetic patients.

Conflicts of interest

None to declare.

References

[1] Türkiye Endokrinoloji ve Metabolizma Derneği DM ve komplikasyonlarının tanı, tedavi ve izlem kılavuzu. 2017.
[2] IDF diabetes atlas - 2017 Atlas [Internet]. [cited 2017 Dec 25];Available from: http://www.diabetesatlas.org/resources/2017-atlas.html.
[3] Centers for Disease Control and Prevention. National diabetes statistics report, 2014: estimates of diabetes and its burden in the United States. 2014.
[4] Satman İ, Alagöl F, Ömer B ve ark. TURDEP-II sonuçlarının özeti. Çalışma grubu adına. 2010. Prof. Dr. İlhan Satman.
[5] Satman I, Yılmaz T, ark Sengul A ve. Population-based study of diabetes risk characteristics in Turkey. Diabetes Care 2002;25(9):1551–6.
[6] Singleton JR, Smith AG, Russel JW, Feldman EL. Microvasculer complications of impaired glucose tolerance. Diabetes 2003;52:2867–73.
[7] Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009 Jan;32:193–203.
[8] DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58(4):773–95.
[9] Hediger MA, Rhoads DB. Molecular physiology of sodium-glucose cotransporters. Physiol Rev 1994;74(4):993–1026.
[10] Sha S, Devineni D, Ghosh A, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metabol 2011;13(7):669–72.
[11] Vivian EM. Dapagliflozin: a new sodium-glucose cotransporter 2 inhibitor for treatment of type 2 diabetes. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm 2015;72(5):361–72.
[12] Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S, Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care 2015;38(3):365–72.
[13] Jabbour SA, Hardy E, Sugg J, Parikh S, Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37(3):740–50.
[14] Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012;35(7):1473–8.
[15] Bolinder J, Ljunggren Ö, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab 2012;97(3):1020–31.
[16] Scheerer MF, Rist R, Proske O, Meng A, Kostev K. Changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy: a primary care database study. Diabetes, Metab Syndrome Obes Targets Ther 2016;9:337–45.
[17] Bell KF, Katz A, Sheehan JJ. Quality measure attainment with dapagliflozin plus metformin extended-release as initial combination therapy in patients with type 2 diabetes: a post hoc pooled analysis of two clinical studies. Risk Manag Healthc Pol 2016;9:231–41.
[18] Shao H, Zhai S, Zou D, et al. Cost-effectiveness analysis of dapagliflozin versus glimepiride as monotherapy in a Chinese population with type 2 diabetes mellitus. Curr Med Res Opin 2017;33(2):359–69.
[19] Storgaard H, Gluud LL, Bennett C, et al. Benefits and harms of sodium-glucose Co-transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2016;11(11), e0166125.
[20] Wilding JP, Ferrannini E, Fonseca VA, Wilpshaar W, Dhanjal P, Houzer A. Efficacy and safety of ipragliflozin. in patients with type 2 diabetes inadequately controlled. on metformin: a dose-finding study. Diabetes Obes Metabol

2013;15:403—9.

[21] Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet Lond Engl 2010;375(9733):2223—33.

[22] Wilding JPH, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med 2012;156(6):405—15.

[23] Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metabol 2011;13(10):928—38.

[24] Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metabol 2013;15(9):853—62.

[25] List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32(4): 650—7.

[26] Kaku K, Inoue S, Matsuoka O, et al. Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: a phase II multicentre, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metabol 2013;15(5):432—40.

[27] Wilding JPH, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care 2009;32(9):1656—62.

[28] Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33(10):2217—24.