International Journal of Diabetes in Developing Countries (April–June 2025) 45(2):294–299
https://doi.org/10.1007/s13410-024-01380-y

ORIGINAL ARTICLE

Safety and efficacy of dapagliflozin in patients with type 2 diabetes mellitus during fasting in the month of Ramadan: an experience from tertiary care hospital

Akhtar Ali Baloch[1] · Khalil Ullah Shabir[1] · Zareen Kiran[1] · Nazish Fatima[1] · Syed Muhammad Hasan[1]

Received: 28 January 2023 / Accepted: 17 July 2024 / Published online: 29 July 2024

Abstract

Objective The data regarding the safety and efficacy of dapagliflozin during fasting is lacking especially in Pakistan. So, the current study aimed to explore the safety and efficacy of dapagliflozin in minimizing the episodes of hypoglycemia during fasting and reducing the HbA1c.

Methods A single-center, prospective observational cohort study was conducted at the National Institute of Diabetes and Endocrinology Department (NIDE), Dow International Medical College (DIMC), from March to June 2022. Diabetic patients who were being treated with stable doses of metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors were included, and then, different doses of dapagliflozin (DAPA) were added in their standard regimen after dividing them into two groups (Group A and B receiving 5 mg and 10 mg of DAPA, respectively).

Results Most of the study participants were females (63.9%) of which 37.7% had ages ranging from 41 to 50 years, were obese, and had diabetes ≤ 3 years with 24.6% participants having hypertension as comorbidity. Post-intervention analysis of the participants showed a significant decrease in HbA1c and blood pressure levels with the DAPA regimen (p-value = 0.000). Additionally, the efficacy of different doses was also significant (p-value = 0.008); however, the negative odds ratio of 0.929 indicated that increasing the dose would decrease the HbA1c.

Conclusions It was found that DAPA was safe and effective for the patients as it improves the HbA1c levels, and there were no significant hypoglycemic events. Further, urinary tract infections and diabetic ketoacidosis were also not reported by the patients.

Keywords Safety · Efficacy · Diabetes mellitus · Dapagliflozin

Introduction

Fasting in the month of Ramadan carries a considerable challenge for people with type 2 diabetes mellitus because it could precipitate episodes of hypoglycemia, hyperglycemia, dehydration, diabetic ketoacidosis (DKA), and venous thromboembolism [1]. Fasting, an essential pillar of Islam, is exempted for those people who are living with medical conditions or illnesses that put them at high risk and diabetes mellitus is one of them. The International Diabetes Federation–Diabetes and Ramadan (IDF-DAR) guidelines categorize people with diabetes into three groups—very high risk, high risk, and moderate/low risk [2]. Very high and high risk patients are advised not to fast while moderate to low risk could fast under the supervision of health care professionals provided that adequate education has been given. However, most of the patients falling in the high and very high risk category insisted to fast at any cost [2].

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study performed in 2001 concluded that the prevalence of fasting for at least 15 days during Ramadan among Muslim world diabetic patients is around 8.7% in type 1 and 91.3% in type 2 diabetes [3]. Optimal care and proper Ramadan-centered focused education must be given to these diabetic patients before and during Ramadan to make sure that they could fast safely.

✉ Akhtar Ali Baloch
Akhtarali80@hotmail.com

[1] National Institute of Diabetes And Endocrinology, Dow International Medical College, Dow University of Health Sciences, Karachi, Pakistan

The key elements of education included training of the participants regarding nutritional and dietary advice, exercise, medications, and dosage adjustment and more importantly knowing when to break the fast if hypoglycemia and hyperglycemia occur [2]. The Ramadan Education and Awareness in Diabetes (READ) study proved that a significant number of hypoglycemic events could be avoided during fasting in Ramadan, if patients have received pre-Ramadan education training programs [4].

Many trials have proven the safety of different anti-hyperglycemic drugs in fasting during the month of Ramadan for diabetic patients [5–7]. Over the last few years, the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors is preferred. Thus, due to its cardio-renal advantages, dapagliflozin (DAPA) is used these days [8, 9]. This newest class of drug has the added advantage that it does not cause severe episodes of hypoglycemia as compared to sulfonylureas [10]. However, the risk of developing thirst, dehydration, postural hypotension, thrombosis, and diabetic ketoacidosis increases with the use of SGLT2 inhibitors during Ramadan as evident by different trials done worldwide [10–12].

The available data regarding the safety and efficacy of dapagliflozin during fasting in Ramadan is lacking especially in Pakistan. Thus, this study aimed to explore the safety of dapagliflozin in minimizing the episodes of hypoglycemia during fasting in Ramadan and measure the efficacy of different dosages of dapagliflozin in reducing the HbA1c along with the standard of care received by the type 2 diabetic patients in the month of Ramadan.

Materials and methods

Study design

This was a single-center, prospective observational cohort study conducted at the National Institute of Diabetes & Endocrinology (NIDE), Dow International Medical College, Dow University of Health Sciences, Karachi, OJHA, Campus, from March to June 2022, that is 4 weeks before Ramadan until 4 weeks post-Ramadan, after ethical approval of the protocol from the ethics committee.

Non-probability convenience sampling technique was used to recruit the participants in the study. All patients with type 2 diabetes mellitus aged between 18 and 65 years old, who intend to fast at least 20 days during Ramadan, had an HbA1c level of 7 or above, and who are being treated with a stable dosage of metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors were included in the study, whereas diabetic patients who were pregnant or were breastfeeding their child and patients who were on insulin or sulfonylureas were excluded as this class of drug is proven to be associated with severe hypoglycemia (blood sugar level below 70 mg/dl anytime during the 24-h period of the day in the fasting month of Ramadan). Further, patients who had a past history of recurrent urinary tract infections, impaired renal function with estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73 m^2, malignancy, cardiovascular events within the last 90 days, or contraindication for fasting were excluded.

The sample size was calculated using Open epi, version 3, open-source calculator. Keeping a 97% confidence interval (CI), a percentage of hypoglycemia in the intervention group of 6.9% as reported in a previous study [13], and a margin of error of 5%, the current study sample size was calculated to be 121 patients. As the current study comprised two groups, so there were 61 participants in each group.

All patients who met the inclusion criteria were enrolled in the study after taking informed consent. Patients were divided into two groups. Group A included those patients who took 5 mg of dapagliflozin before and continued during the study period along with any doses of metformin and DPP-4 inhibitors. Group B included those patients who took 10 mg of dapagliflozin before and continued during the study period along with any doses of metformin and DPP-4 inhibitors. Both groups were enrolled at least 1 month before fasting.

Data was collected from all participants at the initial visit 4 weeks before Ramadan and on a follow-up visit 4 weeks after Ramadan. Patients were advised to document their blood glucose at seven different times per week [2].

All data was entered using a predefined structured proforma for documenting the sociodemographic variables and clinical and laboratory parameters. Data regarding sociodemographic features (age, gender, weight, height, body mass index, comorbidities); clinical data (duration of type 2 diabetes); details of micro- and macrovascular complications of diabetes like nephropathy, neuropathy, retinopathy, ischemic heart disease, or cerebrovascular disease; and measurement of systolic and diastolic blood pressures at baseline (4 weeks before Ramadan) and at 4 weeks post Ramadan and incidents of hypoglycemia during fasting and any adverse events and laboratory data (HbA1c levels, serum sodium, potassium, chloride, bicarbonate, creatinine levels 4 weeks before Ramadan and at 4 weeks post Ramadan and urinalysis) were collected.

Statistical software for social sciences (SPSS version 26) was used to analyze the data. All categorical variables, including age, duration of disease, mean laboratory parameters, the frequency of hypoglycemic episodes, gender, and adverse events, were presented as frequency and percentages and compared using the chi-squared test.

Comparison between groups was analyzed with analysis of variance (ANOVA). Data was presented in the form of tables and bar charts. A p-value of < 0.05 was considered the cutoff for significance.

Results

Although the calculated sample size of this study was 121 patients with 61 patients in each group, however, the sample size was reduced to 61 participants only due to the following reasons: (1) death of the participants ($n=2$) and (2) non-response rate of the participants ($n=20$), patients were not willing to conduct the laboratory assessment after Ramadan due to multiple reasons: one such reason was the financial issues or non-availability of services at their area as most of them were residing in rural areas ($n=11$), and also the participants did not fast in Ramadan as per the inclusion criteria with most of the participants had less than 20 fasts or even zero fasting ($n=26$).

On these bases, the sample size was reduced to 61 participants in total with 30 patients in each group. Out of 61 participants, 63.9% were females. Around 37.7% participants' age ranged in between 41 and 50 years.

Most of the participants (37.7%) were suffering from diabetes since ≤ 3 years. Most of the participants (55.7%) did not have any comorbidity; however, 24.6% were suffering from hypertension. The majority of the participants.

(37.7%) were obese and 72.1% were diabetic as per their HbA1c levels (Table 1).

When the safety of the drug DAPA was assessed, it was found that the number of hypoglycemic and diabetic ketoacidosis events was reduced significantly (p-value = 0.000). There were no significant hypoglycemic events reported by participants which were managed at home. Out of 61 participants, 9 (14.7%) reported to the hospital with high and low blood sugar levels, in which only 4 (6.5%) participants reported hypoglycemia. That was not statistically significant. Further, urinary tract infections were also not reported by the patients at a significant level (p-value = 0.001) (Table 2). The 14 patients reported only mild-intensity urinary tract infections which were managed conservatively and urinary microscopy and cultures were not done. They continued dapagliflozin as symptoms of UTI were mild and improved with increased fluid intake in a non-fasting state (after iftar), safe hygiene practices, and standard antimicrobial medications if required.

When the efficacy of the drug dapagliflozin was assessed in comparison to the dipeptidyl peptidase-4 (DPP-4) inhibitors, that were given previously to the patients, it was found that the HbA1c levels and systolic and diastolic blood pressures were significantly decreased with DAPA regimen (p-value = 0.000) (Table 3).

Additionally, when the efficacy of different doses was assessed, the values were significant (p-value = 0.008) where the negative odds ratio of 0.929 indicated that increasing the dose would decrease the HbA1c further (Table 4). But the safety of the drug decreased with an increase in dose from 5 to 10 mg. Four out of 61 participants reported hypoglycemic events in which 1 was on 5 mg and 3 were on 10 mg.

Table 1 Demographic characteristics of the participants ($n=61$)

Variables		Frequency	Percentage
Gender	Male	22	36.1
	Females	39	63.9
Age	30 to 40	13	21.3
	41 to 50	23	37.7
	51 to 60	15	24.6
	61 to 70	10	16.4
Duration of diabetes	1 month till 3 years	23	37.7
	4 to 6 years	13	21.3
	7 to 9 years	10	16.4
	10 and above years	15	24.6
Comorbidities	Chronic kidney disease (CKD)	1	1.6
	Hypertension (HTN)	15	24.6
	Ischemic heart disease (IHD)	1	1.6
	Retinopathy	4	6.6
	Neuropathy	1	1.6
	Dyslipidemia	2	3.3
	None	34	55.7
Body mass index (BMI)	Underweight	1	1.6
	Normal	16	26.2
	Overweight	18	29.5
	Obese	23	37.7

Table 2 Safety of the drug dapagliflozin towards the patients of type 2 diabetes mellitus during fasting ($n=61$)

Safety variables		Frequency	Percentage	*p*-value
Any admission due to high or low blood sugar level?	Yes	9	14.8	**0.000**
	No	52	85.2	
Any admission due to low blood pressure or extreme dehydration?	Yes	10	16.4	**0.000**
	No	51	83.6	
Any admission with Diabetic Ketoacidosis (DKA)?	Yes	1	1.6	**0.000**
	No	60	98.4	
Any kind or symptom of Urinary tract infection (UTI)?	Yes	14	22.9	**0.001**
	No	47	77.1	

Table 3 Efficacy of the drug dapagliflozin in comparison to dipeptidyl peptidase-4 (DPP-4) inhibitors ($n=61$)

Regimen	DPP-4 inhibitors (pre-intervention)	Dapagliflozin (post intervention)	Correlation	Significance	*p*-value
HbA1c levels	8.05 ± 1.89	7.22 ± 1.60	0.199	0.466	**0.000**
Systolic pressure (mmHg)	132.627 ± 21.160	128.731 ± 16.130	−0.13	0.937	**0.000**
Diastolic pressure (mmHg)	79.069 ± 9.678	78.170 ± 9.669	0.067	0.680	**0.000**
Creatinine (mg/dl)	0.797 ± 0.202	0.812 ± 0.226	0.125	0.455	**0.000**
eGFR (ml/min/1.73m^2)	107.378 ± 27.924	107.787 ± 24.844	−0.13	0.937	**0.000**

Table 4 Efficacy of different doses of the drug dapagliflozin ($n=60$)

Drug dosages	*N*	*p*-value	Odds ratio (OR)	-2 Log likelihood	Cox and Snell R square	Nagelkerke R square
DAPA 5 mg	30	0.008	Ref	37.620[a]	0.000	0.000
DAPA 10 mg	30		0.929			

[a]Estimation terminated at iteration number 4 because parameter estimates changed by less than 0.001

Discussion

This study was conducted with a primary objective to assess the number of hypoglycemic events that occurred by dapagliflozin and a secondary objective to assess the number of events of diabetic ketoacidosis, urinary tract infections, and/or decline in eGFR and effectiveness of dapagliflozin in reducing HbA1c level. Many studies have been conducted in the past to prove the safety and efficacy of different anti-hyperglycemic drugs for diabetic patients [5–7].

Over the last few years, SGLT2 inhibitors are preferred due to their cardio-renal advantages [8, 9]. However, the risk of developing thirst, dehydration, postural hypotension, thrombosis, and diabetic ketoacidosis increases with the use of SGLT2 inhibitors as evident by different researches conducted globally [10–12].

It was found that the available data regarding the safety and efficacy of these SGLT2 inhibitors is lacking during fasting in type 2 diabetes mellitus patients in Pakistan. Thereby, this study aimed to explore the safety of one such drug named dapagliflozin in minimizing the episodes of hypoglycemia during fasting in Ramadan and measure the efficacy of different dosages of dapagliflozin in reducing the HbA1c along with the standard of care received by the type 2 diabetic patients in the month of Ramadan.

This study found that the drug DAPA was safe for the diabetic patients at both diabetic and pre-diabetic levels as it significantly reduced the number of hypoglycemic and diabetic ketoacidosis events (p-value = 0.000) during fasting. Further, urinary tract infections were also not reported by the patients at a significant level (p-value = 0.001). These findings are in agreement with the results of the study conducted by Verma et al. in 2018 and concluded that SGLT2 inhibitors are state-of-the-art pharmacological tools for the prevention of cardiovascular risks as compared to other sugar-lowering drugs [14]. Similarly, another study conducted by Wiviott et al. in 2018 confirmed the safety and efficacy of the drug dapagliflozin towards the cardiovascular events in diabetes patients [15]. One more study explained the cardioprotective effects and safety of SGLT2 inhibitor in addition to volume and diuresis, adipokine kinetics, and myocardial metabolism in diabetic patients [16]. Similarly,

studies conducted by Bonora et al. in 2020 and Neuen et al. 2019 concluded that numerous diverse mechanisms could play their role in the overall cardio and nephron-protective effects as produced by SGLT2 inhibitors in diabetic patients. However, not considering the exact molecular pathway, the ancillary extraglycemic effects approach of SGLT2 inhibitors significantly decreased the risk of hospitalization due to heart failure, cardiovascular events, and diabetic ketoacidosis progression, thereby protecting the heart and kidneys of the diabetic patients [17, 18].

Further, the current study assessed the efficacy of the drug dapagliflozin in comparison to the dipeptidyl peptidase-4 (DPP-4) inhibitors, that were given previously to the patients; it was found that the HbA1c levels were significantly decreased with DAPA regimen (p-value = 0.000) during fasting. Similar to the current study results, a study conducted by Dainele et al. in 2016 reported that dapagliflozin improves insulin sensitivity increasing lipid oxidation in diabetes patients thereby increasing their glucagon to insulin ratio [19]. Thus, DAPA treatment causes an acute reduction in the concentration of plasma glucose thereby decreasing glucose entry into muscle and thus decreasing the HbA1c levels of the diabetic patients.

Additionally, when the efficacy of different doses was assessed, the values were significant (p-value = 0.008) where the negative odds ratio of 0.929 indicated that increasing the dose would decrease the HbA1c further. Likewise, another recent meta-analysis conducted by Abu-Zaid et al. in 2021 found that HbA1c levels, BMI, and total daily insulin dose were significantly reduced in the diabetic patients who received dapagliflozin versus placebo [20].

Conclusion

In conclusion, the current study findings suggested that the drug dapagliflozin is safe and effective for type 2 diabetes patients during fasting in the month of Ramadan. As it improves the HbA1c levels, the number of hypoglycemic and diabetic ketoacidosis events was reduced significantly. Further, urinary tract infections were also not reported by the patients. Although previous studies have shown increased cases of diabetic ketoacidosis and urinary tract infection with long-term use of the dapagliflozin drug, the current study does not show any such incidents. This might be due to the following reasons that many of these previous researches involved type 1 diabetes patients in whom the daily dose of insulin was decreased with SGLT2 inhibitors' therapy as they increase glucose secretion [21, 22], whereas the current study only included patients with type 2 diabetes who were not taking insulin as therapy and it is evident that the insulin dose reduction would result in ketoacidosis. Another common case in many previous researches cases was any associated medical and/or surgical condition which result in moderate-to-severe physical and mental stress for the diabetic patients which leads to catecholamine's predisposition and development of ketoacidosis both by insulin secretion inhibition and ketone production stimulation [23]. Lastly, it has been hypothesized by different studies that this increased plasma ketone concentration [24–26] worked as a readily oxidizable fuel for the myocardium [27, 28] and provided the beneficial cardiovascular effects in type 2 diabetes mellitus patients [29]. The current results are entirely in agreement with all above-mentioned theories and provide a strong explanation for the safety and efficacy of dapagliflozin during fasting in type 2 diabetes patients.

However, there are some limitations of the current study including the lower sample size and being a single-center study. Further, studies with increased sample sizes and including multiple centers are recommended. Moreover, a comparison of type 1 and type 2 diabetic patients is also recommended using dapagliflozin for generalizability of its adverse effects like urinary tract infections and diabetic ketoacidosis.

Author contribution The authors confirm contribution to the paper as follows: study conception and design: AB, KS; data collection: NF, MH; analysis and interpretation of results: AB, ZK, NF; draft manuscript preparation: KS, NF, ZK. All authors reviewed the results and approved the final version of the manuscript.

Data availability All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Consent to participate Written informed consent was obtained from participants.

Competing interests The authors declare no competing interests.

References

1. Abdelgadir E, Rashid F, Bashier A, Al Saeed M, Khalifa A, Alawadi F, et al. Use of flash glucose monitoring system in assessing safety of the SGLT2 inhibitors during Ramadan fasting in high risk insulin treated patients with type 2 diabetes. Diabetes Metab Syndr: Clin Res Rev. 2019;13(5):2927–32.
2. Hassanein M, Al-Arouj M, Hamdy O, Bebakar WMW, Jabbar A, Al-Madani A, et al. Diabetes and Ramadan: practical guidelines. Diabetes Res Clin Prac. 2017;126:303–16.
3. Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Cl Voinet, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care. 2004;27(10):2306–1.
4. Bravis V, Hui E, Salih S, Mehar S, Hassanein M, Devendra D. Ramadan education and awareness in diabetes (READ)

programme for Muslims with type 2 diabetes who fast during Ramadan. Diabetic Med: J Br Diabet Assoc. 2010;27(3):327–31.
5. Bashir MI, Pathan MF, Raza SA, Ahmad J, Khan AKA, Ishtiaq O, et al. Role of oral hypoglycemic agents in the management of type 2 diabetes mellitus during Ramadan. Indian J Endocrinol Metab. 2012;16(4):503–7.
6. Devendra D, Gohel B, Bravis V, Hui E, Salih S, Mehar S, et al. Vildagliptin therapy and hypoglycaemia in Muslim type 2 diabetes patients during Ramadan. Int Jclin Prac. 2009;63(10):1446–50.
7. Bashier A, Bin Hussain A, Mk A. Safety and efficacy of liraglutide as an add-on therapy to pre-existing anti-diabetic regimens during Ramadan, a prospective observational trial. J Diabetes Metab. 2015;6:590.
8. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Eng J Med. 2019;381(21):1995–2008.
9. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. New Engl J Med. 2020;383(15):1436–46.
10. Wan Seman WJ, Kori N, Rajoo S, Othman H, Mohd Noor N, Wahab NA, et al. Switching from sulphonylurea to a sodium-glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia. Diabetes Obes Metab. 2016;18(6):628–32.
11. Bashier A, Khalifa AA, Abdelgadir EI, Al Saeed MA, Al Qaysi AA, Bayati MBA, et al. Safety of sodiumglucose cotransporter 2 inhibitors (SGLT2-I) during the month of Ramadan in Muslim patients with type 2 diabetes. Oman Med J. 2018;33(2):104–10.
12. Shao Y, Lim GJ, Chua CL, Wong YF, Yeoh ECK, Low SKM, et al. The effect of Ramadan fasting and continuing sodium-glucose co-transporter-2 (SGLT2) inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes. Diabetes Res Clin Pract. 2018;142:85–91.
13. Wan Seman W, Kori N, Rajoo S, Othman H, Mohd Noor N, Wahab N, et al. Switching from sulphonylurea to a sodium[Inline Image Removed]glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia. Diabetes Obes Metab. 2016;18(6):628–32.
14. Verma S, Bhatt DL, Bain SC, Buse JB, Mann JF, Marso SP, et al. Effect of liraglutide on cardiovascular events in patients with type 2 diabetes mellitus and polyvascular disease: results of the LEADER trial. Circulation. 2018;137(20):2179–83.
15. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. The design and rationale for the dapagliflozin effect on cardiovascular events (DECLARE)–TIMI 58 Trial. Am Heart J. 2018;200:83–9.
16. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61(10):2108–17.
17. Bonora BM, Avogaro A, Fadini GP. Extraglycemic effects of SGLT2 inhibitors: a review of the evidence. Diabetes, Metab Syndr Obes: Targets Therap. 2020;13:161.
18. Neuen BL, Young T, Heerspink HJ, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019;7(11):845–54.
19. Daniele G, Xiong J, Solis-Herrera C, Merovci A, Eldor R, Tripathy D, et al. Dapagliflozin enhances fat oxidation and ketone production in patients with type 2 diabetes. Diabetes Care. 2016;39(11):2036–41.
20. Abu-Zaid A, Altowairqi AK, Dissanayaka T, Oganesyan A, Bhagavathul AS, Alhabeeb H, et al. A systematic review and dose-response meta-analysis on the efficacy of dapagliflozin in patients with type 1 diabetes mellitus. Pharmacolog Res. 2021;165:105456.
21. DeFronzo RA. 2001 Regulation of intermediary metabolism during fasting and feeding. Endocrinol 737–75
22. Crook ED, Zhou J, Daniels M, Neidigh JL, McClain DA. Regulation of glycogen synthase by glucose, glucosamine, and glutamine: fructose-6-phosphate amidotransferase. Diabetes. 1995;44(3):314–20.
23. McGarry J, Wright PH, Foster DW. Hormonal control of ketogenesis. Rapid activation of hepatic ketogenic capacity in fed rats by anti-insulin serum and glucagon. J clin invest. 1975;55(6):1202–9.
24. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. Diabetes Care. 2016;39(7):1108–14.
25. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis Diabetes care. 2016;39(7):1115–22.
26. Abdul-Ghani M, Del Prato S, Chilton R, DeFronzo RA. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME study. Diabetes Care. 2016;39(5):717–25.
27. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiolog rev. 2005;85(3):1093–129.
28. Bedi KC Jr, Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation. 2016;133(8):706–16.
29. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Eng J Med. 2015;373(22):2117–28.