Original Article

Metabolic and renal outcomes of empagliflozin in patients with type 2 diabetes mellitus attending Armed Forces Hospital in Saudi Arabia

Retrospective cohort study

Ali A. Alshahrani, *MD, MBBS,* ***Saad S. Al Qahtani,*** *B Pharm,* ***Abrar S. Al Qahtani,*** *MD, MBBS,* ***Saeed M. Mashhour,*** *B Pharm,* ***Zayed S. Alkhtani,*** *MD, MBBS,* ***Yahya M. Alragea,*** *MD, MBBS.*

ABSTRACT

الأهداف: تهدف هذه الدراسة لاستكشاف تأثير empagliflozin (25 mg) على المعدلات الأيضية والكلوية في المرضى المصابين بداء السكري من النوع الثاني.

المنهجية: أُجريت هذه الدراسة المقارنة بأثر رجعي بالمستشفى العسكري في مدينة خميس مشيط، جنوب المملكة العربية السعودية. شملت هذه الدراسة كل البالغين المصابين بداء السكري النوع الثاني الذين تزيد أعمارهم على 18 سنة وزاروا عيادات مرض السكري خلال الفترة من اكتوبر 2021 حتى مارس 2022 (لمدة 6 أشهر)، مع او بدون علاج الانسولين.

النتائج: تضمنت هذه الدراسة ما مجموعه 308 مريض تم تشخيصهم بداء السكري النوع الثاني. بعد بدء علاج empagliflozin تم ملاحظة انخفاضات ذات دلالات إحصائية في وزن المرضى (كجم) عند 1، و 3–5، و 6 أشهر. بالاضافة الى انخفاض مستويات البروتين الدهني منخفض الكفاءة بشكل ملحوظ خلال 3–5 أشهر بعد بدء العلاج (p=0.011)، بالرغم من انخفاض مستوى الكيراتين بالدم تدريجياً مع مرور الوقت أثناء استخدام العلاج، من 87.45±31.78 (0.105) الى 78.39±27.43 (0.033). إضافةً لذلك، بعد بدء العلاج انخفضت نسبة urinary albumin–to–creatinine بشكل ملحوظ عند 3–6 و 6 أشهر. كما اظهرت مستويات HbA1c انخفاضاً إحصائياً معتبراً عند 3–5 أشهر (p<0.001) و عند 6 أشهر (p<0.001) بعد بدء العلاج. يجدر بالذكر أن ضغط الدم الانقباضي والانبساطي انخفض بشكل ملحوظ بعد 6 أشهر من بدء العلاج.

الخلاصة: في هذه الدراسة أثبت علاج empagliflozin فعاليته في التحكم بضغط الدم و وزن الجسم، و تحسين كلا من وظائف الكلى، و dyslipidemia على المدى القصير، و التحكم بمستوى السكر بالدم للمرضى المصابين بداء السكري النوع الثاني.

Objectives: To explore the effects of empagliflozin (25 mg) on metabolic and renal parameters in patients with type 2 diabetes mellitus (T2DM).

Methods: This retrospective observational comparative study was conducted at a military hospital in southern Saudi Arabia. All adults (aged >18 years) with T2DM who attended diabetic clinics between October 2021 to March 2022 (6 months), with or without insulin treatment, were eligible for inclusion in the study.

Results: Following the initiation of empagliflozin treatment, statistically significant reductions in patient weight (kg) were observed at 1, 3-5, and 6 months. In addition, low-density lipoprotein levels significantly decreased 3-5 months post-treatment initiation (p=0.011). However, serum creatinine level decreased gradually with time during the treatment with empagliflozin, from 87.45±31.78 (0.105) to 78.39±27.43 (0.033). Furthermore, after empagliflozin treatment, the urinary albumin-to-creatinine ratio significantly decreased at 3-5 and 6 months. Moreover, HbA1c levels exhibited statistically significant decreases at 3-5 months (p<0.001) and at 6 months (p<0.001) following the initiation of empagliflozin treatment. Notably, systolic and diastolic blood pressure significantly reduced 6 months after empagliflozin treatment.

Conclusion: In the current study, empagliflozin has demonstrated efficacy in controlling blood pressure and body weight, and improving renal function, short-term dyslipidemia, and glycemic control in patients with T2DM.

Keywords: empagliflozin, weight, dyslipidemia, glycemic control, renal outcomes

Saudi Med J 2023; Vol. 44 (7): 674-678
doi: 10.15537/smj.2023.44.7.20230094

From the Department of Family Medicine, Armed Forces Hospital, Khamis Mushait, Kingdom of Saudi Arabia.

Received 22nd May 2023 . Accepted 7th June 2023.

Address correspondence and reprint request to: Dr. Ali A. Alshahrani, consultant family medicine and diabetes, Family Medicine Department, Armed Forces Hospital, Khamis Mushait, Kingdom of Saudi Arabia. E-mail: aly.alshahrani@gmail.com
ORCID ID: https://orcid.org/0000-0001-5333-5814

Type 2 diabetes mellitus is a progressive disease.[1] Increasing insulin resistance, progressive decline in β-cell function, dysfunctional adipocytes, gastrointestinal incretin defects, increased glucose reabsorption from the kidneys, hyperglucagonemia, and neurotransmitter dysfunction are potential factors contributing to the pathogenesis of diabetes.[1] With complex pathophysiology, sodium-glucose cotransporter 2 (SGLT2) inhibitors have a unique mechanism of action, leading to the excretion of glucose via urine and the subsequent lowering of plasma glucose. This mechanism is independent of β-cell function; thus, these agents are effective treatments for T2DM at theoretically any disease stage.[2]

Evidence from clinical trials shows reductions in glycated hemoglobin (-0.59%) to (-0.82%) with a low risk of hypoglycemia, except when used with insulin or insulin secretagogues, and moderate reductions in body weight (-2.1 to -2.5 kg) and systolic blood pressure (-2.9 to -5.2 mmHg), thus supporting the use of empagliflozin as monotherapy or in combination with other glucose-lowering agents.[2]

A collaborative meta-analysis of 13 clinical trials involving 90413 participants showed, in addition to the established cardiovascular benefits of SGLT2i, data revealed strong support for their use in decreasing kidney disease progression and acute kidney injury in those with chronic kidney disease or heart failure with or without diabetes.[3] Among patients receiving the recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization than those in the placebo group, regardless of the presence or absence of diabetes.[3,4] Approximately 2.6 million people were estimated to have received dialysis or undergone kidney transplantation for kidney failure in 2010, and this number is projected to double by 2030.[5] Sodium-glucose cotransporter 2 inhibitors can reduce the risk of dialysis, transplantation, and death due to kidney disease in individuals with T2DM and protect against acute kidney injury.[6]

Although numerous international studies have been carried out on the safety and effectiveness of SGLT2 inhibitor, particularly on cardiovascular and renal outcomes, no study in Saudi Arabia has determined its effectiveness and safety, especially in patients with comorbid diabetes of different races and lifestyles.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This retrospective observational comparative study was carried out in the chronic illness clinics of the Armed Forces Hospital, Southern Region (AFHSR), Khamis Mushait City, located in southwestern Arabia. It has a population of 1.353.000, according to the estimated 2017 census.

All adults (aged >18 years) with T2DM who attended these clinics between October 2021 to March 2022 (6 months), with or without insulin treatment, were eligible for inclusion in the study provided that they met the inclusion criteria, that is, being on empagliflozin (SGLT-2 inhibitor) for at least 6 months, including patients with mild kidney impairment and heart failure. In addition, patients on a ketone diet, patients with renal failure (end-stage kidney disease) or stage 4 or 5 chronic kidney disease, patients with estimated glomerular filtration rate (eGFR) <25, patients with severe malnutrition, pregnant women, and patients with any suspicious information from the history or examination of type 1 diabetes mellitus or latent autoimmune diabetes in adults (LADA) were excluded from the study.

A checklist was used to collect information on patients with T2DM from electronic medical records before and after empagliflozin therapy was started. This information included body weight, low-density lipoprotein (LDL) level, triglyceride (TG) level, creatinine level, blood pressure, urinary albumin-to-creatinine ratio (UACR), and glycated hemoglobin level (HbA1c%).

Approval was obtained from the Research and Ethics Committee of the AFHSR (AFHSRMREC/2022/FAMILY MEDICINE/596) prior to the study, which was carried out according to the principles of Helsinki. In addition, written permission was obtained from the medical director of the AFHSR.

Statistical analysis. The data were entered and analyzed using the Statistical Package of Social Science, version 26.0 (IBMCorp, Armonk, NY, USA). Descriptive statistics, such as mean, range, and standard deviation, were calculated to summarize continuous numerical data, whereas frequency and percentage

Table 1 - Age and gender distribution of the participants (N=308).

Variables	Description
Gender, n (%)	
Male	198 (64.3)
Female	110 (35.7)
Age (years)	23-89
Range, mean±SD	58.0±10.6

SD: standard deviation

were used to describe categorical variables. A paired t-test was used to compare parameters before and after empagliflozin therapy at different follow-up periods. Statistical significance was set at $p<0.05$.

Results. In total, 308 patients with T2DM were included in this study. Almost two-thirds (64.3%) of the patients were male. Their ages ranged from 23 to 89 years, with an arithmetic mean of 58 years and a standard deviation of 10.6 years (Table 1).

The weight (kg) of patients decreased significantly at 1 month from 83.3 ±15.9 to 80.5±15.5 ($p=0.010$), 3-5 months from 84.9±15.1 to 82.±15.7 ($p<0.001$), and >6 months from 83.4±13.9 to 79.4±12.8 ($p<0.001$) after the start of empagliflozin treatment. Low-density lipoprotein (LDL) levels decreased significantly from 2.53±0.91 to 2.36±0.84 ($p=0.011$) at 3-5 months after the initiation of empagliflozin treatment but increased non-significantly from 2.55±0.77 to 2.6±0.87 ($p=0.584$) at 6 months after starting empagliflozin. Triglyceride levels did not decrease significantly at any follow-up point. Although serum creatinine levels were consistently higher than pretreatment levels, they gradually declined over time, from 87.4±31.78 (0.105) to 78.3±27.4 (0.033). The UACR ratio decreased significantly from 123.86±348.6 to 91.87±226.3 ($p=0.043$) at 3-5 months and from 133.4±391.8 to 71.9±169.3 ($p=0.022$) at 6 months after starting empagliflozin. Glycated hemoglobin level (HbA1c%) decreased significantly from 9.0±1.72 to 8.5±1.4 ($p<0.001$) at 3-5 months and from 8.8±1.5 to 8.3±1.3($p<0.001$) at 6 months after starting empagliflozin. Systolic ($p=0.045$) and diastolic ($p=0.002$) blood pressure decreased significantly 6 months after empagliflozin treatment (Table 2).

Discussion. The current study adds to the literature concerning the benefits of empagliflozin in weight reduction, both systolic and diastolic blood pressure lowering, short-term decrease in LDL and HbA1c levels, and improvement in renal outcomes.

In this study, a decrease in patients' weight was observed even at the 1 month follow-up after the start of empagliflozin therapy and afterward. This has been documented in numerous randomized clinical trials and retrospective cohort studies.[7-12] The weight reduction induced by empagliflozin could be explained by many factors, including glucosuria, which leads to the energy loss of 200–300 Kcal/day,in addition to reductions in visceral adipose tissues, fat mass, and subcutaneous adipose tissue.[13,12]

Table 2 - Comparison of metabolic and renal outcomes of empagliflozin in patients with T2DM at different follow-up periods.

Variables	Before starting empagliflozin Mean±SD	3 weeks to 1 month after starting empagliflozin Mean±SD (*p*-value)	3-5 months after starting empagliflozin Mean±SD (*p*-value)	>6 months after starting empagliflozin Mean±SD (*p*-value)
Weight (kg)	83.3±15.9 (n=45)	80.4 ±15.5 (0.010)		
	84.9±15.1 (n=152)		82.0±15.7 (<0.001)	
	83.4±13.9 (n=117)			79.4±12.8 (<0.001)
LDL	2.31±0.58 (n=19)	2.23±0.63 (0.618)		
	2.53±0.91 (n=166)		2.36±0.84 (0.011)	
	2.55±0.77 (n=73)			2.60±0.87 (0.584)
TG	2.11±1.20 (n=33)	1.88±1.18 (0.115)		
	1.79±0.96 (n=236)		1.77±1.08 (0.766)	
	1.87±0.99 (n=126)			1.77±0.80 (0.223)
Creatinine	83.79±30.14 (n=31)	87.45±31.78 (0.105)		
	77.55±25.18 (n=227)		79.62±28.60 (0.059)	
	76.04±23.46 (n=147)			78.39±27.43 (0.033)
UACR	52.39±92.85 (n=21)	32.87±44.34 (0.208)		
	123.86±348.6 (n=181)		91.87±226.3 (0.043)	
	133.41±391.8 (n=106)			71.92±169.3 (0.022)
HbA1c	8.93±1.50 (n=34)	8.73±1.43 (0.411)		
	9.01±1.72 (n=260)		8.51±1.43 (<0.001)	
	8.85±1.55 (n=166)			8.34±1.35 (<0.001)
SBP	130.45±14.87 (n=22)	129.59±11.63 (0.777)		
	129.35±13.77 (n=115)		129.05±12.71 (0.821)	
	129.52±13.06 (n=83)			126.04±12.33 (0.045)
DBP	75.09±8.62(n=22)	72.41±7.79 (0.066)		
	74.26±8.32 (n=115)		73.20±7.35 (0.221)	
	75.19±7.92 (n=83)			71.61±8.95 (0.002)

T2DM: type 2 diabetes mellitus, SD: standard deviation, N: number of individuals with an event, LDL: low-density lipoprotein, TG: triglycerides, UACR: urine albumin-to-creatinine ratio, HBA1c: glycosylated hemoglobin, SBP: systolic blood pressure, DBP: diastolic blood pressure

Dyslipidemia is a common comorbid condition associated with T2DM, and the current study revealed a significant reduction in LDL levels at 3-5 months after the initiation of empagliflozin therapy, with a non-significant TG decline.[14] Similarly, a significant decrease in LDL cholesterol levels was observed in patients with T2DM treated with empagliflozin in another Canadian study.[8] Furthermore, a non-significant increase in LDL levels was observed after 6 months of empagliflozin use, and other randomized clinical trials have documented similar results.[9,15] The use of statins can explain this finding; it was caused either by dosage change or decreased clearance of LDL from the circulation and increased lipolysis of triglyceride-rich lipoproteins.[16] However, most patients with diabetes in chronic illness clinics aged >40 at our facility take moderate-intensity statins for primary cardiovascular prevention. In a Canadian study, the authors documented reduced LDL cholesterol after initiating empagliflozin, even though most patients continued statin intake without changing the dosage.[8]

In the current study, and in agreement with other studies[7,11,15,17-22], empagliflozin significantly decreased both systolic and diastolic blood pressure after 6 months of therapy, which could be attributed to its effect on weight reduction, osmotic diuresis, and improvement in vascular stiffness and hyperglycemic oxidative stress.[23] In addition, osmotic diuretics and natriuretics help alleviate plasma volume contraction, providing cardiovascular benefits.[23-26]

The present study showed a decrease in HbA1c% starting significantly at 3 months after empagliflozin initiation, although the mean value was above the recommended level of 7%. An improvement in glycemic control has also been observed in a similar Canadian study;[8] however, in the present study, we did not include information regarding whether patients were taking insulin or other antidiabetic oral medications with empagliflozin, which could affect the overall impact of empagliflozin on HbA1c%. In a Canadian study, the authors observed that patients treated with empagliflozin in addition to insulin and no metformin had a smaller HbA1c% decrease than patients treated with empagliflozin in addition to metformin without insulin.[9] Further studies and information on the intake of other antidiabetic medications along with empagliflozin are highly recommended to clarify these issues. A reduction in HbA1c% after empagliflozin initiation has also been observed.[7, 9-11]

The current study's findings showed that, despite all creatinine levels being higher than before treatment, creatinine levels gradually decreased over time once empagliflozin was started. However, no statistically significant increase was observed at the 1 month mark and beyond 3 months. This pattern can be attributed to the mechanism of action of SGLT2 inhibitors, which reduce intra-glomerular pressure and eGFR.[27] However, there was a reduction in the UACR, starting significantly at 3 months after empagliflozin initiation and onwards. Furthermore, improvement in cardiorenal hemodynamics with empagliflozin was reported by Fitchett.[28] In addition, the EMPA-REG OUTCOME[29] study reported a reduction in the incidence of nephropathy by almost 46%, a risk of progression to severely elevated urinary albumin excretion by 38%, a risk of doubling creatinine level by 44%, and a risk of initiating renal replacement therapy by 55% with empagliflozin. However, other studies observed no effect of empagliflozin on serum creatinine levels or estimated glomerular filtration rate.[30]

In conclusion, the strength of this study reflects real-world clinical practices. Confounding factors, specifically the utilization of statins and angiotensin-converting enzyme inhibitors (ACEi), were partially accounted for in this study. All patients included in the study were regularly monitored and treated at chronic illness clinics, where it is standard practice to prescribe statins for patients with diabetes aged 40 and above and ACEi for those with T2DM and moderately or severely elevated urinary albumin excretion. However, the study was limited by its single-center design, which could have affected the generalizability of the findings. Furthermore, the authors could not examine patient compliance with empagliflozin intake, which might have influenced the outcomes. Lastly, missing data posed a limitation, as reliance on medical records for information was necessary.

This study provides further evidence that empagliflozin effectively improves the weight, blood pressure, glycemic control, dyslipidemia (short-term LDL, TG), and renal outcomes in patients with T2DM. However, carrying out additional multicenter longitudinal studies would be advantageous in order to extend the applicability of the findings obtained from this study.

Acknowledgment. *The Authors would like to thank Prof. Moataz Abdel-Fattah, Consultant of Epidemiology and Biostatistics, for providing valuable advice regarding the statistical management of data. We gratefully acknowledge Elsevier for the English language Editing.*

References

1. DeFronzo RA. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; 58: 773–795.

2. Levine MJ. Empagliflozin for type 2 diabetes mellitus: An overview of phase 3 clinical trials. *Curr Diabetes Rev* 2017; 13: 405-423.
3. The Nuffield Department of Population Health Renal Studies Group, and SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022; 400: 1788-1801.
4. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383: 1413-1424.
5. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; 385: 1975–1982.
6. Neuen BL, Young T, Heerspink HJL, 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: 845-854.
7. Ghosh A, Gupta R, Singh P, Dutta A, Misra A. Sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes in North India: A 12-month prospective study in real-world setting. *Int J Clin Pract* 2018; 72: e13237.
8. Brown RE, Gupta N, Aronson R. Effect of dapagliflozin on glycemic control, weight, and blood pressure in patients with type 2 diabetes attending a specialist endocrinology practice in Canada: a retrospective cohort analysis. *Diabetes Technol Ther* 2017; 19: 685-691.
9. 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* 2010; 375: 2223-2233.
10. 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 Metab* 2011; 13: 928-938.
11. Jabbour SA, Hardy E, Sugg J, Parikh S, Group S. 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: 740-750.
12. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, 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: 159-169.
13. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes care* 2009; 32: 650-657.
14. Leiter LA, Berard L, Bowering CK, Cheng AY, Dawson KG, Ekoé JM, et al. Type 2 diabetes mellitus management in Canada: is it improving? *Can J Diabetes* 2013; 37: 82-89.
15. Matthaei S, Bowering K, Rohwedder K, Sugg J, Parikh S, Johnsson E, et al. Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes. *Diabetes Obes Metab* 2015; 17: 1075-1084.
16. Basu D, Huggins LA, Scerbo D, Obunike J, Mullick AE, Rothenberg PL, et al. Mechanism of increased LDL (low-density lipoprotein) and decreased triglycerides with SGLT2 (sodium-glucose cotransporter 2) inhibition. *Arterioscler Thromb Vasc Biol* 2018; 38: 2207-2216.
17. Shin Y, Moon JH, Chin HJ, Ferrannini E, Lim S. Glycemic efficacy and metabolic consequences of an empagliflozin add-on versus conventional dose-increasing strategy in patients with type 2 diabetes inadequately controlled by metformin and sulfonylurea. *Endocrinol Metab* 2020; 35: 329-338.
18. Weber MA, Mansfield TA, Alessi F, Iqbal N, Parikh S, Ptaszynska A. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin–angiotensin system blockade. *Blood Pressure* 2016; 25: 93-103.
19. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373: 2117-2128.
20. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347-357.
21. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644-657.
22. Wilding J, Bailey C, Rigney U, Blak B, Beekman W, Emmas C. Glycated hemoglobin, body weight and blood pressure in type 2 diabetes patients initiating dapagliflozin treatment in primary care: a retrospective study. *Diabetes Ther* 2016; 7: 695-711.
23. Muskiet M, van Bommel E, van Raalte D. Antihypertensive effects of SGLT2 inhibitors in type 2 diabetes. *Lancet Diabetes Endocrinol* 2016; 4: 188-189.
24. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; 129: 587-597.
25. Lim S, Eckel RH, Koh KK. Clinical implications of current cardiovascular outcome trials with sodium glucose cotransporter-2 (SGLT2) inhibitors. *Atherosclerosis* 2018; 272: 33-40.
26. Lee SJ, Lee KH, Oh HG, Seo HJ, Jeong SJ, Kim CH. Effect of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase 4 inhibitors on cardiovascular function in patients with type 2 diabetes mellitus and coronary artery disease. *J Obes Metab Syndr* 2019; 28: 254-261.
27. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* 2016; 134: 752-72.
28. Fitchett DH. Empagliflozin and cardio-renal outcomes in patients with type 2 diabetes and cardiovascular disease–implications for clinical practice. *Eur Endocrinol* 2018; 14: 40-49.
29. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323-334.
30. Mirabelli M, Chiefari E, Caroleo P, Vero R, Brunetti FS, Corigliano DM, et al. Long-term effectiveness and safety of SGLT-2 inhibitors in an Italian cohort of patients with type 2 diabetes mellitus. *J Diabetes Res* 2019; 2019: 3971060.