KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon
ISSN 0022–9032 e-ISSN 1897–4279

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Article type: Short communication
Received: October 12, 2021
Accepted: November 14, 2021
Published online: November 16, 2021

Effect of long-term use of sodium-glucose co-transporter-2 inhibitors on plasma volume status in patients with type 2 diabetes mellitus: sub-analysis of a prospective, observational study during COVID-19 pandemic

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Short title: SGLT-2 inhibitors and plasma volume status

Conflict of interest: None declared

Introduction

Type 2 diabetes mellitus (T2DM) constitutes a 21st century pandemic [1]. Cardiovascular disease (CVD) represents the major cause of death among diabetic subjects. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have revolutionized treatment of T2DM and concomitant CVD [3], also indicated in specific patients' subgroups [4, 5]. However, mechanisms underlying their beneficial effects remain largely unknown [6]. One of those proposed mechanisms is plasma volume (PV) contraction, due to osmotic diuresis and natriuresis. Therefore, we sought to determine the effect of SGLT-2 inhibitors on plasma volume status (PVS), assessed non-invasively.

Methods

This is a single-center, prospective, observational study, conducted in Greece, between January 2020 and July 2021. Study protocol was approved by the Ethics Committee of School of Medicine, Aristotle University of Thessaloniki (protocol number: 4/17.7.2019). Study was performed in accordance with the principles outlined in the Declaration of Helsinki.

Subjects aged 18–75 years old, with a diagnosis of T2DM (≥12 months), glycated hemoglobin (HbA_{1c}) values 6.5%–10.0%, stable antidiabetic and antihypertensive treatment over the last 6 months and an indication for the initiation of a SGLT-2 inhibitor were eligible to participate.

All eligible patients provided a written informed consent before enrollment. Enrolled participants were assigned either to dapagliflozin or empagliflozin. Follow-up visit was planned 6 months after the initiation of SGLT-2 inhibitor treatment. PVS was assessed with the equations described by Ling et al. [7].

Continuous variables are presented as mean (standard deviation [SD]), according to their normal distribution, while categorical variables are presented as relative frequencies (n, %). Shapiro-Wilk test was used to test for normality. We performed hypothesis testing using one-tailed paired t-test, since all variables followed normal distribution. Pearson correlation coefficient (r) was used to assess the correlation of endpoint of interest (change in PVS, Δ PVS) with numerical variables of interest. Point-biserial correlation coefficient (rpb) was used, in order to quantify the correlation between the continuous variable Δ-PVS and the dichotomous variables. *P*-values <0.05 were considered statistically significant. R software was utilized.

Results and discussion

Fifty-one subjects participated in the study. Two subjects denied undergoing follow-up visit, while 3 subjects discontinued treatment with SGLT-2 inhibitors due to mild adverse events. A total of 46 subjects with T2DM completed the study.

Their mean age was 62.89 (8.53) years, while mean T2DM duration was 9.72 (6.37) years. From enrolled participants, 29 were male, all Caucasian. Thirty patients were prescribed dapagliflozin and 16 empagliflozin. Despite the prespecified date of follow-up visit, COVID-19 pandemic regulations delayed follow-up visits, leading to a mean treatment duration of 9.98 (3.27) months.

Mean body mass index of enrolled subjects was 31.25 (5.8) kg/m^2, while their mean HbA_{1c} was 7.48 (1.51)% at baseline (Table 1). A significant proportion of participants suffered from hypertension (69.5%) and dyslipidemia (60.8%), while 56.5% had pre-existing CVD.

Regarding their antidiabetic treatment, 93.5% received metformin, 28.3% received insulin, 32.6% was prescribed glucagon-like peptide-1 (GLP-1) receptor agonists and 39.1% was administered dipeptidyl-peptidase-4 (DPP-4) inhibitors.

We demonstrated that long-term treatment with SGLT-2 inhibitors did not significantly affect PVS, since PVS changed from –0.13 (0.08)% at baseline to –0.15 (0.09)% at the end of follow-up period (Δ PVS = –0.02%; P = 0.99). Of note, empagliflozin resulted in a non-significant change in PVS from –0.16 (0.06) to –0.1575 (0.1)% (P = 0.5), while dapagliflozin also led to a non-significant change in PVS from –0.11 (0.08) to –0.14 (0.08)% (P = 0.99). Interestingly, history of pre-existing CVD did not significantly affect the observed results.

Pearson correlation co-efficient analysis revealed that PVS correlated significantly with haematocrit (r = –0.68; P <0.0001) and haemoglobin (r = -0.66; P < 0.0001). PVS did not correlate with rest numerical variables.

We also documented a negative correlation between Δ PVS and history of coronary artery disease (rpb = –0.033; P = 0.025) and a positive correlation with prior use of DPP-4 inhibitors (rpb = 0.3; P = 0.042). No significant correlation was shown with history of rest major co-morbidities and prior antidiabetic or antihypertensive medication.

We demonstrated that long-term use of two different SGLT-2 inhibitors does not significantly affect PVS in patients with T2DM.

Dekkers and colleagues demonstrated that dapagliflozin significantly decreased estimated PV at 24 weeks after initiation, showing a significant correlation with glycemic control, body weight and creatinine clearance [8]. Hoshika et al. showed that empagliflozin produced a significant decrease in estimated PVS at 24 weeks in patients with T2DM and acute myocardial infarction [9]. Similarly, Jensen et al. observed that empagliflozin significantly decreased estimated PV at 12 weeks in patients with HF with reduced ejection fraction [10]. Rapid attenuation of PV at 12 weeks has been shown with canagliflozin in patients with T2DM [11]. Finally, in the longest available study, long-term monotherapy with tofogliflozin in patients with T2DM produced a significant decrease in estimated PV 52 weeks post-initiation of treatment, however, that effect was rapidly ameliorated [12].

An interesting hypothesis has been suggested by Hallow and colleagues [13]: in healthy subjects, dapagliflozin led to a 3-fold decrease in interstitial fluid volume (IFV) compared to blood volume (BV), while the predicted decrease in IFV with bumetanide was only 80% of BV reduction [13]. A significant decrease in extracellular water volume with dapagliflozin has been shown in subjects with T2DM and established diabetic nephropathy [14]. Of note, Jensen et al.

[10] showed that empagliflozin compared to placebo resulted in a significant decrease in estimated extracellular volume.

We consider as major strengths of our study the long follow-up period, the administration of two different SGLT-2 inhibitors and the conduction during COVID-19 pandemic, which has inevitably imposed significant limitations in patients' adherence to treatment, physical status and access to healthcare services. We acknowledge that our eligibility criteria were relatively board, potentially missing the chance to address a significant effect of SGLT-2 inhibitors on PVS in specific patients' population.

Summarizing, we demonstrated that long-term administration of two different SGLT-2 inhibitors in patients with T2DM does not affect PVS. Other mechanisms might be implicated with the beneficial effects of this class. Osmotic diuresis, natriuresis and blood pressure reduction, along with hematocrit and hemoglobin increase, decrease in serum uric acid, and improvement in albuminuria have been shown [6]. According to mechanistic studies, SGLT-2 inhibitors exert anti-inflammatory effects, enhance fat utilization and browning and suppress myocardial and renal oxidative stress. Improvement in myocardial energetics, reduction of cardiomyocyte apoptosis and attenuation of sympathetic nervous system activity have also been proposed [6]. Some of these effects might also be valuable against COVID-19, which can prioritize the use of SGLT-2 inhibitors in subjects with T2DM during this hazardous pandemic [15].

Whether SGLT-2 inhibitors modify fluid volume regulation in the long-term has to be clarified in future trials. In addition, it must be proven if the hypothesis suggested by Hallow and colleagues [13], applies in clinical practice and in some patients' populations, such as those suffering from heart failure or diabetic nephropathy.

*Study has been registered in the International Standard Registered Clinical/soCial sTudy Number (ISRCTN) registry (registration number: ISRCTN88851713).

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Table 1. Participants' baseline characteristics

Baseline characteristic	Value
Enrolled subjects	46
Male gender	29 (63.04%)
Age, years	62.89 (8.53)
Body weight, kg	90.04 (17.4)
Body mass index, kg/m^2	31.25 (5.8)
Glycated haemoglobin, %	7.48 (1.51)
Type 2 diabetes mellitus duration, years	9.72 (6.37)
Arterial hypertension	32 (69.6%)
Dyslipidemia	28 (60.9%)
Cardiovascular disease	26 (56.5%)
Coronary artery disease	14 (30.4%)
Heart failure	5 (10.9%)
Atrial fibrillation	1 (2.2%)
Cerebrovascular disease	7 (15.2%)
Peripheral artery disease	2 (4.4%)
Chronic kidney disease	3 (5.5%)
Chronic obstructive pulmonary disease	10 (21.8%)
Obstructive sleep apnea	7 (15.2%)

*Data are presented as mean (standard deviation) or absolute numbers, unless otherwise stated