Effect of sodium-glucose co-transporter-2 inhibitors on right ventricular function in patients with type 2 diabetes mellitus: A pilot study

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) and cardiovascular disease are interconnected [1]. Subjects with T2DM feature an excess risk for heart failure (HF) development [2] although mechanisms are not fully defined [3].

Right ventricular (RV) function is adversely affected by both prediabetes and T2DM [4, 5]. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown outstanding cardiovascular and renal benefits in T2DM. Recently, they have been incorporated into the treatment algorithm of HF with reduced left ventricular ejection fraction (HFrEF), according to the 2021 European Society of Cardiology (ESC) guidelines [6] while national societies have also adopted this evidence [7]. However, there is no evidence of their effect on RV function.

Therefore, we conducted a pilot study, to assess the effect of SGLT2i on RV function in patients with T2DM.

METHODS

This is a single-arm, prospective, observational study, conducted between January 2020 and August 2021. The study protocol was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki, and performed in accordance with the Declaration of Helsinki.

Subjects aged 18–75 years old, with an established 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 an SGLT2i, were eligible to participate, after providing written informed consent. Enrolled participants were initiated to dapagliflozin or empagliflozin once daily.

We set as the primary efficacy outcome the change in tricuspid annular plane systolic excursion (TAPSE). We also assessed a number of echocardiographic parameters: basal linear RV end-diastolic diameter (4-chamber view), RV end-systolic (RVES) area, RV end-diastolic (RVED) area, RV s', RV e', RV a', RV e'/a', and RV systolic pressure (RVSP) [8].

We assessed several anthropometric and laboratory markers of interest. Blood samples were drawn after overnight fasting. We also evaluated major safety outcomes.

An echocardiographic study was performed by the same cardiologist, highly trained and blinded to clinical information, according to the current guidelines for the echocardiographic assessment of RV, at baseline and at the end of the prespecified follow-up period [8]. An echocardiographic assessment of left ventricular (LV) function was also performed.

Statistical analysis

Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), according to the normality of distribution, while categorical variables are presented as relative frequencies and percentages (n [%]). The Shapiro-Wilk

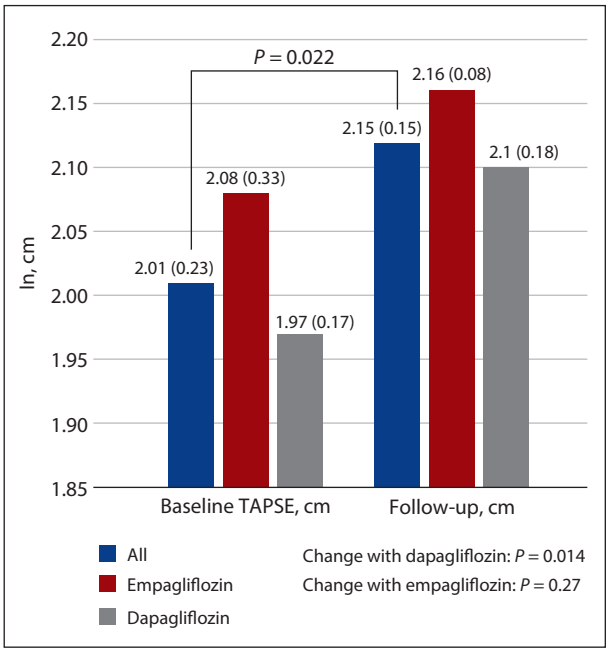

Figure 1. Effect of sodium-glucose cotransporter-2 inhibitor, empagliflozin, and dapagliflozin on right ventricular systolic function as assessed with tricuspid annular plane systolic excursion

Abbreviations: TAPSE, tricuspid annular plane systolic excursion

test was used to test for normality. In the case of normal distributions, we performed hypothesis testing using a one-tailed paired t-test, otherwise we used a one-tailed Wilcoxon signed-rank test. Pearson coefficient correlation test was used to assess the correlation of endpoint of interest (change in TAPSE) with numerical variables of interest. *P*-values <0.05 were considered significant. R-4.1.3 software for Windows (The R Foundation) was utilized for statistical analysis.

RESULTS AND DISCUSSION

Twenty subjects were included. Their mean age was 62.8 (7.87) years, while the median T2DM duration was 9.5 (4.5–12.25) years. Fifteen patients were male. Mean value of HbA_{1c} was 7.43% (1.76%), while mean body mass index (BMI) was 31.31 (5.59) kg/m^2. Main baseline characteristics are summarized in Supplementary material, *Tables S1* and *S2*. A follow-up visit was planned 6 months after the initiation of an SGLT2i. Due to special regulations imposed in the context of the COVID19 pandemic, the mean treatment duration and follow-up period finally lasted 9.35 (3.4) months.

SGLT2i resulted in a significant increase in TAPSE from 2.01 (0.23) to 2.12 (0.15) cm ($P = 0.02$; Figure 1). No difference between the two SGLT2i was documented ($P = 0.7$). Change in TAPSE was significant in subjects with prior cardiovascular disease ($P = 0.024$), while it was non-significant for subjects without such history ($P = 0.26$). No significant effect of SGLT-2i on other indices of RV systolic and diastolic function was demonstrated (Supplementary material, *Table S3*).

We did not document a significant correlation between change in TAPSE and rest echocardiographic, anthropometric, or laboratory parameters during the trial, except for a significant positive correlation between change in TAPSE and change in RV diameter at the mid-cavitary level ($r = 0.46$; $P = 0.042$; Supplementary material, *Figure S1*). Improvement in blood pressure (BP), body weight, and glycemic control with SGLT2i were not significant, possibly due to small sample size. No significant correlation between change in TAPSE and change in BP, body mass index, or HbA_{1c} was demonstrated. No major safety issues were reported.

In this pilot study, treatment with SGLT2i resulted in a significant improvement in TAPSE. In a former trial, empagliflozin did not affect RV mass index (RVMi), RV end-diastolic and end-systolic volume index (RVEDVi, RVESVi), and RV ejection fraction (RVEF), while echocardiographic assessment documented a non-significant decrease in TAPSE [9]. In another trial, 3-month treatment with empagliflozin resulted in a significant decrease in the pulmonary artery (PA) diastolic pressure in patients with HF regardless of left ventricular ejection fraction or presence of T2DM [10]. Results concerning PA systolic pressure and mean PA pressure were consistent [10]. Experimental data have suggested that empagliflozin decreases RV hypertrophy and fibrosis, while it also inhibits PA remodeling in a model of pulmonary hypertension [11].

At present, it seems impossible to determine the mechanisms underlying this beneficial effect on TAPSE. Osmotic diuresis and natriuresis [12], along with inhibition of Na^+/H^+ exchanger (NHE) activity and increase in mitochondrial Ca^{2+} concentration [13], amelioration of cardiac fibrosis and inflammation [14], and improvement in coronary microvascular function [15] might be among those mechanisms. Preload and afterload reduction, mainly by natriuresis, might be the most significant factor that leads to TAPSE increment and improved RV function.

The small sample size and study design represent the main limitations. We should also highlight the specific limitations of 2D echocardiography in clinical practice. cMRI is the modality of choice for accurate anatomic and cardiac tissue characterization although is much more expensive and not widely available. In addition, it would be interesting to assess the impact of SGLT-2i on RV function in patients with HF, in whom the beneficial effect could hypothetically be more pronounced. Unfortunately, only one patient in our cohort had a history of HF.

Finally, our results should be interpreted with caution. Both TAPSE and RV s' velocity assessed by tissue Doppler imaging (TDI) are angle-dependent and reflect only the longitudinal function of the basal segment of the RV, neglecting the contribution of the apical and RV outflow tract components to RV global systolic performance. While usually they exhibit similar changes, TAPSE is more load dependent than TDI S' velocity. Thus, one can

speculate that since SGLT2i may promote natriuresis and reduce preload, TAPSE might show an improved value after SGLT2i therapy, in contrast to RV S′, which is less load-dependent and possibly needs more time to show a significant change.

To sum up, this is the first study to assess the effect of SGLT2i on RV function in patients with T2DM. These results should be a motive for further assessment of the effect of SGLT2i on RV function, based on its prognostic role. Larger studies will shed further light on this interesting topic.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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