Benefits of SGLT2 inhibitors on renal and cardiovascular protection, in diabetic patients

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KEYWORDS

Cardiovascular, inhibitor, glycosuri, heart failure

ABSTRACT

Introduction: Type 2 Diabetes Mellitus is major risk factors for both cardiovascular and renal diseases. Managing cardiovascular risk and the progression of renal disease is therefore essential in treating diabetic patient. Sodium-glucose cotransporter-2 inhibitors have been linked to a substantial decrease in cardiovascular and renal mortality, reduced hospitalizations for heart failure and slower progression of renal damage and albuminuria.

Objectives: Our study aimed to evaluate the impact of SGLT2i on cardiovascular and renal protection in diabetic patients.

Methods: Our study involved elderly patients, with type 2 diabetes, who were divided in two groups, one group received SGLT2i, while the other did not. Data were collected at the start of treatment, as well as at 3, 6, 9 and 12 months thereafter. During each evaluation, we assessed HbA1C, BMI, GFR and renal parameters, uric acid, NTproBNP, echocardiography, and both PAS and PAD values, in both groups.

Results: Out of 300 elderly diabetic patients included in the study, 200 were started on dapagliflozin 10 mg. At 12 months, HbA1c, weight, systolic blood pressure, NTproBNP, uric acid, albuminuria, were decreases in group with dapagliflozin versus the other group without it, and estimated glomerular filtration rate was higher (75.3 – 87.19mL/min/1.73m2; $p<0.005$). Follow up in patients with SGLT2i showed a significant decrease in left ventricular end-diastolic dimension (LV-EDD) (62.86 mm to 54.85 mm; $P< 0.001$) and improvement in LV-EF.

Conclusions: The use of Dapagliflozin demonstrated metabolic benefits in patients with T2DM, including notable decreases in HbA1c, blood pressure, weight, uric acid, and NTproBNP. Additionally, cardiovascular and renal benefits were observed. Therefore, SGLT2i have a significant impact on both cardiovascular and renal protection in diabetic patients.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a multifaceted, chronic disease with increasing prevalence over time. It is associated with a higher risk of various cardiovascular diseases (CVD), with heart failure (HF) often presenting earlier than myocardial infarction (MI). Heart failure (HF) and Chronic Kidney Disease (CKD) commonly occur together, both being influenced by diabetes as a major risk factor. This interplay creates vicious circle that leads to a worsened prognosis (1). Diabetic patients with concurrent CV or renal diseases face a greater risk of death and CV events compared to those without these additional conditions. Although conventional risk factor control can reduce ischemic complications, heart failure risk remains an unsolved problem in diabetes mellitus for which intensive glycaemic control has had little benefit. So, in 2008, the US Food and Drug Administration required pharmaceutical companies to evaluate the cardiovascular outcomes of antidiabetic treatments in addition to glycaemic control (2). Until the introduction of gliflozins, no antidiabetic therapy demonstrated significant improvements in HF hospitalization (3). Sodium-glucose cotransporter-2 (SGLT2) inhibitors manage blood glucose levels by inhibiting SGLT2 in the kidneys. The DAPA-HF trial (4) and the EMPEROR-Reduced trial (5) indicated that dapagliflozin and empagliflozin, respectively, might reduce the occurence of cardiovascular adverse events in patients with heart failure. Numerous studies, have demonstrated the beneficial effects of SGLT2-inhibitors, highlighting their benefits not only for reducing cardiovascular risk, including heart failure and diabetic renal disease. So, SGLT2 inhibitors, also known as gliflozins, represent an effective and innovative treatment option for patients with T2DM, with established cardiovascular risk.

Objectives

Our study aimed to asses benefits of SGLT2-i on cardiovascular risk of our diabetic patients.

2. Methodology

The study group included 300 diabetic patients with established cardiovascular risk, hospitalized at Internal Medicine. They were divided in two subgroups: 200 patients who were started on dapagliflozin 10 mg, one tab/day, plus their previous existing therapy and 100 who continued with their therapy. Patients who received SGLT2-i before the study, and patients with urinary tract infection, end stage of renal disease and Heart Failure with Reduced Ejection Fraction by more than 20%, were excluded. The clinical data were extracted from the patient's medical history and by previously registered hospitalizations. After ten hours overnight fast, blood samples were collected and the following tests were conducted: glycosylated hemoglobin (HbA1C), renal parameters, uric acid, NTproBNP. All of them, included BMI, eGFR, echocardiography, SBP and DBP values, were evaluated in every meetings, in both groups Diabetes was defined by fasting plasma glucose levels ≥126 mg.dl or by specific treatment. Patients receiving antihypertensive treatment or they with blood pressure higher than 130/80 mmHg, were characterized as hypertensive. Blood pressure was measured by validated mercury sphygmomanometers with relaxing patient. BMI was calculated by standard formula and expressed as kg/m2. Estimated GFR (eGFR) is calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation (2021), from standardized creatinine, sex, race and age for each patient. Two-dimensional echocardiogram of the left ventricle (LV) was used. The left ventricular end-diastolic dimensions (LVEDD), the left ventricle ejection fraction (LVEF) as risk factors for HHF, were carried out in accordance with the American Society of Echocardiography recommendation. Normal LV size was 42 to 59 mm for men and 39 to 53 mm for women and up to this size was dilated ventricle. EF was calculated using Simpson's method and severe LV dysfunction was defined as EF ≤35%. Data were collected at the beginning of treatment, 3, 6, 9 and 12 months after.

Statistics

Statistical analysis was done using SPSS version 25. Differences in parameters of interest between groups were defined by the U Mann Whitney test. For comparison of qualitative variables Fisher's exact test and Student's test for quantitative variables was used. Statistical significance was assumed if $p < 0.05$.

3. Results and Discussion

Among 300 patients, 169 (56.3%) were females and 131 (45.7%) males, respectively, 97 females and 84 males in dapagliflozine group and 82 females and 47 males at the control group. Mean age for study group was 67 (± 11.8) years and for the control group 64.8 (± 9.7) years. Two patients from the first group didn't complete the study, because of repeated urinary tract infections, and 14 patients died till the end of study, respectively, six of them from dapagliflozine group and eight from the other group. At 12 months of follow up, HbA1c, weight, NTproBNP, uric acid, were significantly lower in exposed group versus the other group. Albuminuria at SGLT2i group had a significant reduction from one meeting to the other (1325.9 mg/24 h to 768 mg/24h; P< 0.001). (Fig. 1).

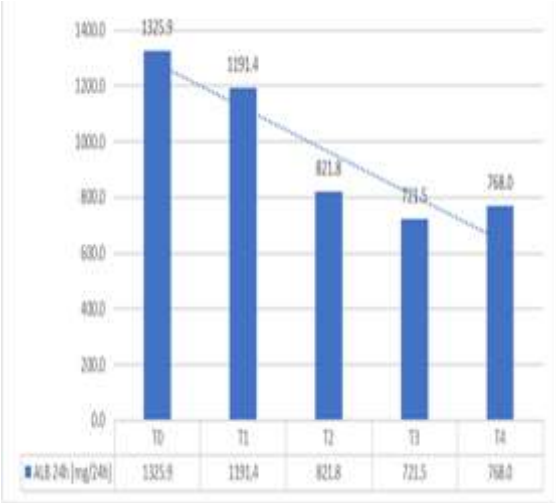

Figure 1. The mean value of albuminuria at the SGLT2i group, at each meeting.

Follow-up of echocardiographic parameters, in patients with SGLT2i, showed a significant decrease of LVEDD (62.86 mm to 54.85 mm; P< 0.001) (Fig. 2) and improvement in LV-EF. At the other side, the eGFR was higher (75.3 – 87.19 mL/min /1.73m2; p<0.005) (Fig. 3). A significant reduction of SBP (145.51 to 119.70mmHg; P< 0.001) and DBP (85.53 to 78.02 mmHg; P< 0.01) was noticed, also, at SGLT2i group, compared to the control group (Fig. 4).

The improvements in cardiac function by using SGLT2i were more pronounced in HF patients compared to those without HF.

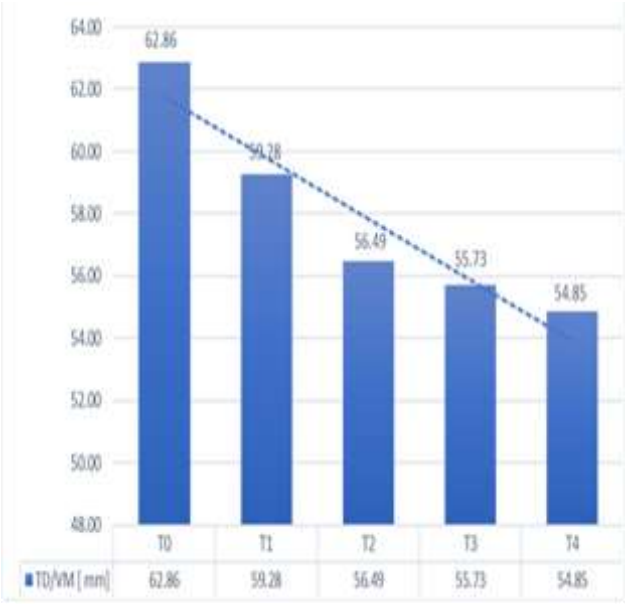

Figure 2. The mean value of the LVEDD at the SGLT2i group, at each meeting.

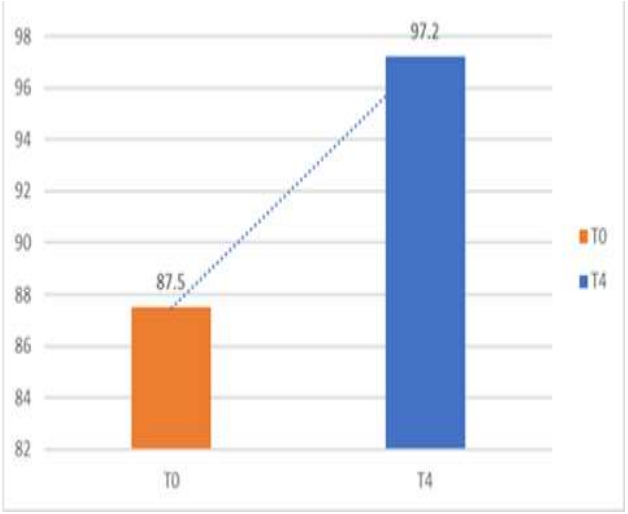

Figure 3. The mean value of the eGFR at the start and at the end of study, at the SGLT2i group.

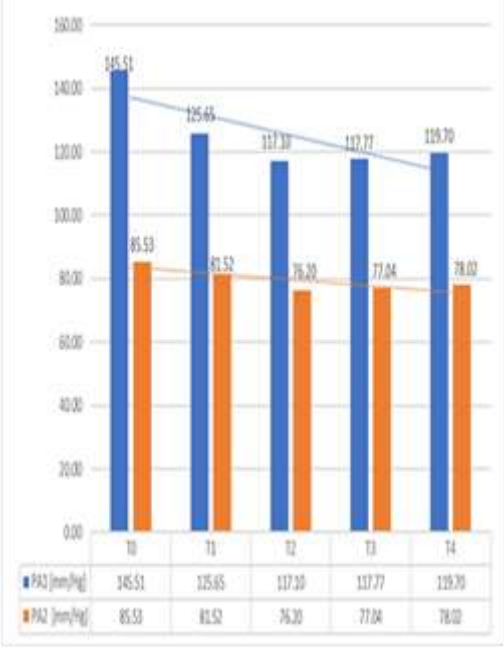

Figure 4. The mean value of SBP and DBP at the SGLT2i group, at each meeting

4. Conclusion and future scope

Discussion

The present study provides evidence, that use of SGLT2i may be associated with reduction of risk factors of CVD in diabetic patients, beyond glycaemic control. We tried to identify clinical risk predictors of HF and CKD, in patients with diabetes, and to evaluate the impact of SGLT2i in these factors.

An important parameter that reflects cardiac function is LVEDD and a dilated LVEDD is a predictor for left ventricular insufficiency. LV dilation independently contributed to adverse outcomes in patients with advanced HF (6). Concurrently, a dilated LVEDD is associated with an elevated risk for heart failure and cardiovascular events (7). Prior research has shown the substantial effectiveness of SGLT2 inhibitors in reducing LV dilation and enhancing LV function. (8,9) At our study we used this parameter to assess the heart failure risk at our diabetic patients and the impact of dapagliflozin at this risk factor. Our study shown that dapagliflozin patients had a significant reduction in LV dimensions

along with an improvement in cardiac function. There are so many exploratory clinical trials that demonstrated this result, effects of SGLT2 inhibitors on cardiac functions (9,10,11). A meta-analysis, included 13 studies comprising 1437 patients, found that SGLT2 inhibitors reduced LV volumes, and increased LVEF, improving clinical outcomes of HF (11) Additionally, the DAPA-HF (4) and DECLARE-TIME 58 (14) with dapagliflozin, EMPEROR-Reduced (5) and EMPA-REG OUTCOME (12) with empagliflozin, CANVAS Program (13) with canagliflozin, and VERTIS CV (15) with ertugliflozin, revealed that SGLT2 inhibitors could reduce the occurrence of HF and cardiovascular events, as well as atherosclerotic cardiovascular disease, or diabetic nephropathy.

Early clinical sign of diabetic nephropathy is the presence of albumin in urine, known as microalbuminuria, categorizing patients with this condition as having incipient nephropathy. Albuminuria predicts renal failure in diabetic patients. Proteinuria now serves as a prognostic indicator for CVD disease, and detection of albuminuria is a signal to screening for potential vascular disease, and is needed aggressive intervention to mitigate all cardiovascular risk factors (16.17). Epidemiological and experimental evidence indicates that proteinuria is linked to heightened risk of mortality from all-causes and cardiovascular issues, cardiac abnormalities, cerebrovascular disease, and, possibly, peripheral arterial disease (18, 19)

We evaluate albuminuria for each patient at each meeting, and we saw a significant reduction at dapagliflozin group. In DECLARE-TIMI 58, as secondary exploratory analysis, dapagliflozin exhibited a beneficial impact on albuminuria, and was found consistently to demonstrate a significant positive long-term improvement on UACR, regardless of initial eGFR and UACR levels, including patients who had normoalbuminuria at baseline (20).

Another multicenter, double-blind, placebo-controlled, randomised trial, was DAPA-CKD, done at 386 sites in 21 countries. In this trial, dapagliflozin led to a significant decrease in albuminuria, among patients with chronic kidney disease, both, with and without type 2 diabetes, showing a relatively greater reduction in patients with type 2 diabetes (21). The CREDENCE trial randomized 4401 participants, assessed the effect of canagliflozin on the intermediate outcomes of albuminuria, etc, and canagliflozin reduced albuminuria compared with placebo (22).

Also, we assessed diabetic nephropathy with another parameter, estimated glomerular filtration, at each examination. After 12 months follow-up, eGFR had significant improvement under dapagliflozin treatment. DAPA-CKD, a randomised controlled trial, using dapagliflozin, showed significantly slowed long-term eGFR decline in patients with chronic kidney disease compared with placebo (23). The CREDENCE study, using canagliflozin, provided renal and cardiovascular protection for individuals with type 2 diabetes and chronic kidney disease (24). SGLT2 inhibition at the EMPA-REG OUTCOME trial, reduced significantly progression of diabetic kidney disease (25,26). A total of 7020 patients diagnosed with T2D and pre-existing cardiovascular disease were randomly allocated to receive either empagliflozin or a placebo. Treatment with empagliflozin notably decreases the occurrence or worsening nephropathy and the advancement to macroalbuminuria (25,26,27).

So, SGLT2 inhibitors reduce the albuminuria ratio and slowed eGFR decline, in diabetic patients, reducing the progression of diabetic nephropathy and cardiovascular events related.

In our study, the mean value of SBP and DBP at the SGLT2i group was significantly reduced from baseline. Also, DAPA-CKD trial shown this effect of dapagliflozin on systolic blood pressure, small changes in DBP as well in patients with CKD, with and without type 2 diabetes. (28) SGLT2i inhibits absorption of glucose and sodium in the proximal tubule, stimulating glycosuria and diuresis, reducing intravascular volume which can contribute to a reduction in blood pressure (29). So many studies have demonstrated improvement on the control of hypertension in diabetic patients with established cardiovascular risk, by using SGLT2i (30,31,32), and at the same time its beneficial effects on kidney and cardiovascular events.

These benefits of SGLT2i on cardiovascular and renal risk, made this medication to be included, not

only in diabetes guidelines but also cardiovascular and renal guidelines. (33)

In summary, SGLT2 inhibitors have a significant impact on LV structure and function, as well as on slowing the progression of diabetic nephropathy. To achieve maximal renal and cardiovascular protection in our diabetic patients, it's important to treat the global cardiovascular risk rather than a single risk factor, and SGLT2i do this perfectly.

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