Dapagliflozin: Emerging Evidence in the Cardiometabolic Landscape

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Introduction

Dapagliflozin is a potent, reversible and selective sodium-glucose cotransporter-2 inhibitor (SGLT2i) indicated for treating type 2 diabetes (T2D)[1]. As monotherapy and combination therapy, Dapagliflozin has been shown to effectively achieve target glycemic control and reduce bodyweight and blood pressure (BP) across a broad spectrum of patients[1]. More significantly, recent studies have shown that dapagliflozin reduced the rate of cardiovascular (CV) death or hospitalization for heart failure (HHF)[2,3], did not adversely affect major adverse CV events (MACE)[4], and reduced progression of renal disease in patients with established atherosclerotic CV disease (ASCVD)[4]. Due to it santihyperglycemic, cardio protective, and renoprotective properties, dapagliflozin is a well-accepted option for managing T2D.

Recent data on dapagliflozin also provides clinical evidence suggesting newer roles for the agent in patients with cardiometabolic disease. This review explores recent and new evidence on the expanding role of dapagliflozin in this field.

Role in Prediabetes

Prediabetes is an intermediate state of hyperglycemia where in the glycaemic parameters are above normal but below the diabetes threshold. Prediabetes is believed to be a state of high risk for developing diabetes with a yearly conversion rate of 5%-10%. Further, observational evidence suggests an association between prediabetes and complications of diabetes such as early nephropathy, small fiber neuropathy, early retinopathy, and risk of macrovascular disease.[5]

Two recent double-blind, placebo-controlled studies have explored the benefits of dapagliflozin in patients with prediabetes. The first evaluated the effects of dapagliflozin on insulin secretion and insulin sensitivity in 24 adult patients with prediabetes. These patients were not on any pharmacological treatment. [6]

Dapagliflozin in prediabetes / prehypertensive patients

- Decrease in body weight /BMI
- Reduction in FBG/HbA1c
- Improvement in insulin sensitivity
- Decrease in DBP/SBP

Improvement in dipper circadian BP pattern

Patients were randomly assigned into two groups of 12 patients each to receive 10 mg of oral dapagliflozin or placebo once a day for 12 weeks. Dapagliflozin administration resulted in significant decreases in body weight, body mass index (BMI), fasting glucose, and uric acid, with improvement in insulin sensitivity.

The second study evaluated the effect of dapagliflozin on blood pressure variability (BPV) in patients with prediabetes and prehypertension, not on any pharmacological treatment. The study performed in 30 patients aged 30-60 years was divided into 15 patients each. The groups received a 10-mg dose of dapagliflozin daily before breakfast for 12 weeks or a placebo. [7]

Besides a decrease in body weight, BMI, fasting glucose, and glycated hemoglobin A1c, as seen in the previous study, a decrease in

office systolic and diastolic blood pressure (SBP, DBP) night-time SBP, nocturnal mean arterial pressure, and the nocturnal hypertensive load was also seen. Dapagliflozin also significantly increased the percentage of the dipper circadian BP pattern. Interestingly, after the administration of dapagliflozin, up to 30 % of the patients did not meet the diagnostic criteria for prediabetes or prehypertension.

Effects of Dapagliflozin on Lipid Profile

SGLT-2 inhibitors have been reported to increase both low-density lipoprotein (LDL) and high-density lipoprotein (HDL)-cholesterol (C). A recent study appears to suggest that dapagliflozin has a beneficial effect infavorably modulating atherogenic dyslipidemia. Earlier clinical evidence has shown that sd LDL-C particles are more atherogenic than lb LDL-C particles. The predominance of sd LDL-C confers a threefold increased risk for coronary artery disease (CAD). There is a preponderance of sd LDL-C particles in individuals with metabolic syndrome and T2D. HDL-C also has subspecies, namely HDL2-C and HDL3-C. Large, cholesterol-rich HDL2-C is inversely associated with plasma TG and insulin resistance, whereas small, cholesterol-poor HDL3-C is not. A single-center, open-label, randomized, prospective study in 80 patients with T2D received dapagliflozin (n = 40) or sitagliptin (n = 40) as an add-on treatment for 12 weeks, and the effects on lipid parameters were assessed. [8]

Dapagliflozin on lipid profile

- Beneficial effects on subspecies of LDL and HDL-C
- Suppresses potent atherogenic sd LDL-C
- Increases HDL2-C- a favourable cardiometabolic marker

While both dapagliflozin and sitagliptin comparably decreased HbA1c (0.75 and 0.63%, respectively), dapagliflozin-treated patients showed a significant decrease in body weight, systolic blood pressure, plasma triglycerides, and liver transaminases, and increased adiponectin. Sitagliptin did not alter these measurements. Further, dapagliflozin suppressed potent atherogenic sd LDL-C and increased HDL2-C, a favorable cardiometabolic marker. Although LDL-C levels are elevated by treatment with dapagliflozin, this was due to increased concentrations of the less atherogenic lb LDL-C. However, these findings were not observed after treatment with sitagliptin. [8]

Role in NAFLD

Patients with T2D often have comorbid non-alcoholic fatty liver disease (NAFLD), a condition that may progress to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. Recent findings from both randomized controlled trials and open-label studies have also shown that SGLT2 i, such as dapagliflozin, may reduce fatty liver and improve biological markers of NAFLD.[9]

Dapagliflozin (5 mg/d) treatment for 12 -24 weeks is associated with improved hepatic fat content, improved liver biochemistry, decreased visceral fat and bodyweight, and enhanced glycaemic control.[10]

In another study, the effects of dapagliflozin on liver steatosis and fibrosis were evaluated in a randomized, active-controlled, open-label trial involving 57 patients with T2D and NAFLD. Dapagliflozin 5 mg/d improved liver steatosis and attenuated liver fibrosis (only) in patients with significant liver fibrosis. Furthermore, serum alanine aminotransferase and γ-glutamyl transpeptidase levels decreased in the dapagliflozin group, but not in the control group, and visceral fat mass was significantly reduced in the dapagliflozin group.[11]

After treatment with 5 mg/d dapagliflozin for 24 weeks, improvement of liver dysfunction was also associated with a decrease in soluble dipeptidyl peptidase-4

(sDPP-4), an enzyme secreted by hepatocytes that induce adipose tissue inflammation and insulin resistance.[12]

Dapagliflozin in NFALD

- Improvement in liver steatosis
- Attenuation of liver fibrosis
- Reduction in visceral fat mass
- Improvement in liver dysfunction (as seen in liver enzyme levels)

The emerging data on the mechanism of dapagliflozin action suggests a mechanism beyond the reduction of hyperglycemia and body weight and a potential role for decreasing low-grade inflammation and oxidative stress. [9]

Dapagliflozin- Evidence of Renal Protection

A prospective cohort study evaluated the effects of dapagliflozin on renal metabolism assessed by urine metabolome analysis in patients with T2D. 80 patients with hemoglobin A1c > 7% on metformin monotherapy were prospectively enrolled, and 50 patients were treated with dapagliflozin for three months. To exclude that the changes observed in urine metabolome were merely the result of the improvement in glycemia, 30 patients treated with insulin degludec were used for comparison. Changes in urine metabolic profile before and after the administration of dapagliflozin and insulin degludec were assessed by proton-nuclear magnetic resonance spectroscopy.[13]

In multivariate analysis, urine metabolome was significantly altered by dapagliflozin but not insulin. After dapagliflozin, the urine concentrations of ketone bodies, lactate, branched-chain amino acids ($P < 0.001$), betaine, Myo-inositol ($P < 0001$), and N-methylhydantoin ($P < 0.005$) were significantly increased. Additionally, the urine levels of alanine, creatine, sarcosine, and citrate were also increased ($P < 0001$, $P < 0.0001$, and $P < 0.0005$, respectively), whereas anserine decreased ($P < 0005$). The results suggest that dapagliflozin significantly affects urine metabolome in patients with T2D in a glucose lowering-independent way, contributing to the renoprotective properties of the drug.[13]

Conclusion

The leading medical bodies have recommended a patient-centered approach for managing hyperglycemia and CV risk factors in T2D, involving individualized glycaemic targets based on the risk of adverse events such as hypoglycemia and bodyweight gain, and patient comorbidities. Given that CVD is the major cause of mortality in T2D, with myocardial infarction (MI) and stroke accounting for ≈ 80% of all deaths, it is important that the selection of an antihyperglycemic agent, plays a role beyond glycaemic control, does not aggravate, and preferably improves, CV risk factors and reduces CV morbidity and mortality. The growing evidence on dapagliflozin appears to indicate a beneficial role in this clinical scenario.

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