A Medical Literature Review on Canagliflozin and Dapagliflozin and the Role of SGLT2 Inhibitors in Diabetic Management

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Abstract. Diabetes is one of the most common diseases encountered in both the outpatient and inpatient settings. According to data from the 2011 National Diabetes Fact Sheet, approximately 8.3% (25.8 million) of the entire American population have diabetes. Of this population, about 72.9% (18.8 million) have been clinically diagnosed while an estimated 27.1% (7.0 million) remain undiagnosed. According to the study Economic Costs of Diabetes in the U.S. in 2012, the total national cost of diagnosed diabetes, including direct medical cost and reduced productivity was nearly $245 billion. Extensive research efforts have gone into developing new pharmacologic agents to treat diabetes. The newest medications recently approved by the FDA are the SGLT2 inhibitors. This article will explain the mechanism of the action of this class of drugs along with their specific role in diabetic management. This article will focus on canagliflozin and dapagliflozin, the two most well researched and studied drugs of SGLT2 inhibitors, both of which have been approved for use by the Food and Drug Administration. Some of the major trials concerning both of these drugs will be presented in this article.

Keywords: dapagliflozin; canagliflozin; diabetes; SGLT2

1. Methods

Data for this research was obtained from PubMed and Google Scholar. A simple search using terms such as SGLT2 inhibitors, the role of SGLT2 inhibitors in diabetes management, Canagliflozin, and Dapagliflozin was done in PubMed and Google scholar databases.

2. Mechanism of action

Sodium glucose linked transporters (SGLT) are proteins located in the mucosa of the small intestine and kidneys that function in glucose reabsorption. These transporters belong to a family of genes called SLC5A. They were first discovered by American biochemist Robert K. Crane in 1960. Crane demonstrated these sodium glucose linked...
Dapagliflozin 

2.1. Dapagliflozin. In January 2012, Dapagliflozin became the first approved SGLT2 inhibitor by the European Medicines Agency in November of 2012. In a recently accepted article for publication, Raskin et al. [4] analyzed five major trials involving dapagliflozin and its efficacy as monotherapy [5], and as adjunctive therapy to metformin [6] Figure 1, pioglitazone [7], glimepiride [8], and insulin [9]. These twenty-four week placebo controlled phase 3 trials all showed Dapagliflozin to decrease baseline HgA1c and fasting plasma glucose (FPG) levels when used as monotherapy or as adjunctive therapy to metformin, pioglitazone, glimepiride, or insulin. Dapagliflozin at a dosage of 10 mg daily was shown to decrease HgA1c (0.82–0.92%) compared to placebo (0.13–0.42%). The same dosage of Dapagliflozin also demonstrated similar decreases in FPG (21.7–29.6 mg/dl) compared to placebo (+3.0 to −6.0 mg/dl). Post prandial plasma glucose (PPG) was also shown to be decreased when Dapagliflozin was added to glimepiride or pioglitazone. Weight loss of up to 3 kg was also seen at the end of the 24 week treatment period.

Studies have been published, investigating the efficacy of Dapagliflozin when used as adjunctive therapy to sitagliptin with or without metformin [10]. Results demonstrated baseline reductions of HgA1c when compared to the placebo controlled group in the primary cohort (0.48%, P < 0.001), dual therapy with sitagliptin (0.56%, P < 0.001) and triple therapy with sitagliptin and metformin (0.40%, P < 0.001).

A double blind placebo controlled study of 546 patients treated with Dapagliflozin at 2.5, 5, 10 mg, or placebo in addition to metformin (≥ 1500 mg/day) for a 24 week period demonstrated a decrease in baseline HgA1c of −0.67, −0.70, −0.84, and −0.30%, P < 0.05 [11]. This study also demonstrated weight reduction after the 24 week treatment period (−2.66%, −3.66%, −3.43%, and −1.02%).

Another randomized, double blind, placebo controlled study investigated the efficacy of dapagliflozin as add on therapy to patients who were not well controlled on insulin and another oral antidiabetic drug [12]. This study included 71 patients, who were treated with dapagliflozin 10 mg, 20 mg, or placebo as additive therapy to their oral antidiabetic regimen and 50% of their daily insulin dose. The treatment period lasted for twelve weeks. Average HgA1c reductions from baseline in the dapagliflozin 10 mg and 20 mg treatment groups were −0.70 and −0.78, respectively. Approximately 65.2% of the patients in the dapagliflozin treated groups showed an average decrease from baseline HgA1c ≥0.5% compared to 15.8% of the placebo group. These studies also demonstrated average weight loss of −2.6 kg and −2.4 kg in the 10 mg and 20 mg treatment groups, respectively over the twelve week treatment period. These findings suggest the potential role of dapagliflozin as an effective adjunctive therapy for patients poorly controlled on insulin and an oral antidiabetic medication.

A 52 week double blind study compared the efficacy of dapagliflozin versus glipizide as adjunctive therapy in

Figure 1: Bailey et al. 24 week trial assessing efficacy of Dapagliflozin as adjunctive therapy with metformin (> 1500 mg/day).
patients who showed poor glycemic control on metformin, with a baseline mean HgA1c of 7.7% [13] Figure 2. The dosages of dapagliflozin and glipizide were titrated to 10 mg and 20 mg/day respectively. Both the dapagliflozin (n = 406) and glipizide (n = 408) groups showed a similar mean HgA1c decrease of (~0.52%) from baseline. Average weight loss seen in the dapagliflozin group was (~3.2 kg), whereas the glipizide group demonstrated a mean weight gain of 1.2 kg (P < 0.0001). There was also a lower rate of hypoglycemic events in the dapagliflozin group (3.5% versus 40.8%, P < 0.0001). There was however an increase in the occurrence of urinary tract and genital infections amongst the dapagliflozin group, however there was good response to standard treatment.

A double blind randomized control study investigated the efficacy of dapagliflozin as adjunctive therapy in patients poorly controlled on pioglitazone monotherapy [14]. Patients previously treated with metformin, sulfonylurea, thiazolidone, or treatment naïve were entered into a 10 week pioglitazone dose optimization period. During this time, the subjects were exposed to only pioglitazone while all other diabetic medications were discontinued. After the optimization period, patients were randomized into three different arms: dapagliflozin 5 mg (n = 141), 10 mg (n = 140), and placebo (n = 139). Primary endpoints included reductions in baseline HgA1c at week 24 of therapy. The study also compared the incidence of weight gain and edema among the different groups. Results showed reductions in baseline HgA1c of −0.82, −0.97, and −0.42% in the dapagliflozin 5 mg, 10 mg, and placebo groups, respectively. Average weight gain was larger in the placebo group (3 kg) compared to dapagliflozin (0.67–1.4 kg) after 48 weeks of therapy. Decreased rate of edema were also observed in the dapagliflozin (2.1–4.3%) arms versus placebo (6.5%). The study demonstrated that dapagliflozin used as adjunctive therapy in patients poorly controlled on pioglitazone induced reductions in HgA1c, decreased weight gain, and lowered incidence of edema.

2.2. Canagliflozin. A 52 week double blind study was undertaken to investigate the efficacy of canagliflozin versus sitagliptin as adjunctive therapy in patients with poor glycemic control with metformin and a sulfonylurea [16]. The dosages of canagliflozin and sitagliptin used in the study were 300 mg and 100 mg/day respectively. The primary end point of the study was a decrease in mean HgA1c from baseline. Results showed a more significant mean decrease of baseline HgA1c in the canagliflozin group compared to the sitagliptin group (~1.03% and ~0.66%). It also showed greater decreases in fasting plasma glucose, body weight and

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systolic blood pressure in the capigliflozin treatment group. There was an increased rate of mycotic genital infections and osmotic diuresis symptoms observed among those treated with capigliflozin ($P < 0.001$).

Another randomized double blind study was performed looking into the efficacy and safety of capigliflozin use in Type II diabetics with underlying chronic kidney disease stage III [17]. In this study, the subjects ($n = 269$) received capigliflozin 100 mg, 300 mg, or placebo. The primary endpoint was a reduction in HgA1c from baseline at 26 weeks of treatment. Other secondary endpoints included decreases in baseline fasting plasma glucose and in the number of patients attaining HgA1c levels $< 7.0\%$. A decrease in baseline HgA1c levels were observed with capigliflozin 100 mg and 300 mg compared to placebo ($−0.33\%$, $−0.44\%$, and $−0.03\%$, $P < 0.05$). The study also demonstrated an increased proportion of patients who reached HgA1c levels $< 7.0\%$ with capigliflozin 100 and 300 mg compared to the placebo group (27.3\%, 32.6\%, and 17.2\%). Capigliflozin was generally well tolerated by patients with Type II DM and CKD stage III.

A double blind placebo controlled multicenter study investigated the efficacy of canagliflozin in diabetics poorly controlled on metformin monotherapy [18] Figure 3. The study included 451 patients with baseline HgA1c of 7.6–8.0\%. Subjects were randomized to canagliflozin 50, 100, 200, or 300 mg once daily, canagliflozin 300 mg twice daily, sitagliptin 100 mg once daily, or placebo in addition to their metformin. The primary endpoint of the study was reductions in baseline HgA1c by week 12 of therapy. Secondary endpoints included changes in fasting plasma glucose, body weight, and overnight glucose to urine creatinine ratio.

Results showed reductions in baseline HgA1c of $−0.79\%$, $−0.76\%$, $−0.70\%$, $−0.92\%$, $−0.95\%$ for canagliflozin 50, 100, 200, 300 mg once daily and 300 mg twice daily, respectively. There was a $−0.22\%$ in the placebo arm, while the sitagliptin arm showed a $−0.74\%$ reduction. The study also indicated a decrease in fasting plasma glucose of $−16$ mg/dl to $−27$ mg/dl in the canagliflozin treated subjects as well as decreases in body weight ($−2.3$ to $−3.4\%$). An increase in overnight glucose to urine creatinine ration was also observed amongst the subjects treated with canagliflozin. The study also showed non dose dependent increases in rates of genital infections with canagliflozin (3–8\%) versus placebo and sitagliptin arms (2\%). There was also an increased rate of urinary tract infections seen with canagliflozin (3–9\%) versus placebo (6\%) and sitagliptin (2\%). Overall, the study demonstrated that canagliflozin added on to metformin showed significant improvement in glycemic control and weight loss.

Stenlof et al. conducted a 26 week randomized double blind placebo controlled phase 3 trial analyzing the efficacy and safety of canagliflozin as monotherapy in patients inadequately controlled with diet and exercise [19] Figure 4. Subjects were randomized into three groups, receiving canagliflozin 100 mg ($n = 195$), 300 mg (197), or placebo (192). The primary endpoint for the study was reduction of baseline HgA1c by week 26. Secondary endpoints included proportion of subjects that attained HgA1c $< 7.0\%$ along with changes in fasting plasma glucose, 2 hour post prandial glucose, body weight, and systolic blood pressure, HDL and triglyceride levels. Results of the study showed a decrease from baseline HgA1c in the patients treated with canagliflozin 100 and 300 mg compared to placebo ($−0.77$, $−1.03$ and $−0.14\%$, respectively, $P < 0.001$). A greater
proportion of patients in the canagliflozin 100 and 300 mg treatment arms attained a baseline HgA1C less than 7.0% compared to placebo (44.5%, 62.4%, and 20.6%, respectively). Reductions in 2 hour postprandial glucose levels were also noted with canagliflozin 100 and 300 mg (−2.4 and −3.3 mmol/l) compared to placebo (+0.3 mmol/l). Results indicated similar reductions in fasting plasma glucose with canagliflozin (−1.5 and −1.9 mmol/l) against placebo (+0.5 mmol/l). The canagliflozin 100 mg and 300 mg groups showed reduction in body weight (−2.5 and −3.4 kg) in comparison to the placebo group (−0.5 kg). The study also demonstrated decreases in systolic blood pressure in patients treated with canagliflozin 100 and 300 mg (−3.7 and −5.4 mmHg, \( P < 0.001 \)). Increases in HDL were seen with canagliflozin 100 and 300 mg (6.8% and 6.1%, \( P < 0.01 \)). Dose dependent increase in LDL was seen with canagliflozin 100 and 300 mg (2.9 and 7%) compared to placebo (1.0%).

3. Conclusion

SGLT2 inhibitors are the newest group of anti-diabetic medications on the market. Studies show promise in regards to producing reductions in baseline HgA1C and fasting plasma glucose, weight loss, and attaining better overall glycemic control. The two most extensively studied drugs in this class have been canagliflozin and dapagliflozin, both of which have been approved by the FDA for use in the United States. These medications do not stimulate the action of B-cells as sulfonylureas and GLP-1 agonists. In this way it allows for preservation of these cells. It also prevents weight gain and in fact has been shown to lead to weight loss, another benefit from insulin and insulin secretagogues. As research advances in this field, more SGLT2 inhibitors may soon be available for the management of diabetes. As clinical experience with these medications increases, physicians will be better able to incorporate them into their therapeutic regimen. The American Academy of Clinical Endocrinology released their 2013 guidelines for management of Type II diabetes in which SGLT2 inhibitors have been included in the algorithm for management of Type II diabetes, mainly as later options in monotherapy, dual therapy, or triple therapy.

References


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