REVIEW ARTICLE

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Comparison of safety and efficacy of dapagliflozin and empagliflozin in type 2 diabetes mellitus patients in India

Amit Varshney[1]*, Ramakant Rawat[2]

INTRODUCTION

Approximately 422 million people are suffering from diabetes worldwide. Most of the population is living in third world or developing countries, and about 2 million deaths are directly or indirectly caused by diabetes each year. Among the adult population of India, there are 73 million cases of diabetes[1]. "From 11.9 and 14.2% of adults in urban India have diabetes; in rural India, the prevalence is between 3.0 and 7.8%, with a much higher incidence among people over 50" (ICMR-INDIAB Study)[2].

The mechanism of action of novel antidiabetic drugs known as sodium glucose co-transporter (SGLT-2) inhibitors differs significantly from those of traditional antidiabetic medications[3]. Anti-glucose reuptake inhibitors like SGLT-2 achieve their hypoglycemic effect by increasing glucose excretion in the urine. A medication that inhibits SGLT-2 would be perfect in her case because her kidneys reabsorb around 90% of the glucose they filter throughout the PCT process[4]. The FDA has so far approved canagliflozin, dapagliflozin, and empagliflozin as drugs in this group[5]. Numerous studies have shown that SGLT-2 inhibitors have favorable effects on body weight (BW), blood pressure, dyslipidemia, and fatty liver disease in addition to lowering the risk of hypoglycemia. Positive results from several clinical studies on the subject of cardiovascular (CV) and renal safety have been reported[6,7]. According to the current guidelines, SGLT-2 inhibitors should be used as second-line antidiabetic drugs when first-line antidiabetic medications fail to adequately control blood sugar levels. However, they may be used well alone as a therapy. Patients with type 2 diabetes were investigated to determine the safety and tolerability profile of SGLT-2 inhibitors (dapagliflozin and empagliflozin)[8].

METHODS

To collect the information for this review, searches were performed in Scopus, Web of Science, Embase, PubMed, and MEDLINE for "Comparison of safety and effectiveness of Dapagliflozin with Empagliflozin in patients with type 2 DM in India." Articles published worldwide between 2010 and 2022 were included.

HBA1C REDUCTION

The majority of Indian patients (56.3%) who started using dapagliflozin at the beginning had HbA1c levels between 8 and 10% with a mean±SD value of 9.11±1.44. Patients who started on empagliflozin had an HbA1c% of 7.92±0.7018 (mean±SD)[9].

Statistically substantial reductions in HbA1c were observed at 3 months (1.00%) and 6 months (1.49%) in Indian patients who had started dapagliflozin therapy. Therefore, across all of his HbA1c stratified groups (i.e., 8, 8–10, and >10%) from baseline to 3 and 6 months, the HbA1c value considerably decreased ($p<0.001$) in patients taking dapagliflozin. The mean (SD) HbA1c level was 9.11% (1.44%) at baseline, 8.11% (1.22%) at 3 months, and 7.62% (1.04%) at 6 months. Patients using 10 mg of empagliflozin had a 0.81% decrease in HbA1c levels, while those using 25 mg had a 1.11% reduction by week 76. In patients with baseline HbA1c values considerably greater than 7%, both 10 and 25 mg of empagliflozin were able to lower HbA1c levels to below 7% after 76 weeks of therapy (20.8 and 28.0%, respectively)[10].

[1]Kanti Devi Medical College Hospital and Research Center, Department of Emergency Medicine – Mathura (UP), India.
[2]Uttar Pradesh University of Medical Sciences, Department of Medicine – Etawah (UP), India.
*Corresponding author: dr.amit.varshney2020@gmail.com
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WEIGHT REDUCTION

Indian patients using dapagliflozin lost an average of 1.14 (2.21) kg after 3 months and 1.86 (3.04) kg after 6 months (SD). Individuals with a BMI greater than 30 lost their maximum weight [mean (SD): 1.60 (2.50) kg] at 3 months and [2.56 (3.50) kg] at 6 months[9].

Therapy with either empagliflozin 10 or 25 mg for 76 weeks resulted in a decrease in BW in Indian patients (1.41 and 1.50 kg, respectively)[10].

BLOOD PRESSURE AND HEART RATE

After 3 and 6 months of therapy, patients using dapagliflozin had decreases in systolic blood pressure (SBP) of 3.24 (11.44 mmHg) and 3.77 (12.22 mmHg), respectively, from baseline[8]. The SBP of patients using empagliflozin was observed to decrease by 3.3 and 3.8 mmHg, respectively, when the drug is given in doses of 10 and 25 mg[9]. Although dapagliflozin reduced diastolic blood pressure (DBP) by 1.13 (7.67) and 1.46 (8.30) mmHg after 3 and 6 months, respectively, empagliflozin reduced DBP by 1.0 mmHg after 10 mg and 1.6 mmHg after 25 mg. However, these reductions in SBP and DBP are non-significant[9,10].

Heart rate reductions are non-significant with both the drugs in any doses and for any duration of treatment.

ADVERSE EFFECTS

Only 2.9% Indian patients on dapagliflozin treatment had one adverse event, while 2.2% Indian patients on empagliflozin had one adverse event. One patient on dapagliflozin and no patient on empagliflozin had greater than one serious adverse event requiring hospitalization. Adverse events such as vulvovaginitis were reported in 0.4% of patients using dapagliflozin and 0.6% of patients using empagliflozin. Fungal infections are also common in empagliflozin 0.3% than dapagliflozin (0.2%). The incidence of urinary tract infections is equal in both groups (0.2%).

Mild adverse events such as headache, constipation, and temperature are infrequent but present in both groups.

Hypoglycemia is an important side effect that should be mentioned, which is 0.2% associated with dapagliflozin and none with patients using empagliflozin[9,10].

DISCUSSION

Not only there are very small data regarding safety and efficacy of dapagliflozin and empagliflozin at the national level, but also the trials and papers addressing this issue are also inconclusive. Thus, the only comparison left is with western world trials. Studies from southern Europe showed that there is a role of geographical diversity in dapagliflozin effect on decreasing HbA1c levels, as well as CV and renal outcomes. As we all know, India is also a country of geographical diversity, so this may be true in Indian perspective also. There are differences between CV and renal effects in northern as well as southern parts of India because of cultural, dietary, and religious differences, so there is no uniformity in the effects of these two drugs.

The mean HbA1c level of dapagliflozin-treated patients was 7.62% after 6 months of treatment, which is close to the ADA-recommended target HbA1c level of <7.0%. Some studies showed a much higher reduction in HbA1c levels from basal HbA1c levels after 6 months (1.49%), which may be due to higher basal HbA1c levels. Results from various studies that are conducted at different parts of the world have shown a positive association between basal HbA1c levels[11-13] (Table 1). However, a study on Chinese patients treated with dapagliflozin reported similar decrease in HbA1c levels[14]. (The percentage of patients who responded well to medication was 1.04 and 1.11%, respectively, with $p<0.0001$ for both dapagliflozin doses when compared with the placebo group.) Indian patients using empagliflozin have a mean reduction of 0.8–1.1% in HbA1c levels, which is equal to that reported in studies by Ferrannini et al.[15] and Rosenstock et al.[16]. The less reduction in HbA1c levels may be due to lower HbA1c baseline levels. In a meta-analysis, it was shown that a small but non-significant drop in the HbA1c levels was observed in both Asian and non-Asian patients treated with the same dose of SGLT-2 inhibitors. However, when analyzed per patient's baseline HbA1c value, the reduction in HbA1c levels was very clear. For individuals with higher baseline HbA1c levels, the decreases in HbA1c levels at 3 and 6 months were greater. Early intervention with SGLT-2 inhibitors may assist individuals with long-standing type 2 diabetes achieve their HbA1c goals more rapidly as their basal HbA1c levels are often higher than usual[10,15-17] (Table 2).

At 6 months, Indian patients using dapagliflozin had lost an average weight of 1.86 kg. Most of the weight loss occurred in patients with BMIs greater than 30, who lost an average of 1.60 kg after 3 months and 2.56 kg after 6 months[9]. At 76 weeks of therapy, patients using empagliflozin had a significant reduction in BW of 1.50 kg in adjusted mean weight[10]. Neeland et al. carried out the same study throughout the course of two distinct cohorts, at 12 and 24 weeks. As seen here, after 12 weeks of using empagliflozin, the average weight loss was 1.7 kg, and after 24 weeks, the average weight loss was 1.9

Table 1. Comparison of dapagliflozin as monotherapy and combination therapy in different trials.

Clinical trial	Population	No. of patients	Comparison drug	Primary end point	Results	Weight change in kg	Adverse effects
Viswanathan et al.[9] Dapagliflozin *vs.* placebo (Indian Population)	Treatment naïve patients insufficiently managed on diet and exercise	1,941	Dapagliflozin 10 mg *vs.* placebo	Median HbA1c rise or fall between 3 and 6 months	At 3 and 6 weeks: HbA1c reductions in dapagliflozin and placebo w ere -1.00, -1.04, and +0.02%, respectively.	At 3 and 6 weeks: Reductions in weight with dapagliflozin and placebo were -1.14, -1.86, and -0.72 kg, respectively	Urogenital infections (mainly vulvovaginitis and fungal infection) were more frequent with dapagliflozin than placebo
Bailey et al.[11] Dapagliflozin with metformin *vs.* placebo with metformin (North and South American population)	Diabetic patients inadequately controlled with metformin alone	564	Dapagliflozin 10, 5, 2.5 mg, and placebo with metformin (≥1,500 mg/day)	Percentage reduction from baseline HbA1c at 102 weeks	At 102 weeks: Dapagliflozin 10, 5, 2.5 mg, and placebo reduced hemoglobin A1c by 0.78, 0.58, 0.48, and 0.02%, respectively	Weight loss was 2.86 pounds with dapagliflozin plus metformin and 0.89 pounds with placebo	Genital infections were more frequent with dapagliflozin than placebo
Ferrannini et al.[12] Dapagliflozin*vs.* placebo (Multi-national population)	Treatment naïve patients insufficiently managed on diet and exercise alone with HbA1c between 7 and 10%	485	Dapagliflozin 2.5, 5, and 10 mg daily *vs.* placebo	Percentage reduction from baseline HbA1c at 24 weeks	At 24 weeks: Hemoglobin A1c (HbA1c) decreases for dapagliflozin 2.5, 5, and 10 mg were 0.58, -0.77, -0.89, and -0.23%, respectively	In comparison to the placebo, dapagliflozin 10 mg caused a 3.16-pound weight loss	No major episode of hypoglycemia and signs and symptoms suggestive of urogenital infection were more common in the dapagliflozin group
Nauck et al.[13] Dapagliflozin with metformin *vs.* glipizide with metformin (Multi-national population)	Diabetic patients inadequately controlled with metformin alone	814	Dapagliflozin (≤10 mg/day) with metformin (≥1,500 mg/day) *vs.* glipizide (≤20 mg/day) with metformin (≥1,500 mg/day)	Percentage reduction from baseline HbA1c at 52 weeks	At 52 weeks, HbA1c equally reduced -0.52% from baseline	Dapagliflozin with metformin *vs.* glipizide with metformin -3.22 and +1.44 kg, respectively	Dapagliflozin with metformin *vs.* glipizide with metformin (hypoglycemia 3.4 *vs.* 39.7%) and (urogenital infection 12.3 *vs.* 2.7%)

kg[18]. Similarly, in a clinical study by Bolinder et al., patients using dapagliflozin had a significant reduction in BW of 4.54 kg over a period of 152 weeks[19].

Similar to the outcomes of the trial by Papadopoulou et al.[20], Indian patients using dapagliflozin had a decrease in SBP of 3.24 mmHg at 3 months and 3.77 mmHg at 6 months. Indian individuals using 10 or 25 mg of empagliflozin had smaller reductions in SBP (3.3 and 3.8 mmHg, respectively) compared to the results of the research by Kario et al.[21]. This may be due to the geographical difference in study cohorts. However, the DBP reduction in Indian patients using dapagliflozin and empagliflozin was insignificant.

Various complications can occur in diabetic patients, but the most common is genito-urinary infections that occur mainly due to glycosuria and more common in females. Usually, the patients had mild episodes and resolved with conservative management. Studies in Indian patients had shown that genito-urinary infections were common with dapagliflozin when compared to empagliflozin (2.9 vs. 2.2%)[9,10]. Similar findings were reported by Ridderstråle et al.[17].

Safety analyses of dapagliflozin from many double-blind, placebo-controlled trials found that patients using dapagliflozin had an increase in urine output of around 10%. This effect was observed at recommended dosages of both dapagliflozin

Table 2. Comparison of empagliflozin as monotherapy and combination therapy in different trials.

Clinical trial	Population	No. of patients	Comparison drug	Primary end-point	Results	Weight change	Adverse effects
Gupta et al.[10] empagliflozin 10, 25 mg daily, ***vs.*** placebo ***vs.*** sitagliptin (Indian population)	Type 2 diabetes patients (T2DM) who opt to treat their condition organically (with diet and exercise alone)	108	Empagliflozin 10, 25 mg daily ***vs.*** placebo ***vs.*** sitagliptin	Exploratory effectiveness goals were set using changes from baseline in HbA1c, fasting plasma glucose, body mass, systolic and diastolic blood pressure, and blood sugar levels	At 76 weeks: A significant reduction in hemoglobin A1c was seen with daily empagliflozin 10 and 25 mg, with respective values of -0.81 and -1.11% from baseline, compared to +0.58% in the placebo group and -0.31% in the sitagliptin collective	Compared to placebo and sitagliptin, weight reduction with empagliflozin 10 mg/day was larger (0.39 vs. 0.43 kg) (1.01 vs. 1.16 kg)	When compared to placebo, sitagliptin has a similar effect, although UTIs and vaginal infections occur more frequently
Ridderstråle et al.[17] Empagliflozin ***vs.*** glimepiride (Multi-national population)	Type 2 DM patients insufficiently managed on metformin, diet and exercise with HbA1c of HbA1c ≥7 and ≤10%	1,549	Glimepiride 1–4 mg daily vs. empagliflozin 25 mg daily	Percentage reduction from baseline HbA1c at 104 weeks	Empagliflozin25 mg and glimepiride 1–4 mg/day both reduced HbA1c by 0.11% from baseline after 104 weeks	Empagliflozin superior to glimepiride in reducing weight	Hypoglycemic events 2 and 24% in empagliflozin and glimepiride, respectively
Ferrannini et al.[15] Empagliflozin ***vs.*** metformin (Multi-national population)	Patients with a body mass index (BMI) of 40 kg/m^2 and inadequate glycemic management (HbA1c >7.0 to <10.0).	224	Empagliflozin 5, 10, and metformin	Percentage reduction from baseline HbA1c at 78 weeks	At 78 weeks: HbA1c reduction in empagliflozin 5 mg, 10 mg, and metformin were -0.34, -0.47, and -0.56%, respectively	Empagliflozin 5, 10 mg, and metformin -2.2, -2.6, and -1.3 kg, respectively	Genital infections were more frequent with empagliflozin than metformin
Rosenstock et al.[16] Empagliflozin with insulin ***vs.*** placebo ***vs.*** insulin (Multi-national population)	Obese patients (BMI >30 and <45 kg/m^2) with T2DM and insufficient glycemic control (HbA1c >7.5 to <10% at screening) despite diet and exercise counseling and treatment with MDI insulin (total daily dose>60 IU) alone or in combination with metformin (immediate or extended release, equal or more than 1,500 mg/day	563	Empagliflozin 10, 25 mg, and placebo with basal insulin in each group	Percentage reduction from baseline HbA1c at 52 weeks	At 52 weeks: HbA1c changes in empagliflozin 10 ,25 mg, and placebo were -1.18, -1.27, and -0.81%	Empagliflozin 10 mg, 25 mg, and placebo were -1.95, -2.04, and +0.44 kg, respectively	Empagliflozin vs. placebo hypoglycemia 15.4 ***vs.*** 15.6% Genital infection 58 ***vs.*** 51.1%

and empagliflozin. This is also the case with empagliflozin, suggesting that euglycemic ketoacidosis is a potential adverse effect while using SGLT-2 inhibitors. The FDA and EMA have issued warnings about SGLT-2 inhibitors that these agents can cause diabetic ketoacidosis (DKA) (the body produces large amounts of ketone bodies, namely, acetone, acetoacetate, and beta-hydroxybutyrate), which is a serious complication that may require hospitalization. Patients with a history of DKA, those with type 2 diabetes and low C-peptide levels, those with LADA, chronic pancreatitis, severe dehydration, severe alcoholism, and acute medical and surgical illnesses, and those with decreased food intake are also at risk. The safety of these drugs and their dosage in patients with high risk of DKA[22] is continuously investigated by the FDA.

CONCLUSION

Diabetes is one of the several difficult-to-manage chronic diseases in the world. The development of new medications is underway with the expectation that they will have fewer negative effects and allow for more regulatory precision. Complications from diabetes may be avoided with good glycemic control. As a result, we need additional medications to maintain normal blood sugar levels. In the fight against type 2 diabetes, novel adjuvants that inhibit SGLT-2 are being used. These SGLT-2 inhibitors are investigational kidney-specific diabetic treatments. By increasing the glucose excretion in the urine, dapagliflozin and empagliflozin enhance the glycemic control. Additionally, the diuretic actions of these medications lower blood pressure and BW. Improved lipid values have also been observed.

AUTHORS' CONTRIBUTIONS

AV: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **RR:** Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing – original draft.

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