A Comparative Study of efficacy and safety of different Sodium Glucose Co-transporter 2 (SGLT-2) Inhibitors in the Management of Patients with Type II Diabetes Mellitus

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ABSTRACT

Background: There are a handful of sodium glucose co-transporter 2 (SGLT2) inhibitors available in the global and Indian markets to manage type II diabetes mellitus (T2DM). However, head-to-head comparison between different SGLT2 inhibitors is scarce. Therefore, the present study was aimed to analyze the effect of different SGLT2 inhibitors on glycemic control and body weight in Indian patients with T2DM.

Methods: This was a prospective, interventional, nonrandomized study that included patients (N = 480) of either sex, aged ≥30 years, with inadequately controlled T2DM having HbA1c > 8.5% and body weight ≥ 25 kg/m². The patients were randomized to receive either Canagliflozin (100 mg BD), Empagliflozin (10 mg OD), Dapagliflozin (10 mg OD), or Remogliflozin (100 mg OD) for 24 weeks. The glycemic parameters and body weight were compared across the treatment groups at week 12 and 24. The incidence of adverse events was also studied across the treatment groups.

Results: A total of 480 patients who received either Canagliflozin (n = 120), Empagliflozin (n = 120), Dapagliflozin (n = 120), or Remogliflozin (n = 120) were included in this study. There was a significant reduction in levels of HbA1c, FBS, PPBS, body weight, systolic and diastolic blood pressure (SBP, DBP) at week 12 and 24 in all treatment groups. The difference in mean values of glycemic parameters and body weight was comparable across the treatment groups at week 12 and 24 but was not significant. Out of all 480 patients, 10 patients (2.08%) reported urinary tract infection (UTI), and five (1.04%) reported genitourinary infection. All the five patients were females and treatment for UTI and mycotic infection was provided as required. Rest of the patients tolerated the therapy well.

Conclusion: Overall observations indicate that all the four SGLT2 inhibitors are effective in reducing HbA1c, FBS, PPBS, body weight, SBP, and DBP. Therefore, gliflozins can be the best choice to start early in patients with inadequately controlled T2DM receiving triple-drug therapy which helps in controlling the parameters of glycaemia and significantly reducing the body weight. Hence SGLT2 Inhibitors could be considered as an add-on to all antidiabetic agents currently used for the management of diabetes in Indian settings.

INTRODUCTION

Sodium glucose co-transporter 2 (SGLT2) inhibitors are recently approved oral anti-hyperglycemic agents by US Food and Drug Administration (FDA) (2013). Owing to their non-pancreatic action SGLT2 inhibitors have demonstrated efficacy and safety in the management of T2DM through the reduction of hypoglycemia risk. These agents are recommended along with diet and exercise by various international as well as Indian guidelines for diabetes management. In a recent update of the ADA 2020 guideline of diabetes management, SGLT2 inhibitors are recommended especially in patients with diabetes with high cardiovascular risk.1 Likewise, the use of SGLT2 inhibitors in patients with type II diabetes has been recommended by the Research Society for the Study of Diabetes in India.2

Unlike the other oral hypoglycemic agents, SGLT2 inhibitors have a novel mechanism of action that reduces blood glucose levels without triggering insulin secretion.3 In addition, several SGLT2 inhibitors have benefits in terms of reduction in body weight, blood pressure, and cardiovascular risk. Assessment of the safety profile indicates genitourinary infection is more commonly observed among patients with diabetes receiving treatment of SGLT2 inhibitors followed by mycotic infection, polyuria, volume depletion, hypotension, and dizziness.4,5

Currently, there are a handful of SGLT2 inhibitors including Canagliflozin, Empagliflozin, Dapagliflozin, and Remogliflozin available in the global and Indian market to manage type II diabetes either as monotherapy or with concomitant medication.7 Recent real-world studies from Ireland and Southern Europe on the clinical efficacy of SGLT2 inhibitors reported a significant reduction in HbA1c and body weight in patients with type II diabetes.8,9 Similarly, real-world experience from India reported the effectiveness of SGLT2 inhibitor in terms of significant improvement in glycemic control and weight reduction with the insignificant incidence of adverse events.5

Aim of the study: To analyze the efficacy and safety of different SGLT2 inhibitors in patients with T2DM.

Objective: To study the effect of different SGLT2 inhibitors on glycemic parameters, body weight, and blood pressure in patients with T2DM.

METHODS

This was a prospective, interventional, nonrandomized study conducted in MGM Medical College and Hospital, in collaboration with the Department of Medicine and Deogiri Diabetes Care Centre, Aurangabad, Maharashtra, India, between November 2019 and November 2020.

The study protocol was approved by MGM Ethics Committee for Research on Human Subjects (MGM. ECRHS).

Study Population and Data Collection

Patients (N = 480) of either sex, aged ≥30 years, with inadequately controlled T2DM having HbA1c > 8.5% and BMI > 25 kg/m² who were receiving either Canagliflozin (100 mg OD), Empagliflozin (25 mg OD), Dapagliflozin (10 mg OD) or Remogliflozin (100 mg BD) (N = 120 for each group) on the background of triple-drug therapy were included in this study. Newly diagnosed T2DM patients (N = 120) of either sex, aged ≥30 years, with inadequately controlled T2DM having HbA1c > 8.5%, and BMI > 25 kg/m² who were receiving either Canagliflozin, fasting blood sugar (FBS), post-prandial blood sugar (PPBS), body weight, and systolic and diastolic blood pressure at baseline, 12 and 24 weeks.

Starting with a comprehensive examination, the study included blood sugar (FBS), post-prandial blood sugar (PPBS), body weight, and systolic and diastolic blood pressure (SBP, DBP) at week 12 and 24 in all treatment groups. The difference in mean values of glycemic parameters and body weight was comparable across the treatment groups at week 12 and 24 but was not significant. Out of all 480 patients, 10 patients (2.08%) reported urinary tract infection (UTI), and five (1.04%) reported genitourinary infection. All the five patients were females and treatment for UTI and mycotic infection was provided as required. Rest of the patients tolerated the therapy well.

Conclusion: Overall observations indicate that all the four SGLT2 inhibitors are effective in reducing HbA1c, FBS, PPBS, body weight, SBP, and DBP. Therefore, gliflozins can be the best choice to start early in patients with inadequately controlled T2DM receiving triple-drug therapy which helps in controlling the parameters of glycaemia and significantly reducing the body weight. Hence SGLT2 Inhibitors could be considered as an add-on to all antidiabetic agents currently used for the management of diabetes in Indian settings.

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patients, type I diabetes mellitus, gestational diabetes, patients with eGFR value less than 45 ml/min/1.73 m² calculated by MDRD formula, patients on insulin therapy, patients with recurrent UTI, and patients with a history of diabetic ketoacidosis or other comorbid cardiac, hepatic, and renal diseases were excluded.

Data collection included body weight in Kgs measured with the electronic weighing machine, and laboratory data included parameters determining glycemic control [HbA1c % measured using High Performance Liquid Chromatography method (Bio-Rad D 10), FBS, PPBS in mg% were analyzed with fully automated Vitros 250 Dry Chemistry analyzer], SBP and DBP measured with a sphygmomanometer in mm of Hg. These parameters were recorded at different time points, at baseline, at week 12 and 24. Safety assessment was performed by general and systemic examination and as per adverse drug reaction reported by patients.

**Results**

A total of 480 patients who received either Canagliflozin (n = 120), Empagliflozin (n = 120), Dapagliflozin (n = 120), or Remogliflozin (n = 120) were included in this study. The mean (SD) age of the patients was 52.1 (9.35) years in Canagliflozin (C), 51.8 (10.74) years in Empagliflozin (E), 52.0 (12.33) years in Dapagliflozin (D), and 51.9 (12.19) years in Remogliflozin (R) groups. All four groups were having comparable ages (p-value 0.361) with a slightly higher proportion of men than women in each group.

Though the difference in mean values of glycemic parameters like FBS, PPBS, HbA1c, and other parameters such as body weight, SBP and DBP was comparable across the treatment groups at 12-week and 24-week follow-up from baseline; the intergroup comparison between all four groups did not demonstrate a significant difference (Tables 1 and 2).

A significant reduction was observed within the groups in the HbA1C values at the end of 24 weeks with a total mean reduction of 3.08, 2.87, 2.74, and 2.79% in Canagliflozin, Empagliflozin, Dapagliflozin, and Remogliflozin groups, respectively (Table 3). An overall highly significant reduction was recorded in the mean values of other glycemia parameters like FBS and PPBS within all four groups (Table 3). Similarly, body weight reduction was also observed in all the patients along with a reduction in SBP and DBP with highly significant differences within individual groups from baseline to the end of 24 weeks (Table 3). Out of a total of 480 patients enrolled in all the four groups 10 patients (2.08%) reported UTI and 5 (1.04%) patients reported genital mycotic infection. All the five patients were females.

**Statistical Analysis**

Data were analyzed using Statistical Package for The Social Sciences (SPSS) software, version 24.0. Quantitative data were presented as mean [standard deviation (SD)] while qualitative data were presented as number. We have applied paired t-test for within-group comparison (before and after therapy) ANOVA test for intergroup comparison and a comparison of two groups was done using post hoc test of LSD (Latin Square Design). A p-value < 0.05 was considered statistically significant.

### Table 1: Comparison of mean values of glycemic parameters in all groups (ANOVA)

<table>
<thead>
<tr>
<th>Glycemia Parameters</th>
<th>No. of visits</th>
<th>Canagliflozin (Mean ± SD)</th>
<th>Empagliflozin (Mean ± SD)</th>
<th>Dapagliflozin (Mean ± SD)</th>
<th>Remogliflozin (Mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar (FBS) (mg%)</td>
<td>Baseline (visit 1)</td>
<td>195.94 ± 23.69</td>
<td>193.93 ± 22.52</td>
<td>198.58 ± 27.52</td>
<td>200.42 ± 27.17</td>
<td>0.201</td>
</tr>
<tr>
<td></td>
<td>12 weeks (visit 2)</td>
<td>164.11 ± 25.14</td>
<td>161.62 ± 23.77</td>
<td>167.50 ± 30.32</td>
<td>167.31 ± 29.90</td>
<td>0.291</td>
</tr>
<tr>
<td></td>
<td>24 Weeks (Visit 3)</td>
<td>140.32 ± 24.99</td>
<td>139.77 ± 24.71</td>
<td>143.82 ± 36.51</td>
<td>148.31 ± 29.72</td>
<td>0.095</td>
</tr>
<tr>
<td>Post prandial blood sugar (PPBS) (mg%)</td>
<td>Baseline (visit 1)</td>
<td>291.37 ± 62.54</td>
<td>287.72 ± 65.02</td>
<td>289.23 ± 61.36</td>
<td>287.91 ± 63.37</td>
<td>0.968</td>
</tr>
<tr>
<td></td>
<td>12 weeks (visit 2)</td>
<td>246.41 ± 65.92</td>
<td>245.62 ± 66.18</td>
<td>248.63 ± 65.72</td>
<td>246.37 ± 65.90</td>
<td>0.987</td>
</tr>
<tr>
<td></td>
<td>24 weeks (visit 3)</td>
<td>205.94 ± 70.31</td>
<td>203.71 ± 68.65</td>
<td>205.44 ± 70.32</td>
<td>206.80 ± 70.27</td>
<td>0.988</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>Baseline (visit 1)</td>
<td>11.7 ± 1.79</td>
<td>11.6 ± 1.76</td>
<td>11.5 ± 1.80</td>
<td>11.6 ± 1.81</td>
<td>0.854</td>
</tr>
<tr>
<td></td>
<td>12 weeks (visit 2)</td>
<td>10.23 ± 1.62</td>
<td>10.31 ± 1.68</td>
<td>10.83 ± 1.75</td>
<td>10.3 ± 1.52</td>
<td>0.747</td>
</tr>
<tr>
<td></td>
<td>24 weeks (visit 3)</td>
<td>8.62 ± 1.57</td>
<td>8.73 ± 1.70</td>
<td>8.76 ± 1.67</td>
<td>8.81 ± 1.74</td>
<td>0.837</td>
</tr>
</tbody>
</table>

Two groups comparison using a post hoc test of LSD observed nonsignificant differences in the mean values of all the parameters except C vs R and E vs R groups where a significant reduction was observed in mean FBS values at 24 weeks.

### Table 2: Comparison of mean values of other parameters in all groups (ANOVA)

<table>
<thead>
<tr>
<th>Other Parameters</th>
<th>No. of visits</th>
<th>Canagliflozin (Mean ± SD)</th>
<th>Empagliflozin (Mean ± SD)</th>
<th>Dapagliflozin (Mean ± SD)</th>
<th>Remogliflozin (Mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (Kg)</td>
<td>Baseline (visit 1)</td>
<td>72.81 ± 9.88</td>
<td>73.12 ± 13.06</td>
<td>71.82 ± 12.15</td>
<td>72.74 ± 13.11</td>
<td>0.879</td>
</tr>
<tr>
<td></td>
<td>12 weeks (visit 2)</td>
<td>70.43 ± 14.52</td>
<td>71.24 ± 14.54</td>
<td>69.13 ± 13.82</td>
<td>70.24 ± 14.48</td>
<td>0.724</td>
</tr>
<tr>
<td></td>
<td>24 weeks (visit 3)</td>
<td>68.22 ± 13.87</td>
<td>68.43 ± 13.78</td>
<td>67.62 ± 12.34</td>
<td>69.23 ± 13.38</td>
<td>0.828</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP) (mm of Hg)</td>
<td>Baseline (visit 1)</td>
<td>138.81 ± 5.31</td>
<td>139.32 ± 5.78</td>
<td>139.11 ± 5.36</td>
<td>138.94 ± 5.68</td>
<td>0.940</td>
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<tr>
<td></td>
<td>12 weeks (visit 2)</td>
<td>136.90 ± 7.46</td>
<td>137.44 ± 6.40</td>
<td>136.63 ± 5.66</td>
<td>136.0 ± 6.67</td>
<td>0.345</td>
</tr>
<tr>
<td></td>
<td>24 weeks (visit 3)</td>
<td>134.71 ± 8.35</td>
<td>135.21 ± 6.64</td>
<td>134.94 ± 6.38</td>
<td>134.82 ± 7.32</td>
<td>0.863</td>
</tr>
<tr>
<td>Diastolic blood pressure (DBP) (mm of Hg)</td>
<td>Baseline (visit 1)</td>
<td>89.31 ± 5.90</td>
<td>87.63 ± 6.17</td>
<td>87.53 ± 7.92</td>
<td>87.64 ± 7.75</td>
<td>0.163</td>
</tr>
<tr>
<td></td>
<td>12 weeks (visit 2)</td>
<td>88.14 ± 6.06</td>
<td>86.01 ± 6.92</td>
<td>86.34 ± 8.35</td>
<td>86.23 ± 8.09</td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td>24 weeks (visit 3)</td>
<td>86.61 ± 6.14</td>
<td>85.22 ± 4.85</td>
<td>85.11 ± 8.56</td>
<td>85.32 ± 8.96</td>
<td>0.343</td>
</tr>
</tbody>
</table>
and treatment for UTI and mycotic infection was provided as required. The rest of the patients tolerated the therapy well (Table 4).

**DISCUSSION**

An extensive literature search has revealed that there is a scarcity of data that compared the efficacy of several available gliflozins in a single study at the global as well as national levels. The use of gliflozins varies widely due to varied clinical inertia toward a marketed drug. 8,9 A real-world study from Southern Europe carried out the clinical effectiveness of dapagliflozin in various countries and reported geographical diversity may have a significant impact on gliflozins on glycemic control.8

In view of this lacuna, the present study attempted to evaluate the effect of SGLT2 inhibitors on glycemic control and body weight in Indian patients with diabetes. The overall observations of this study suggest a reduction in glycemic level at all visits in all the treatment groups indicating the effectiveness of gliflozins on glycemic control. At 12 and 24 weeks of follow-up, all the four gliflozins in this study showed a significant reduction in HbA1c, blood glucose levels, and body weight from baseline indicating the efficacy of these drugs in achieving good glycemic control and weight reduction. These findings corroborate with the previous studies where each of these gliflozins has shown improvement in glycemic control and better influence on weight reduction.8–10

Empagliflozin is the first gliflozin approved by USFDA followed by Canagliflozin and Dapagliflozin. However, Remogliflozin is recently approved SGLT2 inhibitor by USFDA for the management of diabetes. In the present study, the mean difference in HbA1c at 6-months was comparable across the treatment groups. Similarly, a real-world observational study of 120 Indian patients with uncontrolled type II diabetes that compared Remogliflozin 100 mg with Canagliflozin 300 mg reported similar effectiveness between these two agents in terms of reducing HbA1c level, PPBS, FBS, and body weight.11 India is a developing country with a large proportion of the patient population from lower socioeconomic classes, and the cost-effectiveness of drugs is a crucial factor attributable to drug compliance. Remogliflozin and dapagliflozin were more cost-effective and can be used as alternative SGLT2 inhibitor options.11 SGLT2 inhibitors have also been observed to address cardiovascular and renal outcomes in terms of safety and efficacy through various global cardiovascular outcome trials. Another previous clinical trial (open-labeled, 52-week study) comparing Empagliflozin with dapagliflozin as add-on therapy in patients with uncontrolled type II diabetes showed both SGLT2 agents as effective as previous antidiabetic agents. However, the authors further demonstrated Empagliflozin is more effective in improving glycemic control and other cardiometabolic outcomes along with a reduction in body weight compared to dapagliflozin.12 On the contrary present study reported all the four gliflozins are comparable in terms of achieving glycemic control and weight loss. A recently published randomized active-controlled trial compared Remogliflozin vs dapagliflozin for 6 months in patients with uncontrolled type II diabetes demonstrated noninferiority of Remogliflozin over dapagliflozin in terms of reducing HbA1c, FBS, PPBS, and body weight.13 Similarly, in the present study, the mean difference of HbA1c, FBS, PPBS, and weight were comparable between Remogliflozin and dapagliflozin at 12 and 24 weeks follow-up from baseline.

Sodium glucose co-transporter 2 inhibitors are associated with significant weight reduction in patients with diabetes.14 Likewise, a previous real-world study conducted on 30 Irish patients with diabetes reported a reduction in HbA1c and body weight over 15 months of exposure to SGLT2 inhibitors.9 This is in accordance with the present study that reported all the four gliflozins to have significant weight loss at 12 and 24 weeks follow-up from baseline.

Several limitations of this study should be considered and observations should be interpreted vigilantly. The most important limitation of our study was the small sample size and duration of the study. More prospective clinical studies with head-to-head comparisons of SGLT2 inhibitors will be helpful in validating these observations.

**CONCLUSION**

Overall observations indicate all the four gliflozins (Canagliflozin, Empagliflozin, Dapagliflozin, and Remogliflozin) were similarly effective in achieving target glycemic levels and reduction in body weight. A reduction was also observed in blood pressure with the use of all the four gliflozins. Therefore, gliflozins can be a possible choice for the management of diabetes in Indian settings.

**REFERENCES**


