A Prospective Analysis of the Efficacy and Safety of Sodium Glucose Cotransporter 2 Inhibitors: Real World Evidence from Clinical Practice in India

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Abstract

**Background and Aim:** The number of patients with type 2 diabetes (T2DM) is increasing. Most patients with T2DM are uncontrolled and fail to achieve their target Hba1c. In recent years, newer agents such as SGLT2 inhibitors (SGLT2i) have been approved for clinical use. Though data from clinical trials and subset analysis of Indian patients in global studies are promising, real world evidence from standard clinical practice in India is lacking. The aim of this study was to analyze the metabolic parameters in patients with T2DM on SGLT2i in real world clinical practice.

**Materials and Methods:** This was a prospective, longitudinal study of 100 patients with uncontrolled T2DM attending the outpatient of a specialized diabetes hospital. Their metabolic parameters were evaluated at baseline and after 3 months of follow up. They were categorized based on their baseline anti diabetic medications into four groups (25 in each). The groups were as follows: metformin plus sulfonylurea, metformin plus DPP4 inhibitor, triple drug regimen with metformin plus DPP4 inhibitor plus sulfonylurea, and patients on insulin and on triple drug therapy with metformin plus sulfonylurea plus DPP4 inhibitor. Patients in each group were initiated with an SGLT2i. Descriptive statistical analysis was carried out using Microsoft excel. T test was used to calculate the p value at 5 % level of significance.

**Results:** The mean age of the subjects in the study population was 53.20±12.1 years and the duration of diabetes was 13.1±7.26 years. The mean Hba1c reduction and weight reduction observed was 1.02±0.24% and 2.64±1.27 kg respectively. Genital pruritis was reported in 4% of the patients. There was a 16.6% reduction in the daily insulin requirement at follow up when compared to baseline. No other side effects were observed. The reductions in Hba1c and weight were statistically significant (p<0.05) across all groups.

**Conclusion:** This study demonstrates that when SGLT2i are added at any stage of the disease spectrum with any of the preexisting therapeutic agents for patients with uncontrolled T2DM, there is an improvement in glycemic control and body weight, with minimal side effects. The real world study data on Indian patients appears to be promising.

Editorial Viewpoint

- SGLT2 inhibitor is the latest introduction into the armamentarium of antidiabetic drugs.
- The study demonstrates an improvement in glycaemic control and body weight in previously uncontrolled type 2 diabetes mellitus.

Introduction

International Diabetes Federation estimates show that India is home to 69.2 million people with diabetes.¹ An increase in diabetes prevalence has not only resulted in an increase in the complications associated with diabetes but has also exponentially added to health care costs while decreasing the quality of life.²

Even though we have several agents for the treatment of T2DM one or two are rarely sufficient to maintain normal or near normal glycemia and continuous reevaluation and up titration is often necessary. This

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may be attributed to the beta cell decline that occurs as a part of the natural history of T2DM. Cost of health care, lack of education, side effects of existing medications like weight gain and hypoglycemia, lack of lifestyle modification, fear of injections and even physician inertia to up titrate medications are other factors amongst many that contribute to hyperglycemia.

Sodium glucose transporter receptor 2 inhibitors (SGLT2 i) are now recognized as a novel therapy for T2DM management. They act by blocking the sodium glucose co transporter located at the proximal convoluted tubule of the nephron which is responsible for about 90% of glucose reabsorption. These agents decrease the renal threshold for glucose and cause glycosuria. This in turn results in improvement in glycemia and provides extra glycemic benefits like weight loss attributed to osmotic diuresis, calorie loss and decrease in visceral fat. Extra glycemic benefits also include decrease in uric acid levels and improvements in systolic and diastolic blood pressure.4-8

The risk of hypoglycemia with these agents is low, but it has been reported in patients on insulin and insulin secretagogues. An increase in mild genital mycotic infections and urinary tract infections has been reported. Most of these have subsided with antifungal therapy, have been isolated cases and have rarely warranted discontinuation of treatment.4,8-10 Euglycemic ketoacidosis when used off label in patients with type 1 diabetes and in post operative type 2 diabetes patients with reduced oral intake or in those who have been taken off of insulin therapy is a known side effect.11 An increase in fracture risk when used in elderly patients with moderate renal impairment and additional comorbidities like osteoporosis and renal osteodystrophy is also reported.9,12

While the results of the CV safety trials for dapagliflozin and canagliflozin are awaited, the results of the EMPA REG OUTCOME TRIAL, the cardiovascular safety randomized control trial with empagliflozin13 is noteworthy. The results of this trial demonstrated a relative risk reduction of 38%, 35% and 32% with respect to death from a cardiovascular event, hospitalization due to heart failure and all cause mortality respectively.13

SGLT2 inhibitors have been approved for the treatment of T2DM as mono therapy, as an add on second or third line agent in combination with any other known therapeutic options for diabetes, both oral and injectable by the ADA, EASD and the AACE. These class of agents may be used at any stage of T2DM owing to their novel insulin independent mechanism of action, provided the renal function is above a certain threshold.4,13-18

Though data from randomized control trials (RCTs) are promising, real world evidence from standard clinical practice needs to be analyzed.4,8,13 RCTs which are the gold standard method of assessing the efficacy and safety of new drugs usually involve a small group of patients, for a short period of time in a controlled environment. However, clinical practice constitutes treating a heterogeneous population in a realistic uncontrolled environment. The aim of this real world study was to analyze the metabolic parameters, tolerability and side effects of SGLT2i on patients with T2DM in standard clinical practice.

Materials

This was a prospective longitudinal study of 100 patients with uncontrolled T2DM attending the outpatient of a specialized diabetes hospital from May 2015 to August 2015. Each patient gave a written informed consent to participate in the study and the institutions’ ethics and review board approved the study protocol.

Inclusion Criteria: Patients with T2DM and a Hba1c > 8 % meeting one of the criteria below
1. Patients on dual therapy (metformin + sulfonylurea/ DPP4i)
2. Patients on triple oral therapy with metformin + sulfonylurea + DPP4i
3. Patients on insulin and triple oral therapy with metformin + sulfonylurea + DPP4i

Exclusion Criteria: Patients with history of genital mycotic infections, recurrent urinary tract infections, pyelonephritis, acute illness, type 1 diabetes, pregnant or lactating women and those with an eGFR below 45.

All patients were evaluated and screened for complications of diabetes as per standard of care. All patients were subjected to the following investigations: Fasting plasma glucose (FPG) postprandial plasma glucose (PPG) hemoglobinA1c (Hba1c), lipid profile, renal function tests and urine analysis.

Patients who were only on oral anti diabetic medication were advised insulin initiation. Only those who refused insulin initiation were included in the study and categorized into group 1, 2 or 3 as given below based on their baseline medications. Group 4 included patients on insulin. Patients in each group were initiated with a SGLT2i and the preexisting medications were continued. SGLT2i was added to even those on insulin to assess the weight reduction and improvement in glycemic control. All patients were counseled regarding the possible side effects of SGLT2i.

The patients were categorized into 4 groups of 25 each as follows:
Group 1 or G 1 - metformin + sulfonylurea + SGLT2i
Group 2 or G 2 - metformin + DPP4 inhibitor + SGLT2i
Group 3 or G 3 - metformin + DPP4 inhibitor + sulfonylurea+ SGLT2i
Group 4 or G 4 - Insulin
Table 1: Changes in weight and Hba1c

<table>
<thead>
<tr>
<th></th>
<th>Baseline weight kg</th>
<th>Weight at 3 months Kg</th>
<th>Δ Weight Kg</th>
<th>P value</th>
<th>Baseline Hba1c</th>
<th>Hba1c at 3 months %</th>
<th>Δ Hba1c</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G 1</td>
<td>83.02±27.42</td>
<td>76.6±13.56</td>
<td>6.42±12.28</td>
<td>&lt;0.05</td>
<td>9.51±1.17</td>
<td>8.71±1.07</td>
<td>0.8±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>G 2</td>
<td>74.67±9.68</td>
<td>73.95±12.28</td>
<td>0.72±1.28</td>
<td>&lt;0.05</td>
<td>8.86±0.97</td>
<td>7.71±0.95</td>
<td>1.15±0.02</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>G 3</td>
<td>74.36±6.15</td>
<td>72.06±5.01</td>
<td>2.3±1.14</td>
<td>&lt;0.05</td>
<td>9.54±1.16</td>
<td>8.88±1.13</td>
<td>0.66±0.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>G 4</td>
<td>74.35±11</td>
<td>73±10</td>
<td>1.35±1</td>
<td>&lt;0.05</td>
<td>9.51±1.23</td>
<td>8.49±0.99</td>
<td>1.02±0.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>76.6±13.56</td>
<td>73.95±12.28</td>
<td>2.64±1.27</td>
<td>&lt;0.05</td>
<td>9.51±1.17</td>
<td>8.71±1.07</td>
<td>0.8±0.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Group 4 or G 4 - insulin + metformin + DPP4 inhibitor + sulfonylurea + SGLT2i

The preexisting medications included sulfonylurea’s (glimipizide 4 mg/day and glimepiride XR 120mg/day), DPP4 inhibitors (sitagliptin 100mg/day, saxagliptin 5 mg/day, vildagliptin 100mg/day, linagliptin 5mg/day, teneligliptin 20mg/day) along with metformin 2 gm/day. The patients on insulin were continued with the preexisting dose of insulin and dose titration was taught to them based on the insulin regimen they were on (basal/basal bolus/premixed). Diet and lifestyle was intensified.

The commercially available SGLT2i at that point of time in India, i.e. dapagliflozin 10 mg and canagliflozin 100 mg were prescribed once a day alternately in a 1:1 ratio to all patients. The patients on insulin were educated on the importance of self monitoring of blood glucose (SMBG) and were asked to perform SMBG and insulin dosage adjustments based on their individualized targets twice a week. All patients on insulin and insulin secretagogues were educated on the possibility of hypoglycemia and were asked to contact the hospital for adjustment of insulin/ sulfonylurea dosages. The duration of follow up was three months. The tolerability, side effects, the efficacy and safety parameters like Hba1c, weight, renal function tests, urine analysis, fasting lipid profile and complete blood count were evaluated at the follow up clinic visit.

Statistical Analysis

The statistical analysis was carried out using Microsoft excel and results on continuous measurements have been presented as mean ± standard deviation (SD) and results on categorical measurements have been presented in percentages (%). P value at 5% level of significance was calculated using the T test.

Results

The mean age, duration of diabetes, weight and Hba1c in the study population was 53.20±12.1 years, 13.1±7.26 years, 76.6±13.56 kg and 9.51±1.23 % respectively. The duration of diabetes in Group 1, Group 2, Group 3 and Group 4 was 16.75 ± 9.43, 8.87 ± 7.18, 14.4 ± 6.7 and 12.4 ± 5.76 years respectively.

The mean weight and Hba1c reduction at follow up was 2.64±1.27 kg (p<0.05) and 1.02±0.24 % (p<0.05) respectively. The changes in weight and Hemoglobin A1c were statistically significant across all groups and are represented in Table 1.

Genital pruritis was reported as a side effect in 4% of the patients. None of them had mycotic genital infection on examination and all four chose to discontinue the SGLT2 inhibitor as a result of pruritis at follow up. Side effects reported in literature like urinary tract infections, polyuria, thirst, giddiness, postural hypotension, hypovolemia, dehydration, hemoconcentration, euglycemic ketoacidosis, worsening of eGFR, electrolyte imbalance, increase in LDL were not observed and the medication was well tolerated.

Hypoglycemia was reported only in the group on insulin. The exact number of episodes of hypoglycemia was not documented but none of the patients had severe hypoglycemia/ loss of consciousness requiring hospitalization or intravenous dextrose administration. The patients themselves had gradually reduced their insulin dose based on SMBG. The baseline daily insulin dose was 42 ± 29 units and at three months was 35 ± 24 units. Thus a 16.6% reduction in the daily insulin requirement at follow up when compared to baseline was noted.

Discussion

There is substantial evidence to show that SGLT2 inhibitors help in reducing Hba1c, FPG and PPG in patients with T2DM. SGLT2i also have non-glycemic benefits such as weight loss, reduction in abdominal circumference, visceral fat, blood pressure reduction, and reduction of albuminuria.4-8,19 If the CV safety data seen with empagliflozin is also observed as a class effect with the other drugs in this group, these medications might even have the potential to occupy a higher place in the treatment algorithm as the first class of antidiabetic agents to have reduced cardiovascular and all cause death.13,20-22

While evidence from RCTs is the highest level of evidence while analyzing the efficacy of a drug, the performance of an agent outside of a controlled environment may be variable. Real world evidence (RWE) is necessary to ascertain if the efficacy and safety profiles seen in RCTs can be extrapolated from efficacy to clinical effectiveness in practice.

This real world study demonstrates that when SGLT2i are added at any stage of the disease spectrum with any of the preexisting therapeutic agents for patients with uncontrolled type 2 diabetes, there is a clinical and statistically significant
improvement in glycemic control and body weight, with minimal side effects.

A significant Hba1c reduction (p<0.05) was seen across all groups of patients studied, irrespective of duration of diabetes and the baseline therapy. The maximum Hba1c reduction was seen in Group 4 patients (insulin + metformin + DPP4 inhibitor + sulfonylurea + SGLT2i). This reduction may not be solely attributed to the drug, as intensification of lifestyle changes and frequent dosage adjustment of insulin based on SMBG also contributes to improved glycemic control. As the highest baseline Hba1c was seen in this group, this could also have resulted in greater Hba1c reduction at follow up.

The patients in group 2 (metformin + DPP4 inhibitor + SGLT2i) showed a greater Hba1c reduction than those in group 1 (metformin + sulfonylurea + SGLT2i) and Group 3 (metformin + DPP4 inhibitor + sulfonylurea + SGLT2i). Patients in group 2 had a lesser duration of diabetes compared to those in group 1 and 3.

Changes in FPG and PPG were not analyzed, as clinic based estimation was done only at baseline and patients used their own glucose monitors for SMBG. The patients on insulin showed a reduction in their daily insulin dose by 16.6% (42 ± 29 to 35 ± 24 units). This is in concordance with other studies that have reported a reduction in insulin requirements with the addition of SGLT2.

All groups demonstrated a significant decrease in body weight (p<0.05) and those on metformin plus sulfonylurea with the highest baseline weight had the highest weight loss of 4 kg. This was followed by those in group 2 and group 3 respectively. Patients in group 4 on insulin demonstrated the least weight loss. However it is important to note that those on insulin had the highest baseline Hba1c, demonstrated the maximum Hba1c reduction and even with improvement in glycemic control, there was no additional weight gain. They further demonstrated a weight loss of 1.3 kg compared to baseline. Weight loss with improved glycemia is pivotal to diabetes care as meta analysis of cardiovascular outcome trials with glucose lowering therapies have demonstrated that with each kilogram of increase in weight the risk of heart failure increase by 7%. 26

This study has several limitations. The study sample was small and the while the patients continue to be on follow up at the hospital, the findings presented here only include data of the initial 3 months of follow up. Changes in blood pressure were not analyzed as patients in clinical practice as per routine care had an office blood pressure measurement at baseline and follow up and several variables are known to contribute to single office blood pressure readings. Changes in albuminuria, uric acid levels and visceral fat were not studied.

While longer follow up and further study into this new class of drugs is needed on several areas, the evidence on Indian patients appears to be promising. 27 In spite of showing Hba1c reduction, none of the groups in this study reached their target Hba1c. Will patients reach a target Hba1c over the next three to six months? If patients reach their target Hba1c, can this justify a delay in insulin initiation in patients who can afford SGLT2i? If the Hba1c target is not met, how many of our patients will go on to require insulin initiation? How many of our patients on insulin, will need insulin intensification? What will be the durability of weight loss in our patients? Time may give us a clear answer.

References

2. Standards of Medical Care in Diabetes.


