ORIGINAL ARTICLE

Efficacy of SGLT2 Inhibitors as the Fifth Drug in the Management of Type 2 Diabetes Mellitus in Asian Indians not Controlled with at least 4 Oral Antidiabetic Drugs

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Abstract

Aim: To evaluate the efficacy of SGLT2 inhibitors as an add-on therapy along with stricter lifestyle modification in Asian Indian type 2 diabetes mellitus (T2DM) patients with inadequate glycemic control despite receiving an optimum dose of at least 4 oral antidiabetic drugs (OADs).

Methods: A retrospective analysis of data of 808 T2DM patients being treated with an SGLT2 inhibitor (Dapagliflozin, Empagliflozin or Canagliflozin) as an add-on drug in patients with inadequate glycemic control despite receiving optimum doses of at least any four OADs(metformin, sulphonylureas, pioglitazone, DPP4 Inhibitors, alpha-Glucosidase Inhibitors) and who preferred not to initiate insulin.

Results: The average age of the patients included was 51.63 years (SD ± 9.88). 57.7% were males. Average weight was 81.95±16.08 kg. Mean duration of diabetes was 34.08±39.04 months. The mean baseline fasting plasma glucose was 198.21 ± 38.21 mg/dl and mean post prandial plasma glucose was 264.22 ± 45.22 mg/dl. The baseline HbA1c was 8.92 ± 1.47 %. Total 87.4 % of the cases responded to addition of SGLT2 inhibitors during a mean follow-up period of 6 months.

The fasting plasma glucose (FBS) was reduced by -63.65 ± 19.93 mg/dl to a mean FBS of 134.57 ± 33.65 mg/dl (P=0.001). The post prandial plasma glucose (PPBS) was reduced by -79.28 ± 23.57 mg/dl to a mean PPBS of 184.94 ± 38.34 mg/dl (P=0.001). The mean HbA1c reduced significantly by -1.63 ± 0.99 % (P= 0.001).

The mean weight reduction at 6 months of therapy was -3.03± 01.84 kg that is 3.8 % decrease from baseline (p=0.001).The response in age group <55 years was 90.9 %, whereas in ≥55 years, it was 82.2% (p=0.001). The males responded more (91.0%) compared to females (82.5%) (p=0.001). Those with BMI <23.5 kg/m2 had marginally higher but insignificant response of 93.0% as compared to 87.1% in patients with high a BMI (≥23.5 kg/m2) (p=0.253). Patients with <5years duration of diabetes responded better (91.8%) as compared to patients with a ≥ 5 years of diabetes (85.4%).

Conclusion: SGLT2 inhibitors are effective in achieving desired glycemic goals even when used as a fifth add-on drug along with strict lifestyle modification in patients with inadequate glycemic control despite receiving an optimum dose of at least 4 oral antidiabetic drugs (OADs). SGLT2 inhibitors can be effectively used at any stage of diabetes.

Introduction

According to International Diabetes Federation (IDF), India has second largest number of people living with diabetes worldwide (69.2 million) after china (109.6 million). It is predicted that by 2040, India will have approximately 123.5 million diabetes patients; which makes up 10.7% of total adult population aged 20-79 years.[1]

Type 2 diabetes mellitus is characterized by progressive beta-cell failure.[2] Most patients are not able to maintain good glycemic control on dual, triple or quadruple therapy with oral anti-diabetic drugs (OADs) for prolonged periods and will ultimately require insulin. ADA 2017 guidelines recommend that a patient, on failing to achieve HbA1c targets with a maximum of three OADs must be initiated with insulin therapy.[3] However, with the advent of new OAD's whose mechanism of action is independent of beta cell function; this treatment paradigm may be challenged.

Insulin treatment has many issues including patient noncompliance, negative outlook and treating physician's uncertainty to initiate insulin. Barriers to initiation or intensification of insulin therapy exist which include risk of hypoglycemia and adverse effects such as weight gain.[4] In addition, proper storage conditions are required for insulin, especially during travel and fluctuating temperatures. In cases where the patients prefer to avoid initiation of insulin, adding another OAD in lieu of insulin offers an attractive alternative. The availability of newer classes of OADs have widened the scope and possibility of such a treatment plan. These drugs act by different and often complementary mechanisms, addressing different pathophysiological processes that perpetuate hyperglycemia.[5] SGLT2 inhibitors are the newest class of oral anti diabetic agents, licensed in India for the treatment of T2DM since 2012. SGLT2 inhibitors currently available in India are Dapagliflozin, Empagliflozin and Canagliflozin.

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Table 1: Demographic data of the study population

Parameters	N = 808
Age (years)	
Mean	51.63 (SD ± 9.88)
Weight (kg)	
Mean	81.95 (SD ± 16.08)
Duration of diabetes (months)	
Mean	34.08 (SD ± 39.04)
Sex (%)	
Male	466 (57.7 %)
Female	342 (42.3 %)

There are very few studies available which have looked at the benefits of using multiple oral anti diabetic agents (triple or quadruple therapy) with complementary mechanisms of action.[6-8] In addition, patients who refuse to initiate insulin are now more receptive and committed to follow diet, exercise and other lifestyle interventions strictly in their desire to avoid insulin initiation.

According to our knowledge, the current study is the first of its kind to evaluate the efficacy of the currently available SGLT2 inhibitors as an add-on therapy along with stricter lifestyle modification in Asian Indian T2DM patients who were treated with at least 4 OADs and failed to attain glycaemic control.

Methods

A retrospective observational study was carried out in patients with T2DM who were being treated and regularly visiting the Diabetes Specialty Clinic, Mumbai. Patients with poor glycemic control despite receiving optimum doses of at least any four OADs (metformin, sulphonylureas, pioglitazone, DPP4 Inhibitors or alpha-Glucosidase Inhibitors) were treated with any one of the SGLT2 inhibitor (Dapagliflozin, Empagliflozin or Canagliflozin) as an add-on drug. The treatment regimen was decided during consultation.

Inclusion Criteria

- Patients who had records of regular follow up for≥ 6 months.
- Patients who had poor glycemic control despite taking at least 4 oral hypoglycaemic drugs (metformin, sulphonylureas, pioglitazone, DPP4 Inhibitors or alpha-glucosidase Inhibitors). (Poor glycemic control was defined as FPG≥130 mg/dl, PPG≥ 180 mg/dl, HbA1c >7.0)
- Patients who wanted to avoid insulin initiation.
- Patient who had no contraindication for SGLT2 inhibitors.

Exclusion Criteria:

- Patients who were on insulin or previously were on insulin.
- Patients in whom SGLT2 inhibitor therapy were stopped due to:
  - Urinary tract infection
  - Mycotic genital infection
  - Unable to bear cost
  - Symptomatic / troublesome polyuria due to SGLT2i.

Patient's weight, fasting plasma glucose (FPG), post prandial glucose (PPG) and HbA1c, was regularly assessed during routine clinic visits. All clinical parameters were electronically recorded. At each visit to the clinic, patients were motivated to strictly adhere to the suggested diet, exercise and life style modifications by the treating physician, dietician and diabetic educator. At each visit compliance to both drugs and adherence to lifestyle were recorded.

A total of 808 patients who met the inclusion criteria were considered for the final analysis. Glycemic control was defined by FPG level of ≤130 mg/dl and PPG level of ≤180 mg/dl. Changes in patient's weight, HbA1c, post prandial glucose (PPG) and fasting Plasma glucose (FPG) before and after 6 months of SGLT2 inhibitor treatment were recorded and analysed. Statistical calculations were performed with SPSS software. Statistical tests (Student's t test and Chi square test) were considered significant if P-value was <0.05 at confidence interval of 95%.

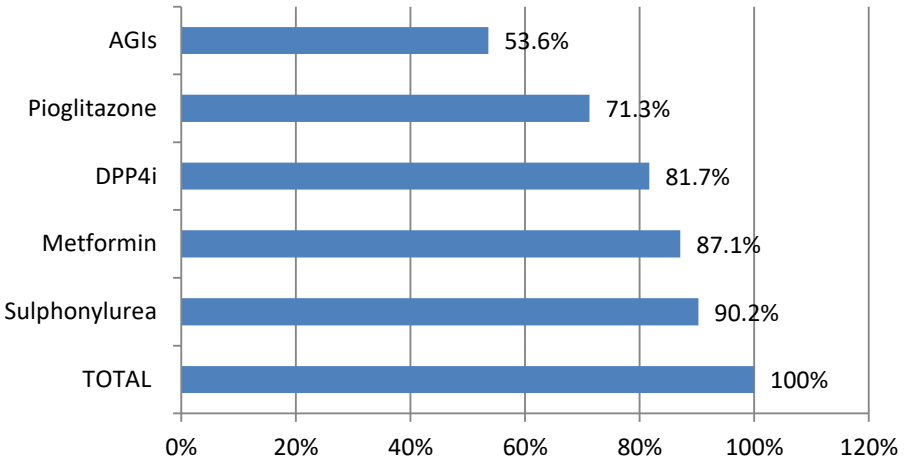

Fig. 1: Pre-existing OADs

Results

A total of 808 patients meeting the inclusion criteria were selected for this study. Out of 808, 57.7% (n=466) were male and 42.3 % (n=342) were females. Patient population had a mean age of 51.63 years (SD ± 9.88) and a mean weight of 81.95 kg (SD ± 16.08). The mean duration of diabetes was 34.08 months (SD ± 39.04) (Table 1).

The percentage of patients on pre-existing OADs such as Sulphonylureas, Metformin, DPP4 inhibitors, Pioglitazone and / or Alpha Glucosidase Inhibitors (AGIs) were as follows in Figure 1.

The baseline treatment regimen included any of the four OAD's prior to starting on SGLT2 inhibitors. SGLT2 inhibitor therapy was commenced soon after quadruple OAD therapy failure to maintain target blood glucose levels (FPG level of ≤130 mg/dl and PPG level of ≤180 mg/dl). The mean time for follow up was of 6 months. Out of total 808 patients, 87.4% (n=706) responded to the addition of SGLT2 inhibitors as a fifth drug and were able to achieve glycemic control of FPG ≤130 mg/dl and PPG≤180 mg/dl. Only 12.6 % (n=102) failed to achieve target glycemic levels (Table 2).

The FPG, PPG and weight were analysed initially at baseline and then at each visits after starting add on SGLT2 therapy. The Mean FPG and PPG before adding of SGLT2 inhibitor were 198.21 ± 38.21 mg/dl and 236.9 ± 29.5 mg/dl respectively, which were reduced to 134.57 ± 33.65 mg/dl and

184.94 ± 38.34 mg/dl. There was a statistically significant reduction from baseline of mean FPG (-63.65 mg/dl, P =0.001) and PPG (-79.28 mg/dl, P =0.001) (Table 3). The mean HbA1c was 8.92% at baseline and after addition of SGLT2 inhibitor, the mean HbA1c showed a significant fall of -1.63% (SD± 0.99) to 7.29 % (SD ± 1.15)(p=0.001). The mean baseline weight was 81.03 kg (SD± 16.73) .With the addition of an SGLT2 inhibitor, the subsequent mean reduction from the baseline in weight was of 3.03 kg (P =0.001) i.e. 3.8 % from baseline (Table 3).

The time required for patient to achieve their glycemic target levels varied significantly. 40.1% of the patients required <2 months to control diabetes. 40.8% patients were able to achieve glycemic targets in 2-4 months. 9.3% patients required 4-6 months while 9.8 % patients required > 6 months to control diabetes (Table 4). Approximately 80% of patients responded favorably at 4 months of add-on therapy.

90.9% of patients belonging to age group < 55 years responded to the treatment which was significantly more as compared to 82.2% of patients whose age was ≥ 55 years (p=0.001). 91.0% of the male patients responded to the treatment which was significantly more as compared to 82.5% of the female patients (p=0.001). 90.8% of the patients who had a history of diabetes for < 5 years significantly responded to add-on treatment compared to 85.9% of the cases who had diabetes for ≥ 5 years. (p=0.011). It was observed that male patients, young patients and those with lesser duration of diabetes responded better to SGLT2 inhibitor treatment.

Table 2: Outcome of patience achieving target glycemic levels

Outcome	No of Cases (N=808)	Percentage
Response	706	87.4
Failure	102	12.6

Table 3: Changes in mean FPG, PPG, HbA1c and weight among study population

	Baseline ($\bar{X}$ ± SD)	End ($\bar{X}$ ± SD)	Difference (Baseline – End) (X ± SD)	P value
Fasting blood glucose (mg/dl)	198.21 ± 38.21	134.57 ± 33.65	-063.65 ± 19.93	0.001
Post-prandial blood glucose (mg/dl)	264.22 ± 45.22	184.94 ± 38.34	-79.28 ± 23.57	0.001
Mean HbA1c (%)	8.92 ± 1.47	7.29 ± 1.15	-1.63 ± 0.99	0.001
Mean weight (kg)	81.03 ± 16.73	77.98 ± 16.42	-03.03 ± 01.84	0.001

Discussion

In this study we have found that addition of an SGLT2 inhibitor as a fifth drug to the treatment regimen of patients uncontrolled on 4 OAD's can achieve good glycemic control and can delay the initiation of insulin therapy. It is important to note that the patients were motivated to adhere to a stricter lifestyle.

The 2015 ADA position statement and European Association for the Study of Diabetes about the management of hyperglycaemia in T2DM recommends SGLT2 inhibitor as one of the treatment options in metformin-failing T2DM patients.[9] Various randomized controlled trials have established the efficacy of SGLT2 inhibitors as monotherapy, dual and triple oral therapy.

The American Diabetes Association/ European Association for the Study of Diabetes Joint Task Force recommends triple OAD therapy in some patients where agents with complementary mechanisms of action should be used.[10] However there are no studies which have reported the efficacy of SGLT2 inhibitors as an add-on to triple or quadruple oral combinations. There is only one case study in which SGLT2 inhibitor has been added as an add-on to triple combination therapy of metformin, glimepiride, and sitagliptin. After three months of therapy, the patient HbA1c was 6.9% with fasting and postprandial values of 97 and 138 mg/dL, respectively. Additionally, a weight loss of 1.9 kg was documented.[11] OAD's such as sulphonylureas and pioglitazone as well as insulin therapy often result in weight gain. Hence, any add-on therapy that can cause weight loss is worth taking into consideration.

Our study has shown significant reduction in HbA1c using SGLT2 inhibitor as the fifth drug along with strict lifestyle modification. The improvement was found to be statistically significant where mean FPG and PPG levels reduced by -63.65 mg/dl and -79.28 mg/dl respectively (P =0.001) and majority of the patients (87.4%) were able to control FPG and PPG levels to target levels. The mean HbA1c showed a significant fall of -1.63%, which can be a synergistic effect of multiple OADs working on different pathophysiologic mechanisms of type 2 diabetes along with stricter adherence to lifestyle modification. The synergistic effects of two OADs, which work on different pathophysiologic mechanisms of type 2 diabetes, have already been studied and have shown synergistic HbA1c reduction beyond simple addition.

The current study also did emphasize on strict adherence to lifestyle modification in study population, who were highly motivated due to their desire to avoid insulin initiation. In current study, addition of an SGLT2 inhibitor was able to reduce mean weight by 3.03 kg from baseline, which may have further helped in reducing insulin resistance and ultimately superior HbA1c reduction. In addition, almost 80% patients were able to control their diabetes within 4 months of treatment, out of which around 40 % had achieved goal in initial 2 months. Our study reflects real life experience and demonstrates that addition of SGLT2 inhibitors as a fifth drug along with strict lifestyle modification will help patients control their diabetes for a prolonged period, delaying insulin initiation.

This study has some limitations because of its retrospective nature. Other important features, such as

Table 4: Duration required for attaining target glycemic control in 706 (87.37%) responders in the study

Outcome (Months)	No. of cases (N = 706)	Percentage
< 2 m	283	40.1
2 – 4 m	288	40.8
4 – 6 m	066	09.3
> 6 m	069	09.8

Table 5: Association between age group, sex, duration of diabetes and response among study population

Characteristics	No of cases (N = 808)	Response No. (%)	P value
Age < 55 years	483	439 (*90.9)	P = 0.001
Age ≥ 55 years	325	267 (82.2)	
Male	466	424 (91)	P = 0.001
Female	342	282 (82.5)	
Duration < 5 years	245	225 (*91.8)	P = 0.011
Duration ≥ 5 years	563	481 (85.4)	

patient compliance and side effects' profile, could not be assessed in the present analysis. However, they do not significantly affect the importance of this study.

Conclusion

Patients with type 2 diabetes who require further improvement in glycaemic control despite the being on 4 OADs, SGLT2 inhibitor as a fifth drug can be considered. They are highly efficacious when added as fifth drug along with strict lifestyle modification and can effectively reduce HbA1c and weight. They act similarly in Obese as well as Non-Obese patients. They can be effectively used at any stage of diabetes and can delay insulin initiation in Type 2 diabetes patients not controlled on multiple OADs.

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