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**ORIGINAL ARTICLE**

# Efficacy of Initiating Sodium Glucose Co Transporter 2 Inhibitor (SGLT2I) for Treatment of Type II Diabetes Mellitus

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## INTRODUCTION

Sodium glucose co-transporter 2 (SGLT 2) inhibitors are hypoglycemic agents that have action on kidneys. They cause increased excretion of glucose via kidneys by reducing its absorption.

In healthy individuals, kidneys filter almost all of the glucose and return it back into circulation, excreting only a minimum amount in the urine. This reabsorption is facilitated by SGLT 2 receptors which are found in early proximal tubule, with some assistance by sodium glucose co-transporter 1 (SGLT 1).

In patients with type 2 diabetes mellitus (T2DM), activity of SGLT 2 is increased. This results in increased absorption of glucose in the bloodcausing further hyperglycemia.

**Objectives:** To determine the efficacy of initiating sodium glucose co transporter2 inhibitor (SGLT2i) in patients with type 2 diabetes mellitus.

**Study design:** Descriptive, case series study

**Study duration:**28th April 2020 to 27th October 2020.

**Settings:** Department of Medicine, Aziz Fatima hospital, Faisalabad and Diabetes & Endocrinology Ward of Hayatabad Medical Complex, Peshawar

**Materials & Methods:** 150 patients with T2D aged between 18 to 60 years. Patients with pregnancy, CHF, those who had received an oral hypoglycemic medication other than metformin for more than 14 days were excluded. All the patients were given Dapagliflozin 10 mg once daily for 26 weeks. For evaluation of HbA1c, blood sampleswere checked and reported by pathologist at hospital. Efficacy was assessed after 26 weeks of treatment.

**Results:**In this study, participants were in the age range from 18 to 60 years with mean age of 40.77 ± 9.42 years. Eighty three patients (55.33%) were between 18 to 40 years of age. Out of 150 patients, 93 (62.0%) were male and 57 (38.0%) were females with male to female ratio 1.6:1. In our study, efficacy of initiating sodium glucose co transporter -2 inhibitor (SGLT2i) in patients of type 2 diabetes mellitus was found in 65 (43.33%) patients.

**Conclusion:** This study concluded that "the efficacy of initiating sodium glucose co transporter - 2 inhibitor (SGLT2i) in patients of type 2 diabetes mellitus is quite high.**"**

**Keywords:** type 2 diabetes mellitus, sodium glucose co transporter -2 inhibitor,efficacy.

## INTRODUCTION

Diabetes mellitis (DM) is basically categorized in four main groups: Type I Diabetes (also called insulin dependant or juvenile diabetes), Type II diabetes (also called non-insulin or adult onset diabetes) ,Secondary diabetes( Specific types of diabetes due to other causes) and gestational diabetes (occurring during pregnancy for the first time).[1,2]

Globally, prevalence of diabetes mellitus has been reported to be 10-14%. Majority of these cases are seen in Asian continent, making over 60% of the world's population with diabetes.[2]

Type 2 DM (T2DM) is the most common among all the four types of diabetes. It is characterized by increased concentrations of glucose in the blood, which in turn occurs due to insulin resistance in the body. As a result, the body produces lesser amounts of insulin, and relative insulin deficiency ensues. [3] T2DM is different from T1DM in the sense that in latter, there is autoimmune destruction of islet cells in pancreas, causing absolute deficiency of insulin in the body.[4]

As discussed above, T2DM is the most common form of diabetes and has the most devastating consequences. In adult population, it is reported to be around 9%.[1] This number is increasing very rapidly, almost equalizing to epidemic criteria. Currently 415 million of the world's population is estimated to have acquired the disease, and this number is estimated to rise to 642 million by 2040.

T2D has a complex pathophysiology due to its multifactorial nature. On a short note, it is characterized by dysfunction of β-cell of pancreas, insulin resistance in other parts of the body and increased glucose production by the liver. In presence of obesity, this is added upon by increased rate of lipolysis, further contributing to diabetes and its harmful effects.[3]

T2DM is a progressive disease, requiring treatment modification and intensification over time for its control. The first and gold standard drug therapy is considered to be metformin, but this has to have adjuncts if hyperglycemia is not controlled well. The recommendations on adding these adjuncts vary and there are no specific guidelines on the step-ladder fashion of controlling diabetes. [4]

However, this choice needs to be made with extreme

caution because of the presence of a large range of glucose lowering pharmacological agents. Of these, biguanides (metformin), sulfonylureas (SUs), meglitinides, dipeptidyl peptidase-4 inhibitors (DPP-4i), thiazolidinediones, alpha-glucosidase inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors are the commonly used oral antidiabetic agents (OADs) both as mono- and combination-therapy in T2DM patients.[5]

Sodium glucose co-transporter 2 (SGLT2) inhibitors are another class of oral hypoglycemic agents that have action on kidneys. They cause increased excretion of glucose via kidneys by reducing its absorption.

In healthy individuals, kidneys filter almost all of the glucose and return it back into circulation, excreting only a minimum amount in the urine. This reabsorption is facilitated by SGLT 2 receptors located in early proximal tubule, with some assistance by sodium glucose co-transporter 1 (SGLT 1). The latter is located in late proximal tubule.

In patients with type 2 diabetes mellitus (T2DM), activity of SGLT 2 is increased. This results in increased absorption of glucose in the blood, hence causing further hyperglycemia.[6]

A study conducted assessing efficacy of SGLT2i showed efficient control of diabetes in 62.4% of the patients.[2]In LOCF study, controlled diabetes was seen in 11.6% of the patients with T2DM.[7]

However, data regarding the above is scarce in our setup. Despite the increasing prevalence of T2DM in our society and its uncontrolled number, yet the newer therapies are not studied for benefits of the masses. Therefore the current study is designed to study the efficacy of SGLT2i for management of T2DM in Faisalabad.

**Objective:** To determine the efficacy of initiating sodium glucose co transporter_2 inhibitor (SGLT2i) in patients with type 2 diabetes mellitus.

**Operational Definitions:**

**Type 2 Diabetes mellitus:** If the patient had FBS >126 mg/dl and RBS >200 mg/dl along with classic symptoms of hyperglycemia or HbA1c> 6.5 was said to have type 2 diabetes mellitus.

**Efficacy:** It was assessed in terms of controlled diabetes. The patient said to have controlled diabetes if they had HbA1c < 7% after 26 weeks of treatment.

## MARERIAL AND METHODS

**Study Design:** Descriptive, case series study.

**Setting:** Department of Medicine, Aziz Fatima hospital, Faisalabadand Diabetes & Endocrinology Ward of Hayatabad Medical Complex, Peshawar

**Duration of Study:** 28th April 2020 to 27th October 2020.

**Sample size:**

By using WHO sample size calculator
P = 62.4%[2]
Confidence level = 95%
Absolute precision = 8%
Sample size = 150.

**Sample Technique:** Non-probability, consecutive sampling.

**Sample Selection:**

**a. Inclusion Criteria:**

- Patients having age between 18-60 years of both genders.
- Patients having type II diabetes mellitus as per operational definition with HbA1c > 8-12%.

**b. Exclusion Criteria:**

- Pregnancy
- Uncontrolled hypertension (SBP ≥ 160 mmHg and diastolic blood pressure ≥ 10 mmHg
- Fasting plasma glucose (FPG) ≥ 270 mg/dL during the 4-week lead-in period
- History of cardiovascular diseases within 3 months of screening
- Congestive heart failure
- An estimated glomerular filtration rate < 60 mL/min/1.73 m2 or serum creatinine ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women
- Hepatic disease
- Received an antidiabetic medication other than metformin for more than 14 days during the 12 weeks before screening.

**Data Collection Procedure:** Study approval was taken from hospital ethical committee. Patients were selected as per inclusion criteria from outpatient department of Medicine/Endocrinology. Informed consent was taken. All the patients were taking Dapagliflozin 10 mg once daily for 26 weeks. For evaluation of HbA1c blood sample was sent to hospital pathology laboratory and it was reported by pathologist. Efficacy was assessed after 26 weeks of treatment as per operational definition. Follow up was done by taking patient's contact number.

**Data Analysis Procedure:** Data was analyzed using SPSS version 22. Mean ± Standard Deviation were calculated for all quantitative variables like age, BMI, duration of disease and HbA1c level. Frequency and percentages were calculated for all qualitative variables like gender and efficacy. Chi-square test was used to compare efficacy between two groups.

Effect modifiers like age, duration of disease, BMI and gender were stratified, and post-stratification and chi-square test was applied. p-value ≤ 0.05 was considered significant.

## RESULTS

The study comprised of 150 patients.They were chosen from 18 to 60 years of age. Mean age and SD was40.77 ± 9.42 years. Greater number of the patients, i.e 83 (55.33%) lied between 18 to 40 years of age (Table 1).

93 of the study participants (62.0%) were male and 57 (38.0%) were females with male to female ratio 1.6:1 (Figure 1). Mean duration of disease was 5.80 ± 2.48 years (Table. 2). Mean BMI was 28.44 ± 3.63 kg/m2 (Table. 3). Mean HbA1c levels were 6.79 ± 0.58.

In our study, efficacy of initiating SGLT2i in diabetic population was found in 65 (43.33%) patients (Figure 2).

Table 1: Distribution of patients as per age (n=150).

| Age (in years) | No. of Patients | Percentage |
|---|---|---|
| 18-40 | 83 | 55.33 |
| 41-60 | 67 | 44.67 |
| Total | 150 | 100.0 |

➢ Mean ± SD = 40.77 ± 9.42 years

Stratification of efficacy with respect to age groups and gender is shown in Table.4 & 5, respectively. Table 6 & 7 have shown the stratification of efficacy of initiating SGLT2i in diabetic participants of the study with respect to duration of DM and BMI, respectively.

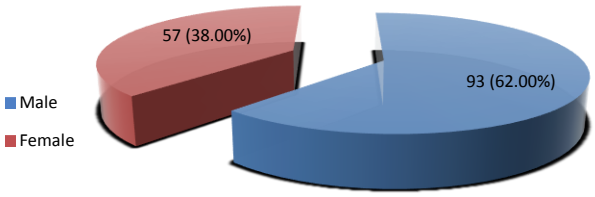


Figure 1: Distribution of patients as per gender (n=150).

Table 2: Distribution of patients as per duration of disease (n=150).

| Duration of disease (in years) | No. of Patients | %age |
|---|---|---|
| ≤5 years | 92 | 61.33 |
| >5 years | 58 | 38.67 |

- Mean ± SD = 5.80 ± 2.48 years

Table-3: Distribution of patients according to BMI (n=150).

| BMI (kg/m$^2$) | No. of Patients | %age |
|---|---|---|
| ≤27 | 76 | 50.67 |
| >27 | 74 | 49.33 |

- Mean ± SD = 28.44 ± 3.63 kg/m$^2$

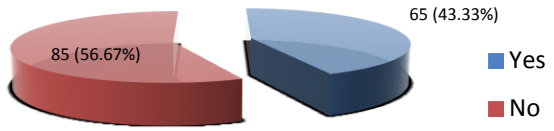


Figure 2: Efficacy of initiating sodium glucose co transporter_2 inhibitor (SGLT2i) in patients of type 2 diabetes mellitus (n=150).

Table 4: Stratification of efficacy with respect to age groups.

| | Efficacy | | p-value |
|---|---|---|---|
| Age (years) | Yes | No | |
| 18-40 | 34 | 49 | 0.515 |
| 41-60 | 31 | 36 | |

Table 5: Stratification of efficacy with respect to gender.

| | Efficacy | | p-value |
|---|---|---|---|
| Gender | Yes | No | |
| Male | 38 | 55 | 0.435 |
| Female | 27 | 30 | |

Table 6: Stratification of efficacy with respect to duration of DM.

| | Efficacy | | p-value |
|---|---|---|---|
| Duration (years) | Yes | No | |
| ≤5 years | 35 | 57 | 0.439 |
| >5 years | 30 | 28 | |

Table 7: Stratification of efficacy with respect to BMI.

| | Efficacy | | p-value |
|---|---|---|---|
| BMI (kg/m$^2$) | Yes | No | |
| ≤27 | 33 | 43 | 0.982 |
| >27 | 32 | 42 | |

## DISCUSSION

Sodium glucose co transporter-2 inhibitors (SGLT2i) are another category of antidiabetic pharmacological agents for curbing diabetes. These agents block the sodium glucose cotransporters present in the kidneys at the proximal convoluted tubules. Hence glucose is not reabsorbed and excreted in the urine. As a result, glucose in the blood is kept controlled because of absence of absorption from the kidneys and also has beneficial effects like weight loss, calorie loss, decrease in visceral fat, decrease in uric acid levels and improvement in blood pressure.[8-12]

The present study pinpoints the effectiveness of SGLT2i for treatment of T2DM. We included participants from 18 to 60 years of age, with mean age of 40.77 ± 9.42 years. A large number of our patients 83 (55.33%) were from 18 to 40 years of age. From the total number of participants, 93 (62.0%) were male and 57 (38.0%) were females, in ratio 1.6:1.

In our study, efficacy of initiating SGLT2i in diabetic population was found in 65 (43.33%) patients. In a study, controlled diabetes was observed in 62.4% patients in patients of T2DM initiating SGLT2i.[2] In a high glycemic sub-study (LOCF), controlled diabetes was observed in 11.6% patients in patients of T2DM initiating SGLT2i.[7]

A meta-analysis involving 45 clinical trials studied SGLT2i and reported that treatment with this medication alone helped in 0.79% decrease in HbA1c levels and with combination therapy, up to 0.61%.[13]

SGLT2i also have beneficial effects in both fasting glucose levels and those checked after meals, in addition to improved time-in-range (TIR). This is asper continuous glucose monitoring (CGM).[14,15]

Gupta et al conducted a study in 2017 regarding efficacy of SGLT2i and found that patients treated with SGLT2i achieved a higher rate of reduced HbA1c (7%) after 76 weeks of treatment.[16]A better level of glucose in the blood and better body weight has also been shown in pooled analysis of four randomized control trials in their Phase III.[17]Another post hoc analysis in 2016 showed similar outcome.[18]

Tamez Perez et al in 2013 conducted a study for efficacy of SGLT2i in 2013 in which reduction of HbA1c was reported to be 1% for group C and 1.1% for group D.[19]Liakoset al in 2014 studied the same and reported a reduction in HbA1c by 0.7% in group E.[20]Observations of these studies coincide with observations of our study.

K. Stenlöfet al and Devi et al also assessed efficacy of SGLT2i in 2012 and 2016 respectively. Patients were given trial of SGLT2i for three months and HbA1c was checked after that period. Both studies gave a positive result of reduction in HbA1c by 1%.[21,22]

In their meta-analysis done in 2010, Sherifaliet al studied the efficacy of SGLT2i in combination therapy and found even further improved results in achieving good blood glucose levels and improved HbA1c. However this effect could be obvious as more than one drug is employed

for the same purpose.[23]

Research has exhibited that SGLT2i have a very effective role in reducing blood glucose levels when used as combination therapy in face of poor glycemic control. Those patients who have their diabetes well managed but do not tolerate their existing regime, replacing their therapy with SGLT2i has not been very effective. But it is imperative to note that SGLT2i have not only benefitted patients in monotherapy or combination therapy, but they also offer other advantages like weight loss, drop in visceral fat, improvement in blood pressure,

## CONCLUSION

Efficacy of initiating sodium glucose co transporter_2 inhibitor (SGLT2i) in diabetic population is quite high.We recommend that there should be routine use of SGLT2i in every T2D patient, thus proper management can be done in these particular patients for good glycemic control and in order to reduce the morbidity.

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