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A Prospective Study to Compare the Glycemic Control of An Individual with Type 2 Diabetes Mellitus After Adding an SGLT2 Inhibitor to Therapy.

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A B S T R A C T

Background & Methods: The aim of the study is to compare the glycemic control of an individual with Type 2 Diabetes Mellitus after adding an SGLT2 inhibitor to therapy. Study will include the patients admitted at Jaslok Hospital and Research Centre or patients coming to Jaslok Hospital and Research Center OPD. We stratified patients based on baseline HbA1c into 3 categories; HbA1c <8%, HbA1c 8-10 % and > 10 %. Number of patients in each category was respectively observed to be 19 patients (22.4%), 46 patients (54.1 %) and 20 patients (23.5 %) on enrolment. It was observed that majority of patients had HbA1c between 8-10 %. Baseline anti- diabetic therapy of all these patients included metformin and a DPP4 inhibitor. An SGLT2 inhibitor was then added to the treatment of diabetes and change in HbA1c at the end of 6 months was observed.

Conclusion: Maximum number of Diabetic Patients belonged to the age group of 46-55 years in the group. Mean Age of the study population was found to be 53.27 years. 58.8% i.e., 50 patients were males in the study group and 41.2 % i.e., 35 patients were females. It was observed that there was a significant reduction in HbA1c with the drug over a period of 6 months. It was also observed that more the initial Hba1c, more is the reduction in Hba1c. The Clinical Prospective Follow-up study conducted at Jaslok Hospital and Research Centre shows that SGLT2 inhibitors, help in improving not only blood sugar control in Diabetics but also have significant positive outcomes in various other Clinical, Biochemical and metabolic parameters.

Study Design: Prospective Study.

INTRODUCTION

Diabetes Mellitus is fast gaining the status of a potential epidemic in India with more than 101 million diabetic individuals currently diagnosed with the disease and a prevalence of 11.4%, Pre-Diabetes prevalence 15.3%.[1] 537 million adults are currently living with diabetes worldwide according to a recent report from the International Diabetes Federation (IDF).[2] 10th edition of the IDF Diabetes Atlas published on December 6 2021 mentions these details. The report also adds that another 40 million adults have impaired glucose tolerance (IGT) in India, placing them at high risk of developing Type-2 diabetes. More than half (53.1 per cent) of people living with diabetes in India are undiagnosed. Diabetes becomes a significant challenge to the health and well-being of individuals with the increasing number of people living with diabetes and at risk of developing the condition in

India. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country.[2]
Although diabetes often cannot be prevented, its complications can be minimized through appropriate glycaemic control; for every one percentage point drop in A_{1c} (e.g., from 8.0% to 7.0%) there is a 40% reduction in the risk of microvascular complications (e.g., retinopathy, nephropathy, and neuropathy).[2]

Type 2 diabetes mellitus (T2DM) is frequently associated with comorbidities that exacerbate cardiovascular (CV) risk, such as obesity and hypertension [3]. The risk of CV disease is increased approximately two to four-fold in adults with diabetes even after adjustment for conventional risk factors (age, sex, smoking status, body mass index [BMI], systolic blood pressure [SBP], and lipids) [4].
Glucose management, lipid lowering, BP control, smoking cessation, and weight loss are recommended strategies for reducing CV risk in patients with T2DM. [4] Improved glycaemic control has been associated with a reduction in microvascular events [5] and there is a clear association between microvascular complications such as albuminuria and an increased risk of CV events in patients with T2DM [6].

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetic agents that reduce hyperglycaemia in patients with T2DM by reducing renal glucose reabsorption and thus increasing urinary glucose excretion (UGE) [7].

In placebo-controlled phase III trials in patients with T2DM, SGLT 2 inhibitors used as monotherapy or add-on therapy improved haemoglobin A1c (HbA1c), reduced body weight and BP, without increasing heart rate, and had small effects on Plasma lipids (increase in HDL-cholesterol, increase in LDL-cholesterol, no change in LDL/HDL cholesterol ratio) [8-12].

MATERIAL AND METHODS

This is a tertiary care hospital based prospective observational study determining the impact of introduction of SGLT2i to a patient on DPP4 inhibitors and metformin therapy on glycaemic control of diabetic individuals including HbA1c, FBS, PPBS and other clinical, metabolic and laboratory parameters
Study will include the patients admitted at Jaslok Hospital and Research Centre or patients coming to Jaslok Hospital and Research Centra OPD, according to the inclusion and exclusion criteria.

Inclusion Criteria:
1. The Patient should be a known case of type 2 Diabetes mellitus, on metformin and DPP4 inhibitors and willing to participate in the study at Jaslok hospital.
2. FBS should be more than 125mg/dl, PPBS should be more than 200mg/dl, HbA1c more than 6.5%

Exclusion Criteria:
1. The patient with impaired renal function(CrCl<40 ml/min), on renal replacement therapy, liver disease.
2. The patient having a history of repetitive genitourinary infections.
3. The patient who is terminally ill/suffering from malignancy.

4. Type 1 DM patients
5. Gestational DM patients/ pregnancy/ lactating mother.
6. Diabetes due to secondary causes (e.g., pancreatic cancer, chronic pancreatitis, steroid-induced diabetes mellitus, Cushing's syndrome, or acromegaly)

RESULTS

Patient Characteristics:

1) AGE:

In our study, patients were stratified into 5 categories based on age, <35 years, 35-45 years; 46-55 years; 56-65 years; and above 65 years in each group. Number of patients in each category have been mentioned in Table 1. Maximum number of patients were found to be in the Age Group of 46-55 years i.e., 33 patients (38.8%).

TABLE **1:** DISTRIBUTION OF THE PATIENTS BASED ON AGE

Age Groups	Frequency	Percentage
<35 years	**6**	**7.1**
35 to 45 years	**14**	**16.5**
46 to 55 years	**33**	**38.8**
56 to 65 years	**23**	**27.1**
Above 65 years	**9**	**10.6**
Total	**85**	**100**

2) GENDER

In Our Study it was observed that 35 patients (41.2%) were females and 50 patients (58.8%) were males.

3) COMORBID CONDITIONS:

In our study, Dyslipidemia was reported as the most common co-morbidity.

TABLE 2: PREVALANCE OF VARIOUS COMORBIDITIES IN PATIENTS

Comorbidities present	Frequency	Percentage
Hypertension (HTN)	**67**	**78**
Dyslipidemia	**85**	**100**
Ischemic Heart Disease (IHD)	**26**	**30.5**

4) Previos Antidiabetic Medications:

All the enrolled patients were on Metformin and DPP4 inhibitor therapy as antidabetic agents and no other medications for treatment of diabetes.

5) HbA1c (Glycaemic control):

Patients were classified into 3 categories based on baseline HbA1c as mentioned in Table 3. Maximum patients were in the 8-10% category.

It was observed that there was a statistically significant reduction in HbA1C with both the drugs at 6-month interval with a mean reduction in HbA1c of 2.19 % ± 0.25%.

It was also observed that; more the initial HbA1c, more is the reduction in HbA1C.

TABLE NO 3: DISTRIBUTION OF PATIENTS BASED ON HbA1c VALUES ON ENROLLMENT AND FOLLOWUP

HbA1c groups	Frequency (Enrollment)	Percentage (Enrollment)	Frequency (Follow up)	Percentage (Follow up)
Less than 08 %	19	22.4	66	77.7
08 to 10 %	46	54.1	19	22.3
>10 %	20	23.5	0	0
Total	85	100	85	100

6) BMI:

We stratified patients at baseline according to their BMI based on latest WHO classification as mentioned in Table 4.

In our study it has been observed that the majority of patients belonged to the WHO Overweight class (BMI 25-29.9 kg/m^2.)

Mean initial BMI was 28.76% ± 3.61 and mean BMI at 6 months was 27.79 ± 3.48. This was statistically significant with a p value of < 0.001.

It was found that there was a statistically significant reduction in BMI at 6-month interval with SGLT2i and that; more the initial BMI, more is the reduction in BMI.

TABLE 4: DISTRIBUTION OF PATIENTS ACCORDING TO BMI ON ENROLMENT AND FOLLOWUP

BMI Groups	Frequency (Enrollment)	Percentage (Enrollment)	Frequency (Follow up)	Percentage (Follow up)
Normal (18.5-24.9)	14	16.5	17	20.1

Overweight (25-29.9)	**41**	**48.2**	**46**	**54.1**
Obese 1 (30-34.8)	**24**	**28.2**	**21**	**24.7**
Obese 2 (35-39.9)	**6**	**7.1**	**1**	**1.1**
Obese 3 (>/=40)	**0**	**0**	**0**	**0**
Total	**85**	**100**	**85**	**100**

7) eGFR

We have stratified patients based on their base line eGFR values into 4 categories as mentioned in Table 5.

Mean initial eGFR was 74.52 ± 41.37 and mean eGFR at 6 months was 91.14 ± 64.41. This was statistically significant with a p value of < 0.001.

There was a significant increase in eGFR with the drug at 6 months follow up.

TABLE NO 5: DISTRIBUTION OF PATIENTS ACCORDING TO BASELINE eGFR

eGFR groups at time of enrolment (ml/min/1.73m^2)	**Frequency (Enrollment)**	**Percentage (Enrollment)**	**Frequency (Follow up)**	**Percentage (Follow up)**
30-44	**24**	**28.2**	**19**	**22.4**
45-59	**19**	**22.4**	**18**	**21.2**
60-89	**17**	**20**	**21**	**24.7**
>90	**25**	**29.4**	**27**	**31.8**
Total	**85**	**100**	**85**	**100**

8) Cardiovascular parameter (LVEF):

We stratified patients based on baseline LVEF into 3 categories as per table 6..

It was observed that there was statistically significant increase in LVEF with the drug.

Mean initial LVEF was 52.9% ± 13.4 % and mean LVEF at 6 months was 55 ± 10.1. This was statistically significant with a p value of < 0.001.

TABLE NO 6: DISTRIBUTION OF PATIENTS ACCORDING TO BASELINE LVEF

LVEF groups at time of enrolment				
	Frequency (Enrollment)	**Percentage (Enrollment)**	**Frequency (Follow up)**	**Percentage (Follow up)**
< 40 %	**18**	**21.2**	**13**	**15.29**
40-49 %	**2**	**2.4**	**3**	**35.29**
More than or equal to 50 %	**65**	**76.4**	**69**	**81.17**
Total	**85**	**100**	**85**	**100**

9) Complications:

It was observed that 7 (8.2%) out of 85 patients in the study group had genitourinary complications

TABLE NO 7: FOLLOW UP ANALYSIS OF METABOLIC AND BIOCHEMICAL PROFILE AT BASELINE AND 6 MONTHS INTERVAL.

Paired Samples Statistics		Mean	Std. Deviation ±	95% Confidence Interval of the Difference		P value
				Lower	Upper	
Weight (kg)	At enrollment	76.45	±6.90	2.22	2.88	<0.001
	At follow up	73.89	±6.77			
BMI	At enrollment	28.76	±3.61	0.84	1.09	<0.001
	At follow up	27.79	±3.48			
SBP	At enrollment	141.60	±9.56	5.10	5.74	<0.001
	At follow up	136.18	±9.68			
DBP	At	81.6	±2.68	4.02	4.24	<0.0

	enrollment	2				01
	At follow up	77.49	±2.71			
FBS	At enrollment	152.87	±9.23	23.35	24.53	<0.001
	At follow up	128.93	±9.76			
PPBS	At enrollment	227.08	±14.49	45.49	46.72	<0.001
	At follow up	180.98	±14.37			
HbA1c	At enrollment	9.26	±1.07	2.14	2.25	<0.001
	At follow up	7.06	±1.04			
LDL	At enrollment	95.27	±14.38	17.65	18.34	<0.001
	At follow up	77.27	±14.09			
TG	At enrollment	183.89	±10.86	32.30	35.12	<0.001
	At follow up	150.19	±12.70			
	At follow up	13.21	±0.88			
Serum Creatinine	At enrollment	1.55	±0.62	0.19	0.20	<0.001
	At follow up	1.35	±0.62			
Creatinine Clearance	At enrollment	74.52	±42.37	-21.66	-11.58	<0.001
	At follow up	91.14	±64.41			
	At follow up	135.74	±6.16			
LVEF	At enrollment	52.9	±13.4	-3.17	-0.93	<0.001
	At follow up	55.0	±10.1			

DISCUSSION

Inhibitors of sodium–glucose cotransporter 2 reduce rates of hyperglycaemia in patients with type 2 diabetes by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion.[13] SGLT2 inhibitors are selective inhibitors of sodium glucose cotransporter 2[14] that have been approved for management of type 2 diabetes.[15] Given as either monotherapy or as an add-on therapy, both the drugs are reported to reduce glycated haemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3a chronic kidney disease.[16-23]SGLT 2 inhibitors are associated with weight loss and reductions in blood pressure without increases in heart rate.[16-24] They also have favourable effects on markers of arterial stiffness and vascular resistance[25], visceral adiposity[26], albuminuria[27] and plasma urate levels[28]. They have been associated with an increase in levels of both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol.[29] SGLT 2 inhibitors by causing glycosuria and natriuresis, reduces hyperglycaemia (antidiabetic effect), body weight, and blood pressure.[29] SGLT 2 inhibitors have shown to reduce hospitalizations for HF in patients with type 2 diabetes mellitus.[30] They have been known to reduce oxidative stress, reduce atrial natriuretic peptide levels and thus delay atherosclerosis. The most common side effects of these drugs are urinary tract infections and genital infections.[31]

Type 2 diabetes is a major risk factor for cardiovascular disease,[32-33] and the presence of both type 2 diabetes and cardiovascular disease increases the risk of death.[31] Evidence that glucose lowering reduces the rates of cardiovascular events and death has not been convincingly shown, although a modest cardiovascular benefit may be observed after a prolonged follow-up period. Furthermore, there is concern that intensive glucose lowering or the use of specific glucose-lowering drugs may be associated with adverse cardiovascular outcomes. Therefore, it is necessary to establish the cardiovascular safety benefits of glucose-lowering agents.[35]

We conducted a prospective observational study at Jaslok Hospital and Research Centre in which 85 patients were enrolled according to inclusion and exclusion criteria. They were started on an SGLT2 inhibitor. Patients were then followed up for six-month interval and various clinical and biochemical parameters were studied at six-month interval in. Results were taken at baseline and at 6 months. The results were recorded and statistically analysed.

Mean HbA1c at baseline was found to be 9.26 ± 1.07%. Mean HbA1c at follow-up was found to be 7.06 ± 1.04 %. Mean reduction in HbA1C with SGLT2i over a period of 6 months was -2.19 ± 0.25. The reduction in HbA1C was found to be statistically significant with a p-value of <0.001 .

In EMPA REG OUTCOME study After 12 weeks, during which glucose-lowering therapy was to remain unchanged, the adjusted mean difference in change in the glycated haemoglobin level between patients receiving empagliflozin and those receiving placebo were −0.54% (95% CI, −0.58 to −0.49). The results were found to be statistically significant[36].

Over the follow-up period it was seen that higher the baseline HbA1c, higher was the mean reduction in HbA1c over the period of 6 months in both the groups. The results were found to be statistically significant with a p-value of <0.05 in all the categories.

CONCLUSION

Maximum number of Diabetic Patients belonged to the age group of 46-55 years in the group, followed by 56-65 years. Mean Age of the study population was found to be 53.27 years. 58.8% i.e., 50 patients were males in the study group and 41.2 % i.e., 35 patients were

females. It was observed that there was a significant reduction in HbA1c with the drug over a period of 6 months. It was also observed that more the initial Hba1c, more is the reduction in Hba1c. The Clinical Prospective Follow-up study conducted at Jaslok Hospital and Research Centre shows that SGLT2 inhibitors, help in improving not only blood sugar control in Diabetics but also have significant positive outcomes in various other Clinical, Biochemical and metabolic parameters.

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