Frontiers in Health Informatics www.healthinformaticsjournal.com
ISSN-Online: 2676-7104
2024; 13: 5 Open Access

Oral GLP-1 RA (Semaglutide) Versus SGLT 2 Inhibitors in Patients with Type 2 Diabetes Mellitus Uncontrolled on Metformin - A Clinical Observational Prospective Study

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Article Info

Article type:
Research

Article History:
Received: 2024-11-19
Accepted: 2024-12-02
Published: 2024-12-21

Keywords:
HbA1c, Oral GLP-1 RA, SGLT 2 Inhibitors, Metformin & Diabetes Mellitus

A B S T R A C T

Study Design & Methods:
Over the study duration of 6 months, 65 patients were enrolled into each group, one on oral Semaglutide(GLP-1RA) and the other on SGLT-2 inhibitors with ongoing background treatments eg; metformin.
The Key end point of the study was to compare the percentage reduction in HbA1c from baseline to month 6 (Primary) and Bodyweight, BMI, BP, Total Cholesterol, LDL ,Serum Creatinine, eGFR (Secondary)

Results:
Fifty Nine (91%) patients on GLP-1RA group And Sixty Three (97%) patients on SGLT-2 Inhibitor group and completed the study.
Mean reduction in HbA1C with Oral Semaglutide over a period of 6 months was 1.9 ± 1.0. ($p<0.001$).
Mean reduction in HbA1C with SGLT-2i group over a period of 6 months was 1.58 ± 0.77 %. ($p <0.001$).
It was found that the mean reduction in HbA1c was more with GLP-1 RA than SGLT2 inhibitor in all the categories of HbA1C.This was statistically significant proving superiority of Oral Semaglutide.

Conclusion:
Oral Semaglutide was superior than SGLT-2 Inhibitors in reducing HbA1c at 6 month in patients with type 2 diabetes uncontrolled on Metformin. Body weight was also significantly reduced in both the groups Mean reduction in BMI with GLP-1 RA was 2.47 ±2.6. ($p <0.001$) and Mean reduction in BMI with SGLT-2i was 1.72 ±1.1 ($p <0.001$).
Mean reduction in SBP and DBP between GLP-1RA and SGLT-2 Inhibitors were 6.4mmHg/6mmHg and 3.6mmHg/4.7mmHg respectively.
Mean reduction in Total cholesterol between both groups was 72.8 mg/dl and 66.1mg/dl respectively.
Oral semaglutide was well tolerated within the established safety profile of GLP-1 receptor agonist.

Study Design: Clinical Prospective Observational Study.

INTRODUCTION

Lifestyle interventions remain a crucial aspect of managing DM; however, most patients do not reach their goal with these interventions alone and require pharmacological therapies. Many classes of medications have been proven safe and effective, most patients do not experience a significant reduction in their blood glucose and require insulin and/or experience microvascular and macrovascular complications [1].

The incretin system has become an important target in the treatment of type 2 diabetes in recent years [2]. Two incretin hormones have been identified: Glucose-dependent insulinotropic polypeptide (GIP) and Glucagon-like peptide 1 (GLP-1) [3].

GLP-1 is a small peptide hormone released from gastrointestinal L cells upon nutrient ingestion. It binds to the GLP-1R (GLP-1 receptor) and exhibits incretin effects that include glucose-dependent insulin secretion from pancreatic β cells, inhibition of glucagon release from pancreatic α cells, and the prolongation of gastric emptying [3]. Together, these actions contribute to a reduction in blood glucose and an improvement in postprandial glucose metabolism. By stimulating GLP-1R–expressing hypothalamic neurons, GLP-1 also induces satiety and leads to weight loss. GLP-1 is generated through the cleavage of pre-proglucagon by convertase PC1/3, re- leasing equipotent peptides GLP-1(7-36 amide) and GLP-1(7-37). However, the half-life of GLP-1 is only a few minutes because of its cleavage by the ubiquitously expressed enzyme DPP4 (dipeptidyl peptidase-4).

In humans, the expression of the GLP-1R has been shown in various tissues, including pancreatic islet, lung, kidney, stomach, brain, endothelial cells, and smooth muscle cells, as well as specific atrial and ventricular cardiomyocytes. It has been shown that secretion of insulin is greater in response to oral glucose ingestion than to an isoglycemic intravenous glucose infusion, a phenomenon referred to as “the incretin effect” [4]. The incretin effect is reduced in people with type 2 diabetes. The most recent understanding of this deficit suggests that it relates to deterioration of the GLP-1 effect, with impaired capacity to secrete insulin, increasing insulin resistance, and hyperglycemia, perhaps leading to a decrease in GLP-1 receptor expression and resulting in GLP-1 resistance [5].

MATERIAL AND METHODS

This is a tertiary care hospital based prospective observational study , determining the impact of introduction of GLP-1RA and SGLT2i with metformin (background treatment) on percentage reduction in HbA1c within 6 months and other aspects of clinical and biochemical profile of diabetic individuals. Comparing the percentage reduction in HbA1c at end of study in both groups would be primary outcome. Both drugs are having evidence to reduce blood sugar and weight and other important parameters which are having significant impact on metabolic profile however their mechanism of action differs. GLP-1RA acting by promoting Incretin effect and SGLT-2i acting by promoting glycosuria. Now I want to compare these drugs in terms of efficacy and all other variables over a defined timeline.

Semaglutide would be given in dosing of 3 mg, 7 mg and final dosage of 14 mg with each dose increased at monthly interval by slowly building tolerability.

Inclusion Criteria:
Patient should be a known diabetic and willing to participate and follow up in the study at Jaslok hospital, including both male and female between age of 30-85 years.

Exclusion Criteria:
- The patient who is terminally ill or having malignancy,Patients not willing to follow-up and patient having Type 1 DM and Gestational DM.
- Diabetes due to secondary causes (e.g., pancreatic cancer, chronic pancreatitis, steroid-induced diabetes mellitus, Cushing's syndrome, or acromegaly)
- The patient with impaired renal function with creatinine clearance of less than 30 ml/min, history of repetitive Genitourinary Infections and Decompensated Liver disease.

RESULT

Table 1: Baseline Characteristics

Age Groups	GLP-1 RA	SGLT-2 Inhibitor
Patients, n	59	63
Age(years), mean (SD)	62.1 (10.3)	62.3 (10.1)
Duration of diabetes(years), mean(SD)	23 (35.4)	25 (38.5)
Female, n (%)	21(32.3)	20 (30.8)
BMI (kg/m2) mean (SD)	29.5 (4.2)	29.45 (4.46)
HbA1c%, mean (SD)	8.9 (1.25)	8.85 (1.31)
eGFR(ml/min/1.73 m2), mean (SD)	80.70 (27.77)	78.48(22.94)

Patients-
A total of 122 patients were screened, with 59 patients receiving oral GLP-1RA (semaglutide) and 63 patients receiving SGLT-2 Inhibitors. 91%patients on GLP-1RA group And 97% patients on SGLT-2 Inhibitor group and completed the study.
Baseline characteristics were balanced between treatment groups.
Patients had a mean age group of 62.28 years and had a baseline HbA1c of 8.87% and average duration of diabetes 24 years and mean BMI of 29.48 kg/m^2.
Metformin was the most common additional anti diabetic medication used.

Table 2: Prevalence of Various Comorbidities in Patients

Comorbidity	SGLT-2 Inhibitor	GLP-1 RA
TB	2 (3%)	2 (3.1%)
Asthma	2 (3%)	1 (1.5%)
HTN	52 (80%)	52 (80%)
IHD	34 (52.3%)	35 (53.8%)
CVA	6 (9.2%)	6 (9.2%)
PVD	2 (3%)	6 (9.2%)
Dyslipidemia	29 (44.6%)	29 (44.6%)

Glycemic Control:
Oral Semaglutide provided a superior reduction in HbA1c compared to SGLT2 inhibitors. Reduction in HbA1C was significantly greater with Oral Semaglutide at 6 months (1.9 ± 1.0. ($p<0.001$) vs 1.58 ± 0.77 %. ($p <0.001$) with the SGLT2 inhibitors group. More patients achieved the predefined HbA1c targets with oral Semaglutide than with SGLT2 inhibitors.

Body Weight:
Superiority of body weight reduction at month 6 with oral semaglutide over SGLT-2 Inhibitors was significant, with BMI changes of 2.47 ±2.6. ($p <0.001$) and 1.72 ±1.1 ($p <0.001$) respectively.

Other Outcomes:
Most patients achieved primary outcome of HbA1c reduction without severe and symptomatic hypoglycaemia.Gastrointestinal symptoms like nausea, fullness of abdomen were greater in semaglutide group whereas Urinary tract infections were reported in few patients receiving SGLT-2 inhibitors.

Blood Pressure-
Mean reduction in SBP and DBP between GLP-1RA and SGLT-2 Inhibitors were 6.4mmHg/6mmHg and 3.6mmHg/4.7mmHg respectively. The difference in SBP between both groups at follow up was statistically insignificant with p value of 0.7 whereas the difference in DBP was statistically significant with p value of <0.001

Lipid Profile-
Mean reduction in Total cholesterol between both groups was 72.8 mg/dl and 66.1mg/dl respectively.In GLP-1 RA group, mean LDL at baseline was 150.53 mg/dl ±29.78 mg/dl and mean LDL at follow up was 126.15 mg/dl ±.29.36 mg/dl. There was a statistically significant reduction in LDL values with GLP-1 RA over a period of 6 months with a p value < 0.001. In

SGLT2 inhibitor group, mean LDL at baseline was 154.51 mg/dl ±30.90 mg/dl and mean LDL at follow up was 134.26 mg/dl ±27.96 mg/dl. There was a statistically significant reduction in LDL levels with SGLT2 inhibitor at follow up with a p value of < 0.001. It was found that the mean reduction in LDL levels was more with GLP-1 RA than SGLT2 inhibitor but difference was statistically insignificant with a p value of 0.01.

Renal Profile-
In GLP-1 RA group, mean Serum creatinine at the time of enrolment was 1.13 mg/dl ±0.37 and at 6 months was 0.86 ± 0.23. This reduction was statistically significant with a p value of <0.001. In SGLT2 inhibitor group, mean Serum creatinine at the time of enrolment was 1.12 mg/dl ± 0.25 and at 6 months was 0.90 ± 0.36. This reduction was statistically significant with a p value of <0.001.

Mean reduction in Serum creatinine was more with GLP-1 RA compared to SGLT2 inhibitor at 6 months interval, however the difference was not statistically significant. (p=0.07)
Thus, SGLT2 inhibitor and GLP-1 RA, both improve renal outcomes in patients with Diabetes mellitus.

Mean eGFR change in semaglutide group was significant with change from 80.70 ± 27.77 to 99.84 ±32.08 ml/min/1.73m^2 at 6 month with p value of <0.001.

Mean eGFR change in SGLT-2 inhibitor group was significant with change from 78.46 ± 22.94 to 95.35 ±33.65 ml/min/1.73m^2 at 6 month with p value of <0.001.

Mean improvement in eGFR was more with GLP-1 RA compared to SGLT2 inhibitor at 6 months interval, however the difference was not statistically significant. (p=0.04)

Cardiovascular Parameters-
It was observed that there was statistically significant increase in LVEF with both the drugs at 6 months follow up.

In GLP-1 RA group, mean initial LVEF was 43.22% $\pm$ 15.85 % and mean LVEF at 6 months was 50.89% $\pm$8.20. The improvement in LVEF with GLP-1 RA was statistically significant with a p value of < 0.001.

In SGLT2 inhibitor group mean initial LVEF was 44.55% $\pm$ 14.08 % and mean LVEF at 6 months was 52.14 % $\pm$ 5.70 %.The improvement in LVEF with SGLT2 inhibitor was statistically significant with a p value of < 0.001.

However, when the mean increase in LVEF with GLP-1 RA and SGLT2 inhibitor was compared this difference was not statistically significant. This could be due to the smaller sample size of our study and small duration of follow up.

Table No 3: Follow Up Analysis of Metabolic and Biochemical Profile at 6 Months Interval with Glp-1 Ra

Groups		Parameters	Mean	Std. Deviation	Paired Differences		95% Confidence Interval of the Difference		P value
					Mean	Std. Deviation	Lower	Upper	
GLP-1 RA	BMI	Baseline	29.5	4.2	2.47	±2.6	1.8	3.15	<0.001
		Follow up	27.07	3.4					
	SBP	Baseline	128.83	11.45	6.4	±0.8	4.7	8.1	<0.001
		Follow up	122.44	7.92					
	DBP	Baseline	77.32	9.00	3.6	±0.5	2.2	4.0	<0.001
		Follow up	74.22	7.89					
	TOTAL CHOLESTROL	Baseline	234.34	57.93	72.81	±4.8	63.2	82.4	<0.001
		Follow up	161.53	40.49					
	S. CREATININE	Baseline	1.13	0.37	0.3	±0.0	0.2	0.4	<0.001
		Follow up	0.86	0.23					
	CREATINE CLEARANCE	Baseline	80.70	27.77	25.6	±3.3	-25.8	-12.5	<0.001
		Followup	99.84	32.08					
	HbA1c	Baseline	8.90	1.25	1.9	±1.0	1.7	2.2	<0.001
		Follow up	6.98	0.76					

Table No 4: Follow Up Analysis Of Metabolic And Biochemical Profile At Baseline And 6 Months Interval With Sglt-2 Inhibitor

Groups		Parameters	Mean	Std. Deviation	Paired Differences		95% Confidence Interval of the Difference		P value
					Mean	Std. Deviation	Lower	Upper	
SGLT-2 Inhibitor	BMI	Baseline	29.45	4.46	1.7	±1.1	1.4	1.01	<0.001
		Followup	27.74	3.4					
	SBP	Baseline	136.19	13.00	6.0	±8.3	3.9	8.1	<0.001
		Followup	130.24	9.34					
	DBP	Baseline	87.78	10.28	4.7	±4.4	3.6	5.9	<0.001
		Followup	83.03	8.50					
	TOTAL CHOLESTROL	Baseline	243.97	30.41	66.1	±29.6	58.5	73.8	<0.001
		Followup	177.85	27.11					
	S CREATININE	Baseline	1.12	0.25	0.2	±0.4	0.1	0.3	<0.001
		Followup	0.90	0.36					
	CREAT CLEARANCE	Baseline	78.46	22.94	16.9	±32.8	-25.1	-8.6	<0.001
		Followup	95.35	33.65					
	HbA1c	Baseline	8.85	1.31	1.58	±0.77	1.4	1.8	<0.001
		Followup	7.27	0.77					

DISCUSSION

We conducted a prospective observational study at Jaslok Hospital and Research Centre in which 130 patients were enrolled over the duration of study according to inclusion and exclusion criteria. Each patient was followed up for a period of 6 months. Over the course of my study, patients were enrolled in two groups. 65 patients were started on SGLT-2 Inhibitor and 65 patients were started on GLP-1RA. Metabolic and biochemical parameters were collected for each individual at baseline and when the individual completed 6 months. Results were taken at baseline and at 6 months in all patients of both the groups. The results were recorded and statistically analysed.

63 (97%) patients on SGLT-2 Inhibitior group and 59(91%) patients on GLP-1RA group completed the trial. My patients were between the age of 35 years to 85 years with a mean age of 62.28 years and median Age of 62 years. In our Study, Patients were stratified into 5 categories based on age, 35-45 years; 46-55 years; 56-65 years; 66-75 years and above 75 years in each group. Maximum number of patients were found to be in the Age Group of 56-65 years i.e., 23 patients (35.4%) in SGLT-2 Inhibitor group. Maximum number of patients in the GLP-1 RA group were found to be in the Age Group of 56-65 years i.e., 25 patients (38.5%).

Number of males in the SGLT-2 Inhibitor group were 45 patients (69.2 %) and in the GLP- 1 RA group were 44 patients (67.7 %). Number of females in SGLT-2 Inhibitor group were 20 patients (30.8 %) and in GLP-1 RA group were 21 patients (32.3%).

In Pioneer 2 trial a total of 1,122 patients were screened, with 822 randomized to oral semaglutide 14 mg once daily (n= 412) or empagliflozin 25 mg once daily (n= 410). Four hundred (97.1%) patients in the oral semaglutide group and 387 (94.4%) in the empagliflozin group completed the trial. Baseline characteristics were well balanced between treatment groups. Patients, of whom half (49.5%) were female [6].

In the GLP-1 RA group, maximum number of patients were found to have Diabetes for a duration of 5-10 years with 22 patients (33.8%) and a duration of 5-10 years with 24 patients (36.9%) in the SGLT-2 Inhibitor group as well.
In Pioneer 2 average duration of diabetes was 7.4 years [6]
Hypertension was reported as the most common co-morbidity in both the groups i.e.,GLP-1 RA and SGLT-2 inhibitor, with 52 patients (80 %) in both groups suffering from hypertension. 58 patient s had dyslipidemia and were on lipid lowering therapy. 69 patient had past history of IHD with ongoing anti platelets. Patients continued on the existing medications as prior to the study.
It was observed that in the study population, 105 patients (80.2%) were on Metformin either as a monotherapy or in combination therapy. Patients receiving Sulfonylureas, Pioglitazone, DPP4 inhibitors, alpha glucosidase inhibitors and Insulin were 57 patients (43.5%); 5 patients (3.8 %); 81 patients (61.8 %); 20 patients (15.3%) and 13 patients (9.9%) respectively. DPP4 inhibitors were withheld in patients whom GLP-1RA was started reason being similar mechanism of

action. Over the course of the study duration, previous medications of the patients were continued and adjusted.

Mean HbA1c at baseline was found to be 8.9 ±1.25% in GLP-1 RA group. Mean HbA1c at follow-up was found to be 6.98 ± 0.76 %. Mean reduction in HbA1C with GLP-1 RA inhibitor over a period of 6 months was 1.9 ± 1.0. The reduction in HbA1C was found to be statistically significant with a p-value of <0.001.

Mean HbA1c at baseline was found to be 8.85 ± 1.31 % in SGLT-2i group. Mean HbA1c at follow-up was found to be 7.27 ± 0.77%. Mean reduction in HbA1C with SGLT-2i over a period of 6 months was 1.58 ± 0.77 %. The reduction in HbA1C was found to be statistically significant with a p value of <0.001.

It was found that the mean reduction in HbA1c was more with GLP-1 RA than SGLT2 inhibitor in all the categories of HbA1C.This was statistically significant. IN SUSTAIN-6 The mean glycated hemoglobin level in the semaglutide group, as compared with the placebo group, was 0.7 percentage points lower in the group receiving 0.5 mg and 1.0 percentage point lower in the group receiving 1.0 mg (estimated treatment difference) (P<0.001 for both comparisons) [7].
The difference in SBP between both groups at follow up was statistically insignificant with p value of 0.7 whereas the difference in DBP was statistically significant with p value of <0.001
STEP-1 TRIAL [8] Showed significant difference in both SBP and DBP in 68 week follow up. Semaglutide group showing -6.16% and placebo -1.06% with difference of -5.10(-6.34 to -3.87 CI), p value<0.001.

It was found that mean reduction in Total Cholesterol and LDL was more with GLP-1 RA when compared with SGLT2 inhibitor. This difference was statistically significant with a p value of <0.001.
In the SUSTAIN 1 trial [9], drug-naive patients with type 2 diabetes were randomly assigned to once-weekly semaglutide (0·5 mg or 1·0 mg) or placebo for 30 weeks.
Significant decreases in total cholesterol, LDL cholesterol, and free fatty acids were only seen in the 1·0 mg semaglutide group compared with placebo.

Mean eGFR change in semaglutide group was significant with change from 80.70 ± 27.77 to 99.84 ±32.08 ml/min/1.73m^2 at 6 month with p value of <0.001 and change of 78.46 ± 22.94 to 95.35 ±33.65 ml/min/1.73m^2 at 6 month with p value of <0.001 in SGLT-2 Inhibitor group.
LEADER, REWIND And SUSTAIN-6 TRIALS [10] favoured use of GLP-1RA for prevention of eGFR decline and reducing albuminuria. According to EMPAREG OUTCOME trial [11] the composite outcome of incident or worsening nephropathy or cardiovascular death was significantly lower in the empagliflozin group than in the placebo group.

It was observed that there was statistically significant increase in LVEF with both the drugs at 6 months follow up, However when the mean increase in LVEF with GLP-1 RA and SGLT2 inhibitor was compared this difference was not statistically significant. This could be due to the smaller sample size of our study and small duration of follow up.

In STEP-HFpEF DM Trial [12] Among patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, semaglutide led to larger reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo at 1 year.

CONCLUSION

Patients from both the groups were serially followed up for 6-month interval after being initiated on GLP-1 RA and SGLT2 inhibitors. It was observed that there was a significant reduction in HbA1c with both the drugs over a period of 6 months. However, it was found that GLP-1 RA was more efficacious than SGLT2 inhibitor in HbA1c reduction and weight reduction over a period of 6 months. It was also observed that more the initial HbA1c, more is the reduction in HbA1c.Our Study in continuation with previous research done shows that SGLT2 inhibitor and GLP-1 RA help in improving the clinical profile of a diabetic individuals. We hence, supporting the latest guidelines in diabetic control, recommend that GLP-1 RA and SGLT2 inhibitors should be a part of Diabetic regimen of patients unless contraindicated and according to latest ADA guidelines 2024 [13]

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