RESEARCH ARTICLE - OPEN ACCESS

Journal Of Pharmacy And Experimental Medicine

Contents lists available at bostonsciencepublishing.us

Journal Of Pharmacy And Experimental Medicine

Efficacy of Empagliflozin in Reducing Cardiovascular Risk and Glycemic Control in Long Standing Diabetic Patients: An Observational Study

S Divya*, Devarakonda Sivakumar[1], D. Likhitha[1], K. Sravani[1], S. Priya[1]

*Department of Pharmacy Practice, Ratnam Institute of Pharmacy, Nellore, Andhra Pradesh
[1]Pharm D, Ratnam Institute of Pharmacy, Nellore, Andhra Pradesh

ARTICLE INFO

Article history:
Received 20 Febraury 2021
Accepted 03 March 2021
Revised 09 March 2021
Available online 15 March 2021

Keywords:
Diabetes mellitus
SGLT2 inhibitors
Empagliflozin
Glycemic control
Cardiovascular risk

ABSTRACT

Diabetes mellitus is a heterogeneous complex metabolic disorder characterized by elevated blood glucose concentrations. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs. This is a leading health disorder with rising prevalence day by day with irrespective of age and gender. The diabetes patients are prone to have cardiovascular risk such as dyslipidemia, hypertension, coronary artery disease, obesity. The management of diabetes mellitus includes insulin and oral anti-diabetic agents. Among them Sodium glucose co-transporter 2 inhibitors are effective in achieving glycemic control in long-standing diabetic patients as single or add-on therapy. A large number of studies had proven that empagliflozin which belongs to the class SGLT2 inhibitors had shown potent glycemic control and reduces the cardiovascular risk in long-standing diabetic patients.

1. Introduction

Diabetes mellitus (DM) refers to a group of common and chronic metabolic disorder that shares the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of a genetics and environmental factors. Coming to the history of type-2 diabetes, it is described as a metabolic syndrome firstly in 1988 [1]. Usually type 2 diabetes arises due to interaction between different factors such as environmental, social habits and genetic factors [2,3]. The metabolic dys-regulation associated with DM causes secondary pathophysiology changes in multiple organ system that imposed a tremendous burden on the individuals with diabetes and on the health care system. According to 2011 census, due to the cause of diabetes 4.6 million deaths were noted [4].

2. Classification

Diabetes is a heterogeneous, complex metabolic disorder characterized by elevated blood glucose concentrations secondary to either resistance to the action of insulin, insufficient insulin secretion or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. A wide spread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries and peripheral vascular insufficiency. According to American Diabetes Association (ADA) 1997, the Diabetes classification includes: 1. Type 1 diabetes mellitus, 2. Type 2 diabetes mellitus, 3. Gestational diabetes and still it is most widely accepted classification [5].

3. Study Design and Methodology

3.1. Aim of the study

To conduct an observational study on efficacy of Empagliflozin [SGLT2 inhibitor] in reducing cardiovascular risk and achieving glycaemic control in long standing diabetes patients who are on more than two Anti-diabetic therapy.

3.2 Type of study

Observational study

3.4 Place of Study

ACSR Government General Hospital Nellore

3.5 Period of the study

6 months [July 2019 to November 2019]

3.6 Study Population

40 Patients

* Corresponding author.
S Divya, Department of Pharmacy Practice, Ratnam Institute of Pharmacy, Nellore, Andhra Pradesh, India.
E-mail address: hari1509@gmail.com

3.7. Patient Enrolment

Patients enrolled in the study based on the inclusion and exclusion criteria.

3.7.1 Inclusion criteria

- Patient's with age between 35-85 years.
- Patient having history of T2DM
- Patient having co-morbidities of hypertension and other cardiovascular related ones.
- Patient's who were willing to take the drug.
- Patient having stable background anti-hyperglycemic therapy.
- Patient's who were on dual or triple therapy. (Metformin, sulfonylureas and gliptins)

3.7.2 Exclusion criteria

- Patient's who are not willing to take the drug.
- Patient using SGLT2: GLP-IRA/ saxagliptin.
- Patient having GFR <60 ml/min/1.73 m2
- Patient having LVEF<30%.
- Patient's with NYHA class 4 or recent HHF.
- Pregnancy and lactation mothers were excluded.

4. Clinical Manifestations

The person with diabetes mellitus mainly present frequent urination, Dry mouth, repeated infections, blurred vision, fatigue, susceptibility to certain infections, slow wound healing, numbness in soles and palms, tingling, acanthosis nigricans (rarely), weight loss [6].

5. Pharmacological Treatment

a) Insulin therapy

Insulin therapy is a critical part of treatment for people with type 1 diabetes and also for many with type 2 diabetes. The goal of therapy is to keep blood sugar levels within the target range. It is administered by subcutaneous route, it been always a drawback for insulin to inject into the body. Oral hypoglycemic agents are also used in lowering the blood glucose level. Insulin should be initiated when A1c is greater than 7% after 2-3 months of dual oral therapy [7].

b) Oral anti diabetic drugs

- Sulphonylureas
- Biguanide
- Thiazolidinediones
- Dipeptidyl peptides-4 Inhibitors
- Meglitinide Sodium glucose cotransporter-2(SGLT-2) inhibitor
- Dopamine D2 agonist

5.1 Sodium-Glucose Cotransporter Inhibitors (SGLT Inhibitors)

Sodium-dependent glucose co-transporters/sodium glucose linked transporter are family of glucose transporters, SGLT localization is different according to their types and listed in Table 1. These are the latest class of diabetic drugs received FDA approval [8].

Table 1: SGLT family, substrates and their distribution in tissues

SGLT Family	Substrates	Distribution in tissues
SGLT1	Glucose, galactose	Intestine, trachea, kidney, heart, brain, testis, prostate.
SGLT2	glucose	Kidney, brain, liver, thyroid, muscle, heart.
SGLT3	glucose	Intestine, testis, uterus, lung, thyroid, brain.
SGLT4	Glucose, mannose	Intestine, kidney, liver, brain, lungs, trachea, pancreas, uterus.
SGLT5	Glucose, galactose	Kidney.

5.2 Clinical Physiology in glucose control

Sodium-glucose cotransporter-2 (SGLT2) is selectively expressed in the human kidney, where it executes re-absorption of filtered glucose with a high capacitance; it may be over active in patients with diabetes especially in the hyper filtering stage of the disease. As a therapeutic target, SGLT2 has been successfully engaged by orally active selective agents and described the use in glucose control in Figure 1. In a meta-analysis published in 2014, 24 week reduction of HbA1C with SGLT2 inhibitors in trials enrolled patients with higher baseline BMI, HbA1C, and fasting glucose results better outcome [9].

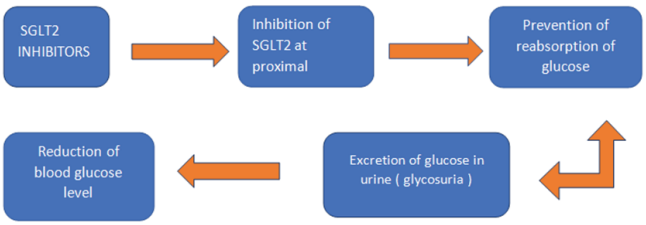


Figure 1: SGLT 2 Inhibitors role in glucose control

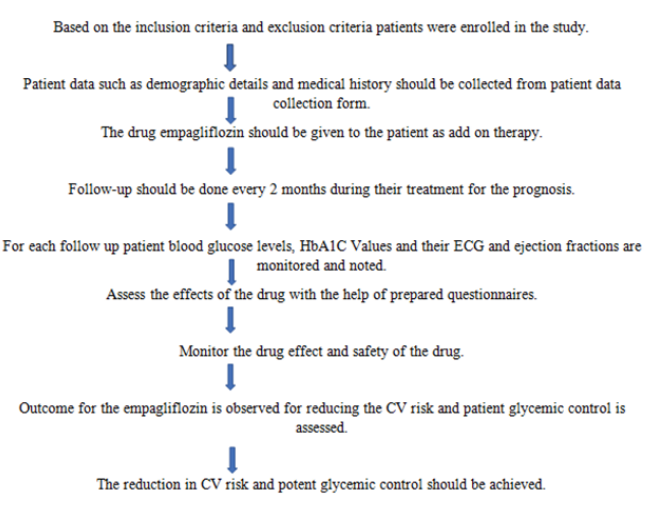
5.3 SGLT2 Inhibitors – Cardiovascular Protection

Sodium-glucose cotransporter 2 (SGLT2) Inhibitors have demonstrated precedent cardiovascular benefits in large scale clinical trials of people who have type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. In the empagliflozin cardiovascular outcome event trail in type 2 diabetes mellitus patients – remove excess glucose (EMPA-REG Outcome) study [10], 7020 individuals with type 2 diabetes who had coronary, peripheral cardiovascular disease or cerebrovascular disease were randomized to receive the SGLT2 inhibitor empagliflozin or placebo, while the primary three-point major adverse cardiac events outcome (cardiovascular death, nonfatal myocardial infarction and non-fatal stroke) was significantly attenuated by empagliflozin, which was particularly noteworthy and the early effects of empagliflozin on cardiovascular death and hospitalization for heart failure, which were reduced by 38% and 35% respectively and in addition all -cause mortality was reduced by 32%. Mechanisms underlying in this function as follows:

- Improvement in cardiac metabolism and bioenergetics.
- Myocardial Na+/H+ exchange inhibition.
- Reduction in necrosis and cardiac fibrosis.
- Alteration in adipokines, cytokine protein production and epicardial adipose tissue mass.

6. Plan of Study

Our plan study was depicted in flow chart. It gives an idea about how we worked on our project.



Flow chart: Plan of study

7. Results and Discussion

7.1 Categorized based on age

Out of 40 patients 7 belong to 35-45 years; 17 belong to 46-55 years; 5 belong to 56-65 years; 4 belong to 66-75 years; 7 belong to 76-85 years.

7.2 Categorized based on gender

Among 70 patients 24 were males and 16 were females.

7.3 Categorized based on co-morbidities

Distribution based on co-morbidities, out of 40 members the patients with co-morbidities were 16 and the patients without co-morbidities were 24.

7.4 Categorized based on duration of type 2 DM

Among 40 patients 16 patients has 6-10 years of duration of type 2 diabetes mellitus; 18 patients has 11-15 years of duration of type 2 diabetes mellitus; 5 patients has 16-20 years of duration of type 2 diabetes mellitus; and 1 patient has >20 years of duration of type 2 diabetes mellitus.

7.5 Categorized based on Social habits

Among total subjects 10 were alcoholics; and 2 were smokers.

7.6 Patient's data during Observational study

Patient's data was tabulated in Table 2 with respective to their visits and glucose levels in order to support the glycemic control of Empagliflozin. Patient's data was tabulated in Table 3 with respective to their ejection factor in order to support the cardiovascular protection of Empagliflozin.

Table 2: Patient's data of glucose levels according to their visits

S.No	values	Visit-1	Visit-2	Visit-3	Visit-4
1.	FBS	210	189	149	183
	PPBS	301	262	179	120
	HbA1c	10.6	9.3	6.8	4.2
2.	FBS	239	152	128	103
	PPBS	343	241	172	142
	HbA1c	12.1	8.1	6.2	5.10
3.	FBS	186	154	102	94
	PPBS	296	190	172	136
	HbA1c	10	7.1	5.75	4.7
4.	FBS	204	170	110	74
	PPBS	326	190	170	142
	HbA1c	11.4	7.5	5.8	4.5
5.	FBS	265	182	172	158
	PPBS	342	280	194	172
	HbA1c	12.6	9.6	7.6	6.8
6.	FBS	178	149	119	76
	PPBS	281	222	183	130
	HbA1c	9.5	7.7	6.2	4.2
7.	FBS	200	169	145	120
	PPBS	259	224	201	170
	HbA1c	9.3	8.1	7.2	6.0
8.	FBS	180	152	120	85
	PPBS	240	210	162	138
	HbA1c	8.7	7.5	5.8	4.4
9.	FBS	195	160	127	100
	PPBS	250	210	180	140
	HbA1c	9.2	7.70	6.3	5
10.	FBS	220	180	135	114
	PPBS	296	240	176	150
	HbA1c	10.7	8.7	6.4	5.5
11.	FBS	212	184	130	90
	PPBS	224	210	162	138
	HbA1c	9.0	8.2	6.0	4.7
12.	FBS	230	158	110	96
	PPBS	331	227	157	118
	HbA1c	11.6	8.0	5.5	4.4
13.	FBS	246	172	146	106
	PPBS	358	256	209	155
	HbA1c	12.5	8.8	7.3	5.4
14.	FBS	260	179	162	108
	PPBS	320	280	176	148
	HbA1c	12.5	9.5	7.1	5.3

15.	FBS	212	200	164	114
	PPBS	354	236	186	140
	HbA1c	11.7	9.0	7.2	5.2
16.	FBS	289	182	139	108
	PPBS	384	280	200	144
	HbA1c	14.0	9.6	8.5	5.2
17.	FBS	232	168	129	105
	PPBS	406	289	236	140
	HbA1c	13.2	9.5	7.6	5.1
18.	FBS	286	244	168	116
	PPBS	353	324	284	162
	HbA1c	13.3	11.8	9.4	5.7
19.	FBS	226	164	114	104
	PPBS	354	250	164	148
	HbA1c	12.0	8.6	6.7	5.2
20.	FBS	230	175	140	128
	PPBS	440	340	280	220
	HbA1c	13.9	10.7	8.7	7.2
21.	FBS	260	192	171	132
	PPBS	354	236	200	156
	HbA1c	12.7	8.9	7.7	6.0
22.	FBS	241	192	186	140
	PPBS	379	236	220	162
	HbA1c	12.7	10.6	8.4	6.2
23.	FBS	220	196	177	122
	PPBS	291	250	200	170
	HbA1c	10.6	9.2	7.8	6.0
24.	FBS	256	216	183	145
	PPBS	320	296	237	190
	HbA1c	12.0	10.6	8.7	7.0
25.	FBS	196	172	141	123
	PPBS	259	220	186	152
	HbA1c	9.4	8.2	6.8	5.7
26.	FBS	276	206	187	130
	PPBS	312	262	201	178
	HbA1c	12.2	9.7	8.0	6.4
27.	FBS	251	215	197	156
	PPBS	296	246	211	170
	HbA1c	11.3	9.6	8.5	6.7
28.	FBS	306	237	176	154
	PPBS	416	302	257	190
	HbA1c	13.9	11.2	8.5	7.1
29.	FBS	269	229	190	140
	PPBS	300	290	230	186
	HbA1c	11.8	10.8	8.7	6.7
30.	FBS	287	229	187	146
	PPBS	340	290	229	170
	HbA1c	13.0	10.1	8.6	6.5
31.	FBS	198	162	157	116
	PPBS	276	230	196	154
	HbA1c	9.8	8.2	7.3	5.6
32.	FBS	230	196	170	130
	PPBS	310	254	197	168
	HbA1c	11.2	9.3	7.6	6.2
33.	FBS	210	177	156	125
	PPBS	296	239	187	159
	HbA1c	10.5	9.3	7.1	5.9
34.	FBS	281	239	181	141
	PPBS	354	276	200	172
	HbA1c	13.2	10.2	7.9	6.5

35.	FBS	222	194	177	136
	PPBS	299	239	201	180
	HbA1c	10.8	9.0	7.8	6.5
36.	FBS	180	169	132	97
	PPBS	240	210	176	136
	HbA1c	8.7	7.8	6.4	4.8
37.	FBS	200	176	152	114
	PPBS	259	210	185	142
	HbA1c	9.5	8.0	7.0	5.3
38.	FBS	162	137	110	87
	PPBS	201	187	154	120
	HbA1c	7.5	6.7	5.5	4.3
39.	FBS	239	196	149	110
	PPBS	284	245	186	137
	HbA1c	10.8	9.1	6.9	5.1
40.	FBS	178	146	120	76
	PPBS	275	201	176	130
	HbA1c	9.3	7.2	6.1	4.2

Using SPSS statistical Software (SPSS 2.O) the probability Value is calculated as:

FBS: p value is <0.00001 and the result is significant at $p<0.05$

PPBS: p value is <0.00001 and the result is significant at $p<0.05$

HbA1c: p value is <0.00001 and the result is significant at $p<0.05$

Table 3: Patient's data of ejection factor before and after initiation of empagliflozin therapy

S.No	ECG		EJECTION FRACTION	
	before	After	before	After
1.	Abnormal	Better	54	62
2.	Abnormal	Better	45	69
3.	Abnormal	Better	45	71
4.	Abnormal	Better	39	51
5.	Abnormal	Better	45	63
6.	Abnormal	Better	45	59
7.	Abnormal	Better	39	50
8.	Abnormal	Better	42	67
9.	Abnormal	Better	48	72
10.	Abnormal	Better	62	70
11.	Abnormal	Better	52	68
12.	Normal	Normal	70	70
13.	Normal	Normal	64	67
14.	Normal	Normal	57	59
15.	Normal	Normal	68	70
16.	Normal	Normal	61	61
17.	Normal	Normal	55	58
18.	Normal	Normal	57	62
19.	Normal	Normal	65	65
20.	Normal	Normal	58	60
21.	Abnormal	Better	49	52
22.	Normal	Normal	56	57
23.	Normal	Normal	65	65
24.	Normal	Normal	64	68
25.	Normal	Normal	70	70
26.	Normal	Normal	55	58
27.	Normal	Normal	57	60
28.	Normal	Normal	70	71
29.	Abnormal	Better	48	55
30.	Normal	Normal	69	70
31.	Normal	Normal	57	60
32.	Normal	Normal	60	60
33.	Normal	Normal	63	65

34.	Normal	Normal	59	63
35.	Normal	Normal	70	70
36.	Normal	Normal	65	65
37.	Normal	Normal	64	67
38.	Abnormal	Better	52	68
39.	Abnormal	Better	46	57
40.	Abnormal	Better	45	54

From the above data, among 40 subjects; 16 patients had the abnormal ECG and abnormal ejection fraction before initiation of therapy i.e. 16 subjects are having the cardiovascular risk before initiation of Empagliflozin therapy.

8. Conclusion

Empagliflozin has a consistent cardio protective effect in patients with T2DM and CVD, regardless of the number of CV risk factors that are controlled. Empagliflozin can be taken along with the other oral anti-diabetes medications such as metformin, sulfonylureas, mono or poly therapy but strict monitoring, awareness regarding dietary modifications are needed during the continuous period of treatment along with the betterment of CV symptoms, empagliflozin was achieved the better glycemic control especially in patients with cardiovascular disease. It is a good alternative to the uncontrolled hyperglycemic patients who are already using triple therapy at maximum dose and not willing to take insulin despite of having minimal adverse effects, it is having very good proven cardiac safety, which makes diabetic management more potent.

Conflict of Interest

None

Ethical Concern

We have obtained informed concern from every patient participated in the study.

Source of Funding

None

Acknowledgements

None

References

1. Patlak M. New weapons to combat an ancient disease: treating diabetes. FASEB J 2002. Dec;16(4):1853 Doi: 10.1096/fj.02-0974bkt [Pubmed]
2. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. Nature reviews endocrinology. Available at: www.nature.com/uidfinder (Accessed 12 December 2020) [PubMed]
3. Genetic basis of type 1 and type 2 diabetes, obesity, and their complications. Advances and emerging opportunities in diabetes research: a strategic planning report of the DMICC. (Accessed 12 December 2020) [PubMed]
4. Global burden of diabetes. International Diabetes federation. Diabetic atlas fifth edition 2011, Brussels. Available at http://www.idf.org/diabetesatlas (Accessed 14th December 2020)
5. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81-90. [PubMed]
6. Alberti KGMM, Zimmet P, Shaw J. International Diabetes Federation: a consensus on type 2 diabetes prevention. Diabet Med. 2007;24:451-63. [PubMed]
7. Geyelin HR, Harrop G, Murray MF, Corwin E. The use of insulin in Juvenile diabetes. J Metabolic Res. 1922;2:767-792. [Google Scholar]
8. D S Hsia, Owen G, W T Cefalu. An Update on SGLT2 Inhibitors for the Treatment of Diabetes Mellitus. Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):73-79. doi: 10.1097/MED.0000000000000311. [PubMed]
9. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2014 May;16(5):457-66. [PubMed]
10. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine. 2015 Nov 26;373(22):2117-28. [PubMed]