ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

A comparative study on the effect of sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors as an add on therapy in patients with type 2 DM

Vishnupriya S[1], Andhuvan G[1], Saravanan T[2], Velammal P[*2]

[1]Department of Pharmacy Practice, PSG College of Pharmacy, Peelamedu, Coimbatore, Tamil Nadu, India
[2]Department of General Medicine, PSG IMSR, PSG Hospitals, Coimbatore, Tamil Nadu, India

Article History:

Received on: 13.07.2019
Revised on: 19.10.2019
Accepted on: 24.10.2019

Keywords:

Type II DM,
SGLT-2 Inhibitors,
DPP-4 Inhibitors

ABSTRACT

There were about 65 million diabetic population in 2016 in India. There were studies which concluded that the Dipeptidyl Peptidase-4 Inhibitors and Sodium Glucose Co-Transportor 2 Inhibitor were providing non-glycaemic control and cardiovascular benefits. Hence, it is important to find out the effect of those drugs on various parameters among the Indian Type 2 Diabetes Mellitus population. The aim is to evaluate and compare the effects of SGLT-2 inhibitors and DPP-4 inhibitors in Type 2 DM patients. The objective is to find out &compare the effects of both class of drugs on the physical profile [Body Weight (BW), Body Mass Index (BMI), Hip-Waist ratio), Diabetic Profile [Fasting Blood Sugar] (FBS), Glycated Haemoglobin (HbA1C)] & Side Effect Profile. The patients were categorized into two Group 1 & 2. Both groups were containing 50 patients, each based on the inclusion &exclusion criteria. The collection of demographics and history were done. Group 1 patients were initiated with DPP-4 Inhibitor, Group 2 patients with SGLT-2 Inhibitors, respectively. At baseline and during follow-up, the parameters like the physical profile, Diabetic Profile were noted. In Body Weight, the mean difference between the groups was found to be 2.9 $\pm$0.79 ($p<0.05$). Similarly, for BMI, it was 2.9$\pm$1.36 ($p<0.04$). For the Hip-Waist ratio, it was 0.07 ($p<0.05$). For FBS, it was 22.08 mg/dl (0.0001), for HbA1c it was 1.09 ($p<0.0043$). On the Side effect profile, SGLT-2 Inhibitors were showing higher incidence for the occurrence of Urinary Tract Infection (UTI) while comparing with DPP-4 Inhibitors. This can be overcome by proper patient counseling. This study concluded that SGLT-2 inhibitors may serves as the best medication choice for add on therapy in Type 2 DM patients.

[*]Corresponding Author

Name: Velammal P
Phone: 9486807712
Email: revathyvelammal@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i1.1867

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases which is present in almost all nations. It is the most common non-communicable disease (Shaw *et al.*, 2010). About 65 million diabetic population in 2016 in India, whereas it was 26 million in 1990. In India, the prevalence of Diabetes Mellitus among adults aged 20 years or older was increased from 5.5% to 7.7% between the years of 1990 to 2016, respectively. In 2016, the highest prevalence is seen in the states of Tamil Nadu

& Kerala, which were stated as High Epidemiological Transition Level (High ETL) & Delhi as Higher-Middle ETL, which is followed by Goa, Punjab & Karnataka (Tandon *et al.*, 2018). The micro and macro vascular complications will be reduced by obtaining fair glycaemia control (Mary *et al.*, 2018). Early initiation of pharmacologic therapy is associated with improved glycaemic control and reduced long-term complications in type 2 DM. In the case of uncontrolled type 2 DM, the drug classes like SGLT-2 inhibitors and DPP-4 inhibitors are used as add on therapy, sometimes as monotherapy also.

DPP-4 inhibitors (Sitagliptin, Teneligliptin, Evo gliptin) produce its effect by activating incretin, which is released by the intestinal cells after food intake. It is usually given as a once-daily dose. DPP-4 is an enzyme that degrades various biologically active peptides, including the GLP-1 and GIP. GLP-1 is playing a major part in releasing insulin (Aschner *et al.*, 2010). Along with glucose control, these drugs were found to have cardiovascular benefits due to its pharmacological augmentation of GLP-1R (Dicker, 2011).

SGLT-2 inhibitors (Dapagliflozin, Canagliflozin, Empagliflozin, Remogliflozin, Ertugliflozin) are a newer class of OHAs (Oral Hypoglycaemic Agents) which are approved to be used as monotherapy or in combination with metformin, sulfonylurea, or insulin. Work by preventing the reabsorption of glucose in PCT and by facilitating its excretion in urine. Hence, the glycaemic control is achieved along with the glucose excretion. The mechanism of action of these drugs is dependent on blood glucose levels and independent of the actions of insulin. So, there are minimum incidences for the occurrence of hypoglycaemia, and there is no risk of overstimulation or fatigue of the beta cells (Mary *et al.*, 2018).

Since both classes of drugs are being used either as monotherapy or as part of dual and triple therapy in type 2 diabetes patients, it is important to compare the effects of those drugs in the Indian type 2 diabetes population. This study involves the comparison of Physical (weight, BMI, Hip-waist ratio), Diabetic (FBS, HbA1C) & Side effect profiles of both classes of drugs.

MATERIALS AND METHODS

The study was conducted in the Department of General Medicine in PSG Hospital, Coimbatore. It was approved by the Institutional Human Ethics Committee, PSG Institute of Medical Sciences and Research (Proposal no: 19/072). It is an observational study which included a total of 100 subjects who were divided into two treatment groups. Both groups contain 50 patients each. Group 1 (G1) contains 28 Males & 22 Females whereas Group 2 (G2) contains 30 Males & 20 Females.

The inclusion criteria include Type 2 DM patient of age above 18 years with poor diabetic control and on regular follow up, Patients who are going to be initiated respectively with SGLT 2 Inhibitors & DPP-4 inhibitors as add on therapy for controlling DM and the patients with normal liver function, renal function. Exclusion criteria include patients with Type 1 DM, renal failure, psychiatric, paediatric, gestational diabetes mellitus, history of diabetic ketoacidosis & primary renal glucosuria, and patients who are unwilling to participate.

Group 1 patients were initiated with DPP-4 Inhibitor, Group 2 patients with SGLT-2 Inhibitors, respectively. At baseline and during follow-up after 3 months of drug initiation, the parameters like the physical profile, Diabetic Profile, and side effects were noted and statistically compared. The effect of drugs within a group was compared by using Paired *t*-Test and between groups were by using Independent *t*-Test.

RESULTS AND DISCUSSION

Effects of DPP-4 Inhibitors

The total of 50 G1 patients who were initiated with DPP-4 inhibitors, drugs given were Teneligliptin 20mg (14 patients), Evo gliptin 5mg (07 patients), DPP-4 Inhibitor +Metformin 500mg (16 patients), DPP-4 Inhibitor +Repaglinide 0.5 mg (06 patients), DPP-4 Inhibitor +Glimepiride 1mg (07 patients).

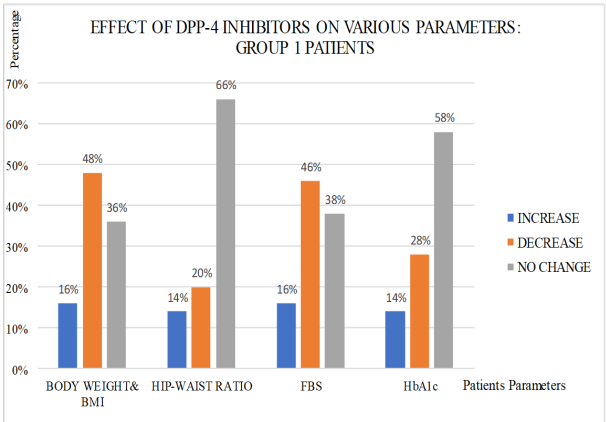

Figure 1: Cluster chart showing the effect of DPP-4 inhibitors on various parameters among Group 1 patients [BMI-Body Mass Index FBS-Fasting Blood Sugar HbA1c-Glycated Haemoglobin]

Once after the drug initiation, the patients were

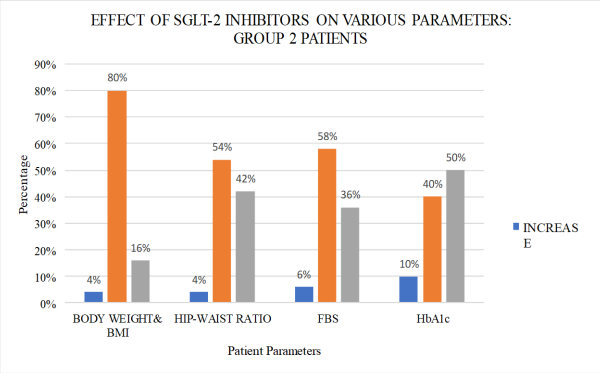

Figure 2: Cluster chart showing the effect of SGLT-2 inhibitors on various parameters among Group2 patients [BMI-Body Mass Index FBS-Fasting Blood Sugar HbA1c-Glycated Haemoglobin]

followed up for three months, and their physical and diabetic profile are monitored, and the changes were noted. According to the effect of drugs on individuals, their parameters get varied. They were depicted in Figure 1.

Figure 1 showing the effect of DPP-4 Inhibitors on various parameters among G1 patients. The mean baseline weight (68.44±3.81) was reduced to 64.45±1.71) (p=0.04), the mean baseline BMI (26.73±1.31) was reduced to (25±1.38) (p=0.05), the mean difference between Hip-Waist ratio was 0.13 (p=0.05), the mean difference between FBS was 59.87 mg/dl (p=0.03), the mean difference between HbA1c was 1.2% (p=0.04).

A retrospective sub-analyzed study of sitagliptin effect on glucose and lipid metabolism, blood pressure, body weight and renal function in type 2 DM patients for a period of 6 months by dividing 173 patients of Type 2 DM into obese group (BMI $\geq$ 25) and non-obese group (BMI < 25), concluded that the body weight was significantly reduced in obese patients from the baseline values despite the ages and HbA1c also decreased in both the groups significantly (Katsuyama *et al.*, 2014).

A review of sitagliptin brought a conclusion that on the addition of sitagliptin (100mg/d) to already existing oral antidiabetic treatment produce a significant reduction of HbA1c. After 24 weeks of the addition of sitagliptin (100mg/d) to metformin produced a significant reduction of HbA1c (0.65%), FBS (25.4 mg/dl), Post Prandial Glucose (2h) (50.6 mg/dl) (Gallwitz, 2007).

GLP-1 also found have cardioprotective action in experimental models of heart failure and myocardial infarction. DPP-4 inhibitors may have cardiovascular effects either by depending or independent of GLP-1 (Jose and Inzucchi, 2012).

An Indian study reported the results of a 16-week, multicentric, double-blind, placebo-controlled, Phase 3 studies of teneligliptin 20 mg daily in drug-naive T2DM patients. This study (N = 237) reported a significant −0.55% glycated hemoglobin (HbA1c) reduction (placebo-subtracted) in teneligliptin arm (P = 0.0043) compared to control. While a significant reduction in 2 hours postprandial glucose (PPG) (−25.8 mg/dl, P = 0.0070) versus placebo was observed, an insignificant reduction in fasting plasma glucose (FPG) was seen (−8.8 mg/dl, P = 0.18) in teneligliptin 20 mg arm. Similarly, a higher percentage of patient achieved the target HbA1c of <7% in teneligliptin arm (43.4% vs. 27.3%, P = 0.026) compared to the control and "overall" the drug was well tolerated (Suryawanshi *et al.*, 2016).

Effects of SGLT-2 Inhibitors

The effects of SGLT-2 Inhibitors among various parameter of G2 patients were depicted in Figure 2.

Figure 2 showing the effect of SGLT-2 Inhibitors on various parameters among G2 patients. The mean baseline weight (71.34±3.28) was reduced to 64.45±1.97) (p=0.02), the mean baseline BMI (29.93±4.32) was reduced to (27.03±2.96) (p=0.04), the mean difference between Hip-Waist ratio was 0.27 (p=0.04), the mean difference between FBS was 81.95 mg/dl (p=0.01), the mean difference between HbA1c was 2.29% (p=0.02)

A retrospective study which involves 61 patients who received 12 months of dapagliflozin concluded that After the 12 months intake of drug the body weight was -3.4±2.6 kg reduced significantly from the baseline value, the drug reduces the hyperglycemia and body weight by inhibiting the renal glucose reabsorption in a safe manner in Type 2 DM patients. (Cho *et al.*, 2017).

The study of "Efficacy and Safety of SGLT-2 Inhibitors" in Emirati patients which included 307 patients concluded that at 6 months of drug administration the baseline HbA1c was decreased from the baseline value, from 8.9±1.7% to 8±1.5% & at 1 year the mean HbA1c was 8±1.4% (p=0.0001). Likely, the bodyweight also reduced from the baseline at the sixth month, from 85.7±17.8 kg to 84±12.2 kg (p=0.0001) (Bashier *et al.*, 2017).

Comparision between the effects of DPP-4 inhibitors & SGLT-2 inhibitors

Since both categories of the drugs is used as add on therapy in the treatment of Type 2 DM, it's important to find out the effect of those drugs on various parameters among the Indian Type 2 DM population. This result may help to wisely choose the add

on therapy drugs for the treatment of Type 2 DM.

Effects of drugs on

Body weight and BMI

Table 1: DPP-4 Inhibitors Vs SGLT-2 Inhibitors on Body Weight and BMI

Body Weight& BMI	DPP-4 Inhibitors	SGLT-2 Inhibitors
Increase (%)	16	4
Decrease (%)	48	80
No Change (%)	36	16

BMI-Body Mass Index

Hip-waist ratio

Table 2: DPP-4 Inhibitors Vs SGLT-2 Inhibitors on Hip-Waist Ratio

Hip-waist ratio	DPP-4 inhibitors	SGLT-2 Inhibitors
Increase (%)	14	4
Decrease (%)	20	54
No change (%)	66	42

The comparison of the effect of both the drugs over the patient's body weight and Hip-Waist Ratio were depicted in Table 1 &Table 2 respectively. In Body Weight, the mean difference between the groups was found to be 2.9 ±0.79 ($p<0.05$). Similarly, for BMI, it was 2.9±1.36 ($p<0.04$). For the Hip-Waist ratio, it was 0.07 ($p<0.05$). SGLT-2 Inhibitors were showing significant reduction while comparing with DPP-4 Inhibitors.

In 2017, Min SH et al. conducted a meta-analysis study titled "Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: a systematic review with indirect comparison meta-analysis". Covariate-adjusted indirect comparison using meta-regression analyses revealed that SGLT2i/INS achieved greater reduction in HbA1c [weighted mean difference (WMD) -0.24%, 95% confidence interval (CI) -0.43 to -0.05%], fasting plasma glucose (WMD -18.0 mg/dL, 95% CI -28.5 to -7.6 mg/dL) and body weight (WMD -2.38 kg, 95% CI -3.18 to -1.58 kg) from baseline than DPP4i/INS without increasing the risk of hypoglycemia (Min *et al.*, 2017).

FBS

HbA1c

The comparison of the effect of both the drugs over the patient's FBS & HbA1c were depicted in Table 3 &Table 4 respectively. The mean difference between the groups over FBS was 22.08 mg/dl (0.0001), for HbA1c it was 1.09 ($p<0.0043$). SGLT-2 Inhibitors were showing significant reduction while comparing with DPP-4 Inhibitors.

Table 3: DPP-4 Inhibitors Vs SGLT-2 Inhibitors on FBS

FBS	DPP-4 Inhibitors	SGLT-2 Inhibitors
Increase(%)	16	6
Decrease (%)	46	58
No Change (%)	38	36

FBS- Fasting Blood Sugar

Table 4: DPP-4 Inhibitors Vs SGLT-2 Inhibitors on HbA1c

HbA1c	DPP-4 Inhibitors	SGLT-2 Inhibitors
Increase (%)	14	10
Decrease (%)	28	40
No Change (%)	58	50

HbA1c-Glycated Haemoglobin

Table 5: Side Effect Frequency of the Drugs

Drugs Category	Side Effects (%)
DPP-4 Inhibitors	10
SGLT-2 Inhibitors	14

An observational study on "Safety and Efficacy of Sodium-glucose Cotransporter-2 Inhibitors as Adjuvant to Insulin Add-on Therapy in Uncontrolled Type 2 Diabetic Patients" concluded that the SGLT-2 Inhibitors were more effective in both glycemic control (FBS, HbA1c) and non-glycemic control (Body Weight, BMI, Blood Pressure) and acts as a well-tolerated therapy in patients. This put forth the overall reduction in cardiovascular risks (Mary *et al.*, 2018).

Side effect profile of the drugs

Since 50 patients were enrolled in each group like DPP-4 Inhibitors and SGLT-2 Inhibitors, respectively, along with the effects of two categories of drugs on various patient's parameters, their Side effects are also monitored during the follow-up period of 3 months. It was given in Table 5.

Side effects of DPP-4 Inhibitors: Nausea, Diarrhoea, Stomach pain, Flu-like symptoms, Nasopharyngitis and HSR (Amori *et al.*, 2007)

Side effects of SGLT-2 Inhibitors: UTI, Hyperkalaemia, Hypotension, Hypoglycaemia and Dia-

betic Ketoacidosis (Hsia *et al.*, 2017).

On Side effect profile, SGLT-2 Inhibitors were showing higher incidence for the occurrence of UTI while comparing with DPP-4 Inhibitors

CONCLUSIONS

Both DPP-4 Inhibitors and SGLT-2 Inhibitors were producing significant impact over the Physical and Diabetic profile of Type 2 DM patients. Though while comparing with DPP-4 Inhibitors, SGLT-2 Inhibitors were producing a more prominent effect over patient's parameters, and apart from producing a significant effect on the Physical and Diabetic profile, SGLT-2 inhibitors were also found to have cardiovascular benefits. Side effects like UTI can be overcome by proper patient counseling. On an overall consideration of the effects produced by both the class of drugs, this study concluded that SGLT-2 inhibitors may serves as the best medication choice for add on therapy in Type 2 DM patients.

Acknowledgement

We would like to extend our thanks to PSG Hospital, Coimbatore-04, Tamil Nadu, India, for providing facilities.

REFERENCES

Amori, R. E., Lau, J., Pittas, A. G. 2007. Efficacy and Safety of Incretin Therapy in Type 2 Diabetes. *JAMA*, 298(2):194–194.

Aschner, P., Katzeff, H. L., Guo, H., Sunga, S., Williams-Herman, D., Kaufman, K. D., Goldstein, B. J. 2010. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes, Obesity, and Metabolism*, 12(3):252–261.

Bashier, A., Khalifa, A. A., Rashid, F., Abdelgadir, E. I., Qaysi, A. A., Ali, R., Alawadi, F. 2017. Efficacy and Safety of SGLT2 Inhibitors in Reducing Glycated Hemoglobin and Weight in Emirati Patients With Type 2 Diabetes. *Journal of Clinical Medicine Research*, 9(6):499–507.

Cho, H. A., Jung, Y. L., Lee, Y. H., Lee, Y. C., Lee, J. E., Lee, S. J., Kim, C. H. 2017. Efficacy of Body Weight Reduction on the SGLT2 Inhibitor in People with Type 2 Diabetes Mellitus. *Journal of Obesity & Metabolic Syndrome*, 26(2):107–113.

Dicker, D. 2011. DPP-4 Inhibitors: Impact on glycemic control and cardiovascular risk factors. *Diabetes Care*, 34(Supplement_2):276–278.

Gallwitz, B. 2007. Review of sitagliptin phosphate: a novel treatment for type 2 diabetes. *Vascular Health and Risk Management*, 3(2):203–210.

Hsia, D. S., Grove, O., Cefalu, W. T. 2017. An Update on SGLT2 Inhibitors for the Treatment of Diabetes Mellitus. *Curr Opin Endocrinol Diabetes Obes*, 24(1):73–79.

Jose, T., Inzucchi, S. E. 2012. Cardiovascular effects of the DPP-4 inhibitors. *Diabetes and Vascular Disease Research*, 9(2):109–116.

Katsuyama, H., Adachi, H., Hamasaki, H., Moriyama, S., Sako, A., Yanai, H. 2014. Significant Differences in Effects of Sitagliptin Treatment on Body Weight and Lipid Metabolism Between Obese and Non-Obese Patients With Type 2 Diabetes. *Journal of Endocrinology and Metabolism*, 4(5-6):136–142.

Mary, P. S. A., Varghese, G. S., Sunny, G. K., Prabakar, J. H., Andhuvan, G., *et al.* 2018. A study on safety and efficacy of sodium-glucose cotransporter-2 inhibitors as adjuvant to insulin add-on therapy in uncontrolled type 2 diabetic patients. *Asian Journal of Pharmaceutics*, 12(3):896–900. Suppl.

Min, S. H., Yoon, J. H., Hahn, S., Cho, Y. M. 2017. Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: a systematic review with indirect comparison meta-analysis. *Diabetes/Metabolism Research and Reviews*, 33(1).

Shaw, J. E., Sicree, R. A., Zimmet, P. Z. 2010. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, 87(1):4–14.

Suryawanshi, S. Y., Bhargava, A., Agarwal, P., Chamle, V. 2016. Evaluation of safety and efficacy of teneligliptin in newly diagnosed Indian type 2 diabetes patients. *Springer*, 59:358–358.

Tandon, N., Anjana, R. M., Mohan, V., Kaur, T., Afshin, A., Ong, K., Dandona, L. 2018. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. *The Lancet Global Health*, 6:30387–30392.

