doi.org/10.36721/PJPS.2022.35.6.SP.1733-1738.1

Assessment of empagliflozin add-on therapy to metformin and glimepiride in patients with inadequately controlled type-2 diabetes mellitus

Bilal Jawed[1,2], Shadab Ahmed[1*], Syed Qamar Abbas[1], Zeeshan Ahmed[3], Shomaiza Andleeb[3], Salman Ashfaq Ahmad[3], Muhammad Asif[4], Erum Akhter[2], Salman Ahmed[5], Muhammad Waleed Hussain[6], Adnan Iqbal[1] and Azfar Athar Ishaqui[3]

[1]Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan
[2]Department of Pharmacy, Chiniot General Hospital, Karachi, Pakistan
[3]Department of Pharmacy, Iqra University, Karachi, Pakistan
[4]Iqra University Nursing College, Iqra University, Karachi, Pakistan
[5]Department of Pharmaceutics, Faculty of Pharmacy, University of Sindh, Jamshoro, Pakistan
[6]Department of Pharmacology, Shaheed Benazir Bhutto Dewan University, Karachi, Pakistan

Abstract: Diabetes mellitus is a multifaceted metabolic disorder, which often required frequent blood glucose monitoring, poly-pharmacy and timely adjustments for its management. The present study focuses to check the effectiveness of empagliflozin add-on therapy in diabetic patients already taking metformin and glimepiride. This was observational, comparative and follow-up cohort study, conducted in a tertiary care hospital of Pakistan. Ninety subjects were enrolled and evenly distributed in Group A (patients on oral therapy of Metformin & Glimepiride) and Group B (patients on oral therapy of metformin, glimepiride and empagliflozin) randomly. The results showed that the addition of empagliflozin to metformin and glimepiride standard therapy provided better control over blood sugar with a significant decrease in HbA1c (16.1% decrease in HbA1c for Group B patients against 8.2% in Group A patients), FBS (23.8% decrease as compared to 14.6% decrease) and BMI (1.5% decrease in Group B patients against 0.06% increase in Group A). The addition of empagliflozin did not exacerbate the toxicity of the existing regimen and is safe to be included in multiple drug regimens. Empagliflozin addition to standard antidiabetic therapy might possess beneficial impacts in managing poorly controlled Type-2 Diabetes Mellitus in the Pakistani population.

Keywords: Empagliflozin, metformin, glimepiride, diabetes mellitus, HbA1c.

INTRODUCTION

The American Diabetic Association defines diabetes mellitus as the cluster of metabolic disturbances manifested by increased glucose in the blood due to problems in either release of insulin or resistance to insulin (Mellitus 2006) (Bamashmoos and Ganem 2013). In Pakistan, it is revealed that the prevalence of prediabetes was 11% and the population with a confirmed diagnosis of Type-2 diabetes mellitus was 17%. The prevalence was found to be maximum in 51-60 years (26%), illiterate (18%), obese (35%), familial (31%) and female gender (18%) (Aamir *et al*. 2019).

The main objective for controlling siabetes mellitus is to reduce the symptoms and increase the quality of life (Donald *et al*. 2013). However, it is difficult to achieve these goals with Type-1 Diabetes Mellitus because of its total dependency on insulin. Whereas, the symptoms of Type-2 diabetes mellitus can easily be prevented and controlled by both pharmacological and non-pharmacological intervention. The management generally begins with modulating diet and weight. These changes in daily routine may sometimes is ineffective and stresses the need to take medicines to decrease the plasma glucose concentration (Daubenmier *et al*. 2012).

Many natural and synthetic oral antidiabetic agents control the blood sugar level through different mechanisms. The different oral antidiabetics are classified into the following categories (a) secretagogues; sulfonylureas and non-sulfonylureas (e.g. glipizide, glyburide, glimepiride and gliclazide) (b) sensitizers; biguanides (e.g. metformin) and thiazolidinediones (e.g. rosiglitazone) (c) alpha-glycosidase inhibitors (e.g. acarbose and miglitol) (d) incretin mimetics; glucagon-like peptide (GLP) analogues (e.g. exenatide), dipeptidyl peptidase-4 inhibitor (e.g. sitagliptin) (e) glucosurics; gliflozins (e.g. empagliflozin) (Chu *et al*. 2019).

Empagliflozin belongs to the newer class of antidiabetic drugs known as glucosurics. The mode of action involves blocking the major transporter, i.e., Sodium-glucose co-transporter 2 in the proximal kidney tubules causing re-absorption of glucose (Dziadkowiec *et al*. 2021). The daily dose recommendation is 10mg, which may be increased up to 25mg. The American Diabetic Association recommends empagliflozin as a second-line option, against Type-2 diabetes mellitus, after metformin in subjects with cardiac failure and chronic renal disease (Davies *et al*. 2018). It is considered as a second agent in cases where metformin use alone failed to maintain optimal glucose levels (Garber *et al*., 2019). Another study revealed that the addition of empagliflozin to

*Corresponding author: e-mail: a_shadab@uok.edu.pk

existing therapy involving metformin and sulfonylurea resulted in a better clinical outcome than increasing the dose of original medicines (Shin *et al*., 2020).

The objective of the study was to assess the effectiveness and safety of empagliflozin as add-on therapy in Type-2 diabetes mellitus patients with inadequate blood glucose control against standard therapy. According to our research & knowledge, this is the first study on diabetes treatment focusing on empagliflozin add-on therapy in the Pakistani population.

MATERIALS AND METHODS

Study design
The current study was an observational, comparative and follow-up cohort study.

Study settings
The study was conducted in tertiary care, a private sector non-teaching hospital based in Karachi, Pakistan. The hospital is located in the North district of Karachi with ISO 2010 standard certification.

Study duration
The study was carried out over six months i.e., from January 2020 until June 2020.

Inclusion criteria
Subjects (both genders with informed signed consent) with uncontrolled Type-2 diabetes mellitus having HBA1c>7% already on stable doses of metformin (1500mg/day) and glimepiride (3mg/day) along with a control diet and exercise for≥12 weeks were eligible in this study. Patients with BMI>20kg/m² were eligible.

Exclusion criteria
Exclusion criteria include patients with uncontrolled diabetes, Type-1 diabetes, on insulin therapy, acute coronary syndrome (ACS), stroke, or heart attack within 12 weeks of consent or any type of cancer. Patients on any proven renal (estimated eGFR>30ml/min/1.73) or hepatic disease, including Hepatitis or chronic kidney disease, history of any surgery or plan within six months. Alcoholic, pregnant, or lactating females, women with pregnancy planning within the study period and history of weight loss medicines usage within three months of consent.

Method
The sample size was calculated using an online calculator (Raosoft 2021). The sample size required to identify a statistically significant result with a confidence level of 95% and a narrow margin of error of 0.05, should be 45 patients per group. No medical or surgical intervention was done in this study. The medicinal agents used in the study were already well-known in the market and are commonly prescribed for the treatment of Type-2 diabetes mellitus patients.

A total of 90 patients were selected for the 16 weeks study fulfilling the above defined inclusion criteria. Patients were randomly assigned into two Groups, A and B, with 45 patients each. Group A patients continuously received Metformin (1500mg/day) and Glimepiride (3mg/day) in specified doses; however, Group B patients had received Empagliflozin 10mg/day additionally along with Metformin (1500mg/day) and Glimepiride (3mg/day). Before the commencement of the study, all required baseline demographic parameters were established through physical and biochemical tests. All other medicine doses for co-morbidities in patients will remain the same.

Study outcomes
The outcomes measured among both study groups were a comparison of baseline changes in HbA1c level, baseline changes in body mass index (BMI), baseline changes in waist circumference (WC) and baseline changes in fasting blood sugar levels (FBS).

Ethical approval
The study was approved by the ethical review committee of the hospital (Ethical Approval # ZM/CG-IRNo.07-20). The study was conducted according to the International Conference on Harmonization Harmonized Tripartite Guideline for good clinical practice and the Helsinki declaration (Dixon 1999).

STATISTICAL ANALYSIS

The data is presented as Mean ± Standard deviation (SD) of n=45/group. Nominal quantitative variables were analyzed by using the Fisher-exact test. Continuous variables were analyzed using a two-tailed unpaired t-test for parametric variables. A p-value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS version 20 software.

RESULTS

As per the study protocol, the Group A patients (n=45) were initiated on Metformin and Glimepiride combination therapy while Group B patients (n=45) were initiated on combination therapy of empagliflozin, metformin and glimepiride. No significant statistical difference was observed for the demographic characteristics; age (50.8 years vs. 50.6 years; P<0.05), gender (female patients; 49% vs 56%; P<0.05) and weight (78.8 kg vs. 80.1 kg; P<0.05) of patients among both study groups. The comparison of different demographic characteristics is summarized in table1.

The Mean±SD values of different parameters of both treatment groups are summarized in table 2. For the HbA1c outcome parameter, a 16.1% decrease with a mean difference of -1.4 % was observed for Group B patients compared to an 8.2% decrease with a mean difference of 0.7% for Group A patients. On comparing

both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (7.9±0.14 vs 7.3±0.18; P-value= <0.05) at 16 weeks intervals as presented in fig. 1 (Graph-A).

For the FBS outcome parameter, a 23.8% decrease with a mean difference of -50.3mg/dl was observed for Group B patients compared to 14.6% decrease with mean difference -30.7mg/dl for Group A patients. On comparing both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (179.6±6.48 vs 161.5±6.13; P-value=<0.05) at 16 weeks intervals as presented in fig. 1 (Graph-B).

For the BMI index outcome parameter, a 1.5% decrease with a mean difference of -0.470kg/m^2 was observed for Group B patients compared to a 0.06% increase with a mean difference +0.020kg/m^2 for Group A patients. On comparing both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (31.58±0.64 vs 30.98±0.34; P-value=<0.05) at 16 weeks intervals as presented in fig. 1 (Graph-C).

For the waist circumference parameter, a 1.6% decrease with a mean difference of -1.40cm was observed for Group B patients compared to a 0.2% increase with a mean difference of +0.220cm for Group A patients. On comparing both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (92.46±1.04 vs 90.56±1.36; P-value=<0.05) at 16 weeks intervals as presented in fig. 1 (Graph-D).

DISCUSSION

Diabetes Mellitus is a composite metabolic ailment, which often requires poly-pharmacy and timely decisions for its management. Type-2 diabetes mellitus patients often require a second additional antidiabetic drug when unable to achieve sufficient glycemic levels with standard therapies like metformin with or without sulphonyl urea (Association 2019). The present study was intended to see the effectiveness of empagliflozin as an add-on medicine in Pakistani patients. The current study showed that the addition of empagliflozin to standard combination therapy, including metformin along with sulphonylurea (glimepiride), provided a significant decrease in HbA1c, FBS, BMI & WC, which was superior to findings in the treatment group A (patients initiated on dual therapy of metformin & glimepiride). In the current study, the demographic and baseline attributes of the subjects in both groups resemble each other (table 1). Therefore, the possibility of start point variations is ruled out as a contributing factor in defining the study outcomes.

Adequate glycemic control is mandatory in managing diabetic complications. The HbA1c concentration indicates a measure of glycemic control in Type-2 Diabetes Mellitus patients for the past two to three months. Other than the average HbA1c level, changes in its levels and HbA1c at different disease stages can give valuable information to the physician during investigations of diabetic complications and its relation with raised HBA1c levels (Lind *et al*. 2009). The current study's data observed that the addition of empagliflozin to standard combination therapy of metformin and glimepiride effectively decreased HbA1c levels from baseline, i.e., a 16.1% decrease with a mean difference of -1.4 % was observed for Group B patients compared to an 8.2% decrease with a mean difference of 0.7% for Group A patients.

Although the best measure for evaluation of glycemic control in normal circumstances is still HbA1c. However, with limited resources, especially in poor, remote areas and in conditions where constraints apply for its use, FBS and RBS are alternative measures generally used to screen and monitor efficient glycemic control in diabetic patients (Swetha 2014). The findings of the current study revealed that empagliflozin addition significantly decreased FBS in Group B compared to Group A. The analysis of initial and final readings of treatment groups indicated the supremacy of treatment Group-B patients as there is a 23.8% decrease with a mean difference of -50.3mg/dl was observed for Group B patients compared to 14.6% decrease with mean difference -30.7mg/dl for Group A patients.

In agreement with previous studies, it was found that empagliflozin addition to pioglitazone with or without metformin (Kovacs *et al*., 2015), linagliptin (Søfteland *et al*., 2017), biguanides, thiazolidinedione, alpha-glucosidase, DPP-4 inhibitors (Subrahmanyan *et al*. 2021) and GLP analogues (Terauchi *et al*. 2019) led to better control of glycosylated haemoglobin. Furthermore, our data also aligned with the current recommendation for incorporating empagliflozin as add-on therapy, i.e., "In case of metformin failure as a single agent or with insulin causing hypoglycemia" (Fitchett *et al.*. 2019; Home 2019; Schwaiger *et al.*. 2019).

In this study, comparisons of bodily indicators suggest a statistically significant reduction in average waist measurement and average BMI in treatment Group B patients as compared to Group A patients. The analysis of initial and final findings of treatment groups indicate the advantage of therapy in Group B patients as there is a 1.6% and 1.5% overall decrease in waist circumference and BMI against 0.2% and 0.06% increase in group A patients, respectively. Overweight, diabetic patients have an increased risk of cardiovascular events due to raised insulin resistance; therefore, management is complicated. Hence, achieving optimum control of body weight and insulin resistance is more challenging for patients maintained on antidiabetic medicines causing significant weight gain (Manrique-Acevedo *et al*., 2020).

Drug safety, along with efficacy, is one of the critical factors modulating the prescriber's decision. Hence,

Table 1: Demographic characteristics of enrolled patients

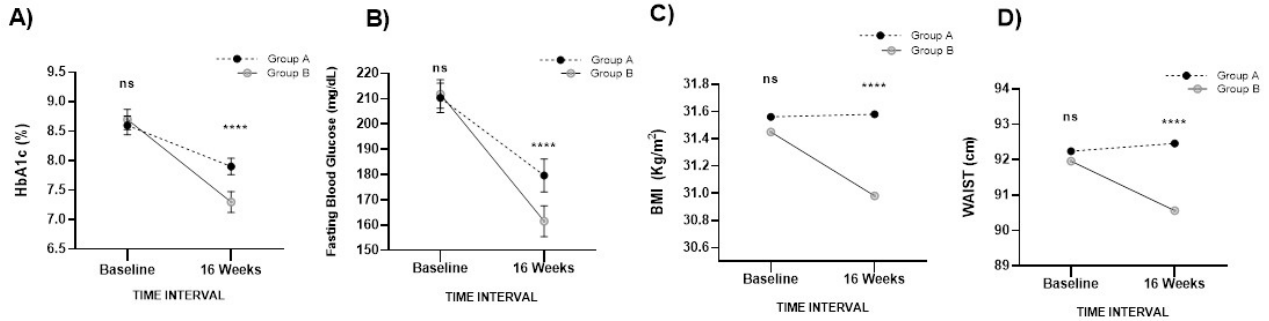
Characteristics	Group A (n=45) (Metformin + Glimepiride)	Group B (n=45) (Empagliflozin + Metformin + Glimepiride)	P-value
Age (years)	50.8 ± 8.4	50.6 ± 9.4	0.92
Male patients	23 (51.1%)	20 (44.4%)	0.67
Female patients	22 (48.9%)	25 (55.6%)	
Smokers (yes)	6 (13.3%)	7 (15.6%)	0.98
Creatinine (mg/dl)	0.88 ± 0.11	0.9 ± 0.14	0.45
Creatinine clearance (ml/min)	98.93 ± 13.8	99.76 ± 15.9	0.79
Family history of T2DM	26 (57.8%)	24 (53.2%)	0.83
Hypertension	25 (55.6%)	28 (62.2%	0.67
Dyslipidemia	29 (64.4%)	25 (55.7%)	0.52
Time of diagnoses of T2DM			
Less Than 1 year	1 (2.2%)	2 (4.4%)	
2- 5 years	8 (17.8%)	7 (15.6%)	
5-10 years	23 (51.1%)	20 (4.4%)	
>10 years	13 (28.9%)	16 (35.6%)	

Where; continuous variables are expressed as Mean ± Standard Deviation, T2DM= Type 2 Diabetes Mellitus.

Table 2: Estimation of different outcome parameters at different time intervals

Parameter	Treatment Group A				Treatment Group B			
	Baseline (Mean±SD)	After 16 weeks (Mean±SD)	% Outcome	*Mean Difference*	Baseline (Mean±SD)	After 16 weeks (Mean±SD)	% Outcome	*Mean Difference*
HbA1c (%)	8.6±0.16	7.9±0.14	8.2%↓	-0.7±0.032	8.7±0.17	7.3±0.18	16.1%↓	-1.4±0.037
FBS (mg/dl)	210.30±5.85	179.60±6.48	14.6%↓	-30.7±1.301	211.8±5.67	161.5±6.13	23.8%↓	-50.3±1.245
BMI (Kg/m^2)	31.56±0.71	31.58 ± 0.64	0.06%↑	+0.020±0.142	31.45±0.50	30.98±0.34	1.5%↓	-0.470±0.090
Waist (cm)	92.24±1.04	92.46 ± 1.04	0.2%↑	+0.220±0.219	91.96±1.21	90.56±1.36	1.6%↓	-1.40±0.271

Whereas; ↓= decrease, ↑=increase, SD= Standard Deviation



Where; (A) represents comparison of mean HbA1c levels among both treatment groups at baseline and 16 weeks interval (B) represents comparison of Mean FBS levels among both treatment groups at baseline and 16 weeks interval (C) represents comparison of Mean BMI values among both treatment groups at baseline and 16 weeks interval (D) represents comparison of Mean Body Waist values among both treatment groups at baseline and 16 weeks interval; ns=P-value>0.05, ****=P-value≤0.05.

Fig. 1: Comparison of different outcome parameters among both treatment Groups at Baseline and 16 weeks interval.

several indicators of toxicities were also observed in the present study. It was observed that both groups were comparable to each other in terms of observed adverse drug reactions like hypoglycemia, urinary tract infection, genital infection, nausea and vomiting.

Enhanced genital infections were also reported to be frequently associated with the use of empagliflozin (Kim *et al*. 2014). On the contrary, our data didn't indicate any such outcome in the treatment group. The hygienic practices in this world can also be attributed to this outcome. However, it requires further investigation for clarification.

The antidiabetic drug that causes hypoglycemia shows a safety risk factor in patients of Type-2 Diabetes Mellitus and may cause problems in treatment adherence and patient compliance (Barnett *et al*. 2010). The findings of the current study indicated no remarkable incidence of severe hypoglycemia in both treatment groups.

The current study is relatively small in duration with limited parameters and a number of patients; therefore, few limitations were observed. The effects and outcomes of empagliflozin for the long-term management of Type-2 diabetes mellitus patients with cardiovascular and renal insufficiency were not analyzed. A double-blind, placebo-

controlled, multi-center study with an increased number of patients can better explain the benefits and disadvantages of this add-on therapy.

CONCLUSION

In conclusion, the present study supports empagliflozin use as add-on therapy in Type-2 diabetes mellitus patients, causing significant improvement in HbA1c and blood glucose levels along with positive impacts on BMI and body waist. Moreover, its addition to the existing regimen did not cause an increase in adverse effects. Therefore, it is concluded that empagliflozin, in addition to standard antidiabetes therapy, might have beneficial impacts in managing Type-2 Diabetes Mellitus in the Pakistani population.

REFERENCES

Aamir AH, Ul-Haq Z, Mahar SA Qureshi FM, Ahmad I, Jawa A, Sheikh A, Raza A, Fazid S, Jadoon Z and Ishtiaq O (2019). Diabetes Prevalence Survey of Pakistan (DPS-PAK): Prevalence of type 2 diabetes mellitus and prediabetes using HbA1c: A population-based survey from Pakistan. *BMJ. Open.* **9**(2): e025300

Association AD (2019). Glycemic targets: Standards of medical care in diabetes-2019. *Diabetes Care.* **42**(Suppl 1): S61-S70

Bamashmoos MA and Ganem Y (2013). Diabetic nephropathy and its risk factors in type 2-diabetic patients in Sana'a City, Yemen. *World J. Med. Sci.,* **9**(3): 147-152.

Barnett A, Cradock S, Fisher M, Hall G, Hughes E and Middleton A (2010). Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. *Int. J. Clin. Pract.* **64**(8): 1121-1129.

Chu C-H, Hsu C-C, Lin S-Y, Chuang L-M, Liu J-S and Tu S-T (2019). Trends in antidiabetic medical treatment from 2005 to 2014 in Taiwan. *J. Formos. Med. Assoc.* **118**(1): S74-S82.

Daubenmier J, Lin J, Blackburn E, Hecht FM, Kristeller J, Maninger N, Kuwata M, Bacchetti P, Havel PJ and Epel E (2012). Changes in stress, eating and metabolic factors are related to changes in telomerase activity in a randomized mindfulness intervention pilot study. *Psychoneuroendocrinology,* **37**(7): 917-928.

Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ and Buse JB (2018). Management of hyperglycaemia in type 2 diabetes. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* **61**(12): 2461-2498

Dixon JR (1999). The international conference on harmonization good clinical practice guideline. *Qual. Assur.* **6**(2): 65-74.

Donald M, Dower J, Coll JR, Baker P and Mukandi B (2013). Mental health issues decrease diabetes-specific quality of life independent of glycaemic control and complications: Findings from Australia's living with diabetes cohort study. *Health. Qual. Life. Outcomes.* **11**(1): 1-8

Dziadkowiec KN, Stawinski PM and Proenza J (2021). Empagliflozin-associated pancreatitis: A consideration for SGLT2 inhibitors. *ACG. Case. Rep. J.* **8**(1): e00530

Fitchett D, Inzucchi SE, Cannon CP, McGuire DK, Scirica BM, Johansen OE, Sambevski S, Kaspers S, Pfarr E, George JT and Zinman B (2019). Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation.* **139**(11): 1384-1395.

Garber AJ, Abrahamson MJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA and Garber JR (2019). Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2019 executive summary. *Endocr. Prac.,* **25**(1): 69-101.

Home PJD (2019). Cardiovascular outcome trials of glucose-lowering medications: An update. *Diabetologia.* **62**(3): 357-369

Kim G, Gerich J, Salsali A, Hach T, Hantel S, Woerle HJ and Broedl UC (2014). Empagliflozin (EMPA) increases genital infections but not urinary tract infections (UTIs) in pooled data from four pivotal phase III trials. *Diabetol. Stoffwechs.* **9**(S 01): P140

Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, Stella P, Woerle HJ and Broedl UC (2015). Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. *Clin. Ther.* **37**(8): 1773-1788.

Lind M, Odén A, Fahlén M and Eliasson B (2009). The true value of HbA1c as a predictor of diabetic complications: Simulations of HbA1c variables. *PloS. One* **4**(2): e4412

Manrique-Acevedo C, Chinnakotla B, Padilla J, Martinez-Lemus LA and Gozal D (2020). Obesity and cardiovascular disease in women. *Int. J. Obes.,* **44**(6): 1210-1226.

Mellitus DJDc (2006). Diagnosis and classification of diabetes mellitus. *Diabetes Care,* **29**(1): S43

Raosoft I (2021). Sample size calculator by Raosoft, Inc. http://www.raosoft.com/samplesize.html

Schwaiger E, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A, Pacini G, Wrba T, Antlanger M, Schmaldienst S and Werzowa J (2019). Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume and patient safety. *Am. J. Transplant.,* **19**(3): 907-919.

Shin Y, Moon JH, Chin HJ, Ferrannini E, Lim SJE and Metabolism (2020). Glycemic efficacy and metabolic consequences of an empagliflozin add-on versus conventional dose-increasing strategy in patients with Type 2 diabetes inadequately controlled by metformin and sulfonylurea. *Endocrinol. Metab.* **35**(2): 329-338.

Søfteland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M and Broedl UCJDC (2017). Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: A 24-week randomized, double-blind, parallel-group trial. *Diabetes Care.* **40**(2): 201-209.

Subrahmanyan NA, Koshy RM, Jacob K and Pappachan JM (2021). Efficacy and cardiovascular safety of DPP-4 inhibitors. *Curr. Drug. Saf.,* **16**(2): 154-164.

Swetha N (2014). Comparison of fasting blood glucose & post prandial blood glucose with HbA1c in assessing the glycemic control. *Int. J. Healthc. Biomed. Res.,* **2**(3): 134-139.

Terauchi Y, Utsunomiya K, Yasui A, Seki T, Cheng G, Shiki K and Lee J (2019). Safety and efficacy of empagliflozin as add-on therapy to GLP-1 receptor agonist (liraglutide) in Japanese patients with type 2 diabetes mellitus: A randomised, double-blind, parallel-group phase 4 study. *Diabetes. Ther.,* **10**(3): 951-963.