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A Multifarious Approach of Sglt 2 Inhibitors: Key Evidence

Vishnupriya s

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ABSTRACT
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are the newer class of drugs introduced into the market for the treatment of uncontrolled type 2 diabetes mellitus (Type 2 DM). It reduces hyperglycaemia by promoting the excretion of urinary glucose. Apart from glycaemia control this category of drugs were showing beneficial effects over body weight, blood pressure, cardio-renal actions. It is generally given as once daily dose. It is reducing glucose by glucose independent insulin reductions by acting on the proximal convoluted tubule of kidneys. Many studies were proven that these drugs were serving as the novel therapy for the treatment of Type 2 DM. Most commonly reported adverse events are genital mycotic infections and urinary tract infections. This review mainly focus on the effects of SGLT-2 Inhibitor's mechanism of action and its effect over Blood Glucose, Body weight & BMI, Lipid Profile, Blood Pressure, Cardiovascular effects, Renal effects and its comparison with DPP-4 Inhibitors which other class of glucose lowering agents been used as an adjuvant therapy in Type-2 DM.
KEYWORDS: SGLT-2 Inhibitors, Type 2 DM, Body weight, Cardiovascular effects ,Glycaemia.

I. INTRODUCTION

Diabetes Mellitus is the most common metabolic disease which is chronic and the most prevailing one among almost all the nations (Shaw et al., 2010). It is one of the most occurring non-communicable diseases. The number of incidences of death is twice more in DM population than in the non-diabetic population. The DM produces micro & macro vascular complication due to hyperglycaemia. The risks can be reduced with proper glycaemic control (Alfeena Mary et al.,2018).

The Beta cells of pancreas progressively deteriorate to cause DM. This kind of deterioration leads to abnormal insulin regulation which in turns leads to worsening of hyperglycaemia on disease progression. There are also other etiological factors which attribute to type 2 DM like the excessive production of glucagon, excessive glucose production in hepatic region, higher lipolysis, and dysfunction of neurotransmitters and abnormal handling of glucose in the renal tubules (Shubrook JH et. al., 2015;DeFronzo Ralph et al., 2009).

EPIDEMIOLOGY OF TYPE 2 DM

In global prevalence, North America has the highest regional prevalence of DM for 2010 (after age standardization to the world population), followed by the EMME and South Asia. By 2030 the Africa is expected to have the largest proportion in adult diabetes numbers, followed by the EMME, though the world's highest prevalence is expected to by North America only. All the regions will have a higher number of adult populations, so over 20 years the diabetes patient's population are going to be increased by 50% (Shaw et al., 2010).

There were about 65 million diabetic populations in 2016 in India, whereas it was 26 million in 1990. The prevalence of Diabetes Mellitus among the adults aged 20 years or older was increased from 5.5% to 7.7% between the years of 1990 to 2016 respectively (Lalit Dandona, 2018).

ADD ON THERAPY

When the original oral hypoglycaemic agent was not showing the sufficient beneficial effects, some other adjuvant therapy is required.

Apart from unfair glycaemic control, the leading factor of mortality & morbidity in type 2 DM is cardiovascular risk. The increased HbA1c, elevated LDL, hypertension, albuminuria & smoking and increases the CVD risk (Kohan et al., 2014). Some new clinicalevidences provide that the fair glycaemic control among newly diagnosed DM patients reduces the occurrence of CVD like MI (Ann Marie Schmidt,2019).

Some new class of anti-hyperglycaemic agents like GLP-1 RAS & SGLT-2 inhibitors are proved to have unexpected cardiovascular benefits in the Cardiovascular Outcome Trials (CVOT). When the original oral hypoglycaemic agent wasnot showing the enough beneficial effects, some other adjuvant therapy is required(Skyler et al., 2009).

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SGLT-2 INHIBITORS

The newer class of anti-diabetic agent, sodium glucose cotransporter-2 (SGLT-2) inhibitors were introduced because of the higher prevalence of uncontrolled type 2 diabetes. SGLT-2 inhibitors include drugs such as dapagliflozin and empagliflozin which are approved to be used as monotherapy or in combination with metformin, sulfonylurea, or insulin(Alfeena Mary et al.,2018)

The SGLT-2 inhibitors have greater advantages over reduction of HbA1c, blood sugar levels, weight and blood pressures. It reduces weight by glucosuria. Glucosuria signals the CNS to change appetite regulation. The beta-oxidation of free fatty acids into triacylglycerol by these drugs reduces the fat deposition & their osmotic diuretic effect and vasodilatation on nitric oxide release decreases the blood pressure(Alfeena Mary et al.,2018).

Along with improving glycaemic control, these drugs are reported to have other beneficial effects on body weight and blood pressure, with a low risk of hypoglycaemia. Increase in HDL-C and LDL-C level are reported with this category drugs but the mechanism by which SGLT2 inhibitor increases LDL-C levels remains unknown and a dose-related increase in LDL-C was observed in patients with SGLT2 inhibitor.

Canagliflozin was the first SGLT-2 inhibitor approved in the US. It requires dose adjustments are in patients with renal impairment (i.e., estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2). If eGFR is < 60 mL/min/1.73 m^2, Dapagliflozin should not be used. Lowering the dose of insulin or insulin secretagogues should be considered when co-administered with SGLT-2 inhibitors in order to reduce the risk of hypoglycaemia(Nainggolan, 2013;FDA 2013).

The canagliflozin of 100 or 300 mg daily for 26 weeks administration resulted in a significant improvement in HbA1C in both doses while compared with placebo in a trial evaluating canagliflozin monotherapy efficacy and safety among 584 adults who were having inadequately controlled with type 2 diabetes mellitus with diet and exercise.(Stenlofet.al, 2013)

Metformin and/or sulfonylureas on combination therapy with Canagliflozin showed a significant reduction in fasting glucose and produces HbA1C level less than 7% in major patient population. On an add-on therapy to insulin & comparative data to thiazolidinedione, the dipeptidyl peptidase-IV inhibitors have also produced improved PPG levels and HbA1C levels(Claret.al, 2012).

Dapagliflozin is given along with diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. (FDA 2013;Tucker M, 2014). It is either indicated as monotherapy or as initial therapy with metformin, or as an add-on to other agents with decreases the glucose level, including metformin, pioglitazone, glimepiride, sitagliptin, and insulin(Wildinget al., 2012 ;Naucket al., 2011 ; Strojeket al., 2011 ; Rosenstocket al., 2012)

As that of dapagliflozin, empagliflozin is also approved to improve glycaemic control as an adjunct to diet and exercise. 7 clinical trials with 4480 patients with type 2 diabetes were evaluated the drug's safety and effectiveness. The pivotal trials showed that empagliflozin has improved the levels of HbA1c while compared with placebo(Rodenet al., 2013 ;Ridderstrale et al., 2014)

The FDA needs post-marketing studies to find out the potential safety issues, including a possible increased risk of bladder cancer (Tucker,2014;FDA 2013). The renal glucose threshold was lower with SGLT-2 inhibition. It results in increased urinary glucose excretion. The FDA approved the dapagliflozinin January 2014and empagliflozin in August 2014(Rodenet al., 2013;Ridderstrale et al., 2014).

The FDA also approved empagliflozin for a new indication in late 2016, particularly for the prevention of CVS disease–related death in type 2 diabetes patients who were also having cardiovascular disease. (Tucker, 2016;Peters, 2016). The new approval was based on results from the EMPA-REG OUTCOME, which included more than 7000 patients. (Zinmanet al., 2015)

Ertugliflozin therapy, which is an adjunct to diet and exercise, is aimed at enhancing the glycaemic control in type 2 diabetic adults. A series of nine phase-3 clinical trials of ertugliflozin which produced a significant improvement over HbA1c, fasting plasma glucose, body weight, systolic and diastolic blood pressures in adult type 2 DM patients put forth its approval. (Terra et al., 2017).

MECHANISM OF ACTION

SGLT-2 inhibitors 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

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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 occurrence of hypoglycaemia and there is no risk of overstimulation or fatigue of the beta cells. (Alfeena Mary et al., 2018)

It reduces the hyperglycaemia by insulin-independent manner. There will be enhanced urinary excretion of glucose is seen (Fig-1 Erikvan Bommel et al., 2017).

EMPA-REG Outcome portrays that apart from SGLT-2 inhibition, this category of drugs is likely to have multi-beneficial effects likes body weight reduction & BP reduction(Erikvan Bommel et al., 2017).

THERAPEUTIC EFFECTS OF SGLT-2 INHIBITORS

1) Effects on blood glucose

A noticeable change on the Blood glucose was seen in patients who were started with SGLT-2 Inhibitors while comparing with other OHAs

After 2 weeks of administration, dapagliflozin increase the urinary glucose excretion to 78±5 g/d & 91±15g/dl on second and third days ($p<0.0001$) when compared with days 0 & 1 (8±1 g/dl). Body weight didn't change in the placebo group but declined modestly in the dapagliflozin treated groups (-1.2 +0.3 kg)(Merovci , et al., 2014)

A review over "SGLT-2 Inhibitors through the windows of EMPA-REG" and CANVAS Trials",concluded that in CV outcomes there were significant differences noted which differs with ethnicity. This also provided an information that canagliflozin produces a far between renal outcome while comparing with empagliflozin because of its concurrent SGLT-1 inhibiting nature along with SGLT-2 inhibition(Ashu Rastogi, et al., 2017).

A study on "Efficacy and Safety of SGLT-2 Inhibitors in Reducing Glycated Hemoglobin and Weight in Emirati Patients with Type 2 Diabetes" which included 307 patientsconcluded 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 body weight also reduced from the baseline at the sixth month, from 85.7±17.8 kg to 84±12.2 kg ($p=0.0001$)(AlaaedinBashier, et.al., 2017).

2) Effects on body weight &BMI

SGLT-2 Inhibitors which are given either as monotherapy or as an add-on therapy to other oral hypoglycaemic agents, has been shown to provide statistically significant and clinically relevant improvements in glycaemic control in uncontrolled Type 2 DM patients.

A study titled "Efficacy of Body Weight Reduction on the SGLT-2 Inhibitor in People with Type 2 Diabetes Mellitus". This study was a retrospective one which involves 61 patients who received 12 months of dapagliflozin. 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 safe manner in Type 2 DM patients(HyunCho, et al., 2017)

A study entitled "Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus" which comprised of 3300 patients who were divided into Cohort 1 of823 patients and Cohort 2 of 2477 patients. In both the group of cohort 1 & 2, empagliflozin significantly reduced the body weight -1.7 kg & 1.9 kg, waist circumference -0.2% & -0.3%, estimated total body fat -0.007 & -0.008, central obesity -0.3 & -0.4 for visceral adipose index respectively. This study concluded that empagliflozin reduced the cardiometabolic in type 2 DM patients by significantly reducing the body weight & adiposity indices(Ian Neeland, et al., 2016).

3) Effects on lipid profiles

There are some beneficial and significant effects of SGLT-2 Inhibitors over triglycerides and High-Density Lipoprotein was reported. A randomised, placebo controlled double blinded study on the dapagliflozin which is administered to Type 2 DM patients who achieved unfair glycaemic control with metformin, revealed that dapagliflozin group has seen with increased HDL-C and decreased triglycerides while comparing with placebo (Bailey et al., 2010).

A study titled "A comparison of the effects of DPP-4 Inhibitors & SGLT-2 Inhibitors on lipid profile in patients with Type 2 DM" concluded that SGLT-2 Inhibitors were associated with significant increase in HDL-C and LDL-C in patients with Type 2 DM while comparing with DPP-4 Inhibitors. Though further studies should be done to access and evaluate the effects of SGLT-2 Inhibitors over lipid profiles (Seon-Ah Cha, 2017).

4) Effects on blood pressure

Generally, most of the diabetic patients are associated with hypertension (HTN) which also attributes to the increased risk of renal dysfunction and cardiovascular diseases. So, there is also a need

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for the strict control of Blood Pressure. There were some proven studies which were concluding that SGLT-2 Inhibitors were also having significant effect over the blood pressure (American Diabetes Association, 2016).

A study titled "Sodium-Glucose Co-transporter 2 Inhibitors for type 2 Diabetes: a systemic review & meta-analysis" concluded SGLT-2 Inhibitors reduce systolic and diastolic blood pressure by 3.77, 1.75 mmHg respectively when compared to placebo groups & it has reduced the SBP by 4.45 and DBP 2.01 when compared to other glucose lowering agents.

The mechanism of BP by SGLT-2 Inhibitors is not completely known. The drug is associated with osmotic diuresis which results in increased urine output about 200-600 ml/day. It may reduce the BP by decreasing the intravascular volume(Erik van Bommel et al., 2017).

Some studies revealed that the anti-hypertensive effect of SGLT-2 Inhibitors is independent of GFR(Kohan et al., 2014;Yale et al., 2013). This results in focusing on the points like reduction in Serum Uric Acid, body weight and oxidative stress and nervous activation (Richette et. al., 2014;Chino et al., 2014; Bailey et al., 2010)

5) Cardiovascular effects

The unpredictable cardio-renal benefits in type 2 DM patients who were either established with cardiovascular diseases or multiple CV risk factors (Neal et al., 2017).

A large multi-national study found reduction in the cardiovascular death and hospitalization for about 38% and 35% respectively in case of heart failures who were administered with SGLT-2 inhibitors for their uncontrolled diabetes mellitus (Mikhail Kosiborod et al., 2017).

In EMPA-REG outcome study, about 7028 patients of type 2 DM with marked coronary, peripheral or cerebrovascular diseases were randomized to get introduced with empagliflozin or placebo. The events like cardiovascular death, non-fatal myocardial infarction and non-fatal stroke were decreased by empagliflozin. The median follow-up was about 2.6 years, the study results revealed that there was 14% significant reduction in CVD related death with the p value of 0.04

Empagliflozin is only the drug from the glucose lowering category which reported with CVD risk reduction in Cardiovascular Outcome Trial (Neeland et al., 2016)

It is associated with reduced CV risk in patients with Type 2 DM who were considered to have low-medium CV risk (Frampton et al, 2018).

6) RENAL EFFECTS

The SGLT-2 Inhibitors may produce the reno-protective effects, by preventing the GFR deterioration and reducing the degree of albuminuria in patients with Type 2 DM along with kidney diseases (Tsimihodimos et al., 2017).

SGLT-2 Inhibitors are considered as the novel choice for combination therapy. Besides the glycaemic control they proved to have direct reno-protective effect and CV safety by albuminuria reduction. The concurrent use of SGLT-2 Inhibitors with RAAS blockers are novel drug strategies to reduce the DKD progression by decreasing the inflammatory and fibrotic markers induced by hyperglycaemia (Honghong Zou et al., 2016).

It decreases the intra-glomerular pressure and alters the renal hemodynamics. Tubular toxicity reduced by this category of drugs. So, it directly protects the kidney (Panchapakesan et al., 2013; Andrianesis et al, 2016; Thomas et al., 2014).

Empagliflozin reduce the incidence or worsening of nephropathy to 12.17% when compared with placebo which reduce the worsening of nephropathy to 18.8%, the progression of microalbuminuria, doubling of creatinine and the need for renal replacement therapies were reduced by SGLT-2 Inhibitors up to 38%, 44% & 55% respectively (Fitchett, 2018).

COMPARISION OF THE EFFECTS OF DPP-4 & SGLT-2 INHIBITORS

Both the classes of drugs are being used as add on therapy to OHAs or as monotherapy to uncontrolled Type 2 DM, their comparison studies provided the results favouring to SGLT-2 Inhibitors. They are many proven studies which are concluded that while comparing with DPP-4 Inhibitors, SGLT-2 Inhibitors were producing more significant effects. The results were concluding that SGLT-2 Inhibitor has significantly prominent effect over the physical profile like Body weight, Body Mass Index and diabetic profile (Fasting Blood Sugar, Glycated Haemoglobin) of the patients.

A meta-analysis studywhich included 14 eligible randomized controlled trials comprising 6980 patients, on 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)

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from baseline than DPP4i/INS without increasing the risk of hypoglycemia. (Min, et al., 2017).

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. (Alfeena Mary, et al., 2018).

The patients who switched to empagliflozin group were compared with patients who were continually taking an original antidiabetic drug of DPP-4 Inhibitors. After 6 months of study, the results revealed that the HbA1c, Body Weight, BMI were significantly reduced in patients who were switched to empagliflozin while the patients who were still on DPP-4 inhibitors has not found with significant reduction in all the above-mentioned parameters. (Chung-Huei Huang, et al., 2018)

SIDE EFFECTS OF THE DRUG

Since, it is reducing the hyperglycemia by increasing the excretion of glucose via urine & by inhibiting the renal tubule reabsorption of glucose, the increased risk of mycotic infections and genital infections were seen (Monami et al., 2014).

It is also prone to cause thirst and rarely orthostatic hypotension. The volume depletion is seen due to osmotic diuresis induced by glucosuria.The patients above 75 years of age, the patients using loop diuretics, those who having GFR < 60ml/min/1.73 are more vulnerable to have volume depletion (Monami et al., 2014). It also leads to ketoacidosis, urosepsis, pyelonephritis (FDA, 2015).

II. CONCLUSION

The SGLT-2 Inhibitors are the recent class of Oral Hypoglycemic Agents. These drugs were acting as the novel drugs in the treatment of Type-2 and as adjuvant therapy in case of Type 1 Diabetes Mellitus. This category of drugs will be the wise choice for lowering the uncontrolled blood glucose despite of their side effects. The side effects can be minimized by carefully selecting the patients. The cardiovascular & safety trials provoked the clinical importance of the drug. Both the glycemic and non-glycemic effects and their tolerability exhibit the superiority of SGLT-2 Inhibitors over other class of oral glucose lowering agents. These may serveas the best choice of add on therapy or monotherapy drug for the treatment of uncontrolled Type 2 Diabetes Mellitus.

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