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DAPAGLIFLOZIN EFFICACY AS AN ADD-ON THERAPY IN DOUBLE AND TRIPLE-DRUG REGIMENS.

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ABSTRACT

Background: Diabetes is one of the most common diseases compared to others. There are many drugs available in the market to treat diabetes. Still, most of them have adverse drug reactions like hypoglycemia, weight gain, and subtherapeutic drug concentrations. SGLT-2 inhibitors are a new class of drugs used as add-on therapy to treat type-2 Diabetes Mellitus. They act by inhibiting glucose reabsorption and increasing glucose excretion via the kidneys. In an average adult, two kidneys filter about 180g of glucose per day. About 98% of the glucose filtered in the kidneys get reabsorbed in the proximal convoluted tubule back into the bloodstream, which can be inhibited by SGLT-2 inhibitors. **Method:** A systematic review and meta-analysis were performed on randomized clinical trial data, extracted from PubMed, Cochrane and Embase. All data, including baseline and shift of baseline, standard deviation, and number of participants, were recorded for HbA1c, Fasting blood glucose (FBG), Bodyweight and SBP/DBP. **Results:** Twelve randomized clinical trials, including 8000 participants, were compared and divided into three groups of drugs: SAXA+DAPA+MET, SAXA+MET and DAPA+MET. The comparison is done for HbA1c (WMD:-6.78; 95% CI:-8.28; P <0.00001) (WMD:-4.88; 95% CI:-6.93; P <0.00001), FBG (SMD: -6.50; 95% CI: -8.55, -4.45; P <0.00001) (SMD: -7.75; 95% CI: -8.84, -6.66; P<0.00005,), body weight (SMD: 0.30; 95% CI: 0.27, 0.33; P =1.00) (SMD: -1.00; 95% CI: -1.90, -0.10; P<0.00001). **Conclusion:** Dapagliflozin, when given in combination, shows a major improvement in HbA1c and FBG levels and does not affect body weight. It was shown to be more effective when given in triple combination therapy.

KEY WORDS : Dapagliflozine, meta-analysis, Sexagliptine, Metformin, Type two diabetes mellitus (T2DM), Sodium-glucose Cotransporter-2 (SGLT2)

INTRODUCTION

The diabetes epidemic has become a major problem. In India, diabetes has become the third-largest cause of overall mortality due to comorbidities. The disease has been diagnosed in 9.3% of elderly people living in rural areas of India, according to a recent estimation by the Union Ministry of Family and Health in 2021 [1]. Among Indians above forty-five years of age, eleven per cent were diagnosed with type-2 diabetes or hyperglycemia. According to the first Longitudinal Ageing Study of India surveyed 72,000 Indians between 2017 and 2018, the prevalence of diabetes was higher in senior citizens. People aged 65 years and above showed a 14% prevalence, while those between 45-59 years were 9%. Early intervention measures include controlling blood glucose levels and reducing the development of cardiovascular and renal diseases.

The role of SGLT-2 inhibitors in Diabetes therapy was studied and researched. This class of drugs works through a unique mechanism of reducing renal tubular glucose reabsorption, producing a decrease in blood glucose without stimulating insulin release. Reduced sodium reabsorption and increased distribution of sodium to the distal convoluted tubule also occur. SGLT2 inhibitors work independently of insulin secretion and beta-cell function, and shows a good impact in long-standing diabetes patients with renal impairment. The prototype SGLT2 inhibitor is Dapagliflozin, and many countries like the European Union and the United States have approved its use. When Dapagliflozin is combined with another oral antihyperglycemic agent, it has the benefit of greater weight loss and blood pressure lowering.

Type II Diabetes in India

The occurrence of diabetes in India has drastically increased despite the abundance and variety of antidiabetic drugs available, due to rapid progress and changes in the demographic. Indians have a higher predisposition to T2DM, a higher risk of coronary artery disease and a low chance of microvascular complications.

Since 1960, the prevalence of T2DM in India has increased in both, the urban and rural sectors, which has marked a big impact on death and increased expenditure on health care. In addition to treating the disease and reducing healthcare expenditure, we have to include the promotion of a healthy lifestyle for the prevention of diabetes.

According to National Health and Nutritional Examination Survey, sixty-two per cent of diabetic patients are at risk of developing hypertension and renal disease before it is diagnosed, eighty-three per cent with hypercholesterolemia, and fifty-six per cent with obesity.

Pharmacodynamics of Dapagliflozin

Sodium-glucose co-transporters are the membrane transporters in the renal tubules involved in the transportation of amino acids, glucose, and other substances from the proximal tubule in the kidney into the bloodstream. This system helps to reabsorb the glucose molecule back in the body, which was removed from the mainstream of blood circulation, by glomerular filtration.

Sodium-glucose co-transporters are classified into two types, SGLT-1 and SGLT-2 [2]. SGLT-1 plays a role in glucose absorption from the gastrointestinal tract and glucose reabsorption from the kidneys. SGLT-2 helps in the transportation of glucose from urine to blood.

SGLT-2 is found in the proximal tubule's apical membrane, in the S1 and S2 segments of the kidney [4, 2]. This SGLT-2 works as a co-transporter of two molecules, sodium and glucose. The glomerular filtrate glucose is reabsorbed about 90% along with sodium from the lumen of the

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proximal tubule into the proximal convoluted tubule cell and then into the capillary endothelial cell via basolateral membrane via GLUT-2. Sodium enters the bloodstream in exchange for potassium.

Dapagliflozin act as a "high-capacity and low affinity" sodium-glucose co-transporter inhibitor. It selectively inhibits the SGLT-2 Protein, which results in decreased renal reabsorption of filtered glucose from the proximal tubule [3]. Several physiological functions may also be influenced, including decreased intraglomerular pressure (believed to be mediated by increased tubuloglomerular feedback) and lowering of both preload and afterload on the heart, and decreased regulation of the sympathetic system [1].

Pharmacokinetic

Dapagliflozin shows a 78% oral bioavailability with a single dose of 10 mg. The maximum plasma concentration of 158 ng/mL steady state was reached in 1-2 hours and was observed at a loading dose of 10 mg/day. The area under the curve was found at 628 h/mL [4,5]. Dapagliflozin gets metabolized by cytochrome P450 to an inactive conjugation compound, mainly dapagliflozin 3-o-glucuronide.

Adverse drug reaction

In recent clinical trials, the most common adverse events found were urinary tract infection, female genital infection, nasopharyngitis, hypotension, diabetic ketoacidosis, hypoglycemia, and hypersensitivity [6].

METHODS AND MATERIALS

The search was made in English, the most common keywords used in the search being "SGLT-2 inhibitor", "Dapagliflozin", "combination of metformin", and "dapagliflozin and add-on therapy".

Study criteria for inclusion were set by following the standard given by America Diabetes Association (ADA). The participants should be above 18 years of age and below 75 years and should have a diagnostic history of uncontrolled diabetes mellitus type 2. Participants who are pregnant, or with oncological disease or serious renal disease were excluded.

Randomized double-blind studies that evaluate the effectiveness of Dapagliflozin in combination and as monotherapy were assessed. The trial should be conducted for >24 weeks and should monitor and record the changes in the HbA1c, FPG, and PPG from baseline.

The data was extracted and then managed and organized in a Microsoft Access database. The data were then filtered according to the inclusion and exclusion criteria. The baseline mean, the standard deviation and the doses given according to the study protocol were then carefully included.

A meta-analysis was performed using the Ren Man software 5.3, all the data which was extracted from different research were entered into the software. The analysis was performed where p and I2 outcomes are used to analyze heterogeneity. The heterogeneity was reduced by making subgroups. Continuous data included the mean change from baseline, standard deviation, and the number of participants in HbA1c, FPG, and PPG. The mean difference was used to express continuous data, and a 95% confidence interval is used to express effective size.

RESULT

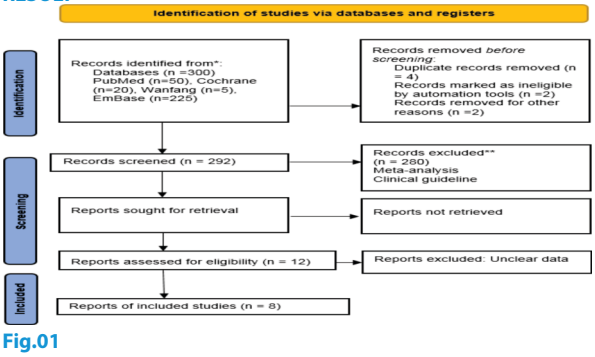

Fig.01

A total of 300 studies were reviewed and searched. After removing the duplicate studies (n=4), records marked as ineligible by the automation tool (n=2) and records removed for other reasons (n=2), 292 studies were excluded after screening for article content review, clinical trials, and meta-analysis. A total of 8 studies were included in the meta-analysis. In this analysis, a total of 2187 patients received triple therapy of Dapagliflozin plus Saxagliptin plus Metformin (DSM), 1450 patients received combined therapy of Dapagliflozin plus Metformin (DM), and 1200 patients received Saxagliptin plus Metformin combination (SM). The doses which were received by the participants were dapagliflozin 10mg, saxagliptin 5mg, and metformin, ranging from 500 to 1500mg per day.

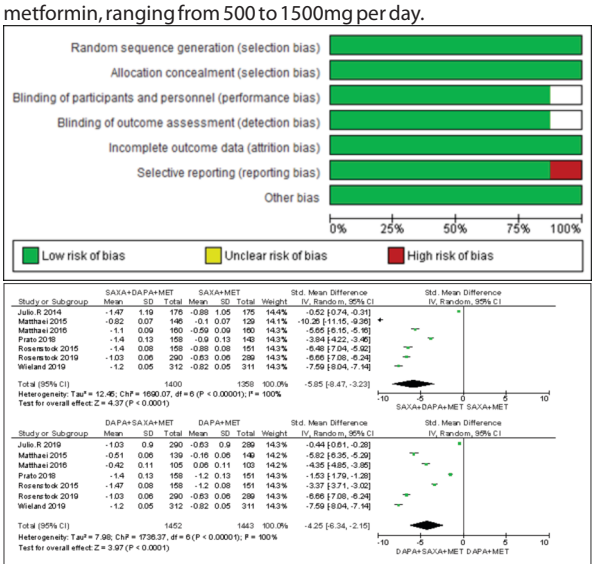

Fig.02 Comparing the effect of DAPA+SAXA+MET with of DAPA+MET and SAXA+MET on the adjusted mean change levels of HbA1c. DAPA+SAXA+MET = dapagliflozin Plus saxagliptin and metformin, DAPA+MET = dapagliflozin plus metformin, SAXA+MET = saxagliptin plus metformin, IV= inverse variance methods.

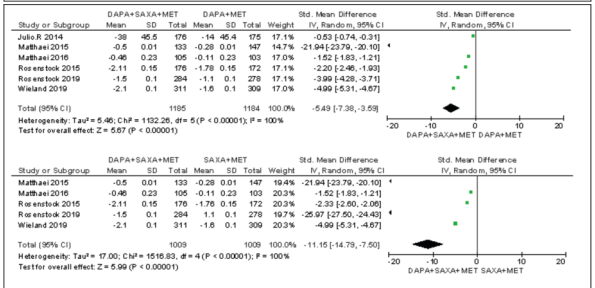

Fig.03 Comparing the effect of DAPA+SAXA+MET with of DAPA+MET and SAXA+MET on the adjusted mean change levels of FPS. DAPA+SAXA+MET = dapagliflozin Plus saxagliptin and metformin, DAPA+MET = dapagliflozin plus metformin, SAXA+MET = saxagliptin plus metformin, IV= inverse variance methods.

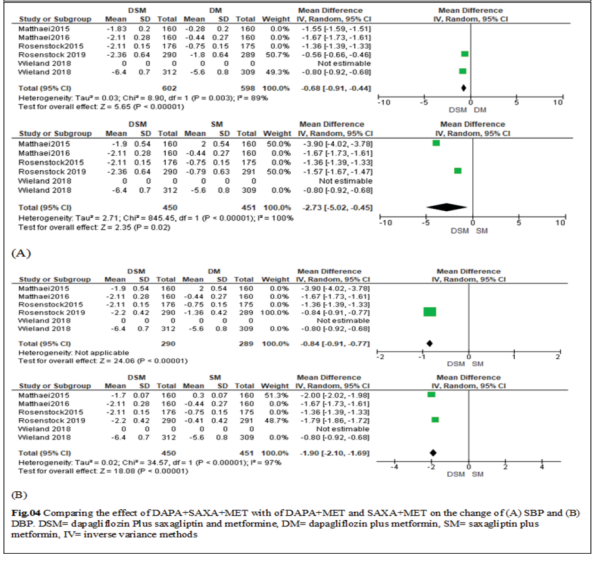

Fig.04 Comparing the effect of DAPA+SAXA+MET with of DAPA+MET and SAXA+MET on the change of (A) SBP and (B) DBP. DSM= dapagliflozin Plus saxagliptin and metformine, DM= dapagliflozin plus metformin, SM= saxagliptin plus metformin, IV= inverse variance methods

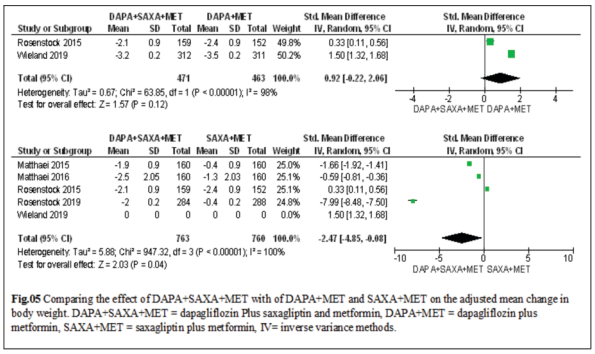

Fig.05 Comparing the effect of DAPA+SAXA+MET with of DAPA+MET and SAXA+MET on the adjusted mean change in body weight. DAPA+SAXA+MET = dapagliflozin Plus saxagliptin and metformin, DAPA+MET = dapagliflozin plus metformin, SAXA+MET = saxagliptin plus metformin, IV= inverse variance methods.

Glycosylated hemoglobin A1C (HbA1c)

In this meta-analysis study, we compared DSM therapy (dapagliflozin plus saxagliptin and metformin) with DM therapy (dapagliflozin plus metformin) and SM (saxagliptin plus metformin) (Fig. 02). 6 clinical trials provided data on HbA1c change from baseline, with 2407 patients for DSM vs SM and 2316 patients for DSM vs DM. To reduce the heterogeneity caused between the groups, random effect models and subgroup analyses are performed. The results showed a drastic change seen in the trial when the DSM combination was used as compared to SM and DM (WMD:-6.78; 95% CI:-8.28; P <0.00001) (WMD:-4.88; 95% CI:-6.93; P <0.00001).

Fasting plasma glucose (FPG)

Five trials were considered for the change in the baseline of FPG (Fig. 03); 4038 patients were involved in the trial of DSM vs DM and SM. Due to heterogeneity, randomized effect models were used, and subgroup analyses were performed to compare DSM vs DM and SM for the change of FPG from the baseline. The result shows that DSM significantly decreases the levels of FPG as compared to DM and SM (SMD: -6.50; 95% CI: -8.55, -4.45; P <0.00001) (SMD: -7.75; 95% CI: -8.84, -6.66; P<0.00005).

Body weight

For the evaluation of change in body weight, four studies were involved, with 1523 participants engaged for the effect of DMS vs SM and two studies for comparing DMS vs DM with 934 participants (Fig. 05). Due to heterogeneity, randomized effect models were used, and subgroup analyses were performed. By comparing both the studies, DSM is proved to be less effective in reducing body weight (SMD: 0.30; 95% CI: 0.27, 0.33; P =1.00) (SMD: -1.00; 95% CI: -1.90, -0.10; P<0.00001).

SBP and DBP

Six studies assessed the effect on systolic blood pressure and diastolic blood pressure. 1779 participants for comparing DSM vs DM and 1802 for DSM vs SM were considered. The results show that DSM produces more effective blood pressure lowering than SM and DM.

DISCUSSION

Diabetes is one of the most prevalent diseases in the world, and a major risk factor for cardiovascular and renal diseases. There are many drugs available in the market to treat diabetes. Still, most of them have adverse drug reactions like hypoglycemia, weight gain, and subtherapeutic drug concentrations.

SGLT-2 inhibitors are a new class of drugs used as add-on therapy to treat type-2 Diabetes Mellitus. Most diabetes medications work by increasing insulin levels or sensitivity in the body, but SGLT-2 inhibitors act by increasing glucose excretion via the kidneys. In an average adult, two kidneys filter about 180g of glucose per day, which is a daily need for 30% energy expenditure in the human body. The filtered glucose is nearly 98% reabsorbed in the proximal convoluted tubule via apical brush borders and basolateral epithelium. Sodium-glucose transporters 1 and 2 are the symporters that are present in the apical membrane of the proximal convoluted tubule. This symporter reabsorbs glucose with Na+, which results in an electrochemical gradient. Na^+/K^+ATPase, which is present in the basolateral, works as a pump in which 3 Na^+ are exported.

Dapagliflozin is an SGLT-2 inhibitor used to reduce blood glucose levels in type 2 diabetes patients. Dapagliflozin has also been found to be beneficial in heart failure by lowering afterload and improving ventricular loading, as well as in chronic kidney disease by lowering the risk of sustained eGFR decline with a favourable safety profile [1]. When used in combination, it has demonstrated effective anti-diabetic activity. The recommended dose of dapagliflozin is 10 mg orally. It is not recommended in patients with GFR greater than 60 mL/min and less than 45 mL/min. In cases of severe hepatic impairment, the dose should be adjusted to 5 mg/day and then increased to 10 mg/day if well tolerated. No dose adjustments are required in patients with mild to moderate hepatic impairment.

Side effects of dapagliflozin include glucosuria, and urinary tract infections, since increased amount of sugar in urine favours the environment for infections like UTIs and candida infections. Glucose in urine causes osmotic diuresis which leads to frequent urination, hypotension, dehydration and weight loss. Diabetic Ketoacidosis is a rare complication.

Metformin monotherapy is the most common treatment for type 2 diabetes. However, to keep glycemic levels under control, metformin is often combined with glucose-lowering agents such as dapagliflozin and saxagliptin. Before starting any combinational drug, the safety and efficacy profile should be thoroughly evaluated. Triple therapy (metformin + dapagliflozin + saxagliptin) has been shown to reduce HbA1c levels more than dual therapy (metformin + saxagliptin or metformin + dapagliflozin). Adverse effects of triple therapy include headache, nasopharyngitis, influenza and urinary tract infection (increased by dapagliflozin and saxagliptin). There was no indication of any serious adverse event (SAE) in individuals who received triple or dual treatment regimens. The incidence of hypoglycemia, a typical consequence of anti-diabetic medication, was not connected to triple or dual therapy, according to multiple studies [1]. Prato et al. observed in their post-hoc analysis that triple therapy with dapagliflozin, saxagliptin, and metformin is a well-tolerated therapeutic regimen for type 2 diabetes patients who require long-term management of high HbA1c levels [1].

In our current study, three combinations were assessed as DAPA+SAXA+MET [dapagliflozin plus saxagliptin and metformine], DAPA+MET [dapagliflozin plus metformin] and [SAXA+MET] saxagliptin plus metformin. The three combinations were compared with each other for their efficacy and safety profile using different components like changes in mean HbA1c levels, fasting plasma glucose levels, body weight, and systolic and diastolic blood pressure.

Due to heterogeneity between the groups, random effect models and subgroup analyses were used to compare the components. The inverse variance method with a 95% confidence interval was used to assess all the parameters. It was observed that Dapagliflozin plus Saxagliptin and Metformine [DSM] combination provided better results in decreasing HbA1c, Fasting plasma glucose, and systolic and diastolic blood pressure levels compared to the other two combinations. However, the DSM combination was less effective in reducing the body weight of subjects than the dapagliflozin plus metformin [DM] combination.

After concluding all analyses, it was reported that the triple-drug regimen of Dapagloflizin along with Saxagliptin and Metformin has greater potential in reducing mean HbA1c, and fasting blood sugar in type-2 diabetics, as compared to the other combinations, in addition to having fewer side effects.

Conflict Of Interest

The authors whose names are listed certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Data Availability Statement

The authors conform that data used in this meta-analysis are open access for other research. Matthaei S, Catrinoiu D, Celiński A, Ekholm E, Cook W, Hirshberg B, et al. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes. Diabetes Care [Internet]. 2015;38(11):2018–24. Available from: http://dx.doi.org/10.2337/dc15-0811 Matthaei S, Aggarwal N, Garcia-Hernandez P, Iqbal N, Chen H, Johnsson E, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes Obes Metab [Internet]. 2016;18(11):1128–33. Available from: http://dx.doi.org/10.1111/dom.12741Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care [Internet]. 2015;38(11):2009–17. Available from: http://dx.doi.org/10.2337/dc15-0779 Mathieu C, Herrera Marmolejo M, González González JG, Hansen L, Chen H, Johnsson E, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. Diabetes Obes Metab [Internet]. 2016;18(11):1134–7. Available from: http://dx.doi.org/10.1111/dom.12737 Del Prato S, Rosenstock J, Garcia-Sanchez R, Iqbal N, Hansen L, Johnsson E, et al. Safety and tolerability of dapagliflozin, saxagliptin and metformin in combination: Post-hoc analysis of concomitant add-on versus sequential add-on to metformin and of triple versus dual therapy with metformin. Diabetes Obes Metab [Internet]. 2018;20(6):1542–6. Available from: http://dx.doi.org/10.1111/dom.13258 Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care [Internet]. 2015;38(3):376–83. Available from: http://dx.doi.org/10.2337/dc14-1142 Müller-Wieland D, Kellerer M, Cypryk K, Skripova D, Rohwedder K, Johnsson E, et al. Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. Diabetes Obes Metab [Internet]. 2018;20(11):2598–607. Available from: http://dx.doi.org/10.1111/dom.13437 Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. Diabetes Obes Metab [Internet]. 2017;19(3):348–55. Available from: http://dx.doi.org/10.1111/dom.12825 Müller-Wieland D, Kellerer M, Cypryk K, Skripova D, Rohwedder K, Johnsson E, et al. Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. Diabetes Obes Metab [Internet]. 2018;20(11):2598–607. Available from: http://dx.doi.org/10.1111/dom.13437

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