Journal of Population Therapeutics & Clinical Pharmacology

Research Article
DOI: 10.53555/p37cha52

EVALUATION OF SAFETY AND EFFICACY OF DAPAGLIFLOZIN AS FIRST LINE MONOTHERAPY WITH METFORMIN IN PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS - A RANDOMIZED OPEN LABEL STUDY

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ABSTRACT
Dapagliflozin, an SGLT2 inhibitor, is compared to Metformin monotherapy in patients with newly diagnosed type II diabetes. Patients newly diagnosed with Type II Diabetes Mellitus were included in the study. It was conducted at the Non-Communicable Disease (NCD) Clinic, under the General Medicine Department at Sri Lalithambigai Medical College and Hospital from February 2023 to February 2024. The study recruited 100 patients, 50 in each arm. As a result of dapagliflozin treatment, patients with metabolic syndrome improved all aspects of the condition. Participants receiving Dapagliflozin experienced greater decreases in body weight, body mass index, waist circumference, fasting blood glucose, and postprandial blood glucose compared to those receiving Metformin. In terms of HbA1c, HDL cholesterol, LDL cholesterol, and triglyceride levels, there were no significant differences. The Dapagliflozin group experienced a higher incidence of UTIs which can be prevented by increased intake of water when compared with the Metformin group. However, there were no serious side effects, or deaths which suggested that although Dapagliflozin increased the risk of urinary tract infections, overall safety profiles of both drugs were good. These findings suggest that Dapagliflozin may offer superior metabolic benefits compared to Metformin for Type II Diabetes Mellitus.

Keywords: Type 2 Diabetes, Dapagliflozin, Metformin, Monotherapy, Blood Glucose

INTRODUCTION
The chronic metabolic disorder diabetes mellitus (DM) causes persistent hyperglycemia. Impairment in insulin secretion or resistance to insulin's peripheral effects may contribute to this. Approximately 415 million adults aged 20 to 79 suffered from diabetes mellitus in 2015, according to the International Diabetes Federation (IDF). In light of the fact that the number of diabetics is expected to rise by 200 million by 2040, the disease is becoming a global public health concern. Various organ systems can be damaged by chronic hyperglycemia as well as metabolic

abnormalities in patients with diabetes mellitus, resulting in life-threatening and disabling complications. In addition, microvascular complications (retinopathy, nephropathy, and neuropathy) increase cardiovascular disease risk [1]. Diabetes patients with type 2 mellitus are educated, evaluated for microvascular and macrovascular complications, achieved near normoglycemia, minimized cardiovascular risk factors, and avoided drugs that can aggravate insulin or lipid metabolism abnormalities. Individual factors, such as age, life expectancy, and comorbidities, must be taken into account when considering these treatments and goals. Bariatric surgery, aggressive insulin therapy, and behavioral interventions have been shown to lead to remissions of type 2 diabetes for several years, but most patients with type 2 diabetes require continuous treatment to remain in remission. As part of glycemic management, insulin availability is increased (either by administering insulin directly or by releasing agents that stimulate insulin secretion), insulin sensitivity is improved, carbohydrate absorption and delivery is delayed, or a combination of these methods is used to increase urinary glucose excretion. Patients with overweight, obesity, or metabolically adverse adipose tissue distribution patterns may also benefit from body weight management. SGLT-2 inhibitors and glucagon-like protein-1 receptor agonists are now available to treat type 2 diabetes mellitus. These drugs not only improve glycemic control, but also have metabolic and cardiovascular benefits [2]. SGLT2 inhibitors are suffixed as gliflozins which have a basic physiology in the urinary tract especially nephrons and also modulates the sodium and glucose channels present in the mucosa of the intestinal tract. The activities of the drugs belonging to this class cause inhibition of glucose reabsorption in the kidneys and so causing low blood sugar. The activity is due to the inhibition of sodium glucose transport protein 2 (SGLT2). They are basically used in the treatment of Type II Diabetes Mellitus and also exhibit cardiovascular effects [3,4]. Many medications of this class of drugs including Empagliflozin, Dapagliflozin, Canagliflozin and Remogliflozin are used to control the blood sugar levels and to lower the body weight. These are also used to control the blood pressure (systolic and diastolic). Gliflozins possess protective effects on various organs like heart, liver and kidneys and exhibit Anti-hyperlipidemic, anti-obesity, Anti-neoplastic activities. They are also reasonably proven to cause homeostasis, glycosuria, and antioxidant activities [5,6]. Surprisingly, SGLT inhibitors have been shown to play a significant role in the inflammatory response. Inhibiting SGLT2 has been reported to reduce inflammation and slow the onset of diabetic nephropathy and other inflammatory-mediated disorders [7]. In a diabetes rat model, Empagliflozin caused the reduction in the inflammatory cytokines, TNFα and IL-6 and also the apoptotic mediators [8]. When the cytotoxicity of the gliflozins like Canagliflozin, Dapagliflozin and Empagliflozin were compared on human RPTEC cells, Canagliflozin showed a SGLT2 dependent cytotoxicity that is mediated by inhibition of glutamate dehydrogenase and mitochondrial electron transport. Also, SGLT2 inhibitors have been recommended as an initial therapy in patients with Type 2 diabetes by the American Diabetes Association's 2022 Standards of Medical Care in Diabetes. Therefore, this study SGLT2 inhibitor Dapagliflozin is selected to compare with Metformin as a first-line drug treatment for Type 2 diabetes.

METHODOLOGY

Study Design

This was a randomized (simple randomization), comparative study.

Study Population

The study included newly diagnosed Type II Diabetes Mellitus patients.

Study Venue

The study was conducted at the Non-Communicable Disease (NCD) Clinic, Department of General Medicine, Sri Lalithambigai Medical College and Hospital.

Study Period

The study period extended from February 2023 to February 2024.

Sample Size

A sample size of 80 patients was determined based on the primary outcome reported in previous study, with a confidence interval of 95% 80% power, resulting in 80 patients required for this study. Considering a 20% dropout rate during the intervention and potential non-adherence to the study protocol, both arms of the study included 100 patients each. [9]

Randomization and Assessment

Patients were randomly assigned to one of two groups using simple randomization. Each participant received the assigned treatment and was assessed periodically throughout the study. It was the efficacy and safety of the treatment regimens that were the primary outcomes measured, with regular follow-ups to monitor patient progress and adherence.

Criteria for selection

Inclusion criteria

- Age 30 – 50 years
- Sex – both genders
- New cases of Type 2 Diabetes
- People with fasting blood glucose levels greater than 126 mg/dl and postprandial blood glucose levels greater than 200 mg/dl
- Glycosylated hemoglobin (HbA1c) >6.5%
- BMI (Body mass index)- >=25
- Patient with abnormal Lipid profile
- Patient willing to participate and give written informed consent.

Exclusion criteria

- Age below 30 and above 50 yrs.
- Old cases of Type 2 Diabetes
- Type 1 Diabetes mellitus.
- Type 2 diabetics with other endocrinological disorders like hypo or hyperthyroidism, Cushing syndrome, acromegaly.
- Type 2 diabetics on drugs like thiazide diuretics, corticosteroids, and oral Contraceptive pills.
- Pregnant and lactating women.
- Patients enrolled in any other study.

Study procedure

Upon approval of the Institutional Ethics Committee, the study was conducted. Participants were informed about the study's purpose and procedures and provided informed consent in their regional language. Patient demographics were recorded, followed by a thorough screening conducted by a doctor, which includes medical history, vital signs, and general and systemic examinations. Eligible patients could enroll and be assigned to the test or control groups through simple randomization.

STUDY GROUP	**TREATMENT**	**FREQUENCY**		**DURATION**
GROUP A (n=50)	Metformin 500mg	BD (twice daily)	After food	24 weeks
GROUP B (n=50)	Dapagliflozin 10mg	OD (once daily)	After food	24 weeks

Laboratory Investigations

Laboratory investigations will be done during Baseline, 1st month, 3rd month, 6th month (End of Study). 5 ml of venous blood will be withdrawn from study subjects under aseptic conditions, then stored & analysed for data under good laboratory practice (GLP) guidelines.

Endpoints

After 24 weeks of therapy, the primary endpoint of the study is the percentage change in HbA1c levels between the two treatment groups. Secondary endpoints include change in fasting blood sugar and postprandial blood sugar, lipid profile, and body mass index (BMI) from baseline after 24 weeks of therapy.

STATISTICS

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 24. After the 24-week study period, the results were analyzed using the unpaired t-test to compare the two treatment groups. The effect of each individual drug was determined using the paired t-test. Using the chi-square test, we analyzed adverse events. Demographic data (age, sex, etc.) and patients' baseline characteristics, which are categorical variables, were summarized by treatment groups using descriptive statistics to assess any differences between them. In order to determine statistical significance, an alpha level of p 0.05 was used.

RESULT

The study included 100 participants, divided equally into two groups: 50 receiving Dapagliflozin 10mg and 50 receiving Metformin 500mg. Baseline characteristics between the two groups were comparable, indicating that randomization of groups for the study in table 1.

Table: 1 Baseline Characteristics of both groups

Characteristics	**Dapagliflozin 10mg (n=50)**	**Metformin 500mg (n=50)**
Sex • Male • Female	 29 (58%) 21 (42%)	 26 (42%) 24 (48%)
Age	44.2±7.4	45.7±6.7
Body weight (kg)	75.1±9.8	77.2±8.2
BMI (kg/m^2)	27.1±3.9	26.9±2.4
Waist circumference	102±8.7	98±4.1
Fasting Blood glucose (mg/dl)	131.2 ± 4.1	131.9±6.3
Post Prandial Blood Glucose (mg/dl)	209.02±5.5	211.11±7.1
HbA1c (%)	7.1±0.2	6.9±0.7
HDL cholesterol (mmol/L)	0.9±0.1	0.7±0.4
LDL cholesterol (mmol/L)	4.1±0.8	3.9±0.7
Triglycerides (mmol/L)	2.8±1.1	2.5±1.4

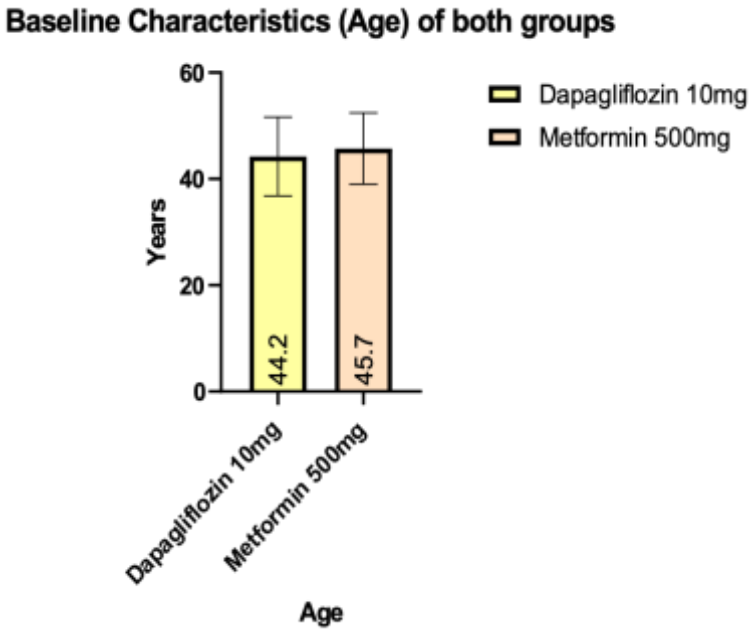

Figure: 1 Baseline characteristics (Age) of both groups

The sex distribution was similar in both groups, with the Dapagliflozin group comprising 28 males (58%) and 21 females (42%), and the Metformin group comprising 26 males (52%). The mean age of participants in the Dapagliflozin group was 44.2 ± 7.4 years, while the mean age of participants in the Metformin group was 45.7 ± 6.7 years. The mean body weight was 75.1 ± 9.8 kg in the Dapagliflozin group and 77.2 ± 8.2 kg in the Metformin group. Similarly, the mean BMI was 27.1 ± 3.9 kg/m2 in the Dapagliflozin group and 26.9 ± 2.4 kg/m² for the Metformin group. Waist circumference measurements showed a mean of 98 ± 8.7 cm in the Dapagliflozin group and 102 ± 4.1 cm in those taking Metformin.

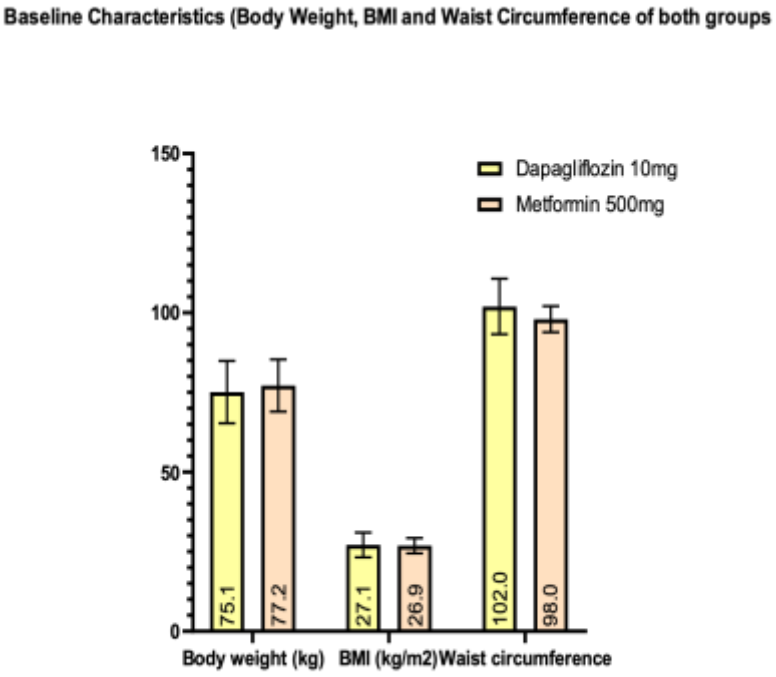

Figure: 2 Baseline characteristics (Body weight, BMI, and Waist Circumference) of both groups

Fasting blood glucose levels were 131.2 ± 4.1 mg/dl in the Dapagliflozin group and 131.9 ± 6.3 mg/dl in the Metformin group. Postprandial blood glucose levels were 209.02 ± 5.5 mg/dl in the Dapagliflozin group and 211.11 ± 7.1 mg/dl in the Metformin group.

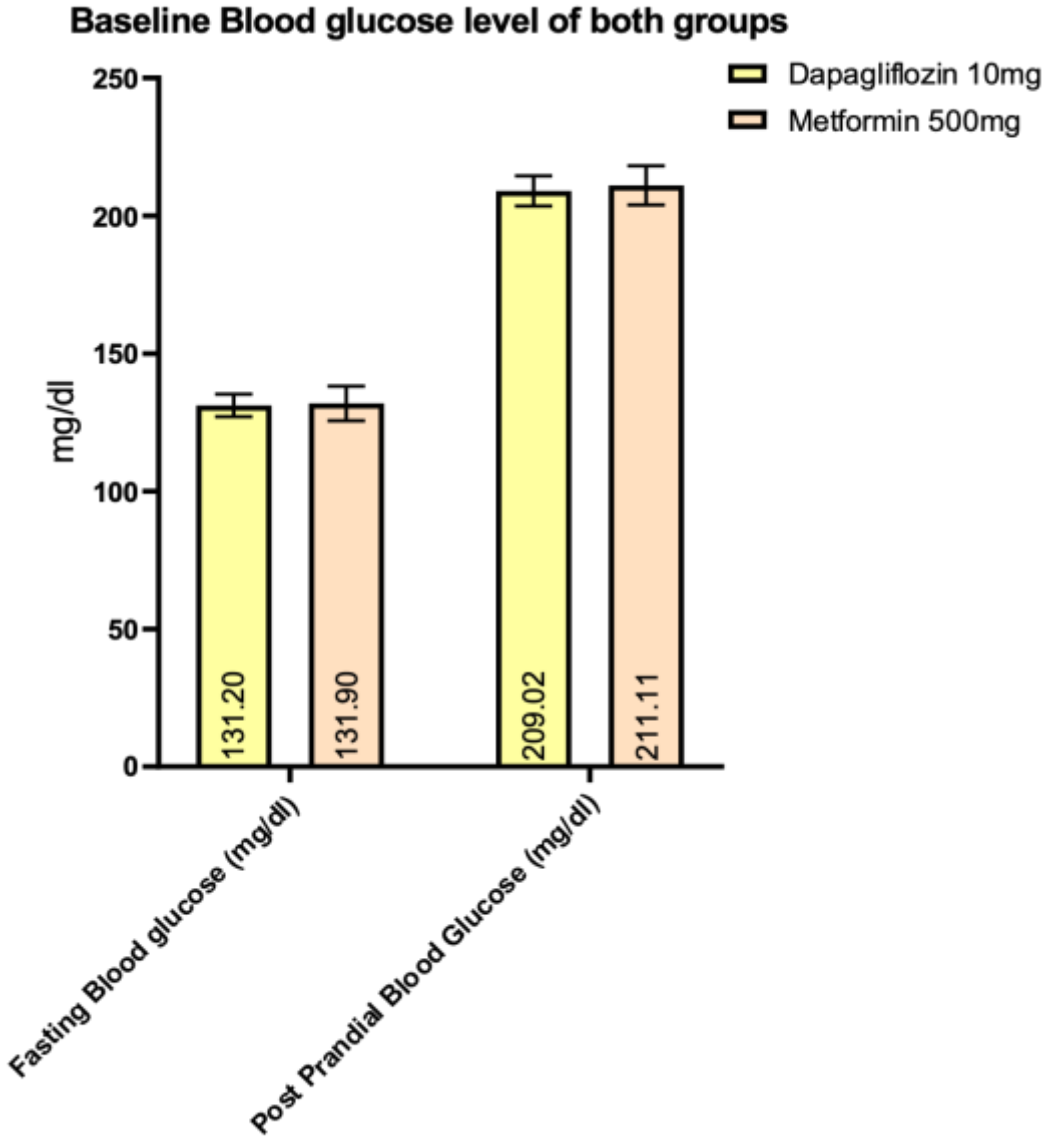

Figure: 3 Baseline Blood glucose level of both groups

There was a mean HbA1c of 7.1 ± 0.2% for the Dapagliflozin group and 6.9 ± 0.7% for the Metformin group. The lipid profile showed that HDL cholesterol levels were 0.9 ± 0.1 mmol/L in the Dapagliflozin group and 0.7 ± 0.4 mmol/L in the Metformin group, respectively. LDL cholesterol levels were 4.1 ± 0.8 mmol/L in the Dapagliflozin group and 3.9 ± 0.7 mmol/L in the Metformin group. Triglyceride levels were 2.8 ± 1.1 mmol/L in the Dapagliflozin group and 2.5 ± 1.4 mmol/L in the Metformin group.

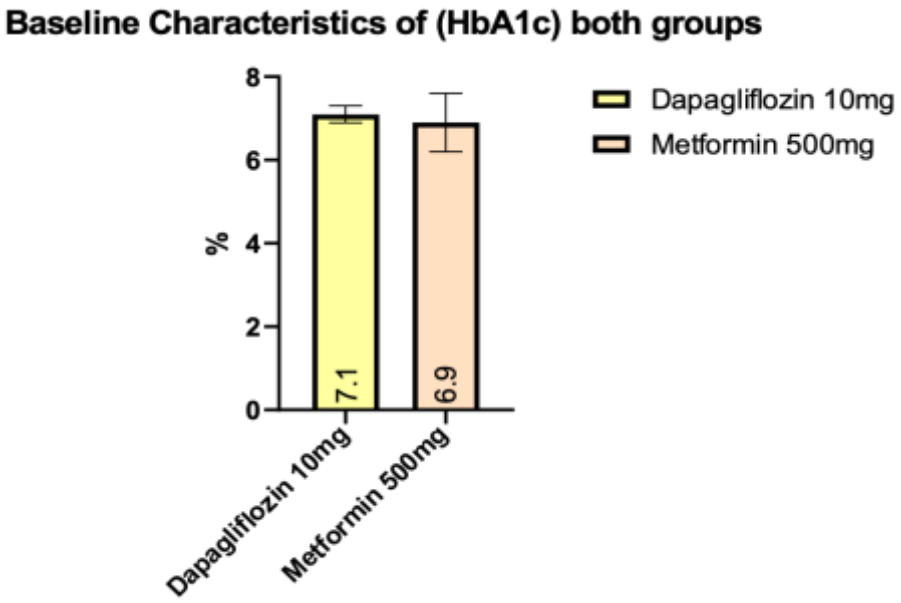

Figure: 4 Baseline characteristics of (HbA1c) both groups

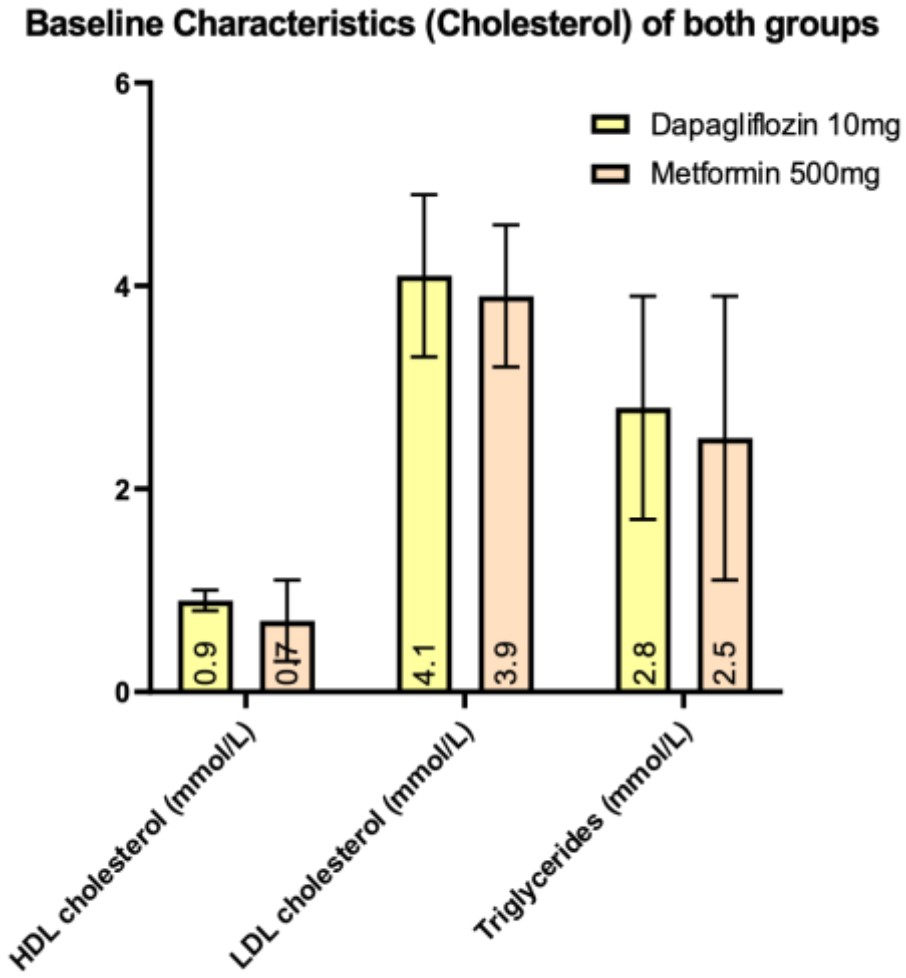

Figure: 5 Baseline characteristics of (Cholesterol) both groups

Table: 2 Clinical endpoints

Characteristics	**Dapagliflozin 10mg (n=50)**	**Metformin 500mg (n=50)**
Body weight	-2.4	-4.2
BMI	-1.3*	-1.1
Waist circumference	-4.4*	-4.1
Fasting Blood glucose	-1.8*	-1.1
Post Prandial Blood Glucose	-1.6*	-1.4
HbA1c	-0.9	-0.9
HDL cholesterol (mmol/L)	0.06	0.05
LDL cholesterol (mmol/L)	0.04	0.03
Triglycerides (mmol/L)	-0.071	-0.090
ADR Events (%) • UTI • Dysuria • Genital infection • Serious adverse effects • Death	 8.3* 0.7 0.3 0.1 -	 4.1 0.9 0.2 0.1 -
Remitting metabolic syndrome	86%	92%*

***p<0.05 significant**

Clinical endpoints of Dapagliflozin vs Metformin

Comparison of clinical endpoints between the Dapagliflozin 10mg and Metformin 500mg groups revealed significant differences in several parameters. Participants receiving Dapagliflozin experienced greater decreases in body weight, BMI, waist circumference, fasting blood glucose, and postprandial blood glucose compared to those receiving Metformin. There was no significant difference between the two groups in terms of HbA1c, LDL cholesterol, HDL cholesterol, or triglyceride levels. These findings suggest that Dapagliflozin may offer superior metabolic benefits compared to Metformin in the treatment of Type II Diabetes Mellitus. Data shown in table 2. Comparison of adverse drug reactions (ADRs) between the Dapagliflozin 10mg and Metformin 500mg groups revealed significant differences in the percentage of patients who developed urinary tract infections (UTIs). As compared to the Metformin group, the Dapagliflozin group had a higher incidence of UTIs. However, there were no significant differences between the groups in the occurrence of dysuria, genital infections, serious adverse effects, or deaths. These results suggest that Dapagliflozin increases the risk of urinary tract infections that can be prevented by increased intake of water and the overall safety profiles of both drugs are comparable. After 24 weeks of therapy, metabolic syndrome remission showed as 86% in Dapagliflozin group and 92% in Metformin group, respectively.

DISCUSSION

In this study, different health parameters were compared in Type II Diabetes Mellitus patients who took Dapagliflozin 10mg and Metformin 500mg based on their response to the treatment. According to the results of this study, both groups had similar sex distributions and mean ages. Dapagliflozin significantly reduced weight, BMI, waist circumference, fasting blood glucose, and

postprandial blood glucose when compared to the Metformin group. A significant difference did not exist between the two groups in terms of HbA1c, LDL cholesterol, HDL cholesterol, or triglyceride levels, which indicates that there was no significant difference between the two groups. In terms of adverse drug reactions, the Dapagliflozin group was observed to have more urinary tract infections (UTIs) than the Metformin group, but both groups showed no incidence of serious adverse effects, or deaths. Both drugs were found to have similar overall safety profiles despite a higher risk of urinary tract infections. In the Dapagliflozin group, 86% of patients were able to achieve complete remission of metabolic syndrome within 24 weeks; in the Metformin group, 92% achieved complete remission. There are several factors that may have confounded the study results. Variability in how adherence to medication regimens varies among participants, which may significantly affect the outcome. Body Weight, Glucose levels, and Lipid profiles could also be affected by differences in diet and lifestyle. Variations in diabetes duration could also affect medication response. Despite similarities in sex distribution and age, other baseline variables might have influenced the results, such as diabetes severity and other co morbidities. Furthermore, variability in measurements could result in inconsistencies, including blood glucose levels. The metabolic benefits of Dapagliflozin were greater than those of Metformin, as it significantly reduced weight, BMI, waist circumference, fasting and postprandial blood glucose levels. Overall glycemic control was equally effective with both drugs, with similar efficacy in controlling HbA1c levels. LDL cholesterol, HDL cholesterol, and triglyceride levels were not significantly different between the groups, suggesting both medications had similar impacts on lipid metabolism. Overall safety profiles of Dapagliflozin and Metformin were comparable, although Dapagliflozin was associated with urinary tract infections (UTIs). Between the groups, there was no significant difference in serious adverse effects, or deaths. In particular, both medications showed similar remission rates 86% for Dapagliflozin, while Metformin had 92% remission rate. Among patients with metabolic syndrome, dapagliflozin improved metabolic indicators. Dapagliflozin's protective effects against metabolic syndrome can be attributed to its mechanism of action. SGLT-2 inhibition causes osmotic diuresis and caloric loss by increasing glucose excretion in urine and decreasing plasma glucose levels. Therefore, dapagliflozin improves glycaemic control, reduces weight, and lowers blood pressure. According to previous studies [9, 10], dapagliflozin or canagliflozin improved all components of metabolic syndrome compared to glimepiride. It is notable that metformin, compared with placebo, decreased metabolic syndrome prevalence by 17% as compared to glimepiride and sitagliptin, which have neutral effects on metabolic syndrome other than glycaemic control. Research [11] showed that dapagliflozin induced remission in 58.3% of patients with metabolic syndrome. A researcher [12] compared dapagliflozin monotherapy and metformin monotherapy with dapagliflozin plus metformin. Unlike them, we found dapagliflozin alone reduced fasting plasma glucose and weight more effectively than metformin alone. As compared to metformin alone, dapagliflozin alone did not significantly reduce glucose levels or body weight as fast as metformin alone did. There is a possibility that the two studies differed because they enrolled patients with type 2 diabetes, whereas this study enrolled patients with metabolic syndrome. In several studies [11-14], SGLT-2 inhibitors were found to be beneficial for people with metabolic syndrome or type 2 diabetes. There were few cases or a short follow-up period in most of these studies, however. Due to the longer follow-up in the present study and the higher number of cases in similar studies, we assessed the effects of long-term administration of dapagliflozin and metformin on metabolic syndrome. The association between glucosuria and UTI was presumed and much debated. In the dapagliflozin studies, UTIs were diagnosed by collecting urine cultures, consulting experienced clinicians, or responding to treatment after a presumed diagnosis. In these trials, relying solely on culture results would have led to an erroneously low infection rate since symptomatic UTIs are commonly treated without obtaining a culture. Women are more likely than men to be diagnosed with UTI clinically. Patients with type 2 diabetes are commonly exposed to these pathogens [15]. A single course of standard antibiotic treatment usually resolved most mild to moderate events. The study participants found these side effects tolerable, as they rarely discontinued dapagliflozin due to UTIs [16]. Blood

glucose levels have been reduced and glucoseuria has been observed with dapagliflozin treatment. In a previous study, the glucose excretion was shown to be progressively increased with increasing doses of dapagliflozin, however there was no similar dose-dependent relationship with UTI incidence. It is also true that glucosuria is associated with genital infection in patients receiving dapagliflozin [17]. It is clearer, however, that genital infections are associated with an increased risk.

CONCLUSION

According to this study, Dapagliflozin might be more beneficial for patients who are overweight and have high blood glucose levels, particularly if they need significant improvements in their metabolic parameters. The effectiveness of Metformin remains high, especially when it comes to remission of metabolic syndrome. As a result of this study, it has been shown that Dapagliflozin also offers significant metabolic benefits when compared to Metformin. The effects of both medications on lowering HbA1c levels is also similar, indicating that both of them are equally effective for managing glycemic control. A key finding of this study was the fact that both drugs are effective in reversing metabolic syndrome. As such, Dapagliflozin is likely to be considered a better option for newly diagnosed Type 2 Diabetes Mellitus patients, especially those younger in age and obese, because of its superior performance in key metabolic parameters.

Conflicts of interest: Nil

Acknowledgement: None

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