EFFECT OF DAPAGLIFLOZIN, SITAGLIPTIN AND METFORMIN COMBINATION ON SOME METABLIC RISK FACTORS IN IRAQI PATIENTS WITH TYPE-2 DIABETES MELLITUS

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Abstract

Diabetes Mellitus is a metabolic disease that requires effective long-term management to achieve optimal glycemic control and minimize chronic complications that may be due to the effect of uncontrolled metabolic risk factors (hypertension, dyslipidemia, and obesity). This study aims to obtain the effect of the combination therapy (Dapagliflozin/Sitagliptin/Metformin) on metabolic risk factors in patients with type 2 diabetes mellitus. A Retrospective cohort study was conducted during the period from February to June 2022. The study involved 50 patients with type 2 diabetes mellitus. Glycated haemoglobin (HbA1c) and lipid profile analysis; in addition to blood pressure and body mass index (BMI) measurements were obtained. The mean systolic blood pressure, HbA1c and BMI before treatment were 131.76±22.49 mmHg, 11.41±2.23% and 31.27±3.92 kg/m2, respectively. They were significantly decreased to 123.44±14.28mmHg, 7.60±1.56%, 30.09±3.54 kg/m2, respectively after treatment. Similarly, the median level of TG, TC, LDL, HDL and vLDL levels before treatment was 153.5 mg/dl, 190.0 mg/dl, 105.0 mg/dl, 35.0 mg/dl and 30.7 mg/dl, respectively, and became 145.0 mg/dl, 154.0 mg/dl, 88.0 mg/dl, 42.0 mg/dl and 28.0 mg/dl, respectively after treatment with significant differences. In conclusion the improvement in the primary endpoint after three months of medication was significantly observed in HbA1c and BMI, which indicates that this type of combination therapy for patients with type-2 diabetes mellitus is highly favourable and efficient.

Keywords: Dapagliflozin, Sitagliptin, Metabolic risk factors, Diabetes Mellitus

Introduction:

Diabetes mellitus (DM) is defined by the American Diabetes Association (ADA) as a metabolic disorders characterized hyperglycemia due to defects in insulin secretion and/or insulin action (1). Type-2 diabetes mellitus represents about 90 to 95% of the overall diabetes types worldwide (2).Management should include medical and nutritional therapy (MNT) and an exercise program to re-establish insulin sensitivity and promote weight reduction (3). Pharmacological treatment of T2DM includes: Biguanides (metformin), Thiazolidinediones (TZDs), Meglitinides, Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), Sulfonylureas, α-Glucosidase inhibitor, Sodium/glucose

co-transporter-2 (SGLT2) inhibitors and bromocriptine (dopamine-2 agonists)(4).Metformin helps to control the amount of glucose by decreases intestinal absorption of glucose and reduces hepatic gluconeogenesis without increasing insulin secretion (5).Dipeptidyl Peptidase-4 (DDP-4) inhibitor enhance beta-cell function, reducing insulin resistance, increase serum glucagon like peptide-1(GLP-1),Glucose-dependent insulinotropic polypeptide (GIP) (6).Sodium Glucose Co-transporter 2 inhibitor (SGLT2)limit glucose reabsorption in the kidney at a lower threshold in the proximal tubular cell in nephron (7).

A study has shown the mechanism, rationale, and evidence from clinical trials for combining two of the newer drug classes, namely, dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter 2 inhibitors, and considers the possible role of such dual therapy in the management of T2DM,(8).DPP-4 inhibitors and SGLT2 inhibitors lower blood glucose by separate, complementary mechanisms. Both are glucose-dependent, accounting for the low risk of hypoglycaemia during treatment (9).

Therefore, this study aims to observe any improvement in the primary endpoint on the metabolic risk factors (HbA1c, lipid profile, hypertension, and BMI) in patients with type-2 diabetes mellitus using the combination therapyDapagliflozin/Sitagliptin/Metformin.

Methods

A Retrospective cohort study was conducted in the Department of Chemistry and Biochemistry/College of Medicine/Al-Nahrain University during the period from February to June 2022. The study involved 50 patients with type-2 DM who attended Endocrinology and Diabetes Specialized Center, Al-Mustansiriya University and Al-Imamain Al-Kadhemain Medical City/Baghdad/Iraq. The parameters in this study (HbA1c, lipid profile, blood pressure, and BMI) were measured at zero-point before taking the combination therapy Dapagliflozin/Sitagliptin/Metformin, then after three months of treatment the primary end-point of these parameters were measured.The study protocol was approved by the Ethical Committee of College of Medicine\ Al-Nahrain University.

Inclusion criteria:

1. Diabetic patients aged ≥30 and <85 years (regardless of gender).
2. Patients who did not change their anti-diabetic therapy for at least 3 months.

Exclusion criteria include:

1. Diabetic patients who require insulin therapy for blood glucose management, or drugs other than the combinations required in this study.
2. Patients with type-1 diabetes mellitus
3. Women with gestational diabetes.
4. Cancer Patients

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Sample Collection and Preparation

Five milliliters (ml) of venous blood samples were taken from patients. About three ml of blood were put in serum separator tube (SST) and the two ml were put in EDTA tube. The blood in the SST tube was let to stand about 20 minutes at room temperature. After clotting the serum was obtained by centrifugation at 3000 rpm for 10 minutes and then used for lipid profile analysis (TG, total Chol., LDL,VLDL, and HDL) inenzymatic, colorimetric method and results obtained byRoche/Hitachi COBAS C 111 Systems.

Whole blood in EDTA was used for (HbA1C) analysis, this method uses TTAB by Roche/Hitachi COBAS C 111 Systems. Body Mass Index was calculated by queteletsindex[BMI= Weight (Kg)/Height^2 (M^2)].

Statistical analysis:

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were subjected to normality test (Shapiro Wilk test), Data with normally distribution were presented as mean and standard deviation, and analyzed with paired t-test (for two groups comparison). Pearson's correlation test was used to explore the possible correlation of lipid profile with other parameters. A p- value less than 0.05 was considered to indicate a statistically significant difference

Results:

The demographic data of the study population which shows the age, genders,and disease duration is given in Table 1.

Table 1: Demographic data of the study population

Age, years *Mean±SD* *Range*	**Gender**	**Disease duration, years** *Mean±SD* *Range*
50.94±7.92 38-70	Male: 18(41.18%) Female: 32(58.82%)	5.03±2.33 2-10

In patients treated with the combination SGLT2 inhibitor (Dapagliflozin)/DDP-4 inhibitor (Sitagliptin)/Metformin, the diastolic BP level was not significantly altered after treatment compared with pretreatment level. On the contrary, the mean systolic BP, HbA1c and BMI before treatment were 131.76±22.49 mmHg, 11.41±2.23% and 31.27±3.92 kg/m^2, respectively compared with 123.44±14.28mmHg, 7.60±1.56%, 30.09±3.54 kg/m^2, respectively after treatment with significant differences. Similarly, the median level of TG, TC, LDL,HDL and vLDL levels before treatment was 153.5 mg/dl, 190.0 mg/dl, 105.0 mg/dl, 35.0 mg/dl and 30.7 mg/dl, respectively,

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and became 145.0 mg/dl, 154.0 mg/dl, 88.0 mg/dl, 42.0 mg/dl and 28.0 mg/dl, respectively after treatment with significant differences (Table 2).

Table 2: Blood pressure, HbA1c, BMI and lipid profile before and after treatment

Variable	Before treatment	After treatment	p-value
Systolic BP, mmHg **Mean±SD** **Range**	 131.76±22.49 100-200	 123.44±14.28 100-150	0.020
Diastolic BP, mmHg **Mean±SD** **Range**	 78.82±8.8 60-100	 80.94±5.88 70-90	0.263
HbA1c% **Mean±SD** **Range**	 11.41±2.23 7.8-17	 7.60±1.56 5-11.2	<0.001
BMI, kg/m^2 **Mean±SD** **Range**	 31.57±3.92 22-40	 30.09±3.54 22-37	<0.001
TG level, mg/dL **Median Range**	153.5 89-460	145.0 72-380	<0.001
TC level, mg/dL **Median Range**	190.0 95-296	154.0 85-255	<0.001
LDL level, mg/DL **Median Range**	105.0 34-217	88.0 18-155	0.004
HDL level, mg/dL **Median Range**	35.0 25-77	42.0 30-56	0.05
vLDL level, mg/dL **Median Range**	30.7 18-92	28.0 18-76	<0.001

Discussion:

The data in this study suggests that the combination of dapagliflozin (SGLT2 inhibitor) and sitagliptin (DPP-4 inhibitor)/metformin therapy is an effective combination for the improvement of metabolic risks other than glycemic indices (obesity, hypertension, and dyslipidemia) as a primary composite outcome in Iraqi patients with T2DM. Together, the DPP-4 and SGLT2 inhibitors fulfill a need for agents with complementary mechanisms of action that can be used in combination with a low risk of adverse events, such as hypoglycemia or weight gain and lower risk of consistent genital infection when glucose-lowering effect from another approach when adding DPP-4 inhibitors to SGLT2 inhibitors. In addition to superior glycemic control reduction in HbA1c goal achieving rate (10).

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This result is in agreement with another study; that found SGLT2 inhibitors and DPP-4 inhibitors have complementary mechanisms of action that address several of the underlying pathophysiologic abnormalities present in T2DM without overlapping toxicities. The combination of these 2 agents has several advantages including a low risk of hypoglycemia, the potential for weight loss, the ability to co-formulate into a pill with once-daily administration, and the possibility to use with other classes of glucose-lowering agents. Cardiovascular outcomes trials reported to date support the safety of the DPP-4 class and suggest possible cardio-protective effects for SGLT2 inhibitors; at least based on the first reported study that used dapagliflozin(11).

In this study BMI was significantly decreased in patients taking the combination of SGLT2 inhibitor/DDP-4 inhibitor/Metformin. The decrease in BMI was 1.19±1.04 (approximately 1.5 kg reduction in weight) after 3 month from taken medication.

This result is in agreement with other studies in which BMI was decreased and weight loss was observed (12,13). The weight loss given by SGLT inhibitors can be attributed to their inhibition of glucose reabsorption, which promotes approximately 75 g of urine glucose excretion with a corresponding caloric loss. (approximately 300 kcal day−1), explaining the weight loss (14). The results also showed that the primary endpoints of lipids after three months of treatment were slightly improved.

Conclusion: The improvement in the primary endpoint after three months of medication was significantly observed in HbA1c, and BMI. Therefore the use of combination therapy (Dapagliflozin/Sitagliptin/Metformin) gives a more favourable and efficient approach for patients with type-2 diabetes mellitus.

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