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Adding empagliflozin to sitagliptin plus metformin *vs.* adding sitagliptin to empagliflozin plus metformin as triple therapy in Egyptian patients with type 2 diabetes: a 12-week open trial

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Abstract. – OBJECTIVE: This study aimed to compare 12.5 mg empagliflozin effectiveness and safety *vs.* 50 mg sitagliptin twice daily as an add-on triple medication in Egyptians with type 2 diabetes.

PATIENTS AND METHODS: Patients with hemoglobin A1c (HbA1c) between 53 and 86 mmol/mol after receiving open-label either sitagliptin 50 mg (n = 85) or empagliflozin 12.5 mg (n = 85) twice daily for 12 weeks were afterward taken into account for the administration of open-label empagliflozin 12.5 mg (n = 40) and sitagliptin 50 mg (n = 28) respectively twice daily for another 12 weeks of treatment as an added-on triple therapy. Both groups of patients kept taking metformin and empagliflozin 12.5 mg or sitagliptin 50 mg twice daily as prescribed. The HbA1c change from baseline after 12 weeks of triple-added-on therapy was the main endpoint.

RESULTS: The sitagliptin group receiving empagliflozin saw a substantial drop in HbA1c, fasting and postprandial plasma glucose levels, body weight, and blood pressure compared to the starting point. As opposed to that, adding sitagliptin to the empagliflozin group non-significantly reduced HbA1c, fasting, and postprandial plasma glucose levels, and systolic blood pressure from baseline but significantly reduced body weight and diastolic blood pressure. Comparing the two groups, adding empagliflozin significantly reduced HbA1c, fasting, and postprandial plasma glucose levels ($p < 0.001$ for all except fasting plasma glucose level, $p = 0.002$). While the patient's weight and blood pressure were not significantly affected.

CONCLUSIONS: Empagliflozin was superior to sitagliptin in relation to glycemic control, weight, and systolic/diastolic blood pressure reduction.

Key Words:
T2DM, Empagliflozin, Sitagliptin, Triple oral antidiabetic combination, SGLT2 inhibitor, DPP4 inhibitor.

Introduction

Diabetes mellitus (DM) is a significant long-term pathological condition marked by the body's failure to perform insulin's physiological role. Over 463 million people worldwide as of today have diabetes; by 2030, that figure is projected to increase to more than five hundred million and to seven hundred million by 2045[1]. The most prevalent form of the disease, Type 2 diabetes (T2D), is now understood to occur due to poor communication between pancreatic ß-cells and organs susceptible to insulin[2]. For those with T2D who are unable or unlikely to regulate their blood sugar levels through lifestyle adjustments, metformin is advised as the primary pharmacological therapy[3]. As T2D advances, metformin treatment alone is typically unable to sustain glycemic control, despite being initially successful[3,4]. Additional therapies are necessary when, as is unavoidable, controlling blood glucose levels cannot be maintained with diet and lifestyle changes, as well as metformin as a monotherapy[3]. Consideration should be given to tolerability, with special attention to weight gain and hypoglycemia based on advice from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), but there are no reliable suggestions regarding which medication to use with metformin[3].

The second-line therapy for T2D is suggested to be one of the five antidiabetic medication groups, on the basis of the most current accepted report from the EASD and ADA[3]. These include glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose cotransporter-2 inhibitors ($SGLT_2i$), and dipeptidyl peptidase-4 inhibitors ($DPP\text{-}_4i$)[5].

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In genuine clinical practice, DPP-$_4$i have been accessible for more than ten years. They have excellent tolerability profiles, predictable glycemic effects, and a low risk of side effects like weight gain and hypoglycemia[6,7]. It has been shown[8,9] that they enhance ß-cell functionality and the propensity to secrete insulin, and as a result, they might be suitable in individuals with diabetes in its early stages who still have some beta-cell function. The first and most often used medication in this class worldwide is sitagliptin[10,11]. Although sitagliptin's effective glycemic qualities have been demonstrated[12-14], its impact on non-glycemic variables like sensitivity to insulin, lipids, and body weight is still debatable.

Empagliflozin, as SGLT$_2$i, are both powerful and selective. Empagliflozin demonstrated various pleiotropic positive outcomes in phase III trials[15-21] in addition to glycemic regulation if utilized alone or as an addition to preexisting medication. Along with a reduction in overall mortality, these benefits include reducing blood pressure, losing weight, and kidney and cardiovascular benefits. Aside from having a reduced risk of hypoglycemia, empagliflozin was well tolerated[15-21]. Moreover, empagliflozin-treated individuals with T2D who had a significant risk of heart disease had a lower rate of death from any cause as well as the primary composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)[22,23]. For individuals with T2D, SGLT$_2$i is one of the 2nd or 3rd-line suggested therapeutic alternatives, and it is advised to combine SGLT$_2$i with DDP-$_4$i plus metformin[24].

Today, it is clear that not all patients respond to anti-diabetic medications in the same way, and the price of treating diabetes is continually rising. Additionally, the safety and effectiveness of sitagliptin or empagliflozin when used alone are well known. There is, however, a paucity of literature-based data on the safety and effectiveness of triple-drug combination therapy. Therefore, the effectiveness and safety of empagliflozin 12.5 mg and sitagliptin 50 mg twice daily, along with metformin and diet, after being added to each other as a triple therapy desiring more glycemic control in Egyptian patients with T2D who were uncontrolled after 12 weeks of therapy with dual therapy (metformin and diet, along with either sitagliptin 50 mg or empagliflozin 12.5 mg twice daily, respectively), were evaluated in our trial.

Patients And Methods

Study Design

Our 12-week, phase II, open-label, investigator-initiated prospective trial (ClinicalTrials.gov No. NCT05359341) was carried out at the Internal Medicine Clinic of October 6 University Hospital from 20th June 2021 to 20th January 2022 without receiving financial assistance from the pharmaceutical industry. Before taking part in the trial, which was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, each subject gave written informed consent.

Patients

Uncontrolled T2D patients (HbA1c > 7 % but ≤ 10%), aged 30-65 years, despite following a diet and fitness plan and the administration of at least 12 weeks of metformin 1,000 mg twice daily, participated in the study. For 12 weeks, eligible patients received open-label treatment with either sitagliptin 50 mg or empagliflozin 12.5 mg twice daily in addition to their baseline metformin dosage (Phase I, not published yet). Patients having an HbA1c level between 53 and 86 mmol/mol (HbA1c > 7 % but 10%) at the end of the 12-weeks of sitagliptin 50 mg or empagliflozin 12.5 mg plus metformin period were then transferred to phase II, where empagliflozin 12.5 mg was added to those who received sitagliptin 50 mg, while for those who already received empagliflozin 12.5 mg, sitagliptin 50 mg was added to them, all administered in addition to the ongoing metformin regimen for an additional 12 weeks.

Exclusion criteria were: pregnancy; high (greater than double the normal upper limit) creatine phosphokinase, alanine aminotransferase, and aspartate aminotransferase; high bilirubin; albumin less than 3.5 g/dl; diabetic ketoacidosis; international normalized ratio > 1-2; the usage of any antidiabetic medication, excluding metformin, within the preceding 12 weeks before the beginning of phase I; any anti-diabetic medication other than study medications and metformin before beginning phase II treatment; HbA1c > 10.5%; epidermal growth factor receptor (eGFR) more than 60 mL/min/1.73 m2; recent ischemic stroke, acute coronary syndrome (ACS), or transient ischemic attack (TIA); recent receipt of weight-loss drugs, especially 3 months before being included in the study; urinary tract infection (UTI), especially for the sitagliptin receiving group; pancreatitis within six months of

enrollment or during phase I, especially for the empagliflozin receiving group; and disregard for scheduled follow-up appointments.

Treatment

Patients who met the criteria and had HbA1c between 7% and 10% despite receiving stable doses of sitagliptin plus metformin (Janumet®, MSD, Rahway, NJ, USA) were enrolled in a group receiving 12.5 mg empagliflozin (Jardiance®, Boehringer Ingelheim, Ingelheim, Frankfurt, Germany) twice daily as add-on therapy, while those with HbA1c between 7% and 10% despite receiving stable doses of empagliflozin plus metformin (Synjardy®, Boehringer Ingelheim, Ingelheim, Frankfurt, Germany) were enrolled in a group receiving an add-on therapy of sitagliptin 50 mg (Januvia®, MSD, Rahway, NJ, USA) twice daily; both groups continued under the triple regimen for 12 weeks. At screening, weeks 12 (week 0; the start of phase II), 18, and 24 of treatment were scheduled for study visits. The trial medications were not subjected to any dosage adjustments.

Outcome Measures

As the HbA1c level is vital to curtail the complications of DM, including cognitive function impairment[25], so, any variation from the baseline HbA1c level at week 12 (week 0 of phase II) to week 24 after addition of one treatment to the other, if HbA1c is still 7-10% was the first key effectiveness variable, in addition to three crucial second efficacy variables: (i) modification of fasting plasma glucose (FPG) and postprandial plasma glucose (PP); (ii) body weight fluctuation; and (iii) variations in systolic and diastolic blood pressure (DBP/SBP).

Vital signs, clinical laboratory results, and adverse events (AEs; using preferred terminology in accordance with version 17.1 of the Medical Dictionary for Drug Regulatory Activities) served as the safety endpoints. All emergent AEs with commencement following the initial dose of sitagliptin or empagliflozin prescribed in our study and for up to 7 days following the study's last medication dosage were managed. The AEs of particular relevance were hypoglycemia, genitourinary infections, hypersensitivity reactions, diabetic ketoacidosis, acute pancreatitis, hypotension, and dehydration. Events with a plasma glucose content of less than 3.9 mmol/L (70 mg/dl) were confirmed to be hypoglycemia AEs.

Statistical Analysis

The full analysis set, or all patients who took phase II medicines for 12 weeks and had post-baseline efficacy variables measured after the treatment period, were used for efficacy analyses. Additionally, assessments of safety characteristics were performed on the safety analysis set, which was comprised of every patient who had taken at least one dosage of the trial drug. The mean standard deviation (SD) for continuous variables and n (%) for categorical variables, respectively, were used to indicate the baseline characteristics of the individuals. Version 22 of the SPSS statistical software program (IB Corp., Armonk, NY, USA) was used for all results. Comparisons between two groups for quantitative parametric values were made using the Student's *t*-test. The Pearson's Chi-square test was utilized to compare categorical variables. If the *p*-value was lower than 0.05, the 95% confidence interval was used. For each treatment group, the numbers and percentages of all adverse events, AEs that resulted in drug cessation, and AEs of particular concern (such as hypoglycemia, UTIs, and diabetic ketoacidosis) were documented.

Results

Patients

In Figure 1, an enrollment flow chart is displayed. Following the completion of written informed consent, in a random assignment, 170 patients were given either 50 mg of sitagliptin (n = 85) or 12.5 mg of empagliflozin (n = 85) as an add-on to metformin and diet, of whom 157 (92.1%) completed all 12 weeks of treatment. In the sitagliptin group, 40 patients with HbA1c 7-10% entered the next phase (another 12-week treatment) by adding 12.5 mg empagliflozin twice daily, searching for more therapeutic control, while in the empagliflozin group, 28 patients entered into phase II by adding sitagliptin 50 mg twice daily. They were all incorporated into the full and safety analysis set after finishing phase II (12-week therapy).

With the exception of a female predominance in the sitagliptin group, baseline characteristics, and demographic variables were evenly distributed amongst the two groups. The average patients' age was 53.5 ± 9.57 years for the sitagliptin group and 53.1 ± 8.96 years for the empagliflozin group. The HbA1c values in the sitagliptin and empagliflozin groups were 8.3 ± 0.71% and 8.1 ± 0.76%, respectively, at baseline. Patients weight, FBG, PP, SBP,

and DBP values were 92.8 ± 15.4 kg, 160.7 ± 45.5 mg/dl, 216.2 ± 53.87 mg/dl, 132.1 ± 10.58 mmHg and 84.1 ± 7.3 mmHg for the sitagliptin group, while they were 92.9 ± 16.1 kg, 147.6 ± 34.97 mg/dl, 221.5 ± 51.36 mg/dl, 131.3 ± 11.0 mmHg, and 80.6 ± 6.2 mmHg for the empagliflozin group, respectively, and all were well compiled in Table I.

Efficacy

Table II demonstrates the efficacy of both groups after 12 weeks of treatment. With sitagliptin, the mean HbA1c values were 7.9 ± 1.8% (p = 0.253), and with empagliflozin, they were 6.7 ± 0.9% (p < 0.001). Empagliflozin caused a statistically significant reduction in HbA1c values (p < 0.001). With sitagliptin, the mean FPG levels were 149.5 ± 54.9 mg/dL (p = 0.412), while with empagliflozin, the mean FPG values were 116.9 ± 28.7 mg/dL (p < 0.001), with a substantially higher decrease in the empagliflozin group (p = 0.002). Mean PP values were 212.1 ± 91.6 mg/dl with sitagliptin (p = 0.829) and 147.8 ± 38.7 mg/dL with empagliflozin (p < 0.001), with a significantly higher decrease in the empagliflozin group (p < 0.001). The body weight reduced dramatically in the sitagliptin group (91.8 ± 15.8 kg; p < 0.003) as well as in the empagliflozin group (91.1 ± 15.9 kg; p = 0.003) without a difference of significance between the two groups (p = 0.870).

As regards blood pressure, DBP significantly decreased in the sitagliptin group as well as the empagliflozin group (p = 0.05 and 0.01, respectively), but the decrease was significantly observed in the empagliflozin group (0.024). However, SBP notably improved in those using empagliflozin (p = 0.008).

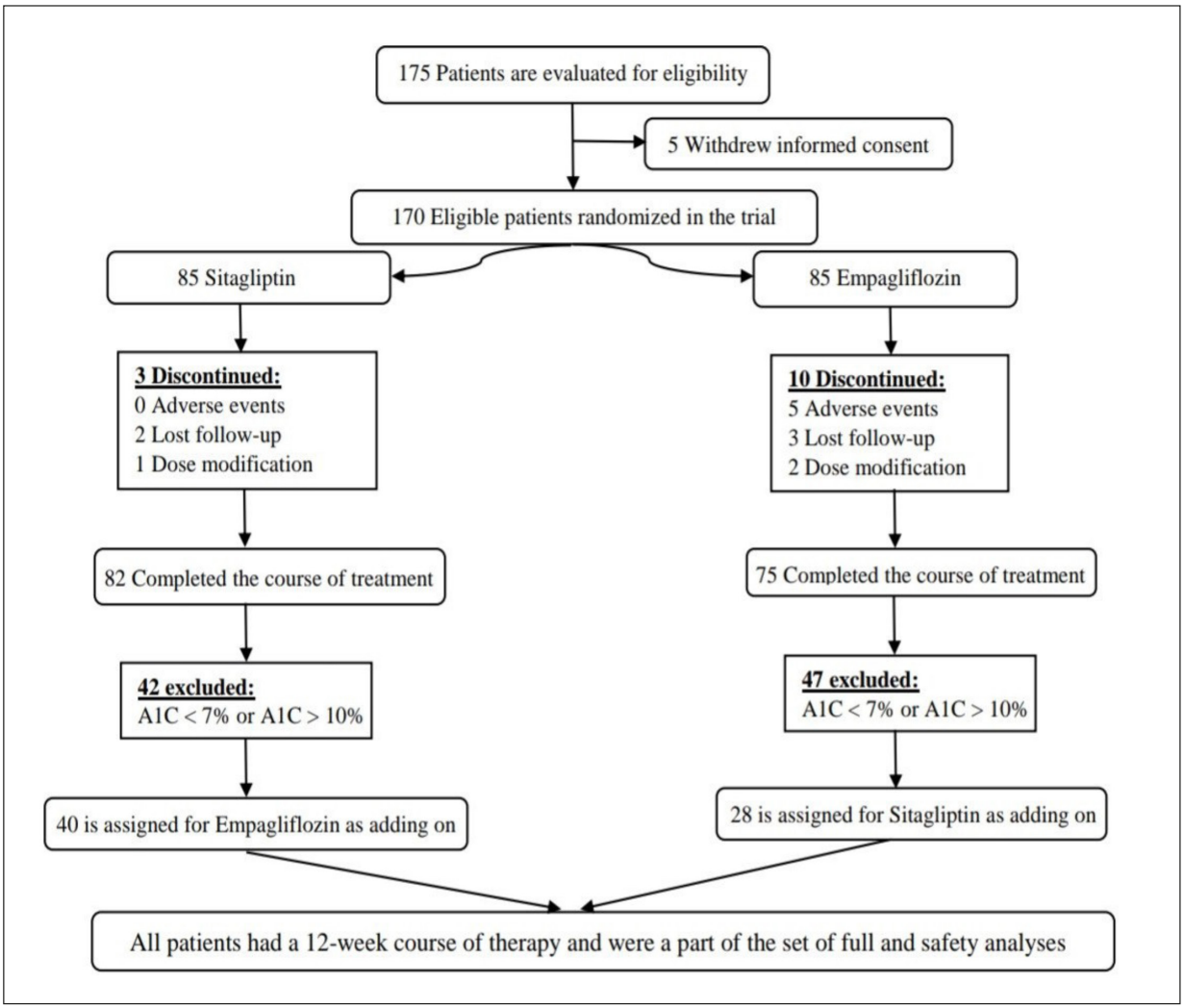

Figure 1. Flow chart of patient enrolment.

Table I. Data on both groups' demographics and baselines.

Parameters	Sitagliptin (n = 28)	Empagliflozin (n = 40)	*p*-value
Gender, n %			
Male	11 (39.3 %)	24 (60 %)	< 0.001
Female	17 (60.7 %)	16 (40 %)	
Age (years)			
Min.-Max.	35 - 70	30 - 66	0.862
Mean ± SD	53.500 ± 9.5704	53.100 ± 8.9637	
Body weight (Kg)			
Min.-Max.	60 - 121	55 - 127	0.979
Mean ± SD	92.839 ± 15.4315	92.943 ± 16.0518	
HbA1c (%)			
Min.-Max.	7.0 - 10	7.1 -10.0	0.285
Mean ± SD	8.275 ± 0.7127	8.080 ± 0.7630	
FPG (mg/dl)			
Min.-Max.	56 - 242	86 - 237	0.207
Mean ± SD	160.679 ± 45.5364	147.600 ± 34.9724	
PP (mg/dl)			
Min.-Max	122 - 313	129 - 314	0.683
Mean ± SD	216.179 ± 53.8730	221.525± 51.3615	
SBP (mmHg)			
Min.-Max.	120 - 170	110 - 160	0.739
Mean ± SD	132.143 ± 10.5785	131.250 ± 11.0215	
DBP (mmHg)			
Min.-Max.	70 - 110	70 - 90	0.039
Mean ± SD	84.107 ± 7.3350	80.625 ± 6.2211	

Fasting plasma glucose (FPG), postprandial plasma glucose (PP), systolic and diastolic blood pressure (DBP/SBP).

Figure 2 reveals significantly ($p < 0.001$) that patients with controlled HbA1c (< 7%) are more likely to be in the empagliflozin group than those treated by sitagliptin (90% *vs.* 35.7 %, respectively). Partially controlled HbA1c (7-10%) patients who needed another treatment option for more control were higher in the sitagliptin group than the empagliflozin group (53.6% *vs.* 10%). At the same time, patients with uncontrolled HbA1c (≥ 10%) who needed an insulin option to be controlled were also lower in the empagliflozin group than the sitagliptin group (0% *vs.* 10.7%).

Safety

The number of AEs over the course of the 12-week study was comparable in both treatment groups, as shown in Table III's AEs statistics. There were no cases of ketoacidosis, pancreatitis,

Table II. Clinical results after 12-week therapy period in both groups were compared to baseline.

Parameters	Sitagliptin as add on (n = 28)	*p*-value	Empagliflozin as add on (n = 40)	*p*-value	*p*-value after comparing both groups
HbA1c (%)					
Mean ± SD	7.943 ± 1.7549	0.253	6.698 ± 0.8592	< 0.001*	< 0.001*
FBG (mg/dl)					
Mean ± SD	149.500 ± 54.8706	0.412	116.925 ± 28.6682	< 0.001*	0.002*
PP (mg/dl)					
Mean ± SD	212.071 ± 91.6111	0.829	147.800 ± 38.7101	< 0.001*	< 0.001*
SBP (mmHg)					
Mean ± SD	129.643 ± 8.7060	0.1	127.250± 7.7584	0.008*	0.238
DBP (mmHg)					
Mean ± SD	81.607 ± 7.3350	0.05*	78.000 ± 5.5238	0.01*	0.024*
Body weight (Kg)					
Mean ± SD	91.768 ± 15.8076	0.03*	91.125 ± 15.9224	0.003*	0.870

Fasting plasma glucose (FPG), postprandial plasma glucose (PP), systolic and diastolic blood pressure (DBP/SBP).

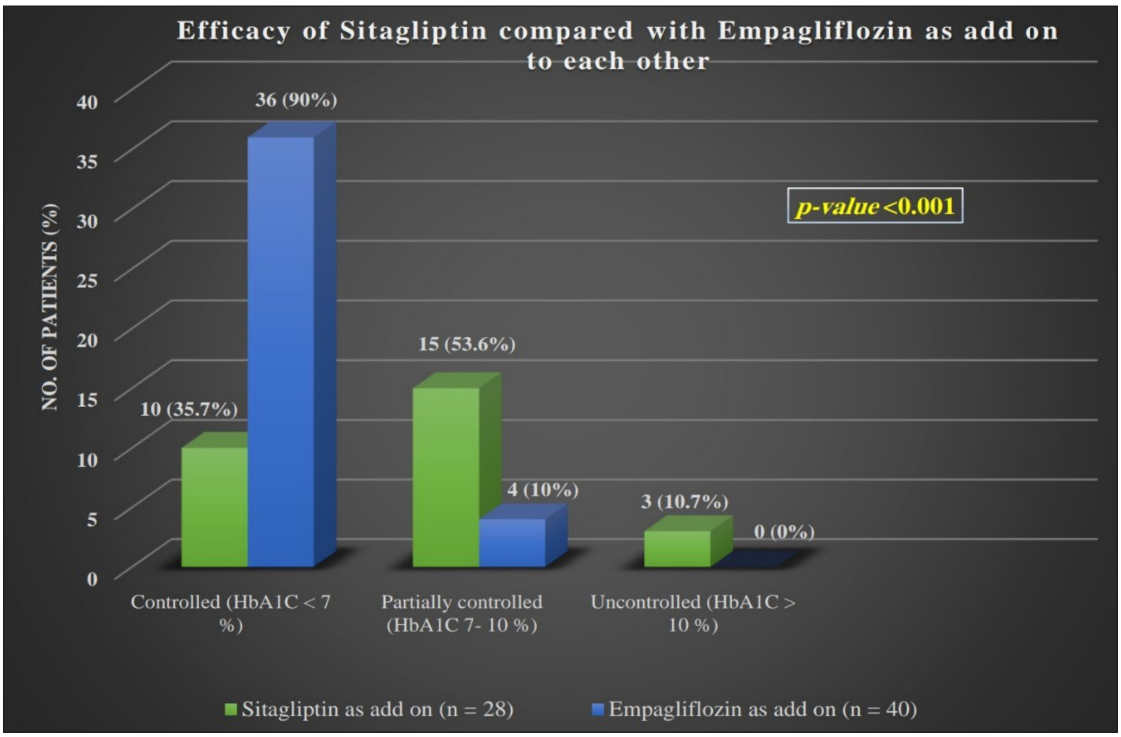

Figure 2. Efficacy of empagliflozin *vs.* sitagliptin on HbA1c when added to each other.

hypoglycemia, dehydration, hypersensitivity, or fatalities during the course of the therapy. However, UTI incidence in the empagliflozin group (7.5%) (the novel medication mechanism, which resulted in high levels of glucose being discharged in the urine, was most likely to blame) was reported to be double than that in the sitagliptin group (3.6%), but it was easily controlled and did not lead to any discontinuation in either group. As with nasopharyngitis, headache, hypotension, and gastrointestinal tract (GIT), upset occurred in both arms in nearly equal proportion and also with no discontinuation. Only one female patient suffered from a genital infection in the empagliflozin arm, but without discontinuation of the study treatment.

Table III. Adverse events in both groups during therapy.

AEs	Sitagliptin as add on (n = 28)	Empagliflozin as add on (n = 40)
One or more adverse effect	4 (14.3%)	2 (5%)
One or more adverse effect leading to discontinuation	0 (0%)	0 (0%)
Nasopharyngitis	1 (3.6%)	1 (2.5%)
Headache	3 (10.7%)	4 (10%)
UTI	1 (3.6%)	3 (7.5%)
Hypoglycemia	0 (0%)	0 (0%)
Genital infection	0 (0%)	1 (2.5%)
Hypersensitivity reactions	0 (0%)	0 (0%)
Pancreatitis	0 (0%)	0 (0%)
Hypotension	1 (3.6%)	1 (2.5%)
Dehydration	0 (0%)	0 (0%)
GIT upset	2 (7.1%)	2 (5%)
Diabetic ketoacidosis	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)

Gastrointestinal tract (GIT), urinary tract infection (UTI).

Discussion

Our study was in agreement with previous research[26] in that it was possible to improve glycemic control in untreated T2D patients without an increase in hypoglycemia by using a combination of metformin and low-hypoglycemic-risk anti-diabetic medications such as DPP_4i or $SGLT_2$i.

Clinically significant decreases in HbA1c levels, plasma glucose concentrations, blood pressure, and body weight were seen when empagliflozin was used alone or as part of combined therapy (as a single-pill treatment or add-on)[27]. It was safe to add it to an oral anti-diabetic regimen for T2D patients whose HbA1c levels had significantly decreased and had inadequate glycemic control[28,29]. Another study[30] revealed that when canagliflozin was introduced to metformin monotherapy-inadequately managed T2D, compared to placebo, it was well tolerated, enhanced glycemic management, and decreased body weight over the course of 24 weeks, compared to sitagliptin over the course of 52 weeks.

DPP-$_4$i are a well-tolerated and efficient second-line treatment for uncontrolled T2D, although they have no effect on body weight[28,29,31-33]. A meta-analysis[34] revealed that combining vildagliptin with metformin significantly decreased HbA1c, FPG, and body weight.

When talking about the triple therapy (DPP_4i plus $SGLT_2$i as an add-on to basic metformin), two studies[32,33] evaluated the single tablet combination with the individual components utilizing empagliflozin and linagliptin in treatment-naive patients[33], and as an addition to metformin[32]. Both studies compared the single-pill combination with the individual components. In both studies, after 24 weeks, when compared to each component alone, the HbA1c reductions for the empagliflozin/linagliptin single-tablet formulation were significantly higher ($p < 0.001$)[33], and at week 52, the efficacy remained unchanged[32].

Also, it was revealed[35] that in patients with poorly controlled T2D, dapagliflozin and metformin were both effective and well-tolerated when combined with gemigliptin as a triple therapy for 24 weeks.

According to safety, compared to placebo, combinations of empagliflozin were well tolerated, and monotherapy was not associated with a higher risk of hypoglycemia or genital infections. Although empagliflozin did not cause diabetic ketoacidosis more frequently than a placebo in clinical studies[27] up until now, doctors should be aware of the risk of this unusual occurrence. Similarly, DPP_4i demonstrated advantages in terms of well-tolerance and no elevated risk of hypoglycemia when used as a second-line treatment for T2D[31].

The percentage of participants experiencing AEs over the course of 52 weeks was comparable across treatment groups when comparing DPP_4i and $SGLT_2$i administered in combination as single-tablet therapy with each drug's separate component. No hypoglycemia-related AEs necessitating treatment were seen[32]. Nevertheless, another clinical trial[30] found that, over a 52-week period, the overall incidences of AEs and discontinuation due to AEs were generally comparable between groups receiving canagliflozin 100 mg, canagliflozin/sitagliptin, and placebo/sitagliptin, with a somewhat greater incidence in the canagliflozin 100 mg group. When comparing the groups, the sitagliptin group experienced more serious AEs and more AEs that resulted in discontinuation.

Because there is little difference in HbA1c with $SGLT_2$i *vs.* DPP-$_4$i as add-ons to metformin, clinical practitioners should base their decision between these glucose-lowering drugs on other efficacy criteria (such as cardiovascular and kidney protection, blood pressure changes, body weight, or safety profiles) rather than HbA1c levels[36].

In more than one trial[37], when comparing $SGLT_2$i to DPP_4i, there was a statistically significant decrease in HbA1c at ≥ 1 year, but there was no statistically significant difference at ≤ 6 months [MD (95% CI) = 0.05% (0.16, 0.05)]. Whether the study was longer than six months or shorter than a year, $SGLT_2$i significantly contributed to greater weight loss than DPP_4i.

Significant drops in body weight were observed in retrospective cohort research[38] on the impact of dapagliflozin addition to the treatment plan for T2D patients in Turkey, from 89.2 kg at baseline to 86.3 kg in the 3rd month (mean difference: -2.49) and to 85.1 kg in the 6th month (mean difference: -3.83; $p < 0.001$ for each). Systolic blood pressure was found to have significantly decreased after therapy, going from 131.9 mmHg at baseline to 126.1 mmHg in the 3rd month (mean difference -6.68) and to 124.1 mmHg in the 6th month (mean difference -7.78) ($p < 0.001$ for each). During the 3rd and 6th months of treatment, the diastolic blood pressure significantly decreased from 81.2 mmHg at baseline to 77.6 mmHg and 76.8 mmHg, respectively (mean difference: -4.16 and -4.29, respectively; $p < 0.001$ for each).

Our current study is almost compatible with the previously mentioned studies[37,38], in which adding empagliflozin for 12 weeks to uncontrolled

(HbA1c is > 7% and <10 %) Egyptian T2D patients after at least 12 weeks being treated with sitagliptin plus metformin caused a significant decrease in HbA1c as well as improvement in blood pressure and a reduction in body weight compared to the opposite (adding sitagliptin to uncontrolled empagliflozin plus metformin patients).

Finally, as a second-line medication to metformin for T2D in the US with or without cardiovascular disease, empagliflozin was more affordable than sitagliptin (at a threshold of $50,000/QALY)[39]. As a result, the utilization of combination therapy with DPP_4i and $SGLT_2$i early in the management of T2D is supported by the benefit of targeting several pathophysiological pathways for T2D. $SGLT_2$i results in a more significant HbA1c decrease, a greater reduction in weight, and a drop in blood pressure, but it also comes with more non-serious AEs, such as UTIs and vaginal infections. These results must be interpreted carefully due to the limited number of trials.

Only three-month patient follow-up is considered one of the important limitations of our study, and low funding and patient non-compliance affected our trial sample size. Also, the COVID-19 pandemic affected the out-patient flow rate to the hospital clinic.

Conclusions

Our study showed that sitagliptin and empagliflozin can be utilized as effective add-on agents in T2D patients who need more than two oral antidiabetics. More precisely, compared to sitagliptin combinations, empagliflozin combinations were more successful in lowering HbA1c, FPG, and PP, as well as improving blood pressure and body weight. Finally, the combination of empagliflozin plus sitagliptin and metformin was concluded to be effective, safe, and tolerable.

Authors' Contributions

H.G.Z., A.M.A., and M.A.A.M. were in charge of the study's concept and execution, processing of data, assessment and interpretation, methodology, and writing; H.M.R. and H.F.S. were in charge of supervision, article drafting, and revision. All authors read and approved the final published version of the manuscript.

Ethics Approval

The Institutional Review Board and Ethics Committee of October 6 University (Approval Number: PDC-Ph-2204018) approved the study. The study was conducted under the principles outlined in the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from all the participants in the study.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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