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RESEARCH

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Empagliflozin versus Sitagliptin as add-on dual therapy in Egyptian patients with type 2 diabetes inadequately controlled with Metformin: a 12-week randomized, open-label, parallel-group trial

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Abstract

Background Diabetes is one of the world's most widespread conditions, and diabetic patients are among the most likely to engage in fierce battles with this chronic disease. Which group should be added-on as a dual therapy for Egyptian patients with type 2 diabetes and inadequate glycemic management, HbA1c ≥ 7.0% and ≤ 10% (≥ 53 and ≤ 86 mmol/mol), following not less than 3 months of metformin and diet therapy, is still up for debate. Based on this ambiguity, we designed our study to compare the safety and efficacy of sitagliptin 50 mg (n = 85) with empagliflozin 12.5 mg (n = 85) twice daily as an adjunctive therapy to metformin and diet for a further 12 weeks. HbA1c after 12 weeks of open-label therapy was the major outcome measure.

Results After 12 weeks of treatment, empagliflozin drastically lowered HbA1c, FPG, PP, body weight, and triglycerides from baseline while significantly increasing LDL, total cholesterol, and HDL. On the other hand, sitagliptin significantly reduced FPG, PP (with a no discernable alteration in HbA1c), body weight, and triglycerides while significantly increasing HDL ($P \leq 0.001$ for all comparisons). Comparing the two groups, empagliflozin significantly reduced HbA1c, FPG, and PP while significantly increasing LDL and triglycerides than sitagliptin ($P < 0.001$ for all except FPG, $P = 0.005$). More patients receiving empagliflozin 12.5 mg than sitagliptin 50 mg twice daily reported adverse events during open-label treatment (11.8% vs. 8.2%, respectively).

Conclusions In type 2 diabetic Egyptian patients uncontrolled with metformin and diet, empagliflozin was superior to sitagliptin as regards glycemic control, weight, and SBP/DBP reduction.

Keywords T2DM, Sitagliptin, Empagliflozin, Dual therapy

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1 Background

A body's failure to perform the physiological function of insulin is what causes diabetes, a significant long-term pathological condition. More than 463 million people worldwide complain of diabetes, and it's predicted that figure will increase to 578 million by 2030 and 700 million by 2045 [1]. It is now understood that type 2 diabetes (T2D), the most prevalent type of the disease, develops as a result of poor communication between ß-cells in the pancreas and insulin-sensitive organs [2].

As 1st line pharmacological therapy for those with T2D who cannot accomplish controlled glucose levels by lifestyle adjustments, metformin is recommended [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 unavoidably the case, blood glucose control cannot be maintained with diet, lifestyle changes, and metformin as a monotherapy [3]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) both claim that the optimal agent to combine with metformin is not always recommended, so tolerability, especially hypoglycemia and weight gain, should be a key factor [3].

As a second-line therapy for T2D, the most recent ADA and EASD consensus report proposes selecting one of five anti-diabetic medication classes. Three of these emerging anti-diabetic drug families include GLP-1RAs (glucagon-like peptide-1 receptor agonists), $SGLT_2$i (sodium glucose cotransporter-2 inhibitors), and DPP_4i (dipeptidyl peptidase-4 inhibitors) [5].

In genuine clinical practice, it has been possible to access DPP_4i (e.g. sitagliptin, vildagliptin, alogliptin, saxagliptin and linagliptin) for more than ten years. They have generally good glycemic efficacy, high tolerability profiles, and a low possibility of adverse effects such as hypoglycemia and weight gain [6, 7]. They have been shown to increase insulin secretory capability and beta-cell activity, and as a result, they may be useful for use in patients who are still at an early stage of the disease and have some beta-cell function [8, 9]. The first and most often used medication in this class worldwide is sitagliptin [10, 11]. Although sitagliptin's effective glycemic qualities have been demonstrated, there is ongoing debate regarding its impact on non-glycemic factors such as body weight, cholesterol, and insulin sensitivity [12–14].

Empagliflozin is a potent and particular $SGLT_2$i. In phase III trials, empagliflozin was connected to clinically meaningful improvements in weight and glycemic control as well as decreases in blood pressure (BP), either alone or in combination with other medications. The risk of hypoglycemia was decreased, and empagliflozin was well tolerated [15–21]. The main combined cardiovascular result (nonfatal myocardial infarction, death from cardiovascular causes, or nonfatal stroke) additionally to overall mortality were both decreased in empagliflozin-treated high cardiovascular risk T2D patients [22, 23]. $SGLT_2$i are one of the 2nd or 3rd line recommended therapeutic options for people with T2D, and it is recommended to combine $SGLT_2$i with DDP_4i and metformin as triple therapy [24].

Today, it is clear that not all patients benefit equally from antidiabetic medications in terms of effectiveness and safety of empagliflozin 12.5 mg to sitagliptin 50 mg twice daily as add-on therapy in uncontrolled T2D Egyptian patients after at least 12 weeks of treatment using metformin and diet.

2 Patient and methods

2.1 Research strategy

This parallel-design, randomized, prospective study was carried out at the internal medicine clinic of University Hospital from 20 September 2020 to 20 January 2022. The study's execution received no financial help from the pharmaceutical sector. Throughout the study's implementation, the Declaration of Helsinki and best clinical practice standards were observed. Before taking part, every participant provided a written statement of informed consent.

2.1.1 Patients

In the trial, patients between the ages of 30–65 with poorly managed T2D (HbA1c > 7% but ≤ 10%) who were also receiving a consistent dose of metformin (1000 mg twice daily, unchanged for not less than 12 weeks before screening) were included. Type 1 diabetes, HbA1c > 10%, pregnancy, chronic liver disease, elevated alanine aminotransferase, aspartate aminotransferase, creatine phosphokinase, albumin < 3.5 g/dl, high bilirubin, INR > 1–2, renal impairment (Crcl ≤ 50 ml/min), pancreatitis, urinary tract infection (UTI), and diabetic ketoacidosis within six months of enrollment were the exclusion criteria Additionally, individuals who had been treated with anti-obesity medications or GLP-1RAs within 12 weeks prior to enrollment, as well as those who failed to attend subsequent consultations, were also excluded.

2.2 Treatment

In addition to the standard metformin (1000 mg twice daily) regimen, we randomized eligible patients in a 1:1 ratio to receive either 50 mg of sitagliptin or 12.5 mg of empagliflozin twice daily for a period of 12 weeks. At screening and at weeks 0 and 12 of therapy, study visits were planned. No dosage changes were permitted for the research drug.

2.3 Outcome measures

The key effectiveness metric was any variation in HbA1c from baseline at week 12 along with four important secondary efficacy variables: (i) change in fasting plasma glucose (FPG) and postprandial plasma glucose (PP); (ii) change in body weight; (iii) change in systolic blood pressure (SBP) and diastolic blood pressure (DBP); and (iv) change in lipid profile: total cholesterol, low density lipoprotein (LDL), triglycerides (TG), and high density lipoprotein (HDL).

Adverse events (AEs), clinical laboratory data, and vital signs were all regarded as safety endpoints (AEs; utilizing suggested terminology in line with version 17.1 of the Medical Dictionary for Drug Regulatory Activities [MedDRA]). Treatment-emergent AEs were defined as any AEs that started after the 1st dose of empagliflozin or sitagliptin and persisted up to one week following the final research medication dose. AEs of special interest included hypoglycemia, genitourinary infections, hypersensitivity reactions, diabetic ketoacidosis, acute pancreatitis, hypotension, and dehydration. Events having a plasma glucose content of less than 3.9 mmol/L were considered to be confirmed hypoglycemia AEs.

2.4 Sample size

A sample size of 85 patients in each group would have 80% power to detect any possible benefits of adding empagliflozin over sitagliptin on HbA1c, assuming a HbA1c mean difference of 0.5, a standard deviation (SD) of 1, an alpha error of 0.05, a beta error of 0.2, and a 20% attrition rate.

2.5 Statistical analysis

The whole analysis set, or all patients who took the study drugs for 12 weeks and had post-baseline values for efficacy variables evaluated after the treatment period, was used to conduct 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 SD and n (%) of patients, respectively, are used to indicate the baseline characteristics of the participants for continuous and categorical variables. All analyses were done using the SPSS statistical software package, version 22. Comparisons between two groups for quantitative parametric values were done using the Student T test. We compared categorical variables using the Pearson Chi-square test. *P*-values lower than or equal to 0.05 will be deemed significant. i.e., a 95% confidence interval was used. For each treatment group, the numbers and percentages of all AEs, AEs that resulted in drug cessation, and AEs of particular concern (such as hypoglycemia, UTIs, and diabetic ketoacidosis) were documented.

3 Results

3.1 Patients

Figure 1 displays a flowchart of the patient enrollment process. After withdrawing 5 patients during the written

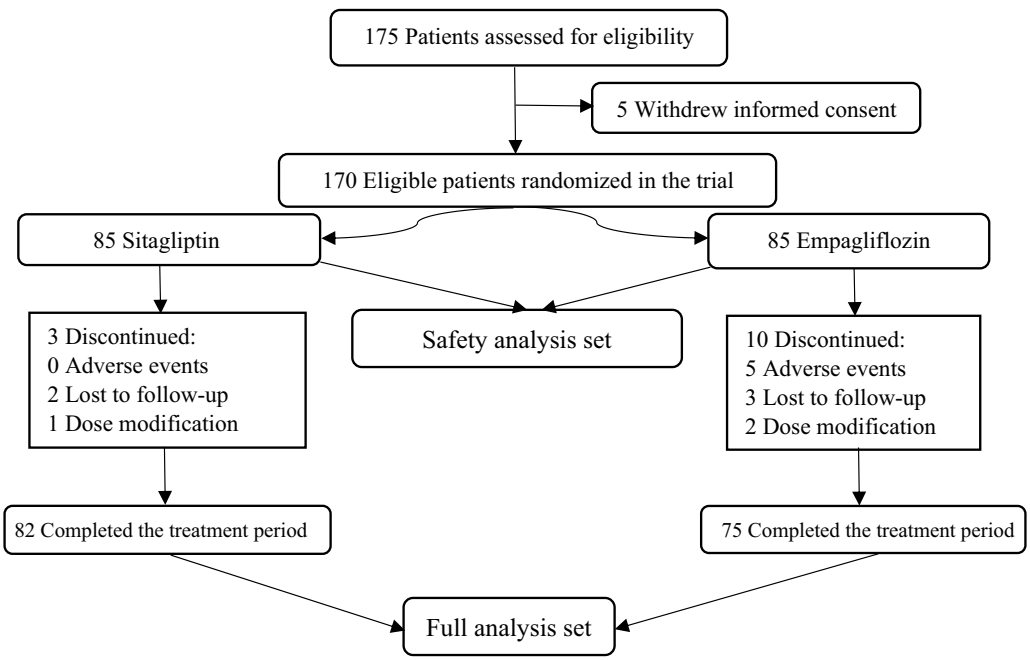

Fig. 1 Flow chart of patient enrollment

informed consent, an overall 170 patients were ascribed at random to receive either 50 mg of sitagliptin (n = 85) or 12.5 mg of empagliflozin (n = 85). Of these patients, 157 (92.1%) finished the full 12 weeks of treatment. Despite being removed from the trial due to adverse events (AEs), lost to follow-up, or dose change, the safety analysis set contained three patients receiving sitagliptin and ten individuals receiving empagliflozin.

A female predominance in the sitagliptin group was the only difference in the demographic and baseline characteristics between the two groups. In the sitagliptin group, the mean patient age was 53.5 ± 8.7 years, whereas in the empagliflozin group, it was 53.4 ± 10.2. The baseline HbA1c values for the sitagliptin and empagliflozin groups were 8.5 ± 1.0% and 8.3 ± 0.84%, respectively. Patients weight, FBG, PP, LDL, total cholesterol, HDL, Triglycerides, SBP, and DBP values were 91.1 ± 15.4 kg, 184.2 ± 64.4 mg/dl, 271.9 ± 89.3 mg/dl, 124.9 ± 28.5 mg/dl, 203.1 ± 39.2 mg/dl, 46.1 ± 10.6 mg/dl, 207.1 ± 72.8 mg/dl, 134.5 ± 16.3 mmHg, and 83.0 ± 13.5 mmHg in the sitagliptin group, while they were 93.3 ± 17.95 kg, 164.6 ± 45.2 mg/dl, 258.6 ± 110.2 mg/dl, 130.1 ± 28.9 mg/dl, 207.0 ± 38.8 mg/dl, 43.96 ± 10.2 mg/dl, 194.8 ± 66.7 mg/dl, 136.7 ± 17.8 mmHg, and 85.6 ± 10.8 mmHg in the empagliflozin group, respectively, and all were well summarized in Table 1.

Table 1 Baseline and demographic data in both groups

Parameters	Sitagliptin (n = 82)	Empagliflozin (n = 75)	*p*-Value
Gender, n%			
Male	33 (40.2%)	40 (53.3%)	< 0.001
Female	49 (59.8%)	35 (46.7%)	
Age (years)			
Min.–Max	30–67	21–70	0.948
Mean ± SD	53.524 ± 8.6670	53.427 ± 10.2300	
Body weight (kg)			
Min.–Max	54–123	59–145	0.411
Mean ± SD	91.055 ± 15.4488	93.267 ± 17.9548	
HbA1c (%)			
Min.–Max	7.0–10.0	7.0–10.0	0.227
Mean ± SD	8.495 ± 1.0000	8.316 ± 0.8350	
FPG (mg/dl)			
Min.–Max	84–401	88–289	0.030
Mean ± SD	184.244 ± 64.4208	164.600 ± 45.1580	
PP (mg/dl)			
Min.–Max	127–481	91–869	0.409
Mean ± SD	271.915 ± 89.2699	258.573 ± 110.2033	
LDL (mg/dl)			
Min.–Max	66–187	42–223	0.258
Mean ± SD	124.902 ± 28.5024	130.120 ± 28.9491	
Total Cholesterol (mg/dl)			
Min.–Max	140–306	112–307	0.532
Mean ± SD	203.098 ± 39.1879	207.000 ± 38.7748	
HDL (mg/dl)			
Min.–Max	30–66	30–67	0.197
Mean ± SD	46.110 ± 10.5993	43.960 ± 10.1893	
TG (mg/dl)			
Min.–Max	90–387	92–463	0.270
Mean ± SD	207.134 ± 72.7629	194.800 ± 66.7472	
SBP (mmHg)			
Min.–Max	110–190	110–240	0.418
Mean ± SD	134.512 ± 16.2847	136.733 ± 17.8298	
DBP (mmHg)			
Min.–Max	70–140	60–110	0.193
Mean ± SD	83.049 ± 13.5345	85.600 ± 10.8416	

3.2 Efficacy

Table 2 demonstrates the efficacy of both groups after 12 weeks of treatment. Mean HbA1c values were 8.3 ± 1.9% with sitagliptin ($P = 0.293$) and 7.2 ± 1.3% with empagliflozin ($P < 0.001$), with a substantially higher reduction in the empagliflozin group ($P < 0.001$), Mean FPG values were 155.3 ± 59.4 mg/dl with sitagliptin ($P = 0.001$) and 131.7 ± 43.3 mg/dL with empagliflozin ($P < 0.001$), with a noticeably larger decrease in the empagliflozin group ($P = 0.005$). Mean PP values were 225.0 ± 87.1 mg/dl with sitagliptin ($P = 0.001$) and 178.2 ± 66.9 mg/dl with empagliflozin ($P < 0.001$), with a noticeably larger decrease in the empagliflozin group ($P < 0.001$). For the sitagliptin group, there was a discernible drop in body weight (89.8 ± 15.5 kg; $P < 0.001$), as well as in empagliflozin group (91.9 ± 18.0 kg; $P = 0.001$), without discernible differences between the two groups ($P = 0.437$).

There was a non-significance difference in SBP and DBP in both groups, either comparing to the baseline of each group or comparing both groups with each other ($P = 0.203$, $P = 0.041$, respectively). According to the patient's lipid profile, there was a non-significant difference in LDL (121.6 ± 29.7, $P = 0.377$) and total cholesterol (194.8 ± 42.4, $P = 0.109$) in the sitagliptin group, while there was a substantial variation (143.96 ± 25.3, $P < 0.001$; 220.6 ± 33.0, $P = 0.001$) in the empagliflozin group, leading to a substantial variation comparing the both groups ($P < 0.001$). Unlike triglyceride, HDL has a significant increase in both groups (49.1 ± 9.4, $P < 0.001$ in sitagliptin; 48.7 ± 8.3, $P < 0.001$ in empagliflozin), but for both triglyceride and HDL, there is no discernible differences between the sitagliptin and empagliflozin groups ($P = 0.049$, 0.788, respectively).

The following figure (Fig. 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 (44 vs. 22, respectively).

Table 2 Clinical outcomes in both groups after 12-week therapy compared by baseline

Parameters	Sitagliptin (n = 82)	*p*-Value	Empagliflozin (n = 75)	*p*-Value	*p*-Value after comparing both groups
HbA1c (%)					
Mean ± SD	8.272 ± 1.9169	0.293	7.177 ± 1.3182	< 0.001	< 0.001
FBG (mg/dl)					
Mean ± SD	155.305 ± 59.4488	0.001	131.693 ± 43.2938	< 0.001	0.005
PP (mg/dl)					
Mean ± SD	225.012 ± 87.0772	0.001	178.173 ± 66.9137	< 0.001	< 0.001
LDL (mg/dl)					
Mean ± SD	121.646 ± 29.6937	0.377	143.960 ± 25.3428	< 0.001	< 0.001
Total cholesterol (mg/dl)					
Mean ± SD	194.841 ± 42.3581	0.109	220.573 ± 33.0410	0.001	< 0.001
HDL (mg/dl)					
Mean ± SD	49.061 ± 9.3800	< 0.001	48.680 ± 8.3004	< 0.001	0.788
TG (mg/dl)					
Mean ± SD	165.866 ± 60.9488	< 0.001	147.947 ± 52.1067	< 0.001	0.049
SBP (mmHg)					
Mean ± SD	128.951 ± 17.4150	0.009	132.067 ± 12.9211	0.016	0.203
DBP (mmHg)					
Mean ± SD	80.463 ± 6.2226	0.074	82.867 ± 8.3494	0.006	0.041
Body weight (kg)					
Mean ± SD	89.807 ± 15.4907	< 0.001	91.907 ± 18.0076	0.001	0.437

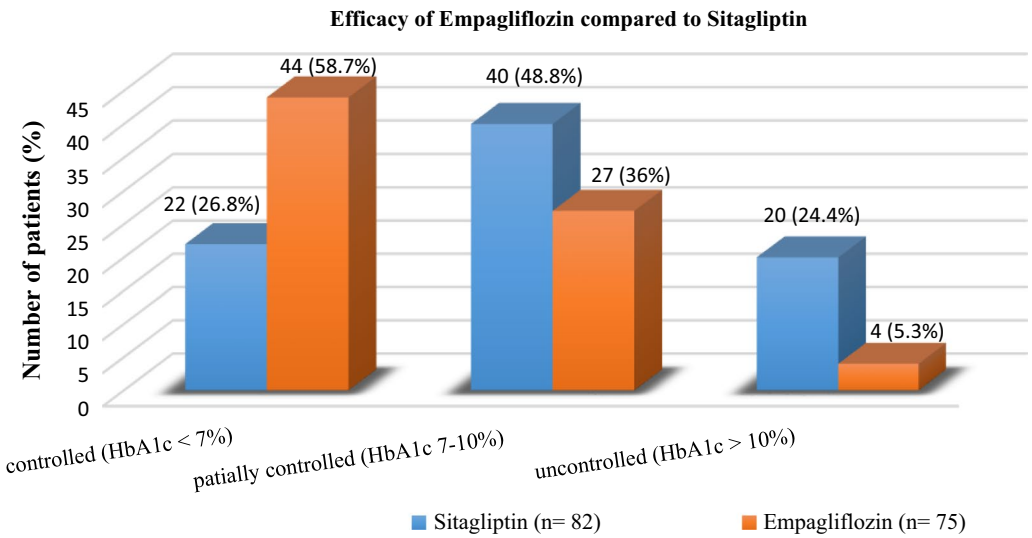

Fig. 2 Effect of empagliflozin vs. sitagliptin on HbA1C

Partially controlled HbA1c (7–10%) patients who needed another treatment option for more control were greater in the sitagliptin group than the empagliflozin group (40 vs. 27). At the same time, patients with uncontrolled HbA1c (≥ 10%) who needed insulin option to be controlled were likewise less in the empagliflozin group than the sitagliptin group (4 vs. 20).

3.3 Safety

Table 3 provides information on AEs, and during the 12-week research period, AE frequency was comparable

Table 3 Adverse events in both groups during therapy

	Sitagliptin (n = 85)	Empagliflozin (n = 85)
One or more adverse effects	7 (8.2%)	10 (11.8%)
One or more adverse effects leading to discontinuation	0 (0%)	5 (5.9%)
Nasopharyngitis	5 (5.9%)	3 (3.5%)
Headache	1 (1.2%)	2 (2.4%)
UTI	2 (2.4%)	3 (3.5%)
Hypoglycemia	0 (0%)	1 (1.2%)
Genital infection	0 (0%)	2 (2.4%)
Hypersensitivity reactions	2 (2.4%)	0 (0%)
Pancreatitis	2 (2.4%)	0 (0%)
Hypotension	0 (0%)	1 (1.2%)
Dehydration	0 (0%)	0 (0%)
Diabetic ketoacidosis	0 (0%)	0 (0%)
GIT upset	3 (3.5%)	2 (2.4%)
Death	0 (0%)	0 (0%)

between the two treatment groups. Neither fatalities nor ketoacidosis were noted while receiving treatment. However, one AE, a urinary tract infection, resulted in the research being stopped in five patients in the empagliflozin group. The most likely reason for this was the distinct pharmacological action, which caused large levels of glucose to be discharged in the urine. While two female patients who were using sitagliptin had UTIs, the medication was not stopped. In the empagliflozin group, there was just one patient (1.2%) who experienced hypoglycemia-related episodes. However, no cases of severe hypoglycemia were reported, and no patients dropped out of the research as a result. Pancreatitis occurred in two (2.4%) patients in the sitagliptin group but did not lead to therapy discontinuation. As with nasopharyngitis, headache and GIT upset occurred in both arms, but also with no discontinuation.

4 Discussion

In this trial, T2D Egyptian patients were compared to sitagliptin and empagliflozin for add-on therapy if glycemic control could not be maintained with diet and metformin. When compared to sitagliptin 100 mg daily, treatment with twice daily 12.5 mg empagliflozin for 12 weeks reduced mean HbA1c, FPG, and PP in individuals with T2D whose condition was insufficiently controlled after at least 12 weeks of metformin therapy along with diet control. With empagliflozin 12.5 mg twice daily added to metformin with diet control, the percentage of individuals with an initial HbA1c (≥7.0%) who reached a HbA1c (<7.0%) after 12 weeks was approximately twice that with sitagliptin 50 mg twice daily added to metformin plus diet control, and empagliflozin-treated patients in comparison to sitagliptin-treated patients had considerably fewer individuals whose HbA1c continued to rise (>10.0%) and required insulin treatment addition.

Patients prioritize losing weight or preventing weight gain [19], since doing so is linked to poorer quality of life and treatment satisfaction in terms of health [20]. Empagliflozin may cause weight loss because of increased urine glucose excretion, which burns calories [17], whereas sitagliptin is considered to be weight-neutral [5, 18]. In our study, both patients receiving either empagliflozin 12.5 mg or sitagliptin 50 mg twice daily significantly decreased their mean body weight from baseline, but without a difference that is statistically significant with regard to the two groups (1.4 vs. 1.2 kg, respectively).

In our study, both the empagliflozin and sitagliptin therapy groups experienced slight, non-significant decreases in the mean DBP and SBP changes from the starting point at week 12. The effects on BP seen in this study could have been altered by alterations in the prescription of antihypertensive medications, which this study did not account for. According to earlier research, empagliflozin lowers blood pressure through potential diuretic impacts, weight reduction, and improved glucose management [21], but gliptins have no BP-lowering effects [22].

As regards lipid profile, our study revealed significant improvement in triglyceride and HDL and non-significant improvement in LDL and total cholesterol in the sitagliptin group, while valuable deterioration in LDL, total cholesterol, and TG but HDL improvement in the empagliflozin group. These outcomes were in harmony with earlier research, which clarified a remarkable increase in LDL [25] and HDL in patients receiving empagliflozin [26], while patients receiving sitagliptin showed improvement in TG, HDL, and LDL. However, it is yet uncertain if sitagliptin treatment can reduce cardiovascular events. [27].

Adding either 12.5 mg of empagliflozin or 50 mg of sitagliptin twice daily to metformin during the study period was tolerated effectively; a smaller number of individuals in the sitagliptin group than in the empagliflozin group reported adverse events. In our trial, neither patients receiving empagliflozin 25 mg nor sitagliptin 100 mg when added to metformin experienced any documented hypoglycemia AEs. Given the current treatment guidelines, it is crucial that both empagliflozin and sitagliptin have a minimal risk of hypoglycemia [1].

Despite the fact that patients receiving empagliflozin 25 mg were more likely to experience these events than those receiving sitagliptin, only a small number of patients in each treatment group experienced UTIs

or genital infections. The same as for pancreatitis, was confined to the sitagliptin group but also occurred in low proportions in patients. When analyzing a limited number of AEs, it is important to keep in mind that our study had a relatively small sample size. In our investigation, the exposure time and follow-up time for AEs were also fairly long. Hence, we aim to conduct phase II of our study to examine the prolonged impact of the medications, as well as its associated AEs.

4.1 Limitations

Only three-month patient follow-up was anticipated to be one of the major drawbacks of our trial, and low funding and patient non-compliance affected our trial sample size. Also, the COVID-19 pandemic affected the outpatient flow rate to the hospital clinic.

5 Conclusion

As add-on therapy for T2D not controlled with metformin and diet, we conclude that although both empagliflozin and sitagliptin were well tolerated and improved body weight and BP, empagliflozin had more significant glycemic control than sitagliptin. Both agents significantly increased HDL and reduced TG and body weight. Despite significant glycemic control, patients receiving empagliflozin showed significant increases in LDL and total cholesterol. DBP and SBP were only slightly reduced by either medication. Based on our findings, when metformin and diet alone are unable to control T2D, we advise empagliflozin as an additional medication.

Abbreviations

T2D	Type 2 diabetes
ADA	American Diabetes Association
EASD	European Association for the Study of Diabetes
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
$SGLT_2i$	Sodium glucose cotransporter-2 inhibitors
DPP_4i	Dipeptidyl peptidase-4 inhibitors
BP	Blood pressure
UTI	Urinary tract infection
FPG	Fasting plasma glucose
PP	Postprandial plasma glucose
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LDL	Low density lipoprotein
TG	Triglyceride
HDL	High density lipoprotein
AEs	Adverse events
SD	Standard deviation

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Author contributions
HGZ, AMA and MAAM the study idea and design, data processing, analysis and interpretation, methodology, conceptualization, and writing; HMR and HFS supervising, drafting the article, and revision. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee and Institutional Review Board of October 6 University (Approval Number: PDC-Ph-2204018) as the trial was conducted at October 6 University Hospital internal medicine clinic. The study (ClinicalTrials.gov no. NCT05359341) was conducted under the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all the participants in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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