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Comparative Study between combination therapy Empagliflozin–Sitagliptin and Empagliflozin–Alogliptin in addition to Metformin assessing the hypoglycemic effect on patients diagnosed with malignancy and poorly controlled Type 2 diabetes mellitus as comorbidity

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) in patients with malignancy poses unique therapeutic challenges, necessitating effective and safe combination therapies. This study compared the efficacy and safety of empagliflozin–sitagliptin–metformin versus empagliflozin–alogliptin–metformin in poorly controlled T2DM with coexisting cancer.

Methods: Prospective, randomized, open-label clinical trial of 12 weeks was performed in 120 patients with T2DM and controlled malignancy. Two groups were randomized: Group A, who received empagliflozin 10 mg combined with sitagliptin 100 mg along with metformin, and Group B, who received empagliflozin 10 mg combined with alogliptin 25 mg along with metformin. Primary endpoint was HbA1c change; secondary endpoints were fasting plasma glucose (FPG), postprandial glucose (PPG), body weight, lipid profile, and adverse events. Data were examined using repeated-measures ANOVA and independent t-tests with $p<0.05$ being significant.

Results: Baseline demographics were similar between groups. At 12 weeks, Group A had a larger mean decrease in HbA1c (−1.4% ± 0.3) than Group B (−1.1% ± 0.4; p=0.02). FPG and PPG also dropped significantly lower in Group A (−37.7 mg/dL and −54.1 mg/dL, respectively) than Group B (−31.7 mg/dL and −46.2 mg/dL; $p<0.05$). Both regimens were tolerated without difficulty, with minimal hypoglycemia and urinary tract infection being the only adverse events noted, and no deterioration of malignancy symptoms.

Conclusion: Empagliflozin–sitagliptin–metformin yielded better glycemic control than empagliflozin–alogliptin–metformin in T2DM patients with malignancy without compromising safety. This combination may be a more potent treatment option for managing complex diabetic populations.

Keywords: *Empagliflozin, Sitagliptin, Alogliptin, Metformin, Type 2 Diabetes Mellitus, Malignancy.*

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a long-standing metabolic disorder often complicated by comorbidities like malignancies, rendering the treatment more difficult and the clinical outcome worse. Optimization of glycaemia in such patients requires effective, safe, and acceptable treatment regimens. Among newer pharmacologic agents, sodium–glucose cotransporter-2 inhibitors (SGLT2i) such as empagliflozin and dipeptidyl peptidase-4 inhibitors (DPP-4i) such as sitagliptin and alogliptin have proved to be beneficial when combined with metformin.

Certain comparative studies had determined the effectiveness of sitagliptin plus metformin, with acceptable glycemic response and safety profiles compared to sulfonylureas like glimepiride [1]. Likewise, research studies have compared the metabolic as well as lipid-altering effects of newer drugs like Terminalia arjuna, with newer interests in combination therapy in metabolic disorders [2-4]. Clinical trials have even compared empagliflozin and sitagliptin as add-on to metformin, determining their antihyperglycemic effectiveness and tolerability in type 2 diabetic patients with suboptimal glycemic control [5,6].

Moreover, combination therapy trials provide evidence of the greater glycemic control by triple-drug treatment compared to dual therapies. For instance, the combination between sitagliptin–metformin and empagliflozin or vice versa demonstrated enhanced glycemic parameters among Egyptian T2DM patients [7]. Similarly, fixed-dose combinations of dapagliflozin, sitagliptin, and metformin also demonstrated equal advantages, which underscore the therapeutic effectiveness of combined therapeutic approaches in poorly controlled T2DM [8].

Lacking comparative effectiveness data on empagliflozin–sitagliptin vs. empagliflozin–alogliptin combination, especially in patients with concomitant malignancy, the current study will compare their clinical activity to metformin treatment.

2. METHODOLOGY

Study Design
This research was a prospective, randomized, open-label, comparative clinical trial spanning 12 weeks. The main aim was to evaluate the efficacy and safety of combination regimens—empagliflozin with sitagliptin compared with empagliflozin with alogliptin—added to metformin in patients with poorly controlled type 2 diabetes mellitus (T2DM) with concomitant malignancy.

Study Population
Patients aged 40 to 70 years with clear diagnosis of T2DM and co-existing underlying malignancy in stable oncological control were enrolled. Participants on constant doses of metformin (≥1500 mg/day) for ≥12 weeks with suboptimal glycemic control were enrolled, with HbA1c levels between 7.5% to 10%. Participants with severe renal impairment (eGFR <45 mL/min/1.73 m²), active liver disease, history of hypersensitivity reaction to study medication, or on insulin were not enrolled.

Randomization and Intervention
Participants were randomly assigned in a 1:1 ratio to two groups through computer-generated block randomization. Group A was given empagliflozin 10 mg once daily and sitagliptin 100 mg once daily, with metformin continued. Group B was given empagliflozin 10 mg once daily and alogliptin 25 mg once daily, with metformin continued at the same dose. Adherence was assessed at each follow-up visit through pill counting and patient diaries.

Clinical and Laboratory Evaluations
Baseline assessment consisted of demographic information, body mass index (BMI), blood pressure, duration of diabetes, type and stage of cancer, and history of previous treatment. Laboratory assessment consisted of fasting plasma glucose (FPG), postprandial plasma glucose (PPG), glycated hemoglobin (HbA1c), lipid profile, renal function tests, and liver function tests. The tests were repeated at 6 weeks and 12 weeks to assess changes in magnitude. Adverse events and complications of cancer therapy were monitored with vigilance during the study.

Outcome Measures
The primary endpoint was the change in HbA1c from baseline to week 12. Secondary endpoints were change in FPG, PPG, body weight, BMI, and lipid profile. Safety endpoints were the frequency of hypoglycemia, urinary tract infections, gastrointestinal disturbance, and any increase in cancer-related symptoms. **Statistical Analysis** Data were tabulated and also analyzed using SPSS software version XX. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as percentage. Group differences were compared with independent t-tests for continuous variables and chi-square tests for categorical variables. For comparing the changes in the glycemic parameters at time points, a repeated-measures ANOVA was applied. A p-value of <0.05 was employed to find the significance of the tests.

3. RESULT

Baseline Characteristics120 patients were enrolled and randomized into two groups, Group A (empagliflozin–sitagliptin–metformin, n=60) and Group B (empagliflozin–alogliptin–metformin, n=60). The two groups were similar at baseline for demographic profiles, the duration of diabetes, malignancy type, and metabolic parameters. The patients' mean ages were 56.4 ± 7.9 years in Group A and 55.8 ± 8.1 years in Group B. The patients' mean baseline HbA1c was 8.7% ± 0.6 in Group A and 8.6% ± 0.7 in Group B, with no statistically significant difference.

Table 1. Baseline Demographic and Clinical Characteristics

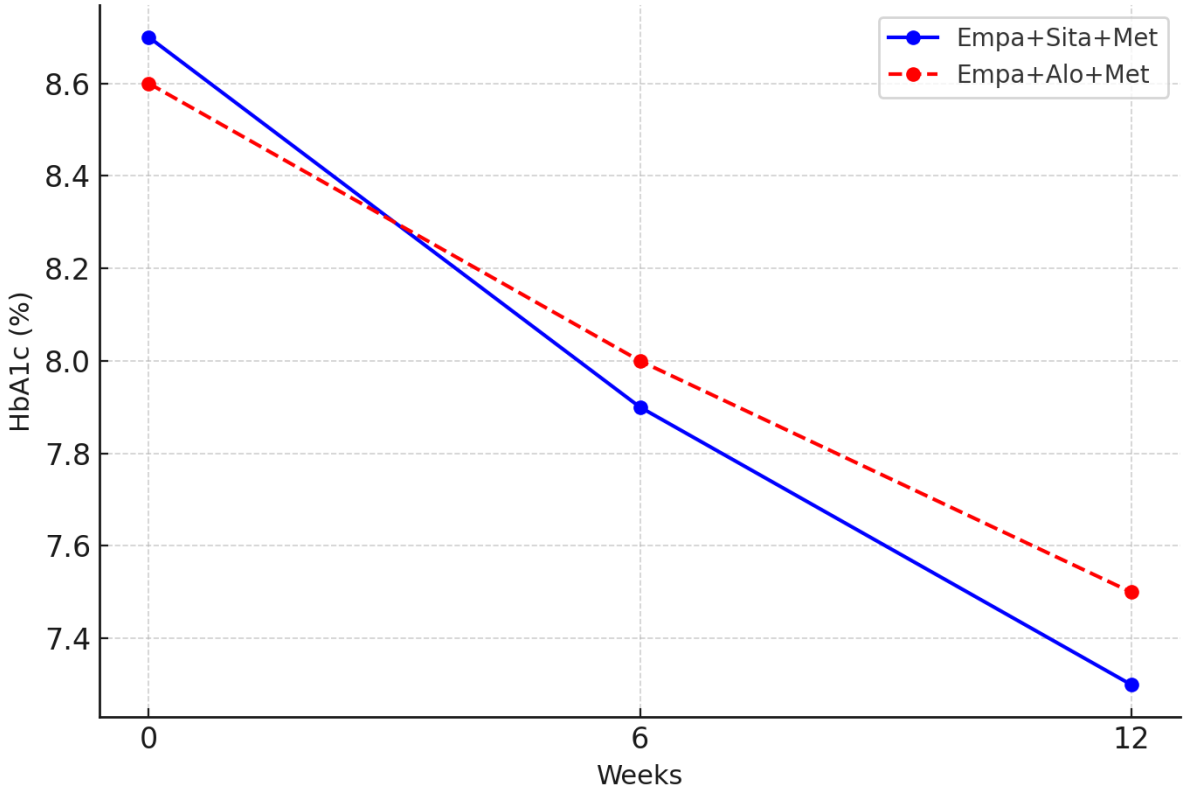
Parameter	Group A (Empa+Sita+Met)	Group B (Empa+Alo+Met)	p-value
Number of patients (n)	60	60	–
Age (years, mean ± SD)	56.4 ± 7.9	55.8 ± 8.1	0.71
Male/Female (%)	52/48	55/45	0.68
Duration of T2DM (years)	8.1 ± 2.3	8.4 ± 2.6	0.54
BMI (kg/m²)	27.3 ± 3.2	27.6 ± 3.1	0.62
HbA1c (%)	8.7 ± 0.6	8.6 ± 0.7	0.44
FPG (mg/dL)	166.2 ± 21.3	165.4 ± 22.1	0.81
Type of malignancy (solid/hematological, %)	78/22	75/25	0.67

Glycemic Outcomes Both groups had substantial decreases in HbA1c, FPG, and PPG at 12 weeks from baseline. The mean HbA1c decrease was more prominent in the empagliflozin–sitagliptin group (−1.4% ± 0.3) than in the empagliflozin–alogliptin group (−1.1% ± 0.4; p=0.02). FPG and PPG also decreased more significantly in Group A.

Table 2. Changes in Glycemic Parameters from Baseline to 12 Weeks

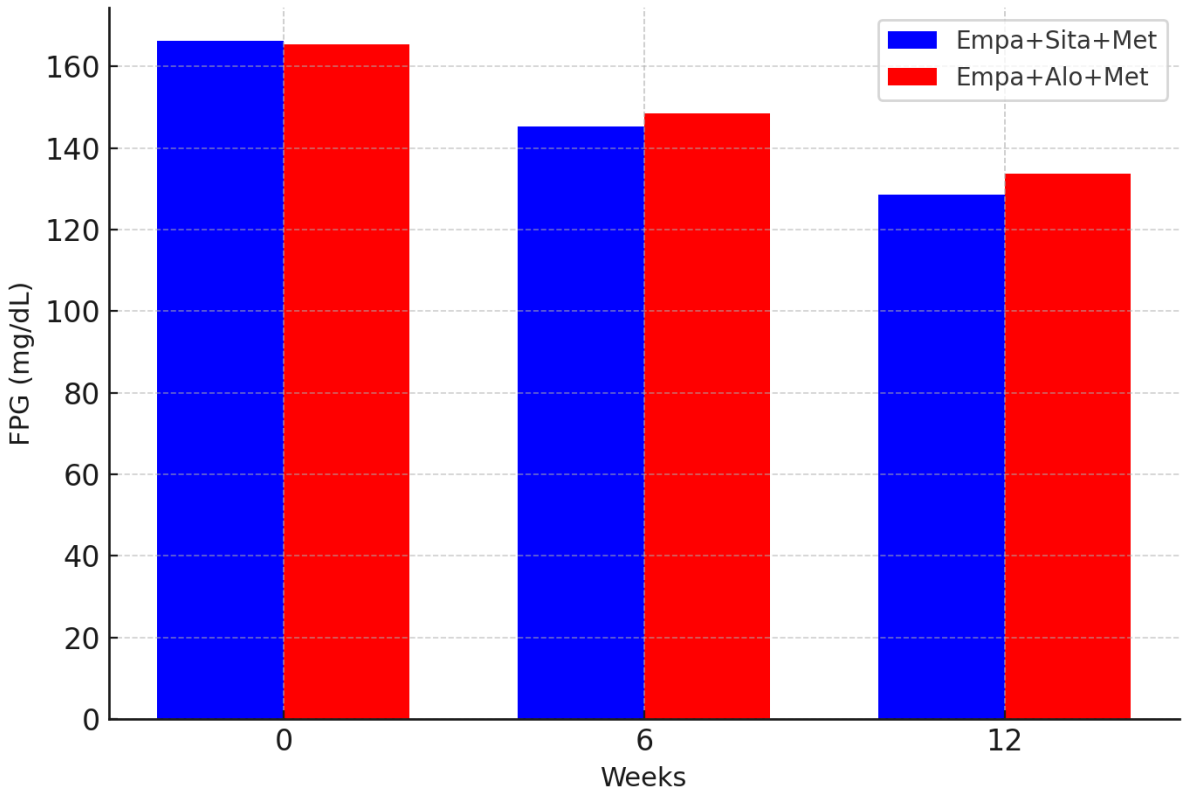
Parameter	Group A (Empa+Sita+Met)	Group B (Empa+Alo+Met)	p-value
HbA1c (%) baseline	8.7 ± 0.6	8.6 ± 0.7	0.44
HbA1c (%) at 12 weeks	7.3 ± 0.4	7.5 ± 0.5	0.02
FPG (mg/dL) baseline	166.2 ± 21.3	165.4 ± 22.1	0.81
FPG (mg/dL) at 12 weeks	128.5 ± 18.6	133.7 ± 19.2	0.04
PPG (mg/dL) baseline	236.7 ± 25.1	235.4 ± 26.7	0.76
PPG (mg/dL) at 12 weeks	182.6 ± 20.5	189.2 ± 21.4	0.03

Safety and Adverse Events Both regimens were tolerated well. Hypoglycemic episodes were infrequent and non-severe, in 2 patients in Group A and 3 patients in Group B. Urinary tract infections were marginally increased with empagliflozin–alogliptin group (8.3%) in comparison with empagliflozin–sitagliptin group (6.7%), though it was not statistically significant. No patient had worsening malignancy-related symptoms due to study medications.



Graph 1. Mean Reduction in HbA1c (%) Over 12 Weeks

Graph 1 comparing HbA1c decline in both groups from baseline to 6 weeks and 12 weeks; steeper decline observed in empagliflozin–sitagliptin group.



Graph 2. Changes in Fasting Plasma Glucose (mg/dL) Across Follow-Up

Graph 2 showing mean FPG reduction at baseline, 6 weeks, and 12 weeks in both groups; greater reduction in empagliflozin–sitagliptin group.

4. DISCUSSION

The current research illustrates that the combination of empagliflozin with sitagliptin and metformin attained better glycemic management compared to empagliflozin added to alogliptin and metformin in patients with type 2 diabetes mellitus complicated by malignancy. Patients in the empagliflozin–sitagliptin group experienced larger decreases in HbA1c, fasting plasma glucose, and postprandial glucose during the 12-week duration, which points to the possible additive effect of the regimen in patients with complicated comorbidities. Both therapeutic approaches were tolerated well, with minimal adverse effects, and no worsening of malignancy-associated outcomes was noted, implying that such combinations are safe in this unique population.

These results corroborate previous evidence of the sustained efficacy and safety of empagliflozin and sitagliptin when added to metformin. Sustained glycemic benefit and tolerability after 78 weeks in patients treated with empagliflozin, sitagliptin, and metformin were reported in a groundbreaking trial by [9], further affirming long-term clinical efficacy of this triple therapy. Our observations extrapolate these to a more difficult-to-treat patient population with concomitant malignancy, a subgroup often excluded from traditional clinical trials.

The superiority of the empagliflozin–sitagliptin combination found in this trial also concurs with more recent comparative evidence. [11] showed that empagliflozin had more beneficial effects on metabolic parameters, including serum asprosin concentration, compared with sitagliptin as add-on treatments with metformin, and pointed to mechanistic distinctions that could account for their combination's improved outcomes. In a similar vein, [14] also observed empagliflozin to be a useful add-on to metformin in patients with mild hyperglycemia, and [13] noted that sitagliptin added to metformin enhanced glycemic control in Chinese patients with T2DM with a very good safety profile. All these results highlight the utility of combining both agents with metformin, especially in patients with suboptimal glycemic control.

Our findings also attest to results from comparative research evaluating empagliflozin versus other oral hypoglycemic drugs. For instance, [10] noted that empagliflozin combination therapy enhanced both glycemic control and weight parameters in patients with obesity and T2DM, in line with the weight-reducing trend in our population. Similarly, comparative studies using incretin-based therapies have indicated that sitagliptin is still effective while GLP-1 receptor agonists liraglutide and semaglutide provide more HbA1c and weight reductions, as indicated by the SUSTAIN 2 trial of [12] and the research of [15]. Nevertheless, due to the oncological comorbidity of our patient population, sitagliptin's favorable tolerability and safety profile rendered it an especially appropriate choice.

Notably, our trial's higher efficacy of empagliflozin–sitagliptin relative to empagliflozin–alogliptin is significant, since there is still limited direct evidence to compare these particular DPP-4 inhibitors when combined with SGLT2 inhibitors. While the two drugs block the identical enzymatic pathway, structural and pharmacokinetic differences might predispose to differences in clinical effect. The consistent superiority of sitagliptin documented here may support its preferential use in high-risk patients who need aggressive glycemic control.

In summary, this research provides new evidence by filling a clinically significant gap: the optimization of combination therapy in diabetic patients with active malignancy. Our results justify the employment of empagliflozin–sitagliptin–metformin as a more efficient approach compared to empagliflozin–alogliptin–metformin for enhancing glycemic metrics without jeopardizing safety. Such results are to be confirmed in larger and longer studies in the future, especially concerning cardiovascular and oncologic outcomes in this complex population of patients.

5. CONCLUSION

In type 2 diabetes mellitus patients with concomitant malignancy, the empagliflozin plus sitagliptin plus metformin combination had greater glycemic efficacy than empagliflozin plus alogliptin plus metformin, with both combinations having good safety and tolerability. The more effective HbA1c and fasting glucose reduction with the empagliflozin–sitagliptin combination highlights its therapeutic value as a better treatment option in this at-risk population. These results underscore the importance of individualizing combination therapy to achieve maximum results in complicated clinical situations and call for further confirmation with large, long-term studies.

REFERENCES

[1] Prakash V, Goel N, Verma S. Comparative study analyzing efficacy and safety of sitagliptin with metformin versus glimepiride with metformin on patients of type-2 diabetes mellitus. Indian J Pharm Pharmacol 2020;7(1):26-33.

[2] Prakash V, Sehgal VK, Bajaj VK, Singh H. To Compare the effects of Terminalia arjuna with Rosuvastatin on Total cholesterol and Low density lipoprotein cholesterol. Int J Med and Dent Sci 2016; 5(1):1056-1066.

[3] Prakash V. Study comparing the hypolipidemic effects of Terminalia arjuna with Rosuvastatin on triglyceride and high density lipoprotein- cholesterol levels. Int J Pharm Chem Anal 2019;6(4):127-35.

[4] Prakash V, Goel N, Giri KR, Goel A. Clinical study evaluating antihyperglycemic efficacy and safety of terminalia arjuna versus sitagliptin in Type-2 diabetes mellitus patients. Bioinformation. 2024;20(12):1862-1868. Published 2024 Dec 31. doi:10.6026/9732063002001862

[5] Salankar H, Rode S, Arjun C, Joseph R, Deshmane GB, Vijayan RP. Comparative Study on Efficacy of Empagliflozin Versus Sitagliptin, as an Add-on Therapy to Metformin in Type 2 Diabetic Patients. J Pharm Bioallied Sci. 2024 Feb;16(Suppl 1):S335-S338. doi: 10.4103/jpbs.jpbs_548_23. Epub 2024 Feb 29. PMID: 38595418; PMCID: PMC11001115.

[6] Kumar S, Prakash V, Kattimani R et al. Evaluation of cardio-protective effects of a Novel SGLT2 inhibitor beyond glycemic control in preclinical models. Bioinformation 21(8): 2459-2463 (2025). DOI: 10.6026/973206300212459.

[7] Zakaraia HG, Salem HF, Mostafa MAA, Ali AM, Rabea H. 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. Eur Rev Med Pharmacol Sci. 2023 Aug;27(15):7289-7298. doi: 10.26355/eurrev_202308_33300. PMID: 37606137.

[8] Sahay RK, Giri R, Shembalkar JV, Gupta SK, Mohan B, Kurmi P, Kumar SR, Sawardekar VM, Mishra A, Murthy LS, Arya VV, Sonawane AR, Soni PN, Gofne SK, Karnawat SR, Rajurkar MN, Patel PM, Lakhwani LK, Mehta SC, Joglekar SJ. Fixed-Dose Combination of Dapagliflozin + Sitagliptin + Metformin in Patients with Type 2 Diabetes Poorly Controlled with Metformin: Phase 3, Randomized Comparison with Dual Combinations. Adv Ther. 2023 Jul;40(7):3227-3246. doi: 10.1007/s12325-023-02523-z. Epub 2023 May 31. PMID: 37258803.

[9] Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, Broedl UC. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013 Dec;36(12):4015-21. doi: 10.2337/dc13-0663. Epub 2013 Nov 1. PMID: 24186878; PMCID: PMC3836134.

[10] Babar M, Hussain M, Ahmad M, Akhtar L. Comparison Of Efficacy And Safety Profile Of Empagliflozin AsA Combination Therapy In Obese Type 2 Diabetic Patients. J Ayub Med Coll Abbottabad. 2021 Apr-Jun;33(2):188-191. PMID: 34137526.

[11] Talebi SS, Rezaie S, Hajmiri MS, Zamanirafe M, Ranjbar A, Moridi H, Mirjalili M, Mehrpooya M. Comparison of the effects of empagliflozin and sitagliptin, as add-on to metformin, on serum levels of asprosin and metabolic parameters in patients with type 2 diabetes mellitus. NaunynSchmiedebergs Arch Pharmacol. 2024 Nov;397(11):9149-9165. doi: 10.1007/s00210-024-03219-z. Epub 2024 Jun 20. PMID: 38900252.

[12] Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017 May;5(5):341-354. doi: 10.1016/S2213-8587(17)30092-X. Epub 2017 Apr 3. PMID: 28385659.

[13] Ji L, Han P, Wang X, Liu J, Zheng S, Jou YM, O'Neill EA, Golm GT, Engel SS, Kaufman KD, Shankar RR. Randomized clinical trial of the safety and efficacy of sitagliptin and metformin co-administered to Chinese patients with type 2 diabetes mellitus. J Diabetes Investig. 2016 Sep;7(5):727-36. doi: 10.1111/jdi.12511. Epub 2016 May 19. PMID: 27181998; PMCID: PMC5009135.

[14] Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013;15(12):1154-1160. doi:10.1111/dom.12185

[15] Zang L, Liu Y, Geng J, et al. Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial. Diabetes Obes Metab. 2016;18(8):803-811. doi:10.1111/dom.12674