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Article

Comparative Efficacy of Tirzepatide, Teneligliptin, and Empagliflozin in HbA1c Reduction in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Eficacia Comparativa de Tirzepatida, Teneligliptina y Empagliflozina en la Reducción de la HbA1c en Pacientes con Diabetes Tipo 2: Una Revisión Sistemática y Meta-Análisis

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ABSTRACT

This study's objective was to evaluate the effectiveness of three different families of drugs (Empagliflozin [an SGLT-2 inhibitor], Tirzepatide [a GLP-1 receptor co-agonist], and Teneligliptin [DPP-4 inhibitor] used in the treatment of type 2 diabetes in lowering HbA1c levels in people with type 2 diabetes mellitus (T2DM). The effectiveness of different families of diabetic drugs was assessed using a meta-analytic approach. Data were gathered from a variety of research publications using ICTRP, CT.gov, and PubMed databases. The data were analyzed, and conclusions were drawn using forest plots. Teneligliptin (a DPP-4 Inhibitor) substantially lowered HbA1c levels in T2DM patients compared to other classes of T2DM drugs with a P-value of 0.0002 and 95% CI -0.63 [-0.97 to -0.30] after reviewing many pertinent articles. The pooled data analysis showed that Tirzepatide and Empagliflozin did not significantly lower HbA1c levels, with the P-value for Tirzepatide being P = 0.55 and for Empagliflozin, it was P = 0.64. According to our research, Teneligliptin may be more effective than Empagliflozin and Tirzepatide as a monotherapy for lowering HbA1c levels in T2DM patients. To corroborate these findings, further research studies are required.

Keywords: Tirzepatide, Teneligliptin, Empagliflozin, Type 2 Diabetes, HbA1c Reduction.

1. Introduction

Diabetes represents a persistent metabolic disorder characterized by heightened concentrations of blood glucose, subsequently leading to detrimental effects on the kidneys, eyes, nerves, circulatory system, and heart over an extended duration. Type 2 diabetes primarily affects adults and emerges when the body exhibits resistance to insulin or fails to generate adequate amounts. A significant portion of the roughly 422 million individuals afflicted with diabetes across the globe can be found in low- and middle-income countries, and diabetes is directly responsible for an estimated 1.5 million fatalities each year. (World Health Organization, 2023) The WHO has been aiming to reduce the new cases of diabetes by 2025 (World Health Organization, 2023), and in the meantime, new treatments have been arising.

In recent years, different approaches have been taken to treat type 2 diabetes mellitus patients; one of those treatments is a novel class of drugs that particularly target the kidneys by inhibiting sodium-glucose cotransporter 2 (SGLT-2), which has just become commercially accessible. (Ndefo et al., 2015) It has been shown that inhibiting SGLT-2 prevents the body from reabsorbing glucose via the kidney, causing glucose to be eliminated in the urine and blood sugar levels to drop. (Isaji, 2007) In the proximal tubules, SGLT-2 functions as an active protein channel and is mostly in charge of the reabsorption of filtered glucose. Increased urine glucose excretion is the physiological result of this inhibition, which benefits diabetic patients by assisting them in maintaining glycemic homeostasis. (Ndefo et al., 2015)

Among the array of SGLT-2 inhibitors, empagliflozin has demonstrated efficacy as both a monotherapy and in combination with other antihyperglycemic agents such as metformin, sulfonylureas, and insulin, reinforcing its role in comprehensive diabetes management. (Gerich, 2010; Ferrannini et al., 2013; Grempler et al., 2012; Richter et al., 2018) This affirmation is echoed by the findings of a Cochrane review, which illuminated the long-term benefits of empagliflozin either as a standalone treatment or in a dual therapy setting for adults with type 2 diabetes mellitus. (Richter et al., 2018) Simultaneously, we included in this study other classes of drugs such as Tirzepatide, a GLP-1 receptor agonist, and Teneligliptin, a DPP-4 inhibitor, which are actively employed in the therapeutic landscape of type 2 diabetes mellitus.

Effectiveness is the capacity of an intervention to bring about the planned or desired result under ideal or regulated circumstances, such as in a clinical study. High blood glucose levels and related problems are a consequence of type 2 diabetes mellitus, a chronic metabolic condition characterized by insulin resistance and relative insulin shortage. Three different families of oral anti-diabetes medications, known as SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1/GIP co-agonists, work to reduce blood sugar levels by preventing the kidneys from reabsorbing glucose, which increases the excretion of glucose in the urine. (Ndefo et al., 2015; Isaji, 2007; Gerich, 2010) As a percentage of glycated hemoglobin, or hemoglobin that has been linked to glucose, HbA1c is a measurement of the average blood glucose level during the previous two to three months. It serves as a measure of long-term glycemic control in diabetic patients.

A meta-analysis is necessary to examine and analyze whether the SGLT-2 inhibitor, DPP-4 inhibitor, or the GLP-1/GIP agonist could be more efficacious compared to others used in patients suffering from type 2 diabetes mellitus in reducing HbA1c in the human body. This would add to the literature and help in reaching a verdict to determine which class of drug is the most efficacious in reducing HbA1c in type 2 diabetic patients.

2. Methods

The recommended reporting items for systematic reviews and meta-analyses (PRISMA) standards (Page et al., 2021) were followed to perform a high-quality and meticulous systematic review and meta-analysis. These recommendations provide a uniform format for disclosing the procedures and findings of systematic reviews and meta-analyses. We conducted a thorough and extensive electronic search of three main databases as part of our methodology: PubMed, CT.gov, and ICTRP from their establishment until April 8, 2023. We put language constraints on our search in an effort to find only research written in English. Our search technique was focused on four main concepts: effectiveness, diabetes mellitus (also known as diabetes), diabetic drugs specifically empagliflozin, tirzepatide, teneligliptin, and HbA1c. We also applied a 10-year filter. To ensure that we were able to include these ideas in our search, we combined the following phrases and Boolean operators using the PICO strategy. For more detailed information on our search terms and strategy, please refer to Supplementary Material 1.

Study Selection. Prior to starting the literature search, certain search criteria were established to include only the most relevant articles. These criteria are as follows:

Inclusion Criteria

- Study design: Randomized controlled trials (RCTs), trials, and clinical studies published in peer-reviewed journals will be included in the review.
- Participants: The study will include adult patients (age 18 years and above) with a diagnosis of type 2 diabetes, as defined by the American Diabetes Association (ADA) or World Health Organization (WHO) criteria.
- Intervention: The study will include trials that compare the use of tirzepatide, teneligliptin, or empagliflozin to placebo.
- Outcomes: The primary outcome of the study will be the mean change in HbA1c levels from baseline to endpoint. Secondary outcomes may include changes in fasting plasma glucose, body weight, blood pressure, and lipid profile.

- Language: Only studies published in English will be included.
- Time: Studies conducted within the last 10 years will be included in this systematic review and meta-analysis.

Exclusion Criteria

- Studies that are not RCTs will be excluded.
- Trials that do not include patients with type 2 diabetes will be excluded.
- Studies that do not compare tirzepatide, teneligliptin, or empagliflozin to placebo, or to any other antidiabetic drug or combination therapy will be excluded.
- Studies that do not report the mean change in HbA1c levels or any of the secondary outcomes of interest will be excluded.
- Studies published in languages other than English will be excluded.
- Trials not published in peer-reviewed journals, such as conference abstracts or unpublished data, will be excluded.
- Trials with a high risk of bias, as assessed by the Cochrane risk of bias tool, will be excluded.
- Trials with a small sample size (fewer than 10 participants per treatment arm) will be excluded.
- Studies that include patients with other types of diabetes (e.g., type 1 diabetes, gestational diabetes) or patients with comorbid conditions that may affect the outcomes of interest (e.g., renal failure, liver disease) will be excluded.
- Trials with a treatment duration of fewer than 4 weeks will be excluded.

These inclusion and exclusion criteria aimed to ensure that the study includes only high-quality RCTs that are relevant to the research question, have a low risk of bias, and provide valid and reliable evidence on the comparative efficacy of tirzepatide, teneligliptin, and empagliflozin on HbA1c reduction in patients with type 2 diabetes.

Data Extraction and Quality Assessment. To obtain genuine and reliable results, a systematic strategy was used to find and assess relevant research. After a thorough search was conducted, articles were imported into the EndNote Reference Library. Duplicates were identified and eliminated to ensure that only original research was included in the analysis. Studies that matched the pre-established selection criteria were thoroughly examined.

A two-step procedure was used for the assessment. First, the relevance of each study to the research question was evaluated by examining its title and abstract. Studies that did not fit the selection criteria were eliminated at this stage. Second, the full texts of the remaining papers were meticulously examined to ensure they complied with the selection criteria and to identify any discrepancies.

An Excel spreadsheet was used to extract and compile the final findings of the trials. All information was meticulously documented and saved for further analysis. The decrease in HbA1c levels was used to evaluate the effectiveness of the three classes of anti-diabetic drugs.

The quality of the studies was evaluated using the Cochrane Risk of Bias Tool, also known as RoB 2.0, a methodology for assessing the risk of bias in randomized controlled trials developed by the Cochrane Collaboration. With the use of this specific tool, the internal validity of the studies was assessed, and each study's plot and risk of bias were summarized. (Higgins et al., 2011)

Assessment of the risk of bias involves evaluating several areas, including randomization, allocation concealment, blinding, attrition, reporting, and other sources of bias. The graph and chart use a color-coded system (low, high, or unclear risk of bias) to summarize the conclusions for each study and for each area. This tool aided in identifying and correcting any potential biases that could have compromised the reliability and applicability of the results (Figures 1 and 2).

Figure 1. Risk of Bias Graph.

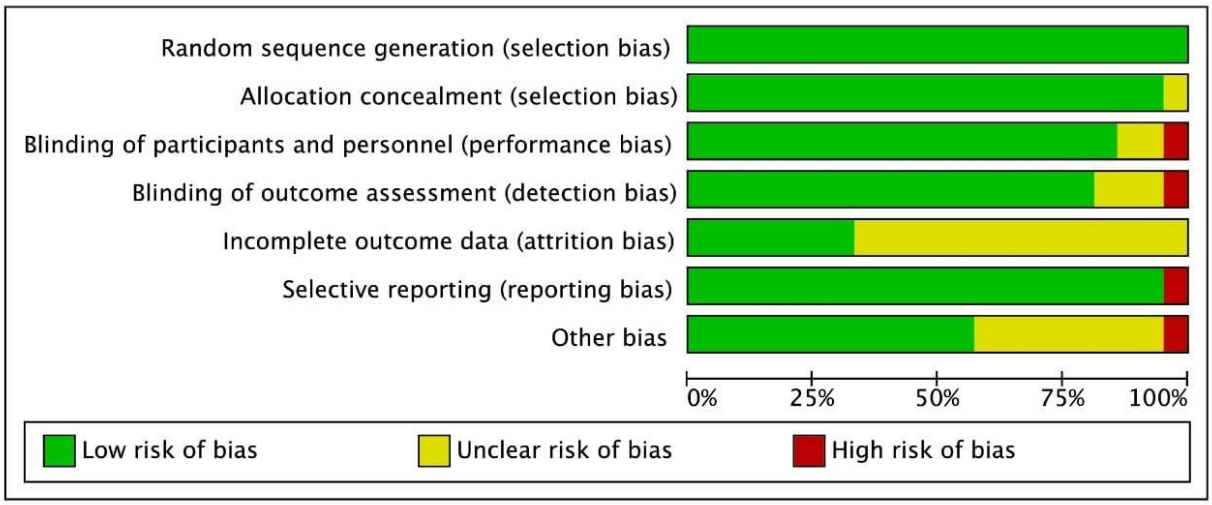
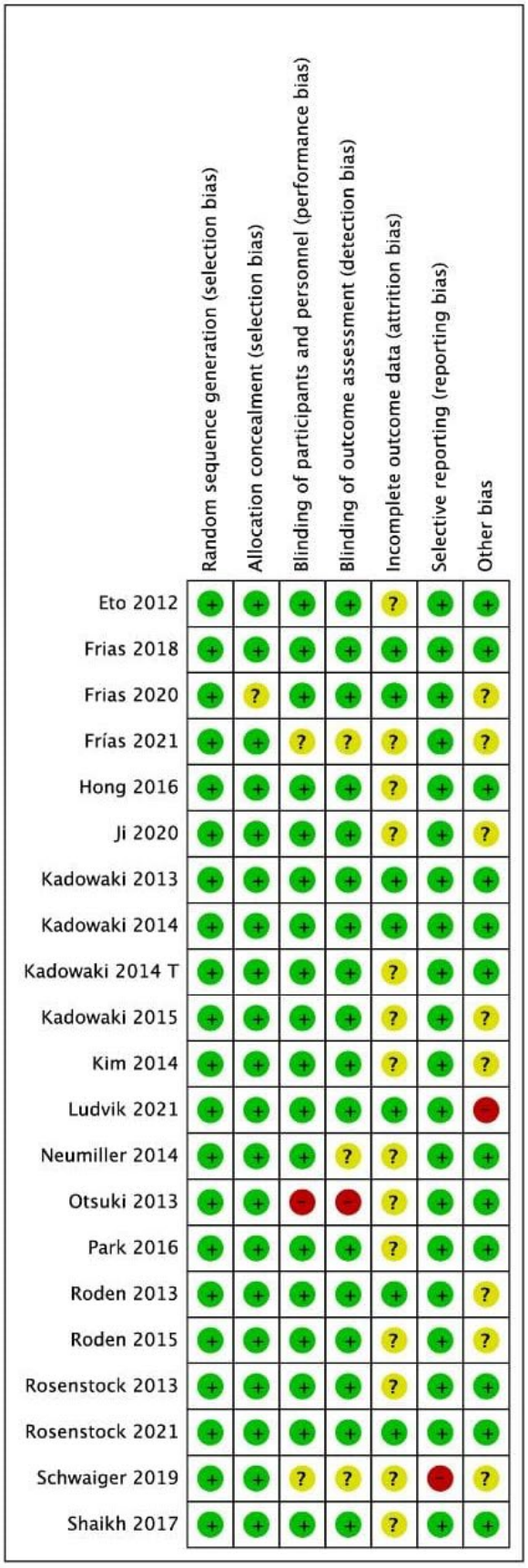


Figure 2. Risk of Bias Summary for Each Study.

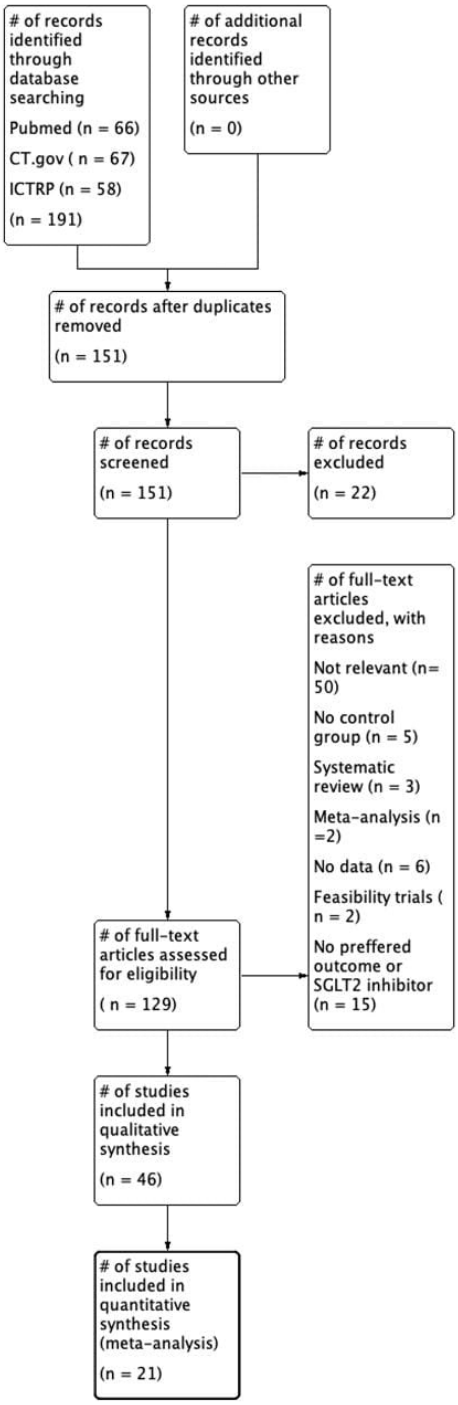


Statistical Analysis. The statistical analysis for this research investigation was carried out using RevMan version 5.3 software, developed by The Nordic Cochrane Centre and The Cochrane Collaboration and released in 2014. It is a widely used method for conducting systematic reviews and meta-analyses in the health sciences. We extracted relevant data and presented it consistently from the studies that met the inclusion criteria. Averages, standard deviations, and 95% confidence intervals (CIs), which demonstrate the reliability of the estimates, were provided in the data. We then combined the data from other experiments using a random effects model. This method relies on the assumption that the studies are diverse and that each one provides an estimate with a distinct effect size. This is how our approach considered the diversity and heterogeneity of the study. To illustrate the results of the meta-analysis, we created forest plots that show the effect sizes, 95% confidence intervals (CI), and pooled estimate for each trial. The forest plots also show the weights assigned to each study based on sample size and variance. We also developed a funnel plot to assess any possible publication bias in the study. Publication bias occurs when studies with positive or important outcomes are more likely to be published than those with negative or insignificant ones. As a consequence, the magnitude of the actual effect could be underestimated or overestimated. Plotting the effect sizes against their standard errors shows how symmetrically or asymmetrically they are distributed around the pooled estimate.

3. Results

Results of Literature Search. Upon applying the criteria of randomized controlled trials and a 10-year time frame, a preliminary search of the three digital repositories yielded 66 potential studies on PubMed, 67 on ClinicalTrials.gov, and 58 on the International Clinical Trials Registry Platform. Following the exclusion process, a total of 21 trials were deemed suitable for further analysis. These 21 selected trials, having satisfied the pre-established requirements, underwent a comprehensive assessment of their complete texts (Figure 3).

Figure 3. PRISMA Flow Diagram Made in RevMan 5.3.



Study Characteristics. This research involved a total of 6173 diabetic patients who participated in 21 studies. The patients were randomly allocated to either the experimental arm or the control arm of the research. The experimental arm consisted of 2682 diabetic patients who received the intervention of interest. The control arm consisted of 2680 diabetic patients who received the usual care or a placebo. The data from these two groups were compared and analyzed to evaluate the effectiveness of the intervention.

Table 1. Basic demographics of studies.

Author	Drug	Study type	Duration of study	Total population	Control population	Intervention population	Age Mean (SD)
Otsuki 2013	Teneligliptin	RCT	28 weeks	51	14	29	69.8 ± 8.5
Kadowaki 2013	Teneligliptin	RCT	12 weeks	324	81	80	57.5 (10.4)
Eto 2012	Teneligliptin	RCT	4 weeks	99	33	32	57.1 (8.7)
Park 2016	Teneligliptin	RCT	24 weeks	142	99	43	
Neumiller 2014	Empagliflozin	NS	24 weeks	164	82	82	NS
Schwaiger 2019	Empagliflozin	Pilot study	4 weeks	NS	14	14	56.5±7.9
Rosenstock 2013	Empagliflozin	RCT	12 weeks	141	71	70	59±8.1
Shaikh 2017	Empagliflozin	RCT	76 weeks	108	28	29	47.1±8.6
Kadowaki 2014	Empagliflozin	RCT	12 weeks	219	109	110	57.2 ± 9.7
Kadowaki 2015	Empagliflozin	RCT	52 weeks	532	267	265	57.9 ± 10.1
Roden 2015	Empagliflozin	RCT	24 weeks	522	288	224	53.8 ± 11.6
Roden 2013	Empagliflozin	RCT	24 weeks	452	228	224	53 ·8 (11 ·6)
Rosenstock 2021	Tirzepatide	RCT	40 weeks	478	121	115	NS
Frias 2021	Tirzepatide	RCT	40 weeks	1878	470	469	NS
Ludvik 2021	Tirzepatide	RCT	52 weeks	1444	359	360	NS
Frias 2018	Tirzepatide	RCT	26 weeks	318	53	54	NS
Frias 2020	Tirzepatide	RCT	12 weeks	54	28	26	57.4 years
Kadowaki 2014	Teneligliptin	RCT	12 weeks	194	98	96	20–75 years
Kim 2014	Teneligliptin	RCT	16 weeks	204	68	136	NS
Hong 2016	Teneligliptin	RCT	24 weeks	142	43	99	>18 years
Ji 2020	Teneligliptin	RCT	24 weeks	151	126	125	52.1 (10.2) years

Results of Meta-Analysis. Twenty-one trials evaluating the effectiveness of three different classes of anti-diabetic drugs were included, i.e., Tirzepatide, Teneligliptin, and Empagliflozin. The analysis for the Teneligliptin class included eight studies with a total sample size of 1202 participants.

Teneligliptin

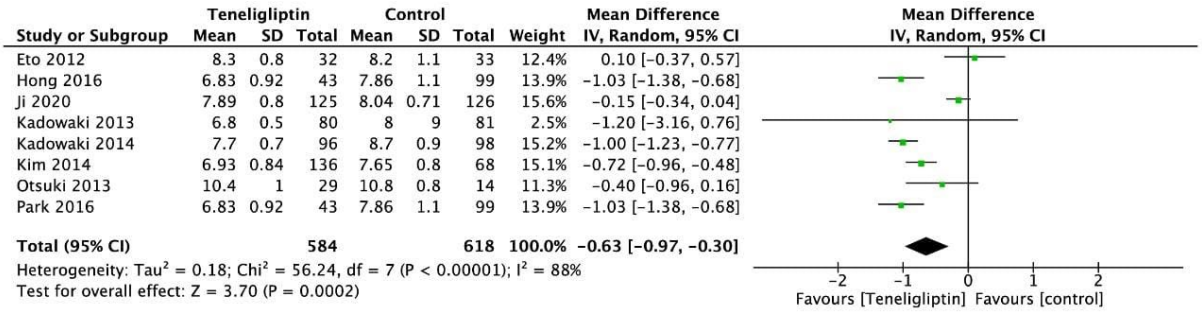
The overall effect size of the treatment was significant, with a Z-score of 3.70 (p = 0.0002) (significant p-value = 0.05), indicating that the treatment was effective in reducing the outcome of interest which was HbA1c levels. The 95% confidence interval for the effect size ranged from -0.63 [-0.97 to -0.30], suggesting that the true effect size is likely to fall within this range.

The heterogeneity statistic I^2 was 88%, indicating that there was substantial variability between the studies in terms of their effect sizes. This suggests that the treatment may have different effects across different populations or contexts.

The forest plot also displayed the individual effect sizes and weights for each of the eight studies included in the meta-analysis. The study with the highest weight was Ji et al. 2020 (15.6%), followed by Kadowaki et al. 2014 (15.2%) and Kim et al. 2014 (15.1%). The study with the lowest weight was Kadowaki et al. 2013 (2.5%).

The experimental group consisted of 584 participants, and the control group consisted of 618 participants. The p-value for the overall effect size was 0.0002, indicating that the probability of observing an effect of this magnitude or greater by chance alone is very low (Figure 4).

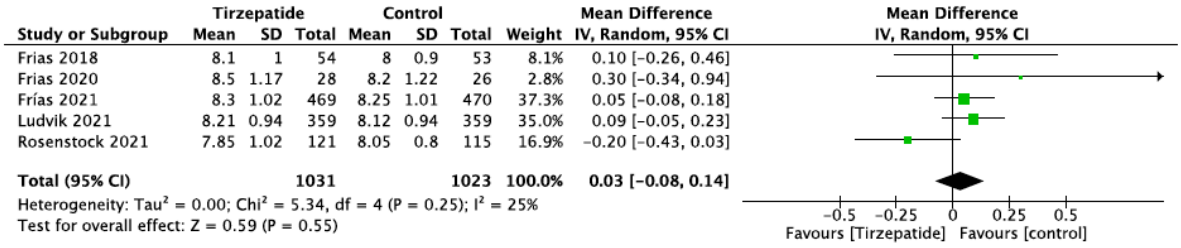
Figure 4. Forest Plot for HbA1c levels in experimental and control group after administering Teneligliptin.



Tirzepatide

The analysis for tirzepatide was performed, which belongs to the GIP/GLP-1 inhibitor class of anti-diabetic drugs. We analyzed the data related to HbA1c levels in both the experimental and control groups who took up the tirzepatide drug. The meta-analysis for this class of anti-diabetic drug included five studies: Frias 2018, Frias 2020, Frias 2021, Ludvik 2021, and Rosenstock 2021. The pooled analysis of these studies showed an overall effect size of Z=0.59 with a p-value of 0.55, indicating that there is no statistically significant difference between the intervention and control groups. The 95% confidence interval for the effect size is 0.03[-0.08, 0.14] suggesting that the true effect size could range from a moderate reduction to a moderate increase in the outcome lowering HbA1c in type 2 diabetic patients. However, the confidence interval includes the null value of zero, indicating that there is no significant effect of the intervention. The I^2 heterogeneity statistic of 25% suggests that there is low variability in effect sizes across the studies, indicating that the studies are relatively consistent in their findings. This is further supported by the weights assigned to each study, with the largest weight given to Frias 2021 (37.3%) and the smallest weight given to Frias 2020 (2.8%); (Figure 5).

Figure 5. Forest Plot for HbA1c levels in experimental and control group after administering Tirzepatide.



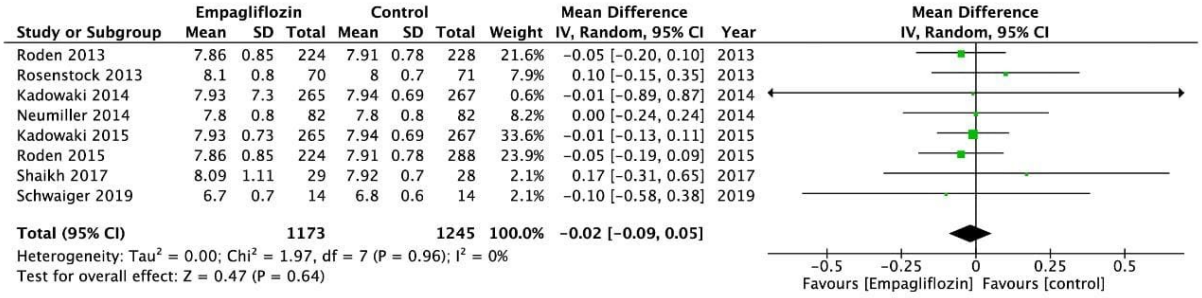
Empagliflozin

Lastly, we analyzed the SGLT-2 inhibitor empagliflozin by pooling the data from the studies for empagliflozin. The forest plot includes data from a total of eight studies with a combined experimental population of 1,173 and control population of 1,245.

The overall effect of the treatment was determined to be non-significant with a Z score of 0.47 (p = 0.64) and a 95% confidence interval of -0.02 [-0.09, 0.05]. The p-value of 0.64 is not statistically significant, suggesting that there is no significant difference between the treatment and control groups.

Additionally, there was no heterogeneity observed among the studies, as indicated by an I^2 value of 0%. The combined weights of the individual studies in the meta-analysis were as follows: Roden 2013 (21.6%), Rosenstock 2013 (7.9%), Kadowaki 2014 (0.6%), Neumiller 2014 (8.2%), Kadowaki 2015 (33.6%), Roden 2015 (23.9%), Shaikh 2017 (2.1%), and Schwaiger 2019 (2.1%; Figure 6).

Figure 6. Forest Plot for HbA1c levels in experimental and control group after administering Empagliflozin.



Overall, these results suggest that teneligliptin may be an effective treatment for lowering HbA1c levels in patients with type 2 diabetes, while tirzepatide and empagliflozin may not be as effective, hence fortifying our research that among the three classes of drugs, teneligliptin proved to be superior to the others. However, further research is needed to confirm these findings and explore potential factors affecting treatment effectiveness.

Publication Bias. Upon examining the funnel plots for all three classes of drugs analyzed in this meta-analysis, evidence of publication bias was observed. In the funnel plots, we observed asymmetry in the distribution of studies, with a greater number of studies located in the upper right quadrant of the plot. This suggests that smaller studies with null or negative results may not have been published, leading to an over-representation of positive studies in the analysis.

While publication bias can be difficult to quantify, it is important to acknowledge its potential impact on the results of meta-analyses. The presence of publication bias can lead to an overestimation of the effectiveness of a treatment, as studies with negative or null results may not be included in the analysis. This highlights the need for caution when interpreting the results of meta-analyses and underscores the importance of conducting high-quality studies and publishing all results, regardless of the outcome. Figures 7, 8, and 9 show the funnel plot for each class of drugs.

Figure 7. Funnel Plot for Empagliflozin.

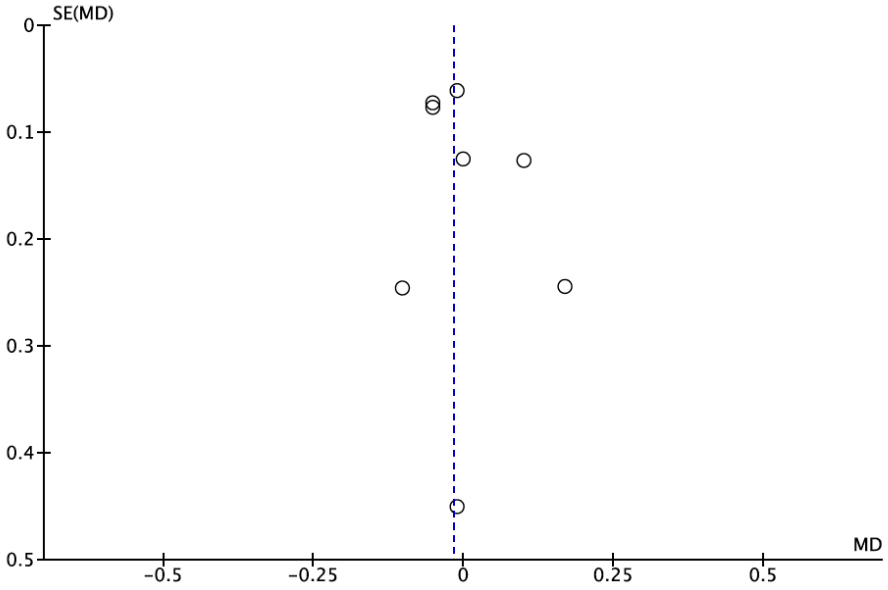


Figure 8. Funnel Plot for Tirzepatide.

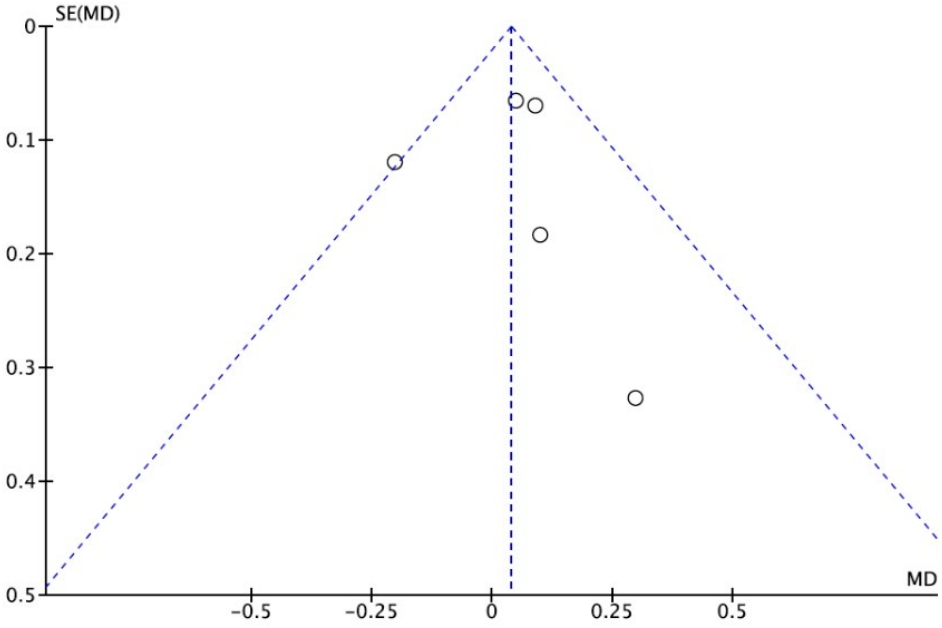
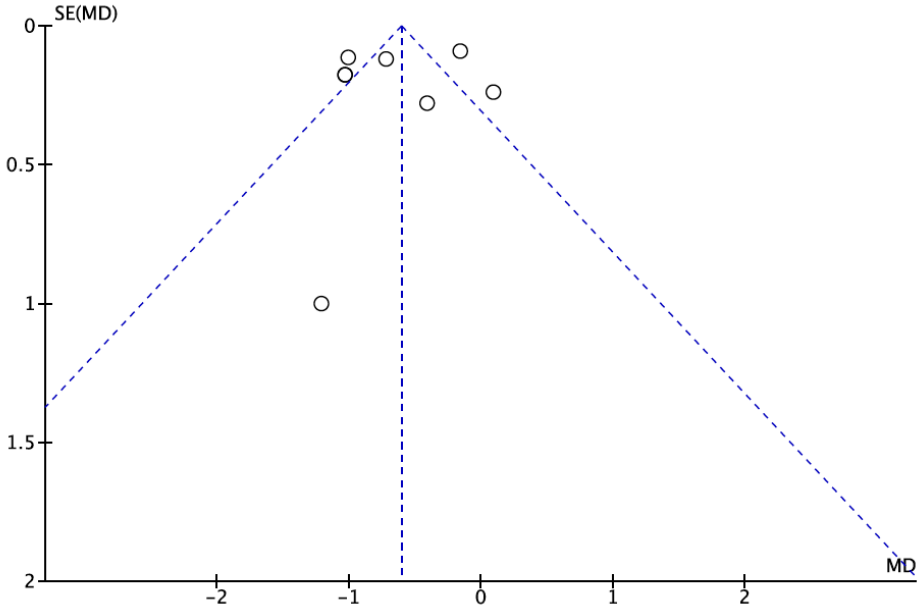


Figure 9. Funnel Plot for Teneligliptin.



4. Discussion

We devised a study to test different classes of anti-diabetic drugs – GLP-1 agonist, SGLT-2 inhibitor, and DPP-4 inhibitor drugs – and explore their possible efficacy results. For this study, we chose Teneligliptin from the DPP-4 inhibitor class, Empagliflozin from the SGLT-2 inhibitor family, and Tirzepatide from the GLP-1 receptor agonist class of anti-diabetic drugs. The results of this meta-analysis suggest that Teneligliptin is the most effective drug among the three in reducing the outcome of interest, HbA1c, in patients with type 2 diabetes. The analysis of Tirzepatide, on the other hand, showed no significant difference between the intervention and control groups. The meta-analysis of Empagliflozin also showed no significant difference between the treatment and control groups. The results suggest that there is no heterogeneity in the Tirzepatide and Empagliflozin groups, whereas there is substantial variability between the studies in the Teneligliptin group. The findings of this study could be useful for clinicians in selecting the most appropriate anti-diabetic drug among the three different classes of anti-diabetic drugs for their patients. When compared to other medications or placebo, the DPP-4 inhibitor lowered HbA1c levels considerably. One of the secondary effectiveness outcomes in the selected studies was a change in body weight. The percentage of participants who reduced their body weight by no less than 5%, 10%, or 15% was also considered.

Teneligliptin, a novel DPP-4 inhibitor, demonstrated a notable decline in the desired outcome of lowering HbA1c, and this finding is corroborated by many studies. However, with technological developments, more high-quality studies are required to validate this theory and the clinical effectiveness of the aforementioned medications at higher doses. In a study conducted by Otsuki et al. (Otsuki et al., 2014), it was presented that the Teneligliptin group's blood glucose level decreased by 36.7 mg/dl from 4 weeks earlier ($p < 0.05$). At 24 weeks, there were 3.1% ($p < 0.05$) and -0.57% ($p = 0.057$) HbA1c differences between the Teneligliptin group and the control group, respectively, which were in line with our analysis as well. (Otsuki et al., 2014)

According to Kim et al., Teneligliptin with ongoing Metformin medication resulted in a mean HbA1c decrease of 0.9% after 16 weeks of treatment, which is comparable to or slightly superior to the findings of earlier trials using other DPP-4 inhibitors, further fortifying our results. (Kim et al., 2015)

There have been other studies where tirzepatide was evaluated for marketing approval under the names of new dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA). For type 2 diabetes, individual trials have compared the clinical profiles of tirzepatide and various comparators. (Karagiannis et al., 2022) Other findings explained that when used by patients with type 2 diabetes, SGLT-2 inhibitors and GLP-1 receptor agonists decreased cardiovascular and renal outcomes, with some variation in benefits and drawbacks (high confidence evidence). SGLT-2 inhibitors reduced mortality from all causes, including cardiovascular mortality, non-fatal myocardial infarction, and kidney failure. SGLT-2 inhibitors decreased the number of hospital admissions for heart failure. SGLT-2 inhibitors, however, can lead to vaginal infections. The impact of SGLT-2 inhibitors and GLP-1 receptor agonists on limb amputation, blindness, eye illness, neuropathic pain, or health-related quality of life was shown to have little to no evidence. In a randomized control trial over a five-year period, SGLT-2 inhibitors prevented 3 to 40 deaths in 1000 patients. (Palmer et al., 2021) Patients with T2DM and CKD who used SGLT-2 inhibitors saw decreases in glycated hemoglobin, blood pressure, body weight, and albuminuria, according to Tadashi Toyama's meta-analysis. The risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke was also decreased by SGLT-2 inhibition. (Toyama et al., 2019)

The majority of type 2 diabetics are overweight, so weight loss and increased physical activity are the main goals of initial treatment. Even a small amount of weight loss can help with blood sugar regulation. Usually, metformin is the medicine of choice in drug treatment situations. However, metformin causes diarrhea in about 10% of people, so it cannot be administered to those with renal impairment since some people cannot tolerate it. When metformin cannot be taken, three of the newest sodium-glucose co-transporter 2 (SGLT-2) inhibitors for monotherapy were evaluated in one study. (Johnston et al., 2017) The glycemic control-improving effects of canagliflozin, dapagliflozin, and empagliflozin were also accompanied by some improvements in blood pressure and weight management, but the three medications did not seem to be economical in monotherapy.

Tirzepatide has become more widely used in the treatment of type 2 diabetes (T2D) due to its favorable effects on body weight, cardiorenal function, and glycemic control. Despite this, it is crucial to continue developing therapies with greater efficacy in order to address the ongoing difficulties many T2D patients face in achieving their metabolic objectives. Ten and 15 mg of tirzepatide exhibited better antidiabetic and weight-loss effects; in particular, 15 mg of Tirzepatide was dominant in reducing HbA1c. Tirzepatide, when compared with insulin in type 2 diabetes mellitus, showed that the medication has a superior, more favorable effectiveness and safety profile. (Guan et al., 2022) However, after pooling the studies and increasing the power in our meta-analysis, it didn't show a significant difference compared to the DPP-4 class or teneligliptin. That's why it would be wise to do more extensive research on this topic to further establish the definite results on this topic.

Moreover, empagliflozin is a widely used SGLT-2 inhibitor. Certain trials favor empagliflozin as a monotherapy and a better performer compared to certain other SGLT-2 inhibitors, but when pooled with different studies, it was not significant in reducing HbA1c as teneligliptin was. (Gupta et al., 2017) According to the meta-analysis's findings, compared to the control group, empagliflozin's overall effectiveness in lowering HbA1c levels was not statistically significant. The EMPA-REG OUTCOME study found no significant change in HbA1c levels between the empagliflozin and placebo groups. (Zinman et al., 2015) However, in other investigations, including the EASE-2 and EASE-3 trials, therapy with empagliflozin resulted in substantial reductions in HbA1c levels. (Rosenstock et al., 2018) The lack of heterogeneity shown amongst the studies in this meta-analysis suggests that changes in research design or patient characteristics may be to blame for the disparities in outcomes. It is also crucial to remember that this meta-analysis only examined empagliflozin's effectiveness in lowering

HbA1c levels and ignored other aspects like cardiovascular outcomes or adverse events. To completely assess empagliflozin's effectiveness and safety in the treatment of type 2 diabetes, further study is required, as is the case with the rest of the classes of anti-diabetic drugs.

Limitations. Despite the significant overall effect size for teneligliptin, the high level of heterogeneity among the included studies (I^2 = 88%) indicates that there may be substantial variability in the effectiveness of the treatment across different populations or contexts. Additionally, the analysis only included studies published in English, potentially limiting the generalizability of the findings to non-English-speaking populations.

For tirzepatide, although the individual studies were consistent in their findings, the overall effect size was non-significant, indicating that the treatment may not be effective in reducing HbA1c levels in type 2 diabetic patients. It is important to note that the analysis only included five studies, which may limit the statistical power of the meta-analysis.

Regarding empagliflozin, while the absence of heterogeneity among the included studies is a strength, the overall effect size was non-significant, indicating that the treatment may not be effective in reducing HbA1c levels in type 2 diabetic patients. The limited number of studies (n = 8) and the relatively small sample sizes of some individual studies may also limit the generalizability of the findings.

Furthermore, the small number of studies and some language and time restrictions in the literature search could have missed some potential studies that would have given us more insight about the effectiveness of these treatments.

Finally, as with any meta-analysis, the potential for publication bias cannot be ruled out. It is possible that studies with null or negative results were not published, which could bias the overall effect size of the treatment.

Future Implications. The findings of this research have important implications for policymakers in terms of providing evidence for the effectiveness of different classes of anti-diabetic drugs, specifically teneligliptin, in reducing the outcome of interest in type 2 diabetic patients. This information can be used to guide decisions related to the inclusion of these drug classes in treatment guidelines for type 2 diabetes. It may also help inform policies related to the reimbursement and coverage of these medications for patients and choosing the best class of drugs in aiding patients with type 2 diabetes mellitus.

However, the lack of significant results for tirzepatide and empagliflozin highlights the need for further research to better understand the effectiveness of these drugs in their respective classes in treating type 2 diabetes. Future research could focus on investigating the potential reasons for the lack of significant effects, such as examining potential moderating factors that may impact treatment efficacy, including age, gender, and comorbidities. Additionally, further research could explore the potential benefits of combinations of drugs or lifestyle interventions.

Overall, the findings of this research provide important information for policymakers in the healthcare field, but also highlight the need for ongoing research to continue to improve treatment options for type 2 diabetes.

Conclusion. In conclusion, our investigation provides substantial insights into the efficacy of various pharmacological classes—namely, SGLT-2 inhibitors, DPP-4 inhibitors, and GIP/GLP-1 receptor agonists—in managing HbA1c levels in type 2 diabetic patients. The evidence underscores the significant therapeutic potential of teneligliptin, a DPP-4 inhibitor, while the drugs tirzepatide

and empagliflozin, despite representing the GIP/GLP-1 receptor agonists and SGLT-2 inhibitors, did not demonstrate marked differences from the control. However, the current scientific understanding in this domain remains relatively nascent and potentially influenced by publication bias, necessitating additional high-quality research. Future endeavors should explore potential moderating variables, such as age, gender, or comorbidities, and consider investigating the synergistic effects of combined therapies or lifestyle interventions. This study thus not only informs healthcare providers and policymakers about the merits of existing treatment options but also emphasizes the importance of persistent scientific inquiry to optimize therapeutic strategies for type 2 diabetes.

References

Ferrannini, E., Berk, A., Hantel, S. et al. 2013. '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, 36(12), pp. 4015-4021.

Gerich, J.E. 2010. 'Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications', Diabet Med, 27(2), pp. 136-142.

Grempler, R., Thomas, L., Eckhardt, M. et al. 2012. 'Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors', Diabetes Obes Metab, 14(1), pp. 83-90.

Guan, R., Yang, Q., Yang, X., Du, W., Li, X. & Ma, G. 2022. 'Efficacy and safety of tirzepatide in patients with type 2 diabetes mellitus: A Bayesian network meta-analysis', Front Pharmacol, 13, 998816.

Gupta, S., Shaikh, S., Joshi, P., Bhure, S. & Suvarna, V. 2017. 'Long-term efficacy and safety of empagliflozin monotherapy in drug-naive patients with type 2 diabetes in Indian subgroup: Results from a 76-week extension trial of phase III, double-blind, randomized study', Indian J Endocrinol Metab, 21(2), pp. 286-292.

Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D. et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. 2011. 'The Cochrane Collaboration's tool for assessing risk of bias in randomised trials', BMJ, 343, d5928.

Isaji, M. 2007. 'Sodium-glucose cotransporter inhibitors for diabetes', Curr Opin Investig Drugs, 8(4), pp. 285-292.

Johnston, R., Uthman, O., Cummins, E. et al. 2017. 'Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation', Health Technol Assess, 21(2), pp. 1-218.

Karagiannis, T., Avgerinos, I., Liakos, A. et al. 2022. 'Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis', Diabetologia, 65(8), pp. 1251-1261.

Kim, M.K., Rhee, E.J., Han, K.A. et al. 2015. 'Efficacy and safety of teneligliptin, a dipeptidyl peptidase-4 inhibitor, combined with metformin in Korean patients with type 2 diabetes mellitus: a 16-week, randomized, double-blind, placebo-controlled phase III trial', Diabetes Obes Metab, 17(3), pp. 309-312.

Ndefo, U.A., Anidiobi, N.O., Basheer, E. & Eaton, A.T. 2015. 'Empagliflozin (Jardiance): A Novel SGLT2 Inhibitor for the Treatment of Type-2 Diabetes', P T, 40(6), pp. 364-368.

Otsuki, H., Kosaka, T., Nakamura, K., Shimomura, F., Kuwahara, Y. & Tsukamoto, T. 2014. 'Safety and efficacy of teneligliptin: a novel DPP-4 inhibitor for hemodialysis patients with type 2 diabetes', Int Urol Nephrol, 46(2), pp. 427-432.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D. et al. 2021. 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews', BMJ, 372, n71.

Palmer, S.C., Tendal, B., Mustafa, R.A. et al. 2021. 'Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials', BMJ, 372, m4573.

Richter, B., Bandeira-Echtler, E., Metzendorf, M.I., Hemmingsen, B. 2018. 'Long-term mono- or dual-combination empagliflozin treatment for adults with type 2 diabetes mellitus', Cochrane Database Syst Rev, (4), CD013007.

Rosenstock, J., Marquard, J., Laffel, L.M. et al. 2018. 'Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: The EASE Trials', Diabetes Care, 41(12), pp. 2560-2569.

Toyama, T., Neuen, B.L., Jun, M. et al. 2019. 'Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis', Diabetes Obes Metab, 21(5), pp. 1237-1250.

World Health Organization. 2023. 'Diabetes - Health Topics.' Available at: https://www.who.int/health-topics/diabetes#tab=tab_1 (Accessed: 23 July 2023).

Zinman, B., Wanner, C., Lachin, J.M. et al. 2015. 'Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes', N Engl J Med, 373(22), pp. 2117-2128.

RESUMEN

El objetivo de este estudio fue evaluar la efectividad de tres diferentes familias de medicamentos (Empagliflozina [un inhibidor de SGLT-2], Tirzepatida [un co-agonista del receptor de GLP-1], y Teneligliptina [un inhibidor de DPP-4]) utilizados en el tratamiento de la diabetes tipo 2 para reducir los niveles de HbA1c en personas con diabetes mellitus tipo 2 (DM2). La efectividad de las diferentes familias de medicamentos para la diabetes se evaluó utilizando un enfoque meta-analítico. Los datos se recopilaron a partir de una variedad de publicaciones de investigación utilizando las bases de datos ICTRP, CT.gov y PubMed. Los datos se analizaron y se extrajeron conclusiones utilizando gráficos de bosques. La Teneligliptina (un inhibidor de DPP-4) redujo significativamente los niveles de HbA1c en los pacientes con DM2 en comparación con otras clases de medicamentos para la DM2, con un valor P de 0.0002 y un IC del 95% -0.63 [-0.97 a -0.30] después de revisar muchos artículos pertinentes. El análisis de datos combinados mostró que la Tirzepatida y la Empagliflozina no redujeron significativamente los niveles de HbA1c, con el valor P para la Tirzepatida siendo P = 0.55 y para la Empagliflozina, fue P = 0.64. Según nuestra investigación, la Teneligliptina podría ser más efectiva que la Empagliflozina y la Tirzepatida como monoterapia para reducir los niveles de HbA1c en pacientes con DM2. Para corroborar estos hallazgos, se requieren más estudios de investigación.

Palabras clave: Tirzepatida, Teneligliptina, Empagliflozina, Diabetes Tipo 2, Reducción de la HbA1c.

SUPPLEMENTARY MATERIAL 1 (SEARCH STRATEGY)

The supplement provides a comprehensive overview of the search strategy employed in our systematic review and meta-analysis, with particular emphasis on the search terms and Boolean operators used in the ICTRP, CT.gov, and PubMed databases.

To ensure a thorough search, we utilized the following phrases and Boolean operators in accordance with the PICO strategy: (Population: 'Type 2 Diabetes' OR 'T2D') AND (Intervention: 'Tirzepatide' OR 'Teneligliptin' OR 'Empagliflozin') AND (Comparison: 'Placebo' OR 'Sugar Pill') AND (Outcome: 'Effectiveness' OR 'Efficacy' OR 'Treatment Outcomes').

The document also outlines the steps taken to manage the search results, including the criteria for the selection and inclusion of studies in the systematic review and meta-analysis.