DOI: https://doi.org/10.53555/nnmhs.v8i11.1400 Publication URL: https://nnpub.org/index.php/MHS/article/view/1400

EFFICACY AND SAFETY OF INCRETIN THERAPY IN TYPE 2 DIABETES MELLITUS : THE SYSTEMATIC REVIEW

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Abstract

Hyperglycemia is the key sign of type 2 diabetes, which is a metabolic disorder characterised by an inadequate production of insulin as well as resistance to the action of insulin. As longitudinal studies of type 2 diabetes continue to provide evidence linking improved glycemic control with a reduction in the rates of diabetes-associated complications, there is a considerable interest in the therapy of type 2 diabetes, with a focus on the development and use of new agents that exhibit improved efficacy and safety in comparison to currently available medicines. Clinical use of incretin-based medicines is growing steadily, and there are numerous additional products being developed at this time. The individual mechanisms by which dual agonism of both GLP-1 and GIP receptors may improve glycemic control require further investigation. We conducted post hoc exploratory analyses of biomarkers associated with pancreatic beta-cell function and insulin sensitivity in order to investigate the mechanisms by which tirzepatide led to greater reductions of hyperglycemia than a selective GLP-1 receptor agonist. According to the findings of this paper, a dose of 15 milligrams of tizepatide was superior in reducing HbA1c levels, despite the fact that it induced higher levels of gastrointestinal side effects.

Keyword: *Diabetes Mellitus; HbA1c; Hyperglycemia; Incretin Therapy*

INTRODUCTION

Hyperglycemia is the primary indicator of type 2 diabetes, which is a metabolic condition defined by a combination of inadequate insulin production as well as resistance to the action of insulin. The incidence and prevalence of type 2 diabetes are continuously growing, which is being fueled in part by a parallel increase in the rates of obesity all over the world.[1,2] Both diagnosed and undiagnosed: Of the 37.3 million individuals who have diabetes, 28.7 million have been diagnosed with the condition, while 8.5 million have not. The proportion of elderly people in the United States is still rather high, coming in at 29.2%, which translates to 15.9 million older people (diagnosed and undiagnosed).[1]

As longitudinal studies of type 2 diabetes continue to provide evidence linking improved glycemic control with a reduction in the rates of diabetes-associated complications, there is a considerable interest in the therapy of type 2 diabetes, with a focus on the development and use of new agents that exhibit improved efficacy and safety in comparison to currently available medicines. This interest comes from the fact that there is a lot of money to be made from treating type 2 diabetes.[3–5]

In recent years, therapies that aim to inhibit the action of incretin hormones have been the subject of a great deal of scrutiny. Postprandial insulin secretion has been shown to be increased by gut-derived substances, which is what the incretin effect is classified as being. Clinical use of incretin-based medicines is growing steadily, and there are numerous additional products being developed at this time.[6] Dipeptidyl peptidase-4 inhibitors, such as sitagliptin and saxagliptin, and glucagon-like peptide-1 receptor agonists are the two primary categories of medications used to treat conditions associated with incretins (exenatide and liraglutide).[7]

Due to their minimal risk of hypoglycemia, capacity to treat postprandial hyperglycemia (DPP-4 inhibitors and short-acting glucagon-like peptide-1 [GLP-1] RAs), and potential for weight loss, GLP-1 RAs and DPP-4 inhibitors are included in current treatment recommendations for T2DM (GLP-1 RAs). Although older persons may be more susceptible to the nausea and vomiting brought on by GLP-1 RA treatment, these qualities may also prove beneficial in older adults, in whom hypoglycemia is particularly undesired. When selecting the right patient for incretin-based therapy, further safety concerns such pancreatitis, C-cell hyperplasia, and renal failure should be taken into account.[5,8]

In this review of the relevant literature, we will present research that demonstrates the advantages of administering convalescent plasma to Covid-19 patients.

METHODS

The full-text papers written in English were used as the source material for the data that was gathered for the purpose of conducting this systematic review. The main objective of this systematic review was to determine the efficacy of incretins in the treatment of patients with type 2 diabetes. The second purpose of this comprehensive study was to investigate the safety of using incretin as a medication for those who suffer from type 2 diabetes.

Pubmed and Google Schoolar are the two databases that were employed during the production of this essay. In this inquiry, the PICO analysis was used to include T2DM patients, and efficacy and safety of incretin therapy as the index. There were comparisons without or other therapy. As component elements, the research included both controlled clinical trials and randomised clinical trials as part of it.

The keywords used in the search were “type 2 diabetes” and “incretin therapy”. This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) paradigm, in which the researchers originally entered keywords into each database. The phrases : (("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "type 2 diabetes"[All Fields]) AND ("incretine"[All Fields] OR "incretins"[Pharmacological Action] OR "incretins"[MeSH Terms] OR "incretins"[All Fields] OR "incretin"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) used in this study. We received four articles, which will be discussed during the discussion **(Table 1)**.

RESULT

Frias, et al showed estimated mean change from baseline in the glycated hemoglobin level was -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg tirzepatide, respectively, and -1.86 percentage points with semaglutide. The estimated differences between 5-mg, 10-mg, and 15-mg tirzepatide groups and semaglutide group were -0.15 percentage points (95% CI, -0.28 to -0.03; P = 0.02), -0.39 percentage points At all dosages, tirzepatide outperformed semaglutide.[9]

The tirzepatide and semaglutide groups had the greatest gastrointestinal side events, mostly mild to moderate (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%). Hypoglycemia (blood glucose level, <54 mg per deciliter) was recorded in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group) of tirzepatide patients and 0.4% of semaglutide patients. Serious adverse events occurred in 5–7% of tirzepatide and 3% of semaglutide patients.[9]

Second study by Rosenstock, et al showed 478 (mean baseline HbA1c 7·9% [63 mmol/mol], age 54,1 years [SD 11,9], 231 [48%] women, diabetes duration 4,7 years, and body-mass index 31,9 kg/m2) were randomly allocated to tirzepatide 5 mg, 10 mg, 15 mg, or placebo (n=115 [24%]). 66 (14%) individuals stopped taking the trial medicine and 50 (10%) quit early. At 40 weeks, all tirzepatide dosages were better than placebo for changes from baseline in HbA1c, fasting serum glucose, bodyweight, and HbA1c goals of 7,0% (<53 mmol/mol) and 5,7% (<39 mmol/mol).[10]

Mean HbA1c decreased from baseline by 1,87% (20 mmol/mol) with tirzepatide 5 mg, 1,89% (21 mmol/mol) with tirzepatide 10 mg, and 2,07% (23 mmol/mol) with tirzepatide 15 mg versus +0·04% with placebo (+0·4 mmol/mol),

resulting in estimated treatment differences versus placebo of -1,91% (-21 mmol/mol), -1,93% (-21 mmol/mol), and -2,11% (-23 mmol/mol) (all p<0·0001). More tirzepatide patients than placebo fulfilled HbA1c goals of less than 7,0% (<53 mmol/mol; 87-92% vs 20%) and 6,5% or less (48 mmol/mol; 81-86% vs 10%), while 31-52% of tirzepatide patients compared to 1% on placebo achieved 5,7% or less (<39 mmol/mol). Nausea, diarrhoea, and vomiting were tirzepatide's most common side effects. Tirzepatide did not cause severe hypoglycaemia (<54 mg/dL [<3 mmol/L]). One placebo patient died.[10]

Del Prato, et al conducted study with 1995 received at least one dose of tirzepatide 5 mg, 10 mg, 15 mg, or glargine (n=1000, 50%) in the modified intention-to-treat population. At 52 weeks, mean HbA1c changes with tirzepatide were -2,43% (SD 0·05) with 10 mg and -2,58% (0,05) with 15 mg, compared to -1,44% (0,03) with glargine. The calculated treatment difference against glargine for tirzepatide 10 mg was -0·99% (multiplicity adjusted 97,5% CI -1,13 to -0,86) and for 15 mg, -1,14% (-1,28 to -1,00), meeting the non-inferiority margin of 0,3%.[11]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Period	Agent	Result
Frias, 2021[9]	United States, Argentina, Australia, Brazil, Canada, Israel, Mexico, and the United Kingdom	RCT, open-label	1,879 patients	July30,2019,andFebruary 15, 2021	Tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg	The estimated mean change from baseline in the glycated hemoglobin level was -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg tirzepatide, respectively, and -1.86 percentage points with semaglutide. The estimated differences between 5-mg, 10-mg, and 15-mg tirzepatide groups and semaglutide group were -0.15 percentage points (95% CI, -0.28 to -0.03; P = 0.02), -0.39 percentage points At all dosages, tirzepatide outperformed semaglutide. The tirzepatide and semaglutide groups had the greatest gastrointestinal side events, mostly mild to moderate (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%). Hypoglycemia (blood glucose level, <54 mg per deciliter) was recorded in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group) of tirzepatide patients and 0.4% of semaglutide patients. Serious adverse events occurred in 5–7% of tirzepatide and 3% of semaglutide patients.
Rosenstock, 2021[10]	United States	RCT, double-blind	705 patients	June 3, 2019, to Oct 28, 2020	Tirzepatide 5, 10, or 15 mg	478 (mean baseline HbA1c 7·9% [63 mmol/mol], age 54,1 years [SD 11,9], 231 [48%] women, diabetes duration 4,7 years, and body-mass index 31,9 kg/m2) were randomly allocated to tirzepatide 5 mg, 10 mg, 15 mg, or placebo (n=115 [24%]). 66 (14%) individuals stopped taking the trial medicine and 50 (10%) quit early. At 40 weeks, all tirzepatide dosages were better than placebo for changes from baseline in HbA1c, fasting serum glucose, bodyweight, and HbA1c goals of 7,0% and 5,7%. Mean HbA1c decreased from baseline by 1·87% with tirzepatide 5 mg, 1,89% with tirzepatide 10 mg, and 2·07% with tirzepatide 15 mg versus +0·04% with placebo, resulting in estimated treatment differences versus placebo of -1,91%, -1,93%, and -2,11% (all p<0·0001). More tirzepatide patients than placebo fulfilled HbA1c goals of less than 7,0% and 6,5% or less, while 31-52% of tirzepatide patients compared to 1% on placebo achieved 5,7% or less. Nausea, diarrhoea, and vomiting were tirzepatide's most common side effects. Tirzepatide did not cause severe hypoglycaemia. One placebo patient died.
Del Prato, 2021[11]	14 countries on five continents	RCT, open-label	1,995 patients	Nov 20, 2018, and Dec 30, 2019	Tirzepatide (5 mg, 10 mg, or 15 mg) or glargine (100 U/mL)	At 52 weeks, mean HbA1c changes with tirzepatide were -2,43% (SD 0,05) with 10 mg and -2,58% (0,05) with 15 mg, compared to -1,44% (0,03) with glargine. The calculated treatment difference against glargine for tirzepatide 10 mg was -0,99% (multiplicity adjusted 97,5% CI -1,13 to -0,86) and for 15 mg, -1,14% (-1,28 to -1,00), meeting the non-inferiority margin of 0,3%. Tirzepatide caused more mild to severe nausea (12-23%), diarrhoea (13-22%), reduced appetite (9-11%), and vomiting (5-9%) than glargine (2%, 4%, <1%, and 2%, respectively); most occurrences occurred after dose-

						escalation. In persons not on sulfonylureas, tirzepatide had a lower rate of hypoglycaemia (glucose <54 mg/dL or severe) (6-9%) than glargine (19%).
Frias, 2018[12]	USA	RCT, double-blind	555 patients	May 24, 2017, and March 28, 2018	Tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1·5 mg), or placebo	Tirzepatide dose-dependently changed HbA1c at 26 weeks. Tirzepatide had mean changes from baseline in HbA1c of -1,06% for 1 mg, -1,73% for 5 mg, -1,89% for 10 mg, and -1,94% for 15 mg, compared to -0,06% for placebo (posterior MD [80% credible set] vs placebo: -1,00% [-1.22 to -0.79] for 1 mg, -1,67% [-1.88 to -1.46] for 5 mg, -1,83% [-2.04 to -1.61] for 10 mg, and -1,89% [-2.11 to -1]. The posterior mean differences (80% credible set) for change in HbA1c from baseline to 26 weeks with tirzepatide dosages were 0,15% (-0.08 to 0.38) for 1 mg, -0,52% (-0.72 to -0.31) for 5 mg, -0.67% (-0.89 to -0.46) for 10 mg, and -0.73% (-0.95 to -0.52) for 15 mg. At 26 weeks, 33-90% of LY3298176 patients reached the HbA1c goal of less than 7.0% (vs 52% with dulaglutide, 12% with placebo) and 15-82% attained at least 6·5% (vs 39% with dulaglutide, 2% with placebo). Tirzepatide decreased fasting plasma glucose by 0.4 to -3.4 mmol/L (vs 0.9 for placebo, -1.2 for dulaglutide). Most treatment-emergent adverse events were gastrointestinal (nausea, diarrhoea, and vomiting). Gastrointestinal events were dose-related (23·1% for 1 mg Tirzepatide, 32·7% for 5 mg, 51·0% for 10 mg, 66·0% for 15 mg, 42·6% for dulaglutide, 9·8% for placebo); most were mild to severe and temporary. Decreased appetite was the second most prevalent adverse event (3·8% for 1 mg Tirzepatide, 20·0% for 5 mg, 25·5% for 10 mg, 18·9% for 15 mg, 5·6% for dulaglutide, 2·0% for placebo). No significant hypoglycaemia occurred. Lung cancer stage IV killed one placebo patient unrelated to study therapy.

Tirzepatide caused more mild to severe nausea (12-23%), diarrhoea (13-22%), reduced appetite (9-11%), and vomiting (5-9%) than glargine (2%, 4%, <1%, and 2%, respectively); most occurrences occurred after dose-escalation. In persons not on sulfonylureas, tirzepatide had a lower rate of hypoglycaemia (glucose <54 mg/dL or severe) (6-9%) than glargine (19%). Tirzepatide did not increase MACE-4 events (cardiovascular mortality, myocardial infarction, stroke, hospitalization for unstable angina) in 109 patients compared to glargine (hazard ratio 0,74, 95% CI 0,51-1,08). The research included 60 fatalities (n=25 [3%] tirzepatide; n=35 [4%] glargine).[11]

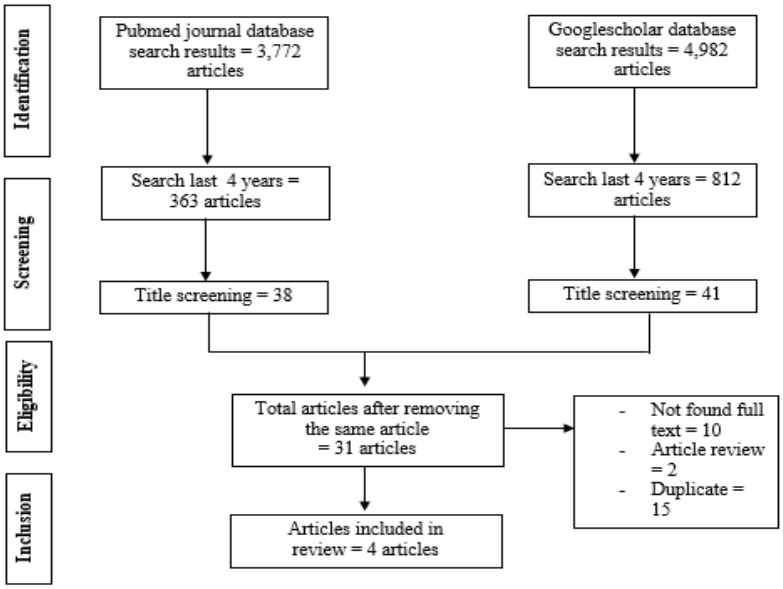

Figure 1. Article search flowchart

Tirzepatide had mean changes from baseline in HbA1c of -1.06% for 1 mg, -1.73% for 5 mg, -1.89% for 10 mg, and -1.94% for 15 mg, compared to -0.06% for placebo (posterior MD [80% credible set]. Posterior MD (80% credible set) for change in HbA1c from baseline to 26 weeks with tirzepatide dosages were 0,15% (-0.08 to 0.38) for 1 mg, -0,52% (-0.72 to -0.31) for 5 mg, -0.67% (-0.89 to -0.46) for 10 mg, and -0.73% (-0.95 to -0.52) for 15 mg.[12]

At 26 weeks, 33-90% of Tirzepatide patients reached the HbA1c goal of <7.0% (vs 52% with dulaglutide, 12% with placebo) and 15-82% attained at least 6·5% (vs 39% with dulaglutide, 2% with placebo). Tirzepatide decreased fasting plasma glucose by 0.4 to -3.4 mmol/L (vs 0.9 for placebo, -1.2 for dulaglutide). Most treatment-emergent adverse events were gastrointestinal (nausea, diarrhoea, and vomiting).[12]

Gastrointestinal events were dose-related (23.1% for 1 mg Tirzepatide, 32.7% for 5 mg, 51.0% for 10 mg, 66.0% for 15 mg, 42.6% for dulaglutide, 9.8% for placebo); most were mild to severe and temporary. Decreased appetite was the second most prevalent adverse event (3·8% for 1 mg Tirzepatide, 20·0% for 5 mg, 25·5% for 10 mg, 18·9% for 15 mg, 5·6% for dulaglutide, 2·0% for placebo). No significant hypoglycaemia occurred. Lung cancer stage IV killed one placebo patient unrelated to study therapy.[12]

DISCUSSION

Hyperglycemia is a symptom of type 2 diabetes (T2D), which can be caused by a number of factors, including a reduction in the amount of insulin produced by pancreatic beta cells as well as a reduction in the amount of insulin's ability to do its job. The individual mechanisms by which dual agonism of both GLP-1 and GIP receptors may improve glycemic control require further investigation. We conducted post hoc exploratory analyses of biomarkers associated with pancreatic beta-cell function and insulin sensitivity in order to investigate the mechanisms by which tirzepatide led to greater reductions of hyperglycemia than a selective GLP-1 receptor agonist. Our goal was to better understand how tirzepatide was able to achieve these results.[13–15]

Study showed tirzepatide in doses of 5 mg, 10 mg, or 15 mg was noninferior and superior to semaglutide in doses of 1 mg when compared in terms of a reduction in the level of glycated hemoglobin in patients with type 2 diabetes who were receiving metformin. This was the conclusion of a study that compared the two drugs. The aim of having a glycated hemoglobin level that is less than 5.7% (normoglycemia) was reached in 27 to 46% of the patients who got tirzepatide, while it was reached in 19% of the patients who received semaglutide. Those who were given tirzepatide at a dosage of 15 milligrams saw a weight reduction that was almost twice as great as that of patients who were given semaglutide at a dose of 1 milligram. At the end of the study's 40 weeks, none of the four therapy groups saw a plateau in their rate of weight loss.[9]

In persons with type 2 diabetes who were treated with diet and exercise alone, the SURPASS-1 study demonstrated a statistically significant improvement in glycemic control and strong bodyweight reductions with all three tirzepatide dosages when compared with the placebo group. Importantly, between 87 and 92% of individuals who were administered tirzepatide achieved the HbA1c goal of less than 7.0% that is suggested by the American Diabetes Association (ADA).[10]

Tirzepatide is a synthetic peptide made up of 39 amino acids. It has agonist action at both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, although it binds more strongly to GIP receptors.[12]

Its structure, which is principally based on the GIP amino acid sequence, has a C20 fatty di-acid moiety that prolongs the duration of action and, as a result, makes once-weekly subcutaneous injection possible.[13] Treatment with tirzepatide (1 mg, 5 mg, 10 mg, and 15 mg) resulted in significant, dose-dependent reductions in glycated hemoglobin A1c (HbA1c) (up to –2.4%) at 26 weeks in subjects with type 2 diabetes (T2D), compared with placebo (+0.1%) and selective GLP-1 receptor agonist, dulaglutide (–1.1%), and dose-dependent reductions in body weight (ranging from –4.8 to – 2).[12]

In this post hoc exploratory biomarker investigation, the effects of tirzepatide, a new dual GIP and GLP-1 receptor agonist that is administered once weekly, were explored on markers of pancreatic beta-cell activity and insulin sensitivity in adult participants who had type 2 diabetes. When compared with dulaglutide, which is a selective GLP-1 receptor agonist, tirzepatide was shown to be superior in terms of its ability to improve beta-cell activity and lower fasting glucagon levels.[16–18]

Tirzepatide was demonstrated to enhance numerous indicators of pancreatic beta-cell function by improving HOMA2-B indices in a dose-dependent manner and reducing proinsulin levels, proinsulin/C-peptide ratios, and proinsulin/insulin ratios. Under situations in which there is an elevated metabolic demand for insulin synthesis, proinsulin, which is the beta cell's most abundant secretory protein, is a significant driver of protein load that is transported to the endoplasmic reticulum.[16,17]

Tabel 2. Effects of administration of medicinal agents on decreasing HbA1c levels

Author	Agent	Reduce HbA1c
Frias, 2021; Rosenstock, 2021; Del Prato, 2021	Tirzepatide 5 mg	1.90%
Frias, 2021; Rosenstock, 2021; Del Prato, 2021; Frias 2018	Tirzepatide 10 mg	2.12%
Frias, 2021; Rosenstock, 2021; Del Prato, 2021; Frias 2018	Tirzepatide 15 mg	2.32%
Frias, 2021	Semaglutide 1 mg	1.86%
Del Prato, 2021	Glargine 100 U/mL	1.44%
	Placebo	0.23%

It is possible that the capacity of pancreatic beta cells to adapt for an increased metabolic requirement for insulin generation in type 2 diabetes depends on their response to endoplasmic reticulum stress. Proinsulin is prone to misfolding. One of the most important aspects of beta-cell dysfunction in type 2 diabetes is an impaired ability to convert proinsulin to insulin. In longitudinal cohorts, elevated proinsulin levels accurately predict both a worsening of hyperglycemia as well as the transition of nondiabetic patients to type 2 diabetes.[19,20]

A decrease in the metabolic load placed on the pancreatic beta cell might be substantially alleviated by improvements in insulin sensitivity. Improvements in proinsulin levels and proinsulin/insulin ratios are two indicators that a reversal of beta-cell dysfunction may be possible when metabolic demand is decreased. This may be the case for certain people. Subjects with type 2 diabetes who react favorably to bariatric surgery by going into remission of their diabetes, for instance, have lower levels of proinsulin and lower ratios of proinsulin to C-peptide than nonremitters do.[21]

On the other hand, an increased metabolic demand together with experimentally induced insulin resistance and increased insulin production may lead to a rise in proinsulin/insulin ratios in animals with type 2 diabetes. The responses of individuals with type 2 diabetes to treatment interventions using insulin secretagogues or insulin sensitizers further highlight the link between stimulating insulin secretion and lowering the amount of stress placed on pancreatic beta cells.[22]

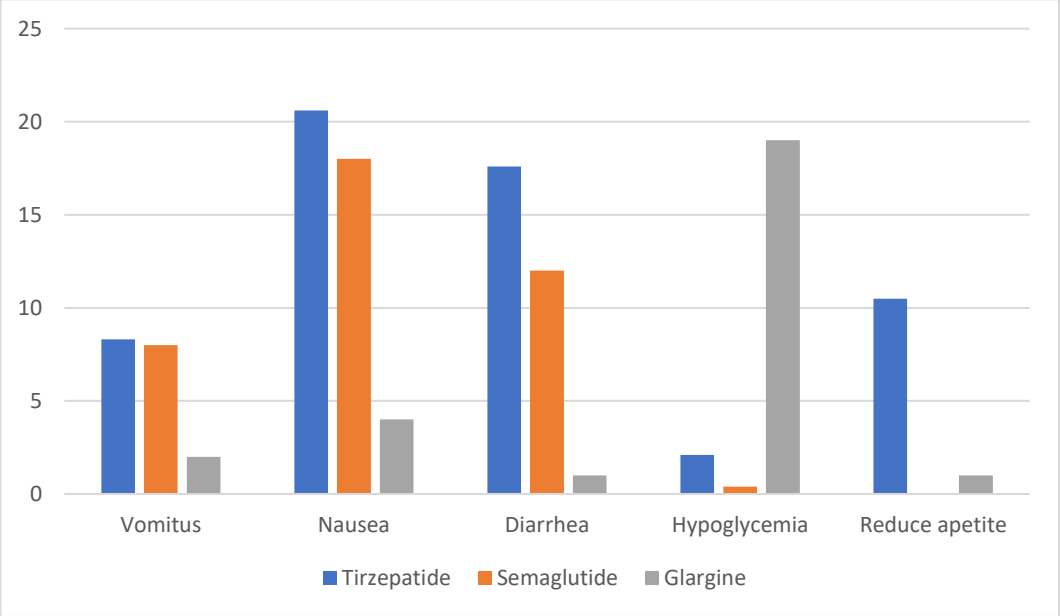

Figure 2. Side effects of treatment agents

In clinical investigations involving type 2 diabetes, the injection of the sulfonylurea glyburide raised both proinsulin levels and the ratio of proinsulin to insulin, while treatment with the insulin sensitizer rosiglitazone considerably lowered the amount of proinsulin that was secreted. Tirzepatide was shown to lower proinsulin/C-peptide ratios in obese adolescents by up to 50 percent, which is a significant reduction when compared to the 21 percent drop that was recorded after bariatric surgery.[21,22]

In general, unpleasant gastrointestinal events were reported more often in the groups receiving tirzepatide as opposed to the groups receiving placebo. Increases in heart rate that were seen in this study were in line with findings from earlier research with GLP-1 receptor agonists.[9,10] GLP-1 receptor agonists have been shown to consistently cause the adverse effects of nausea and vomiting, which are typically harsher at the beginning of treatment and improve as the treatment goes on, whereas DPP-4 inhibitors cause less and less severe side effects.[23]

CONCLUSION

According to the findings of this paper, a dose of 15 milligrams of tizepatide was superior in reducing HbA1c levels, despite the fact that it induced higher levels of gastrointestinal side effects.

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