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BASED ON STUDY OF TIRZEPATIDE IN THE MANAGEMENT OF CHRONIC WEIGHT LOSS IN TYPE 2 DIABETES

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Abstract:

The present study indicates that the Tirzepatide is a promising drug with dual acting glucose dependent insulin tropic polypeptide peptide and glucagon like peptide receptor activation that has revolutionized the treatment of type 2 diabetes mellitus. Tirzepatide is indicated to improve blood sugar control in adults with type 2diabetes as an additional to diet and exercise. It is also indicated as an adjunct to reduced calorie diet and increased physical activity for chronic weight management. Tirzepatide has demonstrated significant benefits in obese patients with a common type of heart failure, preserved ejection fraction in a phase 3 trail.

Over two years,Tirzepatide reduced the risk of major complications including urgent heart failure visits, hospitalizations, increased diuretic treatment and cardiovascular related deaths by 38% compared to placebo.This makes Tirzepatide has been shown to achieve better glycemic control in terms of glycosylated hemoglobin reduction and improve fasting and post pride in a glucose levels as combined with other diabetic medications.Tirzepatide has acceptable side effects in this well tolerated with lower risk of hyperglycemia . In this review we have summarized the clinical trials and their respective outcomes in highlighted the potential future indications for tirzepatide in the management of obesity, heart failure, non alcoholic steatohepatitis. [1]

Key Words: *Tirzepatide, type 2 diabetes mellitus, chronic weight management, benefits in obese patients with a common type of heart failure, preserved ejection fraction in a phase 3 trail.*

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INTRODUCTION:

Tirzepatide is a novel diabetes medication that has been approved by Food and drug administration. It is the first of its kind to act as dual acting glucose dependent Insulin tropic polypeptide (GIP) and glucogon like peptide (GLP- 1) receptor agonist.

Etal coined the term twin cretin to describe their synergistic effect on insulin secretion .After 15 to 20 minutes of meal ingestion ,plasma concentrations of GLP- 1 and GIP increase ,stimulating their receptors on pancreatic cells to activate an insulin tropic response that is glucose dependent and proportional to facilitate the elimination of absorbed carbohydrate and fat load.

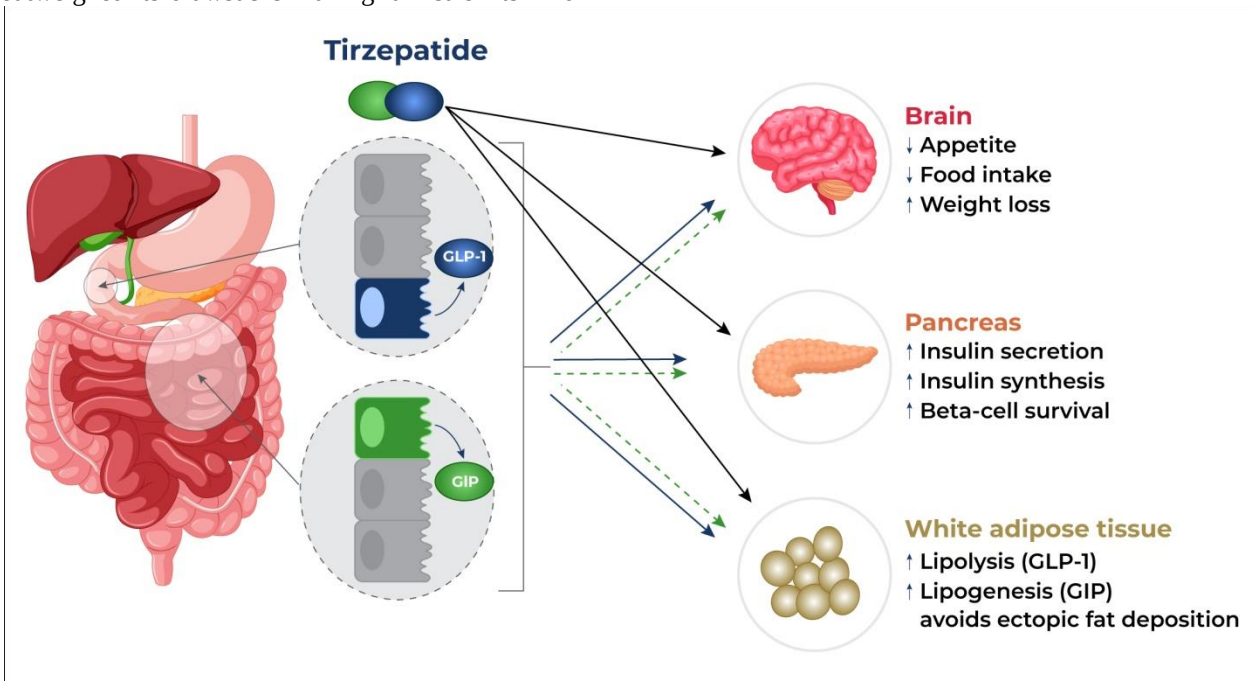
Tirzepatide is viable alternative for supplementing the in cretin effect in achieving glycemic control as this impact is weakened in diabetes with the added benefits of glycosylated hemoglobin reduction ,weight loss and cardiovascular health, a good lipoprotein profile and improvement in non alcoholic steatohepatitis.

In a series of clinical trials, the effectiveness of varying doses has been compared with the other currently prescribed drugs including semaglutide, dulaglutide, insulin degludec, insulin glargine. Metformin, etc [2]

According to the research, Tirzepatide benefits outweighed its drawbacks making it first of its kind to be studied. Nevertheless, given its novelty, further investigation is required to gain a comprehensive understanding of its potential adverse effects .We aim to discuss Tirzepatide in depth this review, highlighting the benefits of this drug in the treatment of diabetes and other conditions such as obesity cardiovascular safety and liver disease. Furthermore, we compare it to other anti diabetic medicines that have been shown to be effective and safe [3]

MECHANISM:

- Tirzepatide is a glucose dependent insulin tropic polypeptide (GIP) receptor and glucogon like peptide (GLP- 1) receptor agonist.
- It is a 39 amino acid modified peptide with a C-20 fatty acid moiety that enables albumin binding and prolongs the half life.
- Tirzepatide selectively binds to and activates both GIP and GLP -1 receptors which are the targets for native GIP and GLP 1.
- Tirzepatide enhances first and second phase insulin secretions and reduces glucagon levels both in a glucose dependent manner.
- Tirzepatide lowers fasting and post prandial glucose concentration, decreases food intake, and reduces body weight in patients with type 2diabetes [4].



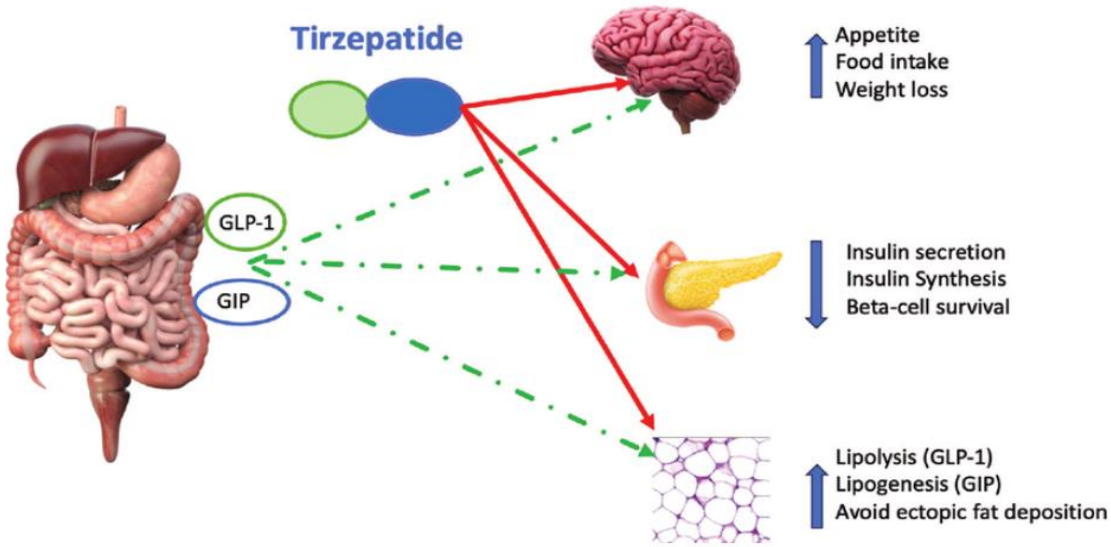
Pharmacokinetics:

Absorption: Tirzepatide has a bioavailability of approximately 80%. The time it takes to reach peak serum levels can range from 8 to 72 hours.

Distribution: The mean steady state volume of distribitution of tirzepatide is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Metabolism: When injected, the peptide structure undergoes proteolytic cleavage. In addition, the C20 fatty di acid composition undergoes beta oxidation and amide hydrolysis. Being a modified polypeptide tirzepatide undergoes metabolism into individual amino acids in various tissues including the liver

Elimination: Tirzepstide has a half life of 5 days facilitating weekly dosing, and is cleared in urine and feces as metabolites [5]



ADMINISTRATION:

Tirzepatide is administered in subcutaneous route and in an oral form

Tirzepatide dosages are available in strengths of 2.5mg/ 0.5ml, 5mg/0.5ml, 7.5mg/0.5ml, 10mg/0.5ml, 12.5mg/0.5ml and 15mg/0.5ml [6].

Adult Dosage: Standard dosing is once weekly, prescribed does can be increased on follow up visits based on efficacy, as defined by HbA1c levels body weight and adverse effects .The patient's ability to tolerate adverse effects plays a significant role in dosing titration. The initial dosage of tirzepatide for treatment initiation is 2.5 mg administered SQ once weekly, with the primary goal of initiation rather than glycemic control after four weeks increase to 5mg SQ once weekly. For additional glycemic control, escalate the dosage by 2.5 mg after at least four weeks on the current dose. The maximum Tirzepatide dosage is 15 mg SQ once weekly .If a tirzapatide dose is missed it should be admitted within four days or 96 hours otherwise keep the missed dose and return to the regular once-weekly schedule[7].

SPECIFIC PATIENT POPULATION:

Hepatic impairment:

According to the manufacturer's product information no dosage adjustment of Tirzepatide is suggested for patients with hepatic impairment

Renal impairment:

No dosage adjustment of Tirzepatide is suggested for patients with hepatic impairment. However tirzepatide is associated with gastrointestinal adverse drug reactions including nausea, vomiting, and diarrhoea leading to dehydration which may cause acute kidney injury. Use with caution in patients prone to dehydration.

Pregnancy considerations:

Available information on tirzepatide use in pregnant women is inadequate to evaluate for a drug related

risk of congenital disabilities and adverse maternal or fetal outcomes exposure to the mother and fetus is associated with poorly controlled diabetes in pregnancy. Animal reproduction studies have shown higher occurrences of external, visceral and skeleton mall formations when exposed to tirzepatide .Potential risks exist in the fetus if ingested during pregnancy .Hence, tirzepatide should only prescribed to pregnant patients of childbearing age when the benefits outweigh the potential risks and after thorough discussion of territogenic effects. Clinicians should also discuss the decreased efficacy of oral contraceptives and offer non oral methods for at least four weeks after beginning of tirzepatide[8]

Breastfeeding considerations:

Novel information exists song Terzepatide in animal or human milk or its effects on the breasted infant .Clinicians should consider the developmental and health benefits of breastfeeding the mothers need for tirzepatide and potential adverse impacts on breastfeeding infant. Tirzepatide is a large molecule with high molecular weight .According to the milk concentration is likely less, and the absorption is unlikely because it is presumably partially destroyed in the infant gastrointestinal tract. Therefore until more clinical data are available should be used cautiously during breastfeeding especially in newborn or preterm infants.

Pediatric patients: Terzepatide has not been established as safe and effective for pediatric patients [9].

ADVERSE EFFECTS OF TIRZEPATIDE:

Based on the available data, most users do not experience significant adverse drug reactions. The primary adverse effects are gastrointestinal -related but other side effects have also been infrequently reported.

Decreased appetite is frequently reported, though this is a potential contributory etiology of intensional weight loss. The adverse drug reactions according to the System organ class (SOC) listed below [10].

Gastrointestinal: Decreased hepatitis often reported nausea and diarrhea may occur in up to 10% of patients in addition to some infrequent reports of vomiting and acid reflux constipation has also been repaired in some users.

Cardiovascular: Sinus tacky cardiac is reported but may be blunted by concurrent medication use.

Renal:

Infrequent cases of acute kidney injury have been reported likely secondary to dehydration from gas to international losses they may occur in healthy preexisting chronic renal disease patients monitoring for signs of dehydration is likely to prevent trainer injury.

Dermatological:

Hypersensitivity reactions have been infrequently reported at the injection site the prevalence is similar to those reported by patients using glp 1 agonies such even should be discussed with a clinician and male warrant medication discontinuation.

Pancreatitis:

GLP 1 medications are a known risk factor for equip pancreatitis the risk level for Terzapati is similar to GLP 1 agonist medications patients should be advised to immediately seek care at the local emergency department if they develop severe abdominal pain on Telesa Patel therapy asymptomatic elevation of lipase in mls may be seen in some patients.

Hepatobilary:

Reports of Kolia Thesis and Korea's 30s have occurred in patients on Teresa Patel therapy these adverse effects may be due to rapid weight loss induced by Terzipathy.

Ocular:

The agents with pre existing diabetic retinopathy should be advised that symptoms may temporarily worsen if glycemic control quickly improves any vision genius should be discussed within a clinician.

Endocrine:

A small risk of hypoglycemia Exits the risk is more significant for insulin therapy patients and those utilizing sulfonyl areas patients should be advised on the potential symptoms of hypoglycemia.

A recent systematic review comprising nine randomized control trials with a total of 9818 patience indicates that there's apartheid's overall safety data is similar to that of glp 1 receptor agonist except for hypoglycemia at doses higher than 10 mg careful attention is required during adverse events like nausea warmth in the area and injection site reactions at higher doses [(11)].

Drug drug interactions:

- Patients using other GLP-1 agents, such as semaglutide or liraglutide, should not be prescribed tirzepatide. Patient on insulin therapy can be initiated on Terzepatide therapy and cautiously have the insulin dose decreased to minimize the risk of hypoglycemia.
- The efficacy of oral hormonal contraceptives is decreased, so patients should be advised to use nonoral contraceptive methods or add a barrier contraceptive for four weeks after initiation and each dose escalation with terzepatide.
- Tirzepatide delay's gastric emptying, impacting the absorption of concurrently administered oral medications .This is particularly significant in those with preexisting delayed gastric emptying, as it exacerbate these symptoms. Caution is advised when using oral medications dependent on threshold concentrations or with a narrow therapeutic index and tirzepatide [(12)]

Contraindications:

Terzepatide is contraindicated in patients with medullary thyroid cancer. Terzepatide is also contraindicated in multiple endocrine neoplasia syndrome type 2 .Patients with known severe hypersensitivity to terzepatide or any excipients as it has been associated with hypersensitivity reactions including anaphylaxis and angiogedema in patients who have experienced angioedema or anaphylaxis due to GLP1 receptor agonist it is important to use terzapatide cautiously[(13)].

Monitoring: Patients should have HbA 1 body weight monitored during follow up visits. Follow up intervals may vary depending on the local standard of care for diabetes management and obesity treatment HbA1c monitoring is usually implemented every 3 months, regarding patient deficiency and pregnancy can lead to references between the A1C result and patients actual glycemic status. Monitoring for side effects such as gastrointestinal related symptoms may be necessary, especially as the prescribed doses increase .In addition the asymptomatic elevation of lipase and amylase levels can be seen in patients using terzepatide. Still clinical data do not suggest utility in monitoring these markers without symptoms.

Toxicity: Patients who overdose on Terzepatide should be monitored for any changes in clinical status .As this medication has a long half life patients may require prolonger monitoring. Clinicians should contact poison control, consultations with a toxicologist may be unnecessary No current antidote for Terzepatide overdose exists and supportive care is most beneficial [(14)].

CONCLUSIONS: Tirzepatide has acceptable side effects in this well tolerated with lower risk of hyperglycemia. Tirzepatide is a promising drug with dual acting glucose dependent insulin tropic polypeptide peptide and glucagon like peptide receptor activation that has revolutionized the treatment of type 2 diabetes mellitus. Tirzepatide is indicated to improve blood sugar control in adults with type 2diabetes as an additional to diet and exercise. It is also indicated as an adjunct to reduced calorie diet and increased physical activity for chronic weight management. Tirzepatide has

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Mechanism in weight loss:

Tirzepatide promotes weight loss by affecting certain brain chemicals involved food intake. Energy topindefere and deposition. It acts on GLP- one receptor which reduces fat cells and enhances fat breake down.

Pathophysiology:

Tirzepatide is a novel dual incretion mimetic, targeting both GLP-1 and GLP receptors. It pathophysiology is based on enchanting the effects of these two incretion hormones which are involved in glucose regulation, insulin secretion and energy metabolism.

GLP-1 ANTAGONISM:

a) Increase insulin secretion: GLP-1 enhances glucose dependent insulin release from pancreatic β cells, helping to lower blood glucose level after meals.
b) Decreases glucagon secretion: by suppressing glucagon release from α cell it reduces hepatic glucose production.
c) Slow gastric emptying: delays nutrient absorption and promotes satiety, leading to reduced caloric intake.
d) Promotes weight loss: GLP-1 activation in brain reduces appetite, contributing to weight loss.

2 GIP AGONISM:

Enhances insulin secretion, like GLP-1 GIP increases insulin secretion in a glucose dependent especially after meals.

Improves insulin sensitivity GIP helps enhance insulin sensitivity in adipose tissue, leading to better utilization.

Potentiates weight loss: although GIP itself is typically associated with weight gain, when combined with weight gain. When combined with glp-1 agonism, it enhances the weight loss effects, possible by synerging with satiety promoting effects of GLP-1.