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Tirzepatide, A New Era of Dual-Targeted Treatment for Diabetes and Obesity: A Narrative Review

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Conflict Of Interest

The authors have no conflicts of interest to declare.

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KEYWORDS

Type 2 diabetes mellitus, Obesity, Tirzepatide, GIP, GLP-1, Dual receptor agonist, Insulin resistance, weight loss, Pharmacodynamic effects, Therapeutic innovation.

ABSTRACT:

This review presents an in-depth exploration of the evolving landscape in managing type 2 diabetes mellitus (T2DM), emphasizing the substantial impact of obesity on its prevalence. The spotlight is on "tirzepatide" (LY3298176), a novel dual agonist targeting Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) receptors. Amid rising obesity-related insulin resistance, this paper underscores the imperative of weight loss in T2DM management as per recent consensus guidelines. Tirzepatide, a synthetic 39-amino acid peptide, exhibits unique dual receptor agonism, fostering a potential synergy in enhancing insulin responsiveness and glucagonostatic activity. Its mechanism of action, chemistry, administration, and pharmacodynamic effects are meticulously elucidated. The review is punctuated with insights from preclinical and clinical studies, particularly the influential SURPASS and SURMOUNT programs, validating tirzepatide's utility in addressing T2DM and obesity. The duality of tirzepatide's receptor agonism holds promise in the intricate realm of T2DM and obesity management. The seamless interplay between scientific advancements and clinical applications presents opportunities for optimizing patient compliance and therapeutic outcomes.

INTRODUCTION

Recent modifications have been undergone to characterize adult-onset diabetes, commonly recognized as noninsulin-dependent diabetes mellitus, by the American Diabetes Association. To make the diagnosis, each of several criteria may be applied independently like the outcome of a 75-gram oral glucose tolerance test, revealing a 2-hour post-ingestion value ≥ 200 mg/dL, and the manifestation of characteristic diabetic symptoms allied with the same blood sugar concentration of ≥ 200 mg/dL, or a recurring fasting plasma glucose concentration measuring ≥ 126 mg/dL on multiple instances.[1] Since 1975, a significant surge in obesity prevalence has been observed, and instances of T2DM have experienced an almost threefold increase.[2] This concerning trend can be attributed to the fact that obesity contributes to insulin resistance, a crucial factor in the onset and progression of T2DM. Obesity stands out as

Journal of Chemical Health Risks

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the most prominent risk factor for this disease. Studies indicate that 44% of individuals worldwide diagnosed with T2DM are either overweight or obese, highlighting the strong association between excess weight and the condition. Furthermore, projections suggest that the incidence of diabetes resulting from obesity will continue to increase in the coming years.[3,4] The most recent consensus guidelines jointly the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have issued a joint statement. Emphasize the significance of incorporating weight loss ranging from 5% to 15% as a crucial aspect of managing T2DM.[5] In response to nutrient ingestion, the intestine secretes hormones commonly referred to as incretins, videlicet GLP-1, and GIP [6,7]. These hormones significantly influence the regulation of glucose equilibrium. Specifically, they exert their effects by stimulating islets of Langerhans cells to liberalize insulin. By acting as signaling molecules in the body, GIP and GLP-1 perform a prelude in sustaining ideal blood glucose levels and are involved in the intricate equilibrium of glucose regulation. Their release in response to nutrient intake highlights their importance in the control of glucose metabolism. As a result, medications that operate on the incretin system, like DPP4 inhibitors and GLP1 receptor agonists, have been used to treat T2DM up to this point. A growing body of research shows that administering GIP and GLP1 together now has a synergistic impact by greatly boosting insulin responsiveness and glucagonostatic activity.[8]

To benefit from this synergistic effect, a novel compound called "twincretin" has been created, acting as an agonist on both GIP and GLP1 receptors simultaneously: (LY3298176) terzepatid. With 39 amino acids, a synthetic peptide functions as an agonist at GLP-1 and GIP receptors. The primary structure of this peptide is derived from the GIP amino acid hierarchy, and it comprises a C20 fatty di-acid element that amplifies its effectiveness, allowing for weekly subcutaneous administration.[9] Since the injectable Exenatide, a GLP-1 RA produced by Eli Lilly and Company and Amylin Pharmaceuticals, Inc., is commercialized under the brand name Byetta®, received approval in the year 2005 a therapy for adult-onset diabetes, there has been notable advancement in this therapy class. Currently, several GLP-1 RA medication items are used and therapeutically prescribed for T2D. Along with promoting adequate glycemic control, these drugs also help people lose weight, lower their chance of developing hypoglycemia, and help preserve the heart and kidneys.[10] The International Diabetes Federation's data indicates that around 415 million individuals, comprising 9.3% of adults aged 20 to 79 years, a global population of people currently experience diabetes, as well as this is anticipated by the year 2040, this amount is projected to rise to 642 million. Approximately 5.0 million deaths worldwide were attributed to diabetes in 2015.[11] Certainly, diabetes is known for its notable genetic predisposition, and the prevalence of high blood sugar in individuals varies among different ethnicities. As, diabetes is more likely to be observed in individuals with African and Hispanic ancestry, as well as in certain minority populations like American Indians and Alaska Natives, because of their distinct genetic composition.[12] The most prevalent form is T2DM, which is over 90% of diabetes mellitus cases, generally found in adults. In the last three decennary, there has been a noteworthy rise in the spreading of adult-onset diabetes in specific nations, regardless of their economic status.[13] Type 2 diabetes is also related to an overall high-cost burden, estimated on a global scale at around $850 billion. T2DM is an ideal target for prevention as it is associated with increased human and financial costs, and challenges in treating it effectively once it is diagnosed.[14] In India, the diabetes problem has been frequently growing since 1990 and with a noticeable acceleration since 2000. The prevalence rate of diabetes has risen from 7.1% in 2009 to 8.9% in 2019. In the global diabetes epidemic, India is ranked second in the world followed by China with 77 million individuals with diabetes. At present, prediabetic conditions are estimated to be found in 25.2 million adults, and it is expected to reach 35.7 million by 2045. Among these, approximately 12 million people are aged over 65, and this figure is expected to increase to around 28 million by the year 2045. Furthermore, in India diabetes remains undiagnosed in nearly 57% of adults which is approximately 43.9 million people. There are a total of 1 million deaths linked to diabetes and on average the mean healthcare expenditure on diabetes per individual is 92 US dollars [15].

Journal of Chemical Health Risks

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MODE OF ACTION:-

The precise procedure through tirzepatide retouching blood sugar control and aids in heft management in type 2 diabetes is not currently understood. It is widely known that GLP-1 R agonism contributes to these beneficial Pharmacodynamic outcomes. Similar to selective GLP-1 RAs, they also have central effects that decrease food intake by enhancing insulin exudation from pancreatic beta-cells in impedance to glucose (known as the incretin effect) and reducing the secretion of glucagon from pancreatic alpha-cells leading to a reduction in intake of nutrients and promoting weight loss.[16] Tirzepatide is a synthetic peptide that works as an agonist for both the GLP- 1 and GIP receptors. It is a gastric inhibitory polypeptide analog and has 39 amino acids. Functionally, it causes the pancreas to release further insulin, which lowers blood sugar situations. Tirzepatide also elevates the level of attention towards adiponectin.[17] In comparison to the utilization of GLP-1 agonist medications alone, its binary agonism capability reduces appetite and markedly lowers hyperglycemia.[18]

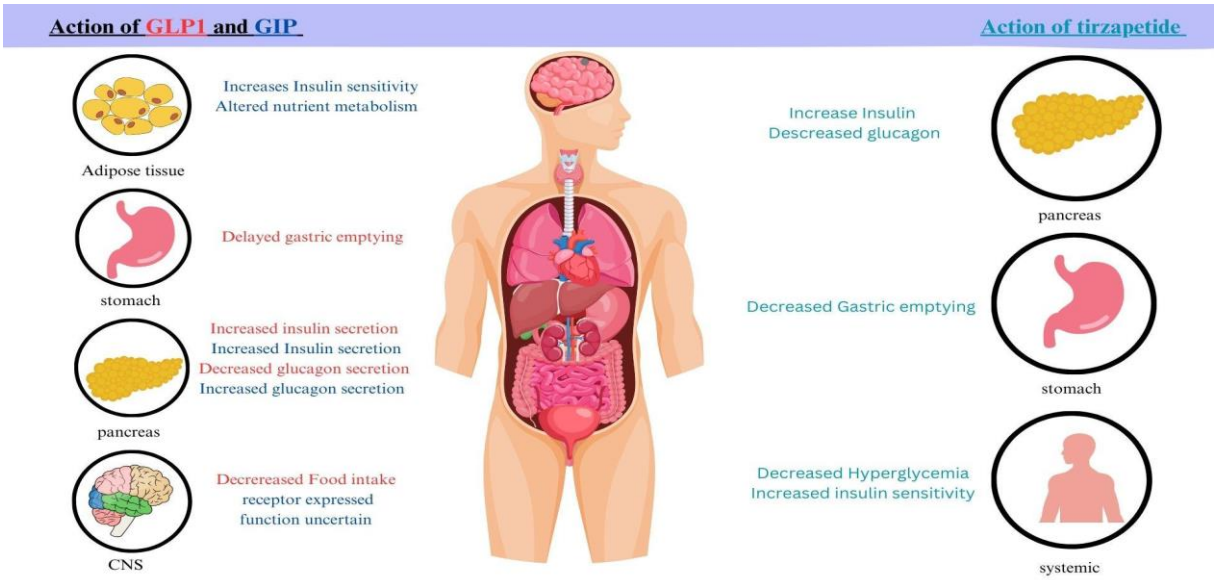

FIG 1 ACTION OF TIRZEPATIDE

PRECLINICAL AND INITIAL CLINICAL INFORMATION REGARDING THE GIP/GLP-1 RECEPTOR AGONIST TIRZEPATIDE:-

Tirzepatide (LY3298176) is the most progressed GLP-1 /GIP receptor agonist in development and was the first FDA-approved drug in its class for treating T2D in May 2022. [19, 20]. The EMA issued a favorable opinion in July 2022, proposing that tirzepatide be given commercial authorization to treat T2DM.[21]

TIRZEPATIDE IN OBESITY—THE SURMOUNT CLINICAL STUDY PROGRAM:-

Liraglutide, a GLP-1 receptor agonist, has obtained approval for addressing obesity through pharmacological management, and in the future, additional GLP-1RAs may also be authorized for this purpose. Additionally, the promise of treating obesity with dual- and triple-receptor agonists exists.[20, 21] Tirizepatide medication led to notable body weight reductions in T2D patients who were overweight or obese. Based on these results, a clinical trial program was launched to assess tirzepatide's efficacy and safety in addressing fatness. The extensive SURMOUNT clinical perusal curriculum on a global scale encompasses 4 distinct randomized controlled trials.[22] In these trials, tirzepatide is administered in aliment of 10 and 15 mg in monitoring SURMOUNT-2 through SURMOUNT-4. The duration of each trial spans at least 72 weeks, facilitating a detailed exploration of tirzepatide's effect and protection in the context of fatness treatment. [23]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(5), 1608-1614 | ISSN:2251-6727

CHEMISTRY AND RECEPTOR-BINDING CHARACTERISTICS:-

Tirzepatide has the chemical formula $C_{225}H_{348}N_{48}O_{68}$. It is an artificial peptide consisting of 39 amino acids, it is directly constructed and shares 19 conserved amino acids by native GIP (1-42) and is grounded on the hierarchy of natural GIP. With agonist action at both the GIP receptor and the GLP-1 receptor, tirzepatide is a single chemical that is linked to a C20 adipose diacid half via a hydrophilic convener positioned at the lysine relics at location 20. This enables the albumin list, extending its $T_{1/2}$ to around 5 days and enabling dosage instead of daily. It has a molecular mass of 4810.52 Dalton. Tirzepatide's list affinity for the GIPR is equivalent to that of natural GIP.[24]

ADMINISTRATION:-

Tirzepatide is injected under the skin to deliver it. Currently, it is not accessible orally. There are other doses available, inclusive of 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL. Once per week is the standard schedule for dosage, with a typical beginning dose of 5 mg/0.5 mL. Based on ascendancy (as determined by hemoglobin A1C scale and body weight) and side effects, prescribed dosages may be raised at subsequent visits. With varying degrees of severity, gastrointestinal-related side effects like nausea and abdominal pain are the most common adverse medication responses. The titration of the tirzepatide dose heavily depends on the patient's capacity to endure side effects.[25]

ADRS DRUG REACTIONS:-

Following the currently available acquaintance, most users do not have substantial unfavorable pharmaceutical reactions. Although additional side effects have been documented, gastrointestinal problems are the most common adverse effects that have been described. Although this is a probable contributing etiology to purposeful weight reduction, decreased appetite is commonly noted. The negative medication responses recorded by System Organ Class (SOC) are listed below:-

SKIN RELATED: Allergic reactions around the location of inject have been noticed sometimes. The number of cases is comparable to what patients using GLP-1 agonists describe. These scenarios should be managed by a doctor, who can contact to have the medicine withdrawn.[26]

GI RELATED: It is typical to encounter a reduction in appetite. Approximately 10% of individuals may experience symptoms of queasiness and diarrhea, with occasional reports of vomiting and gastroesophageal reflux. Additionally, some individuals have reported encountering constveness. Delayed stomach emptying poses a challenge to the absorption of certain oral medications. This is particularly crucial for individuals who already experience delayed gastric emptying since it has the potential to exacerbate their indications.[27]

RENAL: Rare incidences of acute renal damage have been documented; these cases are probably related to dehydration brought on by gastrointestinal losses. These can happen to both healthy people and those who already have chronic renal illness. It is probably best to keep an eye out for indicators of dehydration to avoid kidney damage.

Endocrine the threat of hypoglycemia is minimal and cure-dependent. The threat is lesser for people taking sulfonylureas or entering insulin treatment. The implicit signs of hypoglycemia should be explained in cases. GLP-1 drugs are known to increase the chance of developing acute pancreatitis. Tirzepatide has a comparable degree of risk as GLP-1 agonist drugs. If a patient receiving tirzepatide therapy experiences significant stomach discomfort, they should be urged to visit their local emergency room for treatment. Asymptomatic lipase rises are seen in some patients.[28]

EFFICACY

Tirzepatide is a one-time in hebdomadal hypodermis inject peptide accompanied by agonist undertaking at one and other the gip and GLP-1 receptors that have been developed from the native gip sequence and has been avowed by the Food and Drug Administration FDA for adult-onset diabetes. Preclinical research showed that tripeptides' abutment for gip receptors was continually with native gips affinity for gip receptors however tripeptides' affinity for GLP-1 receptors was around five times weaker than native GLP-1s affinity12 in contrast

Journal of Chemical Health Risks

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JCHR (2024) 14(5), 1608-1614 | ISSN:2251-6727

to GLP-1 receptor mono agonism gip activation appears to work synergistically with GLP-1 receptor activation to promote greaterweight loss in mice12 tripeptide caused clinically significant weight loss in type 2 diabetics during phase 2 tests calling for more research into the ability of the drug to treat obesity. [29] The latest studies show that tirzepatide improves hemoglobin A1C readings far better than an empty pill. Hemoglobin A1C levels were found to drop by -2.11% at a dosage of 5 mg per The latest studies show that tirzepatide improves hemoglobin A1C readings far better than a week in the SURPASS-5 investigation, as opposed to -0.86% with placebo. Hemoglobin A1C roll up by -2.34% while tirzepatide was administered at the recommended amount of 15 mg per week. It was demonstrated throughout forty weeks.[30] Tirzepatide dosages of 5 mg and 15 mg outgrowth in heaviness reductions of 5.4 kg and 10.5 kg, respectively. Semaglutide, an effective GLP-1 drug used to treat weight loss, exhibits a similar dose-related relationship to decreased weight.[31]

In contrast, tirzepatide shows similar pathways of action to GLP-1 medications, albeit with more potency. Owing to its capacity to reduce heft and non-toxicity to the liver, it may also indirectly aid in the control of nonalcoholic fatty liver disease (NAFLD).[32]

An injection is used to give tirzepatide subcutaneously. Currently, there isn't an oral version accessible. There are other dosages available, including 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL. The usual starting dose is 5 mg/0.5 mL, and the dosage is typically administered once per week. During follow-up visits, prescribed doses may be increased in accordance with undesirable effects and efficacy as determined by body weight and hemoglobin A1C levels. The most common adverse medication reactions are digestive tract in character and include sickness and discomfort in the abdomen that might vary in intensity. Tirzepatide dosage titration is heavily influenced by the patient's tolerance for adverse effects. [33]

SAFETY AND TOLERABILITY

During the trial, there were no fatalities. Diarrhoea and an elevated white blood cell count were the two SAEs that single patient in the tirzepatide 12 mg therapy conglomeration indirect. As a binary GIP/GLP-1 agonist, tirzepatide has adverse effects that are similar to those of a GLP-1 receptor agonist. The gastrointestinal (GI) system was responsible for the majority of the side effects, with sickness, scouring, and emesis being the most frequent adverse events.[34]

CONCLUSION

Despite the fact that there is now no known treatment for T2D or obesity, both serious conditions can be managed with the right therapy and lifestyle changes. A novel incretin-based treatment for adult-onset diabetes, tirzepatide is a double GIP/GLP-1 receptor agonist. An increasing body of evidence from the SURPASS and SURMOUNT clinical trial programs supports the effectiveness and safety of one-time hebdomadal subcutaneous tirzepatide in persons with T2DM and/or fatness. After this provides the advantage of a once-weekly dose administration, patient conformity, and dose compliance are well encouraged.

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