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An Overview on Tirzepatide, Dual-Targeted Treatment for Diabetes and Obesity

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Abstract:- Obesity and diabetes prevalence are often referred to as the "twin epidemics" and are becoming a more widespread issue, particularly in developed countries. Advanced therapeutic strategies are therefore required. Tirzepatide, known as "twincretin", is a "first-class" drug and the only agonist of glucagon-like peptide-1 (GLP-1) and glucose-dependent peptide (GIP) receptors, which can significantly reduce blood sugar. levels and improved insulin sensitivity, as well as more than 20% reduction in body weight and improved lipid metabolism. This new antidiabetic drug is a synthetic peptide analog of human GIP hormone with a linkage to C20 fatty acid moiety that, through acylation process, can bind to albumin to deliver a single dose, by a single subcutaneous injection, once a week, consistent with its half-life of approximately five days. The "twincretin" heralded in an era of tremendously important and alluring dual therapy choices for diabetes and obesity, as well as advanced management of closely associated cardiometabolic settings, which are the primary global cause of illness, disability, and mortality. Here, we outline the salient features of tirzepatide's synthesis, structure, and action while also considering its benefits and drawbacks. Additionally, we briefly examine the progression of clinical research and the evolution of this type of medicinal medication.

Keywords:- *Diabetes, Insulin, Incretins, Obesity, Tirzepatide, Twincretin.*

I. INTRODUCTION

Diabetes is a chronic condition caused on by either insufficient insulin production by the pancreas or inefficient insulin utilisation by the body. Blood glucose is controlled by the hormone insulin. Uncontrolled diabetes frequently results in hyperglycaemia, also known as high blood glucose or raised blood sugar, which over time can seriously harm many different physiological systems, including the neurons and blood vessels [1]. Type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes resulting from endocrinopathies, steroid use, etc. are some of the different kinds of DM. Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are the two primary subtypes of DM, and both are typically brought on by defective insulin secretion (T1DM) and/or action (T2DM) [2].

In 1988, type 2 diabetes was initially identified as a part of the metabolic syndrome [3]. Hyperglycemia, insulin resistance, and a relative insulin deficit are the hallmarks of type 2 diabetes, formerly known as non-insulin dependent diabetes [4]. Genetic, environmental, and behavioural risk factors interact to cause type 2 diabetes [5] [6]. Daily cases are growing at a dangerous rate. Over a 34-year period (1980–2014), the number of T2D patients increased fourfold, and from 2000 to 2016, the premature mortality rate from T2D increased by 5%. Due to the predicted 1.5 million direct deaths from T2D in 2019, it was ranked as the ninth-largest cause of mortality [1] [7]. Globally, there were an astounding 537 million adults with T2D in 2021, and that amount is predicted to increase to 783 million by 2045 (with an increase of 12.2%) [8]. According to these findings, 1 in 10 adults today suffer T2D, and this number is rising at pandemic rates.

By regulating the endocrine system for glucose metabolism and glycaemia, beta cells, which are found in the pancreas, play a crucial role in the onset and progression of T2D. In T2D, these cells stop functioning to counteract insulin resistance, resulting in hyperglycaemia, an insulin-deficient state. The pancreatic beta cells' ability to function can be further compromised by hyperglycaemia, which can lead to glucose toxicity and an inadequate supply of insulin in the body [9].

Treatment for T2D include using drugs like metformin along with dietary, activity, and nutritional modifications. To support beta cell activity and reduce harmful inflammatory reactions, varieties of synthetic moieties and herbal formulations have been created [10]. The majority of these medications have side effects depending on how they are administered and other factors. Syncope, vertigo, nervousness, anxiety attacks, depression, and diarrhoea are some of the more typical side effects associated with the sulfonyl urea class of medications. With metformin, gastrointestinal discomfort is the side effect that is most frequently reported, while with repaglinide, it is hypoglycaemia. [11] [12]. In such circumstances, minimal medication really reaches the cells. By delivering such medications to the pancreatic islets or reducing the dose taken, as well as by reducing the negative effects of agents that are regularly administered, the therapeutic impact of such medications can be quickly enhanced [13]. Insulin or its analogues, such as insulin lispro or insulin aspart, and oral medicines, such as glipizide, glimepride, metformin, acarbose, pioglitazone, and saxagliptin, have traditionally been used to treat T2D [14]. Exubera®, a short-acting insulin that can be inhaled soon before nutrient consumption, was authorised for therapeutic use by the US Food and Drug Administration (US

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FDA) in January 2006 in addition to these medications [15]. Additionally, incretins, also referred to as incretin hormones, are substances made by the human body that trigger beta cells to release insulin. They were first identified in the early 1970s. These substances are secreted in the intestine and have an impact on beta cell activity. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide are two of the incretins that are most well-known (GIP) [16]. Tirzepatide is a dual GIP/GLP-1 agonist, hence its adverse drug reaction profile is equivalent to that of GLP-1 agonists. The most frequent side effects of tirzepatide are gastrointestinal in origin, such as nausea, vomiting, and diarrhoea [17] [18]. Based on phase 2 trials, hypoglycemia is not common [17].

According to WHO, Obesity is defined as an abnormal or excessive buildup of fat that creates a health concern. Overweight is defined as a body mass index (BMI) of 25, and obesity as a BMI of greater than 30. According to the global burden of illness, the problem has reached epidemic proportions, with over 4 million people dying annually as a result of being overweight or obese in 2017 [19]. It is important to emphasise the link between obesity and a higher chance of developing various significant disorders and diseases, including diabetes, hypertension, cardiovascular disease, cancer, asthma, and hypercholesterolemia [20]. One of the biggest problems to date has been the struggle against obesity. So far, the only pillars of treatment have been a healthy diet and consistent exercise.

Obesity and diabetes are chronic conditions that are particularly deadly in affluent nations and cause significant morbidity worldwide. As far as the 21st century is concerned, they represent the twin epidemics. Both disorders are complicated health issues incorporating genetic, epigenetic, and behavioural variables, as well as socioeconomic and environmental effects; none is a simple issue [21] [22] [23].

This overview focuses on the synthetic short peptide tirzepatide, the first dual GLP-1 and GIP receptor agonist, as a potential therapeutic agent for the management of either diabetes or obesity. It also discusses how it differs from previous comparable drugs.

Due to recent advancements in science and biotechnology, modified short peptides, which have better bio-functions than their original analogues, hold considerable promise for use in modern biomedicine [24].

II. METHADOLOGY

We used SciFinder®, PubMed, and Scopus to conduct a literature search for the construction of this review. The linked papers were searched using the keywords "tirzepatide and Diabetes," "tirzepatide and Obesity," and "new antidiabetics." There were a total of 90 articles that contained the terms "tirzepatide" and "Diabetes/Obesity," which were closely related to one another. From this, we selected the ones that discussed tirzepatide clinical trials, used synthetic approaches, or conducted in vivo research. Only papers written in English were included; neither conference abstracts nor book chapters were.

III. INSULINOTROPIC PEPTIDES:

The effect of these insulinotropic peptides is known as the 'incretin effect.' This effect is characterized by an increase in glucose secretory response with oral glucose administration compared to intravenous glucose treatment despite equal plasma concentrations. The term comes from the fact that it is thought to occur as a result of foods activating the production of incretin hormones and also acting on pancreatic beta cells in an insulinotropic manner [25].

GIP (gastric inhibitory polypeptide; glucose-dependent insulinotropic polypeptide) is a 42 amino acid hormone synthesized by enteroendocrine K-cells and released into the circulation in response to food stimulation and they have an important function in postprandial metabolism. GIP and glucagon-like peptide-1 (GLP-1) are both incretins that promote insulin release in a glucose-dependent manner [26]. With the discovery of glucose equilibrium, their most advantageous state, the incretin effect, begins to increase glucose-stimulated insulin secretion from the pancreas. GIP is thought to be the key incretin hormone responsible for this action, yet when taken simultaneously, they have a synergistic impact [27].

DPP-4 inhibitors work by preventing the rapid DPP-4-mediated breakdown of endogenous GLP-1 and GIP, hence improving its efficacy. Meanwhile, GLP-1 receptor agonists (RA), which benefit from a structural change, develop resistance to DPP-4 degradation by accelerating the onset of the GLP-1 receptor [28]. GLP-1 RAs also help to reduce pancreatic glucagon release via alpha cells, which reduces stomach emptying time and hunger and food intake, resulting in weight loss in a different way than glucose-dependent stimulation. GIP infusion, unlike externally delivered GLP-1, which partially recovers incretin function in T2D patients, does not produce a substantial insulin secretory response, even at therapeutic dosages [27]. Based on these findings, GIP-selective RAs have not been generally investigated for the treatment of T2D. Semaglutide (Ozempic), a GLP-1 RA, is commonly used to treat type 2 diabetes. The USFDA and EMEA have authorized the subcutaneous use of Semaglutide as an add-on therapy to Metformin. There is also an oral variant of Simaglutide that may be taken once a week [29].

IV. TIRZEPATIDE

Eli Lilly and Company (Indianapolis, IN, USA) was the first to use tirzepatide for glycemic control in early 2016 [30]. Eli Lilly surpassed another milestone on May 14, 2022, when the US FDA approved the highly awaited anti-diabetic medication Mounjaro® (tirzepatide). Tirzepatide is a synthetic peptide compound that works as a receptor agonist on both GIP and GLP-1 receptors. It is also termed as 'twincretin' due to its remarkable dual activity feature. Because it has a half-life of around 5 days, subcutaneous dosing once a week is effective.[31].

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A. STRUCTURE

Tirzepatide is a synthetic peptide that works as a dual agonist for the gastric inhibitory polypeptide (GIP) and the glucagon-like peptide 1 (GLP-1) receptors.[32] It is a 39-amino acid polypeptide analogue of the gastrointestinal inhibitory polypeptide that is conjugated to a C20 fatty diacid moiety through a hydrophilic linkers (γ-Glu-2xAdo, gamma glutamate and bis-aminodiethoxyacetyl) coupled to the lysine20 residue. When compared to a GLP-1 agonist (semaglutide) alone, the dual agonist strategy produces a synergistic effect on insulin and glucagonostatic responses.[33] Tirzepatide's peptide sequence comprises two non-coded amino acid residues (Aib, -amino isobutyric acid) at positions 2 and 13, which lead to its prolonged half-life and high affinity for albumin.[34]

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B. CLINICAL DEVELOPMENT

Tirzepatide's phase 1 clinical studies, which lasted four weeks and were followed by four weeks of safety testing, revealed a significant statistical drop in HbA1c, as well as lower postprandial glucose levels. A 26-week phase 2 clinical study with a dulaglutide group revealed superior effectiveness to dulaglutide. It also helped the individuals lose weight and reduce their hunger. Patients on SGLT2 inhibitors (e.g., dapagliflozin) were enrolled in the SURPASS-1 phase 3 clinical studies, which were conducted in six countries throughout the world. Some trials combined tirzepatide with dapagliflozin, which led in greater HbA1c decrease and weight loss [35]. Furthermore, 1 mg taken once a week exhibited additive benefits in the SURPASS-2 phase 3 clinical study, which compared tirzepatide plus metformin to the selective GLP-1 receptor agonist semaglutide [36].

Other effects of tirzepatide include reduced levels of very low-density lipoproteins and triglycerides, as well as a decrease in blood pressure and an increase in high-density lipoprotein concentration. The most often reported adverse effects were nausea, vomiting, and diarrhea, which were mild to moderate and usually occurred during the dose-escalation phase [37, 38]

Furthermore, a dose-dependent impact on HbA1c and weight reduction was reported in a phase 2 human clinical investigation with tirzepatide in combination with controlled nutrition and lifestyle with or without metformin, which was greater than that of the selective GLP-1 RA dulaglutide. Meanwhile, in a 12-week phase 2 study with moderate dosage-escalation regimens, starting with a lower dose and gradually escalating to the maximum effective doses enhanced gastrointestinal tolerability [39,40,41].

C. PHARMACOKINETICS:

Absorption: Tirzepatide has an estimated bioavailability of 80%. The maximal concentration for tirzepatide was observed within 1-2 days of administration.

Distribution: Tirazepatide has an average apparent volume of distribution (Vd) of around 10.3 L. Plasma albumin has a high level of tirzepatide binding (99%).

Metabolism: The peptide structure is cleaved by proteolysis after injection. The C20 fatty diacid composition also goes through amide hydrolysis and beta-oxidation.

Excretion: The mean half-life (T1/2) was determined to be 116.7 h (i.e., 5 days), demonstrating that a weekly dosing regimen is preferable. [42,43]

According to pharmacokinetics (PK) studies in healthy individuals, the accumulation index was determined to be 1.6 throughout these four weeks, indicating that steady-state exposure with a once-weekly dosage was attained. PK variables were analyzed for a final dosage of 15 mg in subjects with T2D, and Cmax was observed to be 1250 ng/mL and Tmax to be 24 h. [44]

D. PHARMACODYNAMICS:

Tirzepatide is a synthetic peptide that lowers blood glucose levels. It stimulates first- and second-phase insulin secretion by lowering glucagon levels in a glucose-dependent manner [45][46] Tirzepatide has also been proven to prolong stomach emptying, lower fasting and postprandial glucose concentrations, reduce food intake [46], and lower body weight in type 2 diabetic patients [47]. Tirzepatide has the potential to improve insulin sensitivity [46].When the peptide is conjugated to a C20 fatty diacid moiety through a hydrophilic linker at the lysine residue at position 20, the medication is strongly coupled to albumin in the plasma, prolonging its half-life [47].

E. MECHANISM OF ACTION:

Tirzepatide is a synthetic peptide that acts as a dual agonist for the gastric inhibitory polypeptide (GIP) and the glucagon-like peptide 1 (GLP-1) receptors. It promotes pancreatic insulin release, which leads to a decrease in hyperglycemia. Adiponectin levels are also increased with Tirzepatide. Its dual agonism ability results in a greater reduction of hyperglycemia than GLP-1 agonist drugs alone and decreases the user's appetite [48].

F. ADMINISTRATION:

Tirzepatide is given subcutaneously by injection. It is not yet available in oral form. Its available in the following strengths: 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. Dosing is usually given once a week, with a starting dosage of 5 mg/0.5 mL. On subsequent visits, prescribed dosages can be increased based on effectiveness (as assessed by hemoglobin A1C levels and body weight) and adverse effects. The most common adverse drug responses are gastrointestinal in nature, such as stomach pain and nausea, with varying degrees of severity. The capacity of patients to endure side effects is important in the titration of tirzepatide dose [49].

V. CONCLUSION

T2D and obesity are ingrained ailments for which there is unfortunately no known cure, but they may be managed with the optimal therapy, treatment, and lifestyle changes. New scientific innovations are needed in order to ease administration, minimize frequency of dose, and manage various disorders in a single drug owing to the alarming growth in patients worldwide. In phase 1 and phase 2 clinical trials, tirzepatide showed favorable outcomes for controlling HbA1c and body weight. Comparing SURPASS-1 to SURPASS-5 human clinical studies to those of related molecules like semaglutide and dulaglutide, the latter showed promising outcomes. Tirzepatide, sold under the brand name Mounjaro, has received USFDA approval and has emerged as a revolutionary therapy for T2D and weight reduction.

Since it provides the benefit of a once-weekly dosage administration, patient compliance and dose adherence are also encouraged [31] [50,51]. Consequently, tirzepatide may signify a breakthrough in the management of T2D. As a result, there will be an increase in vigour for future research into synthetic peptide treatments.

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