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DUAL BENEFITS OF TIRZEPATIDE: ANTI-OBESITY AND ANTIDIABETIC EFFICACY: A MINI REVIEW

Sriram Praveen, Ananya sarma
Department of Pharmaceutical chemistry, JSS college of Pharmacy, Mysuru, Karnataka, India.

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Abstract

Background: Diabetes mellitus and obesity are two linked conditions that have reached epidemic proportions globally. According to a study published in 2023 by the Indian Council of Medical Research (ICMR), India has 10.1crore people with diabetes. The prevalence of obesity, especially abdominal obesity is increasing continuously due to the intake of foods that are high in carbohydrates and processed foods. Obesity can cause inflammation, insulin resistance, and pancreas overload which lead to diabetes mellitus.

Main Body: The present - review focuses on the medicinal chemistry, organic chemistry and pharmacological aspects of trizepatide. Trizepatide is a new chemical moiety that shows dual agonist activity of glucagon-like peptide-1(GLP-1) receptors and glucose-dependent insulinotropic polypeptide (GIP).Trizepatide is a synthetic peptide that constitutes 39 amino acids. Trizepatide has a potent hypoglycemic effect, and it has antiobesity effects because of its adverse effect.

Conclusion: Trizepatide's capacity to lower blood sugar and promote weight loss makes it an effective treatment for these conditions. Further research will confirm its safety and long-term advantages.

***Keywords*:** Trizepatide, Diabetes mellitus, Obesity, Hypoglycaemia.

***Corresponding Author**
Sriram Praveen

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Introduction

Background

Tirzepatide is a recently developed drug molecule by Eli Lily. The US FDA approved this drug in May 2022. It is the first gut hormonal-based agonist, i.e., a dual GLP-1 and GIP receptor agonist [1].

Methodology

To prepare this review article, we utilizedResearch gate, Google Scholar, SciFinder®, and PubMed to carry out a literature search. To retrieve the words "tirzepatide and type 2 diabetes," "tirzepatide and obesity," and "novel antidiabetics,". We found 39 articles that closely linked the phrases "tirzepatide" and "Diabetes/Obesity". We selected the articles that addressed tirzepatide clinical trials, employed in in vivo research. Only articles published in the English language were considered; book chapters or conference abstracts were included.

Trizepatide is a laboratory-made peptide molecule that is composed of 39 amino acids organized in a linear structure. Because of its distinctive dual function, it is additionally referred to as 'twincretin'. The administrationof this drug is suitable once a week, as its $t^{1/2}$is 5 days [2].Type 2 diabetes (T2D) and obesity are associated with severe complications and pose a risk to cardiovascular health, non-alcoholic fatty liver disease, kidney issues, and other health concerns [3].There is an important correlation between obesity and type 2 diabetes (T2D). Losing weight helps keep blood sugar levels and cardiovascular problems under control. According to the results of the most recent survey by the European Association for the Study of Diabetes (ESD), losing weight is an advice for improving the lifestyle and reducing the chance of developing T2D [4].

GLP-1 and GIP are peptide hormones, and that are secreted by the intestine through the utilization of nutrients and glucose from the food we ingest. GIP is secreted by K cells located in the small intestine [5].These cells are termed enteroendocrine cells, and these cells are responsible for vital functions in postprandial metabolism. The pancreatic release of insulin in response to glucose is enhanced by the incretin effect, which is the most favour condition for identifying glucose equilibrium. While taken concurrently, they have a synergistic effect; GIP is assumed to be the main in cretin hormone responsible for this effect [6].

Pathophysiology of type 2 diabetes (diabetes mellitus)

Diabetes mellitus pathophysiology is very complex and is associated with various hormones including insulin , glucagon and growth hormones. In 1920, most of the researchers

reported that diabetes mellitus is a disorder of the pancreas [7,8]. In1936, Sir Harold Himsworth challenged the old theory of diabetes and proposed that diabetes is be classified into subtypes with respect to insulin sensitivity. In 1960 Rosalyn Yalow and Solomon A. Berson supported the theory of Himsworth and demonstrated that adult diabetic patients had the elevated level of insulin which led to the development of type 1 diabetes and type 2 diabetes [9].

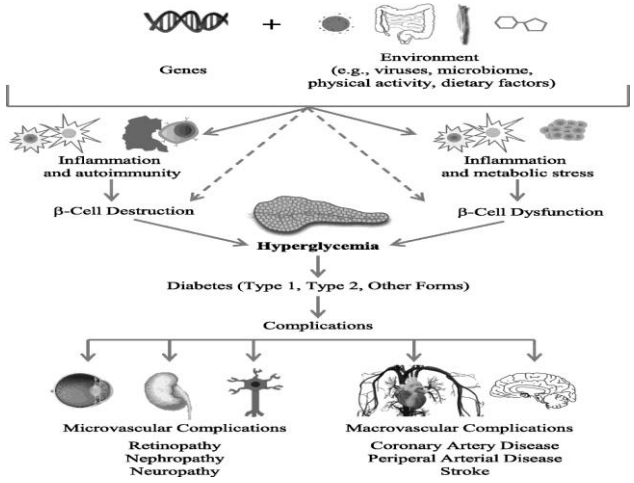

Fig.1 Different Stages of Diabetes [10].

Chemical aspects of trizepatide

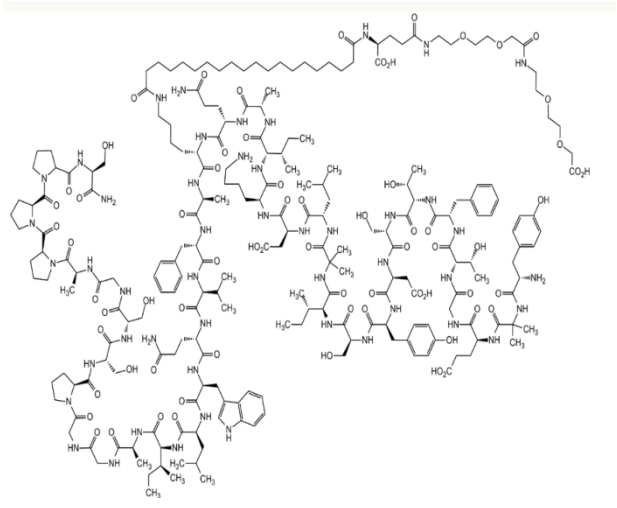

Fig.2: Structure of trizepatide [11].

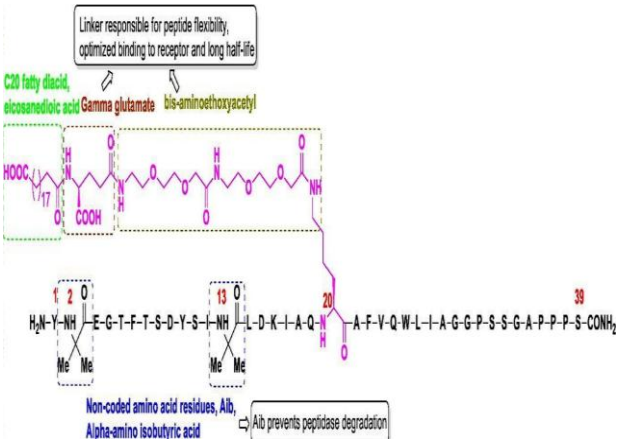

Fig.3 Structural features and aminoacids of trizepatide [12].

Synthesis of trizepatide

The solid-phase peptide synthesis(SPPS)/liquid-phase peptide synthesis (LPPS) method can be used to manufacture trizepatide .Recently Eli Lilly company demonstrated the synthesis of trizepatide via the Continuous Kilogram – Scale GMP manufacturing.Research scientists have chosen four fragments [13].

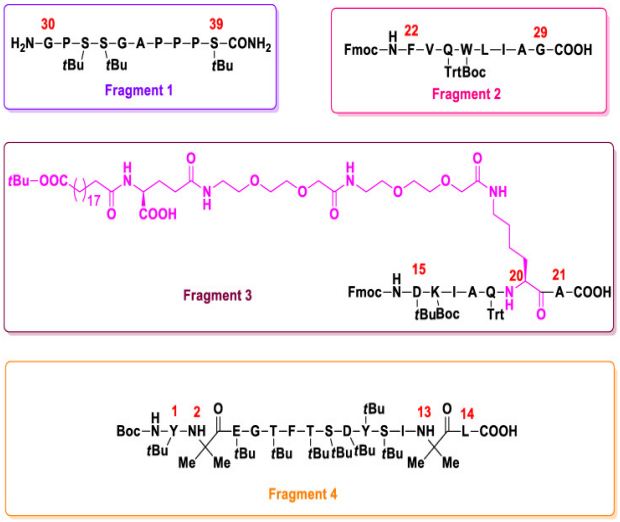

Fig.4 Fragments used in the synthesis of trizepatide [14].

Theabove-mentioned fragments are synthesized via theSPPS method and the coupling of these fragments is performed via LPPS [15].

Step 1–The1st and 2nd fragments were linked to form amino acids. These amino acids are protected by protecting groups, to prevent unwanted reactions during the process of elongation. Fmoc is used as a protective agent.

Step 2 –The Protecting groups were removed and purifiedvia a nanofiltration process. Compounds are separated on the basis of their molecular weight.

Step 3 and Step 4 –Fragments 3 and 4 were coupled. A total of 8.371 kg trizepatide was separated and resulting in a yield of 81% [16].

Chemical formula[17]- $C_{225}H_{348}N_{48}O_{68}$

Molecular weight - 4813.57g/mol

CAS NO – 2023788-19-2

PubChem CID- 163285897

Solubility-It is soluble in water (5.0% mg/ml) and soluble in DMSO [18].

Pharmacological Aspects of Trizepatide

Pharmacodynamics

Mechanism of Action

Trizepatide works by mimicking the action of two incretin hormones, referred to as GLP-1 (glucagon-likePeptide-1) and GIP (glucose-dependent insulinotropic polypeptide-1).Trizepatide activates beta cells of the pancreas to release insulin, which decreases the high blood sugar levels and adiponectin levels are also increased simultaneously [19]. Trizepatide increases insulin sensitivity and it deaccerlates the time required to travel food from the stomach to the small intestine (delay of gastric emptying),which is the reason behind the reduced appetite and inhibits gluconeogenesis in the liver[20].As shown in figure 5 below , the insulin concentration increases with time [21].

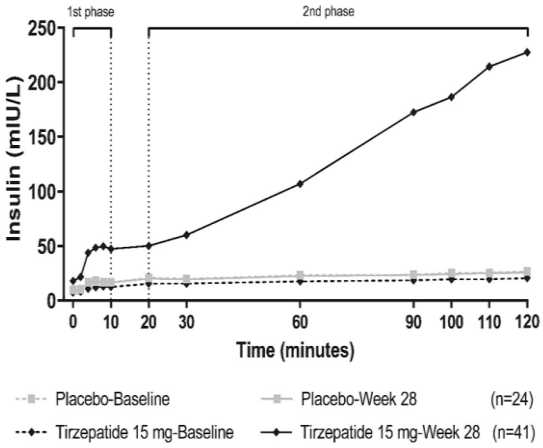

Fig.5 Mean insulin concentrations from 0-120 minutes

Pharmacokinetics

Steady state plasma concentration of trizepatide is achieved by following once in a week of administration for one month

Absorption

with respect to studies conducted by researchers on selected healthy volunteers, the duration required for tirzepatide to reach its maximum plasma (Cmax)after subcutaneous treatment varies between 8 and 72 hours and the dose is between 25-873 ng/mL[22]. Tirzepatide has 80% mean absolute bioavailability after subcutaneous injection. Similar exposure was attained when tirzepatide was administered subcutaneously in the upper arm, thigh, or abdomen.

Distribution

Following the subcutaneous administration of tirzepatide to patients with diabetes mellitus, the mean apparent steady-state volume of distribution is approximately 10.3 Liters. Tirzepatide binds to plasma albumin with 99% affinity [23].

Metabolism

The metabolism of tirzepatide involves amide hydrolysis, beta-oxidation of the C20 fatty acid moiety, and proteolytic cleavage of the peptide backbone [24].

Elimination

Tirzepatide is typically dosed once a week owing to its apparent clearance of 0.061 L/h and elimination half-life of approximately 5 days and no significant amount of trizepatide is found [25,26].

Clinical trials

Researchers have conducted 5 trails of trizepatide as mentioned below

1. SURPASS-1(NCT03954834) – Double-blindrandomized trial with trizepatideas monotherapy. A total of 478 patients participated for 40weeks.The outcomes ofHbA1C were0.09%,1.69%,1.71% and 1.75%(placebo,15mg,10mg,5mg), respectively).[27]
2. SURPASS-2(NCT03987919) – Open label randomized. Semaglutide for 40 weeks. A total of 1879 patients were included for40weeks.The outcomes ofHbA1C were found to be 1.86%,2.30%,2.24% and 2.01%(semaglutide,15mg,10mg,5mg)[28].
3. SUPRASS -3((NCT03882970) – Open label randomized. Atotal of 1947 patients participated for duration of 25 weeks and the outcome of HbA1c was found to be 1.25%,2.14%,2.01%,1.85% (insulin degludec,15mg,10mg,5mg)[29].
4. SUPRASS-4 (NCT03730662) open label randomized. Atotal of2002 patients participated for a duration of 52 weeks and the outcome of HbA1c was found to be 1.39%,2.41%,2.30%,2.11%(insulin glargine,15mg,10mg,5mg) [30].
5. SUPRASS-5(NCT04039503) - Double blind randomized. There were 475 placebo-treated patients were for 40weeks, and the incidence of Hb1AC was 0.86%,2.46%,2.27%, and 2.05%(5mg,10mg,15mg) [31].

The results of these trials revealed that body weight and HbA1csignificantly decreased [32],[33].

Adverse Events

- Pancreas -Acute pancreatitis (!5mg) [34,35].
- Gallbladder -Cholelithiasis (5mg) [36,37].
- Hypoglycemia – The level of glucose in the blood is decreases to≤ 70mg/dL , ≤ 54mg/dL.
- Additionally, some common gastro intestinal Adr's like nausea and diarrhea have been observed with 10mg.
- In rare cases Cardiovascular and Hypertension events, injection site inflammation has been observed. [38,39]

Conclusion

Obesity and diabetes are major health issues, particularly in nations such as India, where their prevalence is increasing. A novel medication called trizepatide is a viable therapeutic option for both obesity and diabetes. It functions by stimulating GLP-1 and GIP, two crucial receptors that aid in blood sugar regulation and weight loss. Trizepatide serves as a useful therapy for these disorders because of its ability to decrease blood sugar and help in weight loss. Its safety and long-term benefits will be verified with additional studies.

Abbreviations

ICMR - Indian Council of Medical Research (ICMR)
GLP-1- Glucagon-like peptide-1
GIP - Glucose-dependent insulinotropic polypeptide (GIP)
US FDA – United States Food and Drug Administration
T2D - Type 2 diabetes
LPPS – Liquid-phase peptide synthesis
SPPS - solid- phase peptide synthesis
GMP – good manufacturing practices
DMSO – Dimethyl sulfoxide
Cmax – Maximum plasma concentration

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Nil

Conflict of interest

No conflict of interest

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Ethical statement

Not applicable

Author contributions

Sriram Praveen, Ananya sarma both are contributed equally.

Informed Consent

We ensure that every person included in this review article has given their express permission for their identities, data, or photographs to be used.

References

1. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402(10402):613–26. doi: 10.1016/S0140-6736(23)01200-X.
2. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Mol Metab. 2018;18:3-14. doi: 10.1016/j.molmet.2018.09.009.
3. Sinha DD, Williams RC, Hollar LN, Lucas HR, Johnson-Javois B, Miller HB, et al. Barriers and facilitators to diabetes screening and prevention after a pregnancy complicated by gestational diabetes. PLoS One. 2022;17(11). doi:10.1371/journal.pone.0277330.
4. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021;385(6):503-515. doi: 10.1056/NEJMoa2107519.
5. Two incretin hormones GLP-1 and GIP: Comparison of their actions in insulin secretion and β cell preservation,Progress in Biophysics and Molecular Biology,Volume 107, Issue 2,2011,Pages 248-256,ISSN 0079-6107,https://doi.org/10.1016/j.pbiomolbio.2011.07.010.
6. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72–130. doi:10.1016/j.molmet.2019.09.010.
7. Irwin S. Primary Prevention and Risk Reduction for Cardiovascular/Pulmonary Disorders—Preferred Practice Pattern 6A. In: Irwin S, Tecklin JS, editors. Cardiopulmonary Physical Therapy. 4th ed. Mosby; 2004. p. 253-269. doi: 10.1016/B978-032301840-1.50014-1.
8. Kim S. H. (2011). Measurement of insulin action: a tribute to Sir Harold Himsworth. *Diabetic medicine : a journal of the British Diabetic Association*, *28*(12), 1487–1493. https://doi.org/10.1111/j.1464-5491.2011.03409.x
9. Ahmed, Awad M. "History of diabetes mellitus." *Saudi medical journal* vol. 23,4 (2002): 373-8.
10. Jay S. Skyler, George L. Bakris, Ezio Bonifacio, Tamara Darsow, Robert H. Eckel, Leif Groop, Per-Henrik Groop, Yehuda Handelsman, Richard A. Insel, Chantal Mathieu, Allison T. McElvaine, Jerry P. Palmer, Alberto Pugliese, Desmond A. Schatz, Jay M. Sosenko, John P.H. Wilding, Robert E. Ratner; Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. *Diabetes* 1 February 2017; 66 (2): 241–255. https://doi.org/10.2337/db16-0806
11. Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: A Systematic Update. Int J Mol Sci. 2022;23(23):14631. doi: 10.3390/ijms232314631.
12. Suryawanshi DM, Bachhav D, Suryawanshi K, Sonavane N, Pooja Mairal. THE EMERGING ROLE OF TIRZEPATIDE, DUAL GLP-1 AND GIP RECEPTOR AGONIST IN THE MANAGEMENT OF T2DM AND OBESITY: A REVIEW [Internet]. International Journal of Novel Research and Development. 2022 Nov. Available from: https://www.ijnrd.org/papers/IJNRD2211104.pdf
13. Frederick M.O., Boyse R.A., Braden T.M., Calvin J.R., Campbell B.M., Changi S.M., Coffin S.R., Condon C., Gowran O., McClary J., et al. Kilogram-scale GMP manufacture of tirzepatide using a hybrid SPPS/LPPS approach with continuous manufacturing. Org. Process Res. Dev. 2021;25:1628–1636.
14. Fields GB. Introduction to Peptide Synthesis. Current Protocols in Protein Science [Internet]. 2001 Dec 1;26(1). Available from: https://doi.org/10.1002/0471140864.ps1801s26
15. May S.A., Johnson M.D., Buser J.Y., Campbell A.N., Frank S.A., Haeberle B.D., Hoffman P.C., Lambertus G.R., McFarland A.D., Moher E.D., et al. Development and manufacturing GMP scale-up of a continuous ir-catalyzed homogeneous reductive amination reaction. Org. Process Res. Dev. 2016;20:1870–1898. doi: 10.1021/acs.oprd.6b00148.
16. Wang Z., Wang Z., Lin S., Jin H., Gao S., Zhu Y., Jin J. Nanoparticle-templated nanofiltration membranes for ultrahigh performance desalination. *Nat. Commun.* 2018;9:2004–2013. doi: 10.1038/s41467-018-04467-3
17. Tirzepatide: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. DrugBank. Available from: https://go.drugbank.com/drugs/DB15171
18. National Center for Biotechnology Information. PubChem Compound Summary for CID 163285897. PubChem [Internet]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/163285897. Accessed 2024 Sep 16.
19. Sattar N, McGuire DK, Pavo I, Weerakkody GJ, Nishiyama H, Wiese RJ, Zoungas S. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nat Med. 2022 Mar;28(3):591-598. doi: 10.1038/s41591-022-01707-4. Epub 2022 Feb 24. PMID: 35210595; PMCID: PMC8938269.
20. Roomy MA, Hussain K, Behbehani HM, Abu-Farha J, Al-Harris R, Ambi AM, Abdalla MA, Al-Mulla F, Abu-Farha M, Abubaker J. Therapeutic advances in obesity management: an overview of the therapeutic interventions. Frontiers in Endocrinology [Internet]. 2024 Apr 23;15. Available from: https://doi.org/10.3389/fendo.2024.1364503.
21. Zhang D, Zhang Y, Sun B. The Molecular Mechanisms of Liver Fibrosis and Its Potential Therapy in Application. International Journal of Molecular Sciences [Internet].

2022 Oct 20;23(20):12572. Available from: https://www.mdpi.com/1422-0067/23/20/12572.

22. Saurabh MK, Ranjan A, All India Institute of Medial Sciences, Dept of Physical and Rehabilitation. Tirzepaptide: A Promising Option for Treating Obesity and Overweight [Internet]. International Journal of Science and Research (IJSR). 2024 Mar. Available from: https://www.ijsr.net/archive/v13i3/SR24305143919.pdf
23. Lin, Fei & Yu, Bin & Ling, Baodong &Lv, Guangyao & Shang, Huijun& Zhao, Xia & Jie, Xiaoling & Chen, Jing & Li, Yan. (2023). Weight loss efficiency and safety of tirzepatide: A Systematic review. PLOS ONE. 18. e0285197. 10.1371/journal.pone.0285197.
24. Ali R, Virendra SA, Chawla PA. Bumps and humps in the success of Tirzepatide as the frst GLP1 and GIP receptor agonist. Health Sci Rev. 2022;4: 100032. https://doi.org/10.1016/j.hsr.2022.100032.
25. Chavda VP, Ajabiya J, Teli D, Bojarska J, Apostolopoulos V. Tirzepatide, a new era of dual-targeted treatment for diabetes and obesity: a mini-review. Molecules. 2022;27(13):4315. https://doi.org/10.3390/molecules27134315.
26. Ali R, Virendra SA, Chawla PA. Bumps and humps in the success of Tirzepatide as the frst GLP1 and GIP receptor agonist. Health Sci Rev. 2022;4: 100032. https://doi.org/10.1016/j.hsr.2022.100032.
27. 27.EliLillyandCompany2021.ClinicalTrials.gov.https://clinicaltrials.gov/study/NCT03954834?tab=table [Accessed 1 Mar 2024]
28. Eli Lilly and Company 2021. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03987919?tab=table [Accessed 1 Mar 2024]
29. ELi Lilly and Company 2022. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03882970 [Accessed 21 Jan 2024]
30. Eli Lilly and Company 2021. — ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03730662 [Accessed 1 Mar 2024]
31. Eli Lilly and Company 2021. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04039503 [Accessed 1 Mar 2024]
32. Permana H, Yanto TA, Hariyanto TI. Efficacy and safety of tirzepatide as novel treatment for type 2 diabetes: A systematic review and meta-analysis of randomized clinical trials. Diabetes & Metabolic Syndrome Clinical Research & Reviews [Internet]. 2022 Oct 14;16(11):102640. Available from: https://doi.org/10.1016/j.dsx.2022.102640
33. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, Mao H, Zhang S, Ahmad NN, Bunck MC, Benabbad I, Zhang XM; SURMOUNT-2 investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023 Aug 19;402(10402):613-626. doi: 10.1016/S0140-6736(23)01200-X. Epub 2023 Jun 26. PMID: 37385275.
34. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Landó LF, Mao H, Cui X, Karanikas CA, Thieu VT. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. The Lancet. 2021 Jul 10;398(10295):143-55.
35. Ludvik B, Giorgino F, Jódar E, Frias JP, Landó LF, Brown K, Bray R, Rodríguez Á. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. The Lancet. 2021 Aug 14;398(10300):583-98.
36. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. *JAMA*. 2022;327(6):534–545.
37. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, Aizenberg D, Wynne AG, Riesmeyer JS, Heine RJ, Wiese RJ. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. The Lancet. 2021 Nov 13;398(10313):1811-24.
38. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, Cui X, Briere DA, Cabrera O, Roell WC, Kuchibhotla U. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. Molecular metabolism. 2018 Dec 1;18:3-14.
39. Frias JP, Nauck MA, Van J, Benson C, Bray R, Cui X, Milicevic Z, Urva S, Haupt A, Robins DA. Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. Diabetes, Obesity and Metabolism. 2020 Jun;22(6):938-46.