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Tirzepaptide: A Promising Option for Treating Obesity and Overweight

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Abstract: ***The Food Drug Administration (United State of America) approved tirzepatide injection in November 2023 for long - term weight management in adults with obesity or overweight and weight - related conditions like high blood pressure, type 2 diabetes, or high cholesterol. It is a 39 - amino acid synthetic peptide, induces insulin secretion, decreases hyperglycemia, and increases adiponectin levels, suppressing appetite more effectively than long - acting glucagon - like peptide - 1 (GLP - 1) agonist compounds alone. Clinically meaningful weight reduction observed with trizepatide. Type 2 diabetes (T2D) and obesity are chronic conditions that cannot be cured but can be controlled via therapy, lifestyle modifications, and medical intervention. Drug's weekly dosing schedule improves patient compliance and adherence, making it a promising option for treating obesity and weight reduction in Indian patients. Safety profile is also favours this drugs, gastrointestinal discomfort was the most common adverse event Undoubtedly, the evident superiority of dual incretin agonist tirzepatide over GLP - 1 will reignite interest in the therapeutic possibilities of GIP in the context of type 2 diabetes, obesity, and associated comorbidities.***

Keywords: tirzepatide , Obesity, adiponectin long - acting glucagon - like peptide – 1

1. Introduction

In 2014, an estimated 39% of the adult population worldwide was categorized as overweigh, they have Body Mass Index (BMI) 25.0–29.9 kg/m^2 or obese (BMI > 29.9 kg/m2), the highest proportion since 1975 [1]. In 1975, the prevalence of obesity was recorded at 6.4% among women and 3.2% among men. By 2014, those figures had increased to 14.9% and 10.8%, respectively [1]. The escalating incidence of overweight and obesity in developing nations, such as India, has occurred concurrently with demographic and epidemiological shifts, characterized by declining mortality and fertility rates and an increase in the prevalence of lifestyle - related illnesses [2–4]. There is absence of exact data about Prevalence of Obesity among Indian Population but a study examining worldwide patterns projected that by 2030, 27.8% of the Indian population would be overweight and 5.0% would be obese [5]. Another study predicts that almost 20% of rural Indian adults will be overweight or obese by 2030 [6].

Non - pharmacological major like lifestyle modifications and calorie restriction are an important part of managing obesity, but it can be hard to keep off the weight. Health education are most appropriate method to prevent obesity but we are getting less success to decreasing its prevalence. Obesity is a dangerous disease that lasts for a long time, gets worse over time, and comes back when ever relax and it is mother of many non - communicable diseases like hypertension, Diabetes and cancer etc.

Several clinical guidelines currently advocate the use of anti - obesity drugs for those who are obese or overweight and have weight - related issues. There is data suggesting that anti - obesity drugs such as long - acting glucagon - like peptide - 1 (GLP - 1) receptor agonists, naltrexone/bupropion, phentermine/topiramate, and orlistat could be useful in maintaining weight loss [7 - 13].

In November 2023, the U. S. Food and Drug Administration approved the use of tirzepatide injection for long - term weight management in adults who have obesity (body mass index of 30 kg/m2 or greater) or overweight (body mass index of 27 kg/m2 or greater) and at least one weight - related condition such as high blood pressure, type 2 diabetes, or high cholesterol [14]. This approval is based upon following a reduced calorie diet and incorporating more physical activity. Tirzepatide, marketed under another brand name is prescribed in conjunction with dietary and exercise regimens to enhance control blood sugar levels in persons diagnosed with type 2 diabetes mellitus. This drug is approved in many countries such as United State of America, many countries of European Union and Japan, as a once - weekly subcutaneous injectable for type 2 diabetes and for the treatment of obesity. GLP - 1 (glucagon - like peptide - 1) and GIP (glucose - dependent insulinotropic polypeptide) are documented incretin hormones originating from the lower (GLP - 1, L cells) and upper (GIP, K cells) intestinal tracts, respectively. Incretin hormones are gastrointestinal peptides released in response to food consumption that promote insulin secretion and regulate blood sugar levels. This narrative review concentrates on emphasizing the synthetic short peptide Trizepatide as the first dual GLP - 1 and glucose - dependent insulinotropic polypeptide (GIP receptor) agonist for treating obesity and highlights its superiority over other related medicines.

Mechanism of action. **Tirzepatide,** a 39 - amino acid synthetic peptide, offers improved bio - functions compared with its original analogs due to their dual agonist activity at the glucose - dependent insulin tropic polypeptide (GIP) and glucagon - like peptide - 1 (GLP - 1) receptors. GLP - 1is responsible for appetite and calorie intake control whereas GIP has been suggested to also contribute to the regulation of food intake. Synergistic effects of activating both GIP and GLP receptors by Tirzepatide which is administered once

weekly by subcutaneous route resulting in increased effectiveness in reducing weight resulting in on appetite, food intake, and metabolic function [15 - 17]. It induces the secretion of insulin from the pancreas, resulting in a decrease in hyperglycemia. Additionally, adiponectin (a protein hormone adiponectin regulates glucose and fatty acid oxidation) levels are increased in response to trizepatide which suppresses the appetite of users and reduces hyperglycemia more significantly than GLP - 1 agonist compounds alone due to its dual agonism effect [18].

Pharmacokinetics; - PK studies were done on healthy volunteers with doses ranging from 0.25 mg to 15 mg. The peak plasma concentration (Cmax) was found to be dose - related and ranged from 26 to 874 ng/mL. The highest amount of fortirzepatide (Tmax) was seen one to two days after it was given, and the mean half - life (T1/2) was found to be 116.7 hours, which is 5 days. This suggests that a dose should be given once a week [19]. An exposure level of steady state was reached after 4 weeks with a once - a - week dose, and the accumulation index was 1.6 during this time. The PK parameters were studied in people with T2D after a final dose of 15 mg. The Cmax was found to be 1250 ng/mL, and the Tmax was found to be 24 hours [20]. Tirzepatide, a highly bound plasma albumin, has a bioavailability of 80% and a distribution volume of 10.3 L. It undergoes proteolytic cleavage and beta - oxidation, with a half - life of 5 days, and is cleared in urine and feces [21].

Evidance for Indicatinion as antiobesity drug: - According to the findings of a study, the average weight of subjects who concluded the 36 - week lead - in period decreased by 20.9% but from week 36 to week 88, the average percent change in body weight was - 5.5 percent with tirzepatide and 14.0% with placebo and Tirzepatide induced a weight loss of 25.3% from week 0 to week 88, compared to 9.9% for the placebo group [22]. The study which was supported by a pharmaceutical company revealed that the average weight change at week 72 was - 15.2 for 5 - mg tirzepatide, - 19.5 for 10 - mg tirzepatide, - 18.5 for 15 - mg tirzepatide, and - 1.9% for placebo.85% of subjects experienced a weight loss of 5% or more with tirzepatide, 89% with 10 - mg tirzepatide, and 91% with 15 - mg tirzepatide [23]. At all doses, Tirzepatide was both noninferior and superior and cause more significant reductions in body weight as compared to semaglutide [24].

Adverse events and Safety [25] The Meta - anylysis of ten trails which had involved 6836 participants found that gastrointestinal adverse events (GI) were the most common, with nausea and diarrhoea being the most frequent. Drug discontinuation due to Adverse Events (AEs) was highest with the 15 mg dose. Rates of fatal AEs, severe hypoglycaemia, and acute pancreatitis were extremely low.

Contraindication: Animal studies suggest that tirzepatide may cause medullary thyroid carcinoma, but its potential use in humans is unknown. Patients with a history of medullary thyroid carcinoma and MEN 2 should avoid tirzepatide. Other thyroid cancer - related risk factors should be advised. Hypersensitivity reaction gallbladder disease or diabetic retinopathy another contraindications drug.

Undoubtedly, the evident superiority of dual incretin agonist tirzepatide over GLP - 1 will reignite interest in the therapeutic possibilities of GIP in the context of type 2 diabetes, obesity, and associated comorbidities. Trial should be conducted for the treatment of obesity or weight reduction among Indian Patient a for maximum benefits. It seems most favourable drug considering safety, efficacy, suitability and convenient also. Research on synthetic peptide medications will continue to find out most suitable drug.

2. Conclusion

Clinically meaningful weight reduction observed with trizepatide. Type2 diabetes (T2D) and obesity are chronic conditions that cannot be cured but can be controlled via therapy, lifestyle modifications, and medical intervention. New scientific advancements are required to accommodate the increasing number of patients globally by simplifying administration, reducing dose frequency, and treating several illnesses with a single prescription. Tirzepatide has shown promising results in reducing body weight clinical trials. The USFDA has approved tirzepatide, as a new therapy for Type 2 Diabetes (T2D) and weight reduction. Due to its weekly dosing schedule, this medication improves patient compliance and adherence. Tirzepatide has the potential to change the treatment of Obesity related condition.

References

[1] Di Cesare M. et al. Trends in adult body - mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population - based measurement studies with 19.2 million participants. Lancet 387, 1377–1396 (2016). https: //doi. org/10.1016/S0140 - 6736 (16) 30054 - X PMID: 27115820.

[2] Tandon N. et al. The increasing burden of diabetes and variations among the states of India: The Global Burden of Disease Study 1990–2016. Lancet Glob. Heal.6, e1352–62 (2018).

[3] Dandona L. Et al. Nations within a nation: variations in epidemiological transition across the states of India, 1990–2016 in the Global Burden of Disease Study. Lancet 390, 2437–60 (2017). https: //doi. org/10.1016/S0140 - 6736 (17) 32804 - 0 PMID: 29150201

[4] Prabhakaran D. et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: The Global Burden of Disease Study 1990–2016. Lancet Glob. Heal.6, e1339–51 (2018).

[5] Kelly T., Yang W., Chen C. - S., Reynolds K. & He J. Global burden of obesity in 2005 and projections to 2030. Int. J. Obes.32, 1431–1437 (2008).

[6] Swain S. & Chowdhury S. Trends of nutritional status among rural adults in six states of India: findings from national survey data. Clin. Epidemiol. Glob. Heal.6, 181–187 (2018).

[7] Rubino D, Abrahamsson N, Davies M, et al; STEP4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA.2021; 325 (14): 1414 - 1425. doi: 10.1001/jama.2021.3224.

[8] Wadden TA, Hollander P, Klein S, et al; NN8022 - 1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low - calorie - diet - induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond).2013; 37 (11): 1443 - 1451. doi: 10.1038/ijo.2013.120

[9] Garvey WT, Batterham RL, Bhatta M, et al; STEP5 Study Group. Two - year effects of semaglutide inadults with overweight or obesity: the STEP 5 trial. Nat Med.2022; 28 (10): 2083 - 2091. doi: 10.1038/s41591 - 022 - 02026 - 4.

[10] le Roux CW, Fils - Aimé N, Camacho F, Gould E, Barakat M. The relationship between early weight loss and weight loss maintenance with naltrexone - bupropion therapy. E Clinical Medicine.2022; 49: 101436. doi: 10.1016/j. eclinm.2022.101436.

[11] Neoh SL, Sumithran P, Haywood CJ, Houlihan CA, Lee FT, Proietto J. Combination phentermineand topiramate for weight maintenance: the first Australian experience. Med J Aust.2014; 201 (4): 224 - 226. doi: 10.5694/mja13.00193.

[12] Sjöström L, Rissanen A, Andersen T, et al; European Multicentre Orlistat Study Group. Randomised placebo - controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lancet.1998; 352 (9123): 167 - 172. doi: 10.1016/S0140 - 6736 (97) 11509 - 4

[13] Hill JO, Hauptman J, Anderson JW, et al. Orlistat, a lipase inhibitor, for weight maintenance

[14] after cnventional dieting: a 1 - y study. Am J Clin Nutr.1999; 69 (6): 1108 - 1116. doi: 10.093/ajcn/69.6.1108

[15] FDA Approves New Medication for Chronic Weight Management, available at https: //www.fda. gov/news - events/press - announcements/fda - approves - new - medication - chronic - weight - management.

[16] Samms RJ, Coghlan MP, Sloop KW. How MayGIP Enhance the Therapeutic Efficacy of GLP - 1? Trends Endocrinol Metab.2020; 31 (6): 410 - 421. doi: 10.1016/j. tem.2020.02.006.

[17] 15. Hammoud R, Drucker DJ. Beyond the pancreas: contrasting cardiometabolic actions of GIP andGLP1. Nat Rev Endocrinol.2023; 19 (4): 201 - 216. doi: 10.1038/s41574 - 022 - 00783 - 3.

[18] 16. Heise T, DeVries JH, Urva S, et al. Tirzepatidereduces appetite, energy intake, and fat mass inpeople with type 2 diabetes. Diabetes Care.2023; 46 (5): 998 - 1004. doi: 10.2337/dc22 - 1710.

[19] Sun B, Willard FS, Feng D, Alsina - Fernandez J, Chen Q, Vieth M, Ho JD, Showalter AD, Stutsman C, Ding L, Suter TM, Dunbar JD, Carpenter JW, Mohammed FA, Aihara E, Brown RA, Bueno AB, Emmerson PJ, Moyers JS, Kobilka TS, Coghlan MP, Kobilka BK, Sloop KW. Structural determinants of dual incretin receptor agonism by tirzepatide. Proc Natl Acad Sci U S A.2022 Mar 29; 119 (13): e2116506119.

[20] Furihat K, Mimura H, Urva S, Oura T, Ohwaki K, Imaoka T, A phase 1 multiple - ascending dose study of tirzepatide in Japanese participants with type 2 diabetes. Diabetes Obes. Metab.2022, 24, 239–246.

[21] Ludvik B, Giorgino F, Jódar E Frias, JP Landó, LF Brown, K Bray, R Rodríguez, A. 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. Lancet 2021, 398, 583–598.

[22] Bucheit J, Ayers J, Pamulapati L, Browning A, Sisson E. A Novel Dual Incretin Agent, Tirzepatide (LY3298176), for the Treatment of Type 2 Diabetes Mellitus and Cardiometabolic Health. J Cardiovasc Pharmacol.2022 Aug 01; 80 (2): 171 - 179.

[23] Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, Ahmad NN, Zhang S, Liao R, Bunck MC, Jouravskaya I. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT - 4 randomized clinical trial. JAMA.2024 Jan 2; 331 (1): 38 - 48.

[24] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A. Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine.2022 Jul 21; 387 (3): 205 - 16.

[25] Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS - 2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med.2021 Aug 5; 385 (6): 503 - 515. doi: 10.1056/NEJMoa2107519. Epub 2021 Jun 25.

[26] Mishra R, Raj R, Elshimy G, Zapata I, Kannan L, Majety P, Edem D, Correa R. Adverse Events Related to Tirzepatide. J Endocr Soc.2023 Jan 26; 7 (4): bvad016. doi: 10.1210/jendso/bvad016. PMID: 36789109; PMCID: PMC9915969.