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Editorial

A Revolutionary Road Map for Obesity Management and Beyond: Tirzepatide as a Dual-Acting Insulinotropic Polypeptide Receptor Agonist

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ABSTRACT

Tirzepatide is a revolutionary and promising medication with a high impact in the treatment of Obesity and T2DM with their complications. Its efficacy was proven through different trials in achieving favorable weight loss and a significant reduction in glycemic index. It also treated a large diversity of related co-morbidities, including fatty liver, cardiovascular disease, dyslipidemia, and more. Tirzepatide is well tolerated, has a good safety profile, and is highly reliable and suitable for use in a population.

It is now widely accepted that Obesity is a long-term, complex, and multifactorial disease rather than a lifestyle and behavioral issue with different negative impacts on health in both personal and community domains (1).

Although debated, Obesity was declared a serious chronic disease by different scientific societies and organizations, and different countries adopted this: Centers for Disease Control and Prevention (CDC), the American Medical Association (AMA) in 2013, and the American Obesity Society in 2008 are examples. However, due to

insufficient data, lacking a clear diagnostic criterion, and acceptable standards and indexing measures that could be applied to everyone, many organizations and countries don't formally recognize Obesity as a disease; the United Kingdom is an example (2-5).

Obesity and being Overweight have multiple, well-recognized adverse effects on health, including but not limited to Type 2 Diabetes Mellitus (T2DM), Cardiovascular events, Hypertension, Lipid disorders, chronic kidney diseases, and Hepatic diseases. Additionally, there is increased evidence linking Obesity as a major etiological factor for malignancy developments, including colorectal, renal, pancreatic, and other cancerous conditions (6-8).

On the other hand, obese persons increasingly experience social stigmatization with possible feelings of depression and even condemnation (9-11).

During the last decades, Obesity has shown a significant increase in prevalence; it has doubled since 1980, with a more ominous figure for adolescents showing a quadrupled increase. About 2% of children and adolescents were diagnosed with Obesity in 1990, compared to a figure of 8% of them in 2022. According to the World Health Organization (WHO), in 2022, 43% of the adult population were obese or overweight, and 16% were obese. In the USA, a higher rate was reported, showing a significant increment in children with a prevalence of 19.7%, according to the CDC. In Iraq, 31.8% of the participants of a national survey were overweight, and 33.9% were obese (5, 12-14).

To achieve favorable health outcomes, different modalities were used for the management of Obesity; lifestyle and nutritional modifications are the initial steps that are widely used; however, failure to achieve a favorable weight with a high relapse rate may be due to multiple factors requires the scientific community to suggest and develop a wide range of medications, however, few of these medications were considered effective and get the required approval. Additionally, different approaches to surgical procedures were tried with variant success rates; however, being an invasive procedure was a major limitation (15-18).

The recent revolution in medical therapy was brought through the emergence of Glucagon-like peptide-1 (GLP-1) receptor agonists targeting GLP-1, a gut-derived hormone belonging to the family of incretin hormones; those agonists were initially used for the treatment of T2DM with a variable efficacy on reducing body weight. Additionally, the application of GLP-1 receptor agonists shows benefits beyond the management of Obesity and T2DM by making favorable modifications, although with variable degrees with different GLP-1 receptor agonists, on other related co-morbidities, including cardiovascular events, Hypertension, lipid disorders, chronic kidney diseases, and nonalcoholic liver diseases (19-20).

The GLP-1 class includes Exantide, Liraglutide, Dulaglutide, and Semaglutide; the Food and Drug Administration approved only Semaglutide and Liraglutide for obesity management (21-22).

Tirzepatide, is a promising, newly released medication with dual-acting insulinotropic polypeptide agonist properties, its dual mechanism synergist efficacy toward T2DM and obesity management with more favorable outcome, this brought through its glucose-dependent insulinotropic polypeptide (GIP) agonist property in addition to its GLP-1 effect, both GLP-1 and GIP are incretin hormones acting through enhancing insulin secretion from pancreatic beta cell, preventing their apoptosis and promoting regeneration, additional actions are through delaying gastric emptying, appetite suppressing, promoting satiety, and inhibiting glucagon secretion. All these effects are more powerful if mediated through dual-acting insulinotropic polypeptide receptor agonists than GLP-1 receptor agonists alone, with increasing evidence of more favorable outcomes regarding managing Obesity, T2DM, and other related co-morbidities (23-26).

Many clinical trials were conducted to assess Tirzepatide benefits, and safety compared to other GLP-1 receptor agonists regarding different variables. The efficacy and safety of Tirzepatide in T2DM management effect were evaluated through the phase three III Global SURPASS program; eight published SURPASS trials were conducted: SURPASS 1-5, SURPASS J-mono, and SURPASS J-combo. Participants for the abovementioned trials were from different countries and patients diagnosed with T2DM. According to the SURPASS trials program, Tirzepatide was superior to other treatment modalities for T2DM management with a greater reduction in HbA1C (27-28).

In the SURPASS J-combo trial, a significant weight loss was noted in addition to glycemic control. Additionally, the recent phase 3 SURMOUMT clinical trial programs (SURMOUNT 1-5) show evidence regarding the efficacy and safety of Tirzepatide in weight reduction through many conducted trials with many of these results published recently, last Study, SURMOUNT 5 is now active aims to evaluate the efficacy and safety of Tirzepatide compared to Semaglutide regarding weight reduction and its related co-morbidities (27-29).

The positive impact on the nonalcohol-fatty liver was noted. The Phase 2 SYNERGY-NASH clinical trial suggests that Tirzepatide was effective in resolving Metabolic dysfunction–associated steatohepatitis without worsening fibrosis (26, 30-31).

Concerning other health impacts, the SUMMIT trial was conducted to evaluate the effect of Tirzepatide on cardiac health. It concludes that Tirzepatide lowers the risk of death from cardiovascular events or heart failure in patients with normal ejection fraction and Obesity (32-33).

Different studies encountered different adverse effects. Gastroinestinal symptoms were the most common when using Tirzepatide like other GLP-1 receptor agonists; these may include nausea, vomiting, diarrhea, dyspepsia, and constipation. Other less-reported adverse effects were cholelithiasis, cholecystitis, and, in rare cases, acute pancreatitis. Generally, most adverse effects were found to be dose-related, which may lead in some instances to discontinue the treatment; a proportion of serious side effects leading to drug discontinuation shows a significant dose-related with an incidence of 7.23%, 8.68%, and 10.39% for the doses of 5 mg, 10 mg, and 15 mg respectively (34-36).

Although rare, yet warrants attention, severe hypoglycemia was reported in some trials. However, these findings were non-significant (34-36).

Psychiatric issues were also reported; however, the incidence was 1.2%, considered as a rare adverse effect; women accounted for two-thirds of the reported cases, and depression was the most common

psychiatric adverse effect, followed by anxiety and suicidal thoughts. Although rare, fatal outcomes of patients who completed suicidal attempts warrant further interest and future investigation (38).

Compared to other GLP-1 receptor agonists, Tirzepatide has a similar profile regarding adverse effects and tolerability (35-36,39).

The main risk for Tirzepatide use was the possibility of developing C cell thyroid cancer, including medullary type. These findings were supported through experimental research on rats; however, this was uncertain and has yet to be proved in humans by different trials. An explanation for this may be due to the less expression of GLP-1 receptors of C cells in humans, which reduces the possibility of developing this type of cancer. Furthermore, C cells in healthy humans have no GLP-1 expression at all. (40-42)

Currently, even though this risk is uncertain, Tirzepatide is contraindicated in patients with a history of medullary thyroid cancer, familial thyroid cancer, and those with genetic susceptibility to thyroid cancer. Although not thyroid cancer, multiple endocrine neoplasia 2 is also contraindicated as a relevant type of malignancy (43).

The expensive cost of Tirzepatide, like other GLP-1 receptor agonists, is the primary limitation for its adoption for many obese patients; more inclusion of Tirzapatide and other GLP-1 receptor agonists in insurance will minimize the healthcare cost for obesity complications and its related co-morbidities. Additional limitations may include the possibility of developing thyroid cancer, although not proven, and the lack of long-term trials to confirm its safety profile rather than efficacy.

In conclusion, Tirzepatide is well established to be considered a revolutionary and promising medication with a high impact in the treatment of Obesity and T2DM with their complications. Its efficacy was proven through different trials in achieving favorable weight loss and a significant reduction in glycemic index. It also treated a large diversity of related co-morbidities, including fatty liver, cardiovascular disease, dyslipidemia, and more. Tirzepatide is well tolerated, has a good safety profile, and is highly reliable and suitable for use in a population. However, ongoing and future long-term trials are still needed to confirm safety and explore more benefits.

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Conflict of Interest

Authors declare no conflict of interest.

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