Effects of Tirzepatide in Spectrum of Metabolic Diseases

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The prevalence of metabolic diseases including type 2 diabetes (T2D), obesity and non-alcoholic fatty liver disease (NAFLD) increases globally. This highlights an unmet need for identifying optimal therapies for the management of these conditions. Tirzepatide is a novel dual incretin receptor agonist (twincretin) that activates both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors.

tirzepatide obesity

1. Introduction

Diabetes mellitus (DM) represents a major public health issue that is characterized as a global pandemic and poses a significant burden upon healthcare systems and societies. The International Diabetes Federation (IDF) estimates that 537 million individuals worldwide are diagnosed with DM, and the figure is expected to rise by 50% over the next 25 years [1]. The continuous rise in the number of people living with DM and especially type 2 diabetes (T2D) is tightly associated with an increased incidence of obesity on a global scale [2]. In 2015, almost 604 million adults in more than 70 countries were estimated to be obese and this prevalence has more than doubled since 1980, reaching epidemic levels [3]. T2D and obesity have also been linked with numerous additional metabolic comorbidities including non-alcoholic fatty liver disease (NAFLD), which is now considered to be the leading cause of chronic liver disease across the globe, resulting in significant hepatic and extra-hepatic morbidity and mortality [4][5][6][7].

Tirzepatide is a novel dual incretin receptor agonist that activates both GLP-1 and GIP receptors, and has demonstrated very promising results in lowering blood glucose levels and reducing body weight [8][9][10][11]. Based on these effects, once-weekly subcutaneous tirzepatide received regulatory approval by the United States Food and Drug Administration (FDA) in May 2022 and marketing authorization by the European Commission in September 2022 for the treatment of patients with T2D as an adjunct to diet and exercise [12][13][14]. It also attained Fast Track designation as an anti-obesity medication independent of concurrent T2D in October 2022 [15]. Although the positive impact of these incretin-based agents has been widely described, it is yet to be clarified whether their beneficial effects on metabolic control can be entirely explained by weight loss or are mediated by direct effects and other independent factors.

2. Metabolic Effects of Tirzepatide

2.1. Impact of Tirzepatide on T2D and Glycaemic Control

The effect of twincretins on glycaemia has been explored in several animal studies. Irwin et al. evaluated the impact of subchronic (14 days) intraperitoneal administration of N-AcGIP (Lys37Myr), exendin(1–39)amide or the combination of both peptides in adult obese mice (ob/ob). Obese mice were administered an intraperitoneal injection of glucose alone or combined with GIP, N-AcGIP, GLP-1 or exendin(1–39)amide. N-AcGIP alone or in combination with exendin(1–39)amide significantly reduced non-fasting plasma glucose levels and glycated haemoglobin HbA1c [16]. Similar results were provided in an experimental study of Gault et al., who assessed the impact of liraglutide and N-AcGIP, a simple combination of liraglutide plus N-AcGIP or Lira-AcGIP preparation (Lira-AcGIP) in diabetic obese mice. The authors demonstrated that the Lira-AcGIP combination resulted in a significant improvement in glycaemic control compared to the other comparator interventions [17]. In 2018, Pathak et al. compared the acute glycaemic effects of Nac(D Ala2)GIP/GLP-1-exe, a peptide that binds to both GIP and GLP-1 receptors, with (D Ala2)GIP or exendin-4 therapy alone. The researchers showed that the twincretin approach could lead to a significant reduction in blood glucose levels at 4 and 8 h after the injection and was associated with an improved insulin secretion [18].

The beneficial glycaemic effect of twincretins has been further confirmed in phase 1 and 2 clinical trials in humans. In 2017, Schmitt et al. conducted a randomized, double-blind, phase 1 trial using NNC0090-2746, also known as RG7697, which is a GIP/GLP-1 dual agonist developed by Novo Nordisk. Patients with T2D were administered a once-daily subcutaneous injection of NNC0090-2746 (0.25–2.5 mg) or the placebo for 14 days. The data of this clinical study showed that the synthetic twincretin significantly reduced HbA1c, fasting and postprandial serum glucose levels in patients with T2D [19]. Frias et al. extended the characterization of NNC0090-2746 and performed a 12-week, randomized, placebo-controlled, double-blind, phase 2a trial, in which individuals with T2D who were inadequately controlled with metformin received either 1.8 mg of NNC0090-2746 or the placebo once daily subcutaneously. The authors have shown that NNC0090-2746 significantly improved glycaemic control compared with the placebo, and was generally safe and well tolerated [20]. These findings were followed by a double-blind, randomized, phase 2b study examining a novel GIP/GLP-1 co-agonist (LY3298176 or “tirzepatide”) developed by Eli Lilly and Company, Indianapolis, IN. In this trial, patients with T2D received either once-weekly subcutaneous tirzepatide (1 mg, 5 mg, 10 mg or 15 mg), dulaglutide (1.5 mg) or the placebo for 26 weeks. The analysis showed that tirzepatide significantly decreased HbA1c in a dose-dependent manner, while there were no reports of severe hypoglycaemia. However, in comparison to the 5 and 10 mg tirzepatide dosage groups as well as dulaglutide, the 15 mg group had a higher incidence of gastrointestinal adverse events including nausea, vomiting and diarrhoea and a higher rate of treatment discontinuation [21]. Based on these data, a 12-week, double-blind, placebo-controlled, phase 2 study was performed to further assess the efficacy and tolerability of higher doses of tirzepatide (12 and 15 mg) using three different dose-escalation regimens (12 mg (4 mg, weeks 0–3; 8 mg, weeks 4–7; 12 mg, weeks 8–11), 15 mg (2.5 mg, weeks 0–1; 5 mg, weeks 2–3; 10 mg, weeks 4–7; 15 mg, weeks 8–11) and 15 mg (2.5 mg, weeks 0–3; 7.5 mg, weeks 4–7; 15 mg, weeks 8–11)). The investigators demonstrated that tirzepatide resulted in clinically meaningful reductions in HbA1c, while lower starting doses and smaller dose increments were associated with a more favourable side effect profile [22].

In SURPASS-1, patients with T2D inadequately controlled with diet and exercise alone were randomly assigned to receive a 40-week course of once-weekly tirzepatide (5, 10 or 15 mg) or the placebo. At 40 weeks, all tirzepatide doses were superior to the placebo for changes from baseline in HbA1c. Specifically, HbA1c decreased by 20 mmol/mol from baseline with tirzepatide, 5 mg; 21 mmol/mol with tirzepatide, 10 mg; and 23 mmol/mol with tirzepatide, 15 mg. Significantly more participants in the tirzepatide groups compared to the placebo group reached HbA1c glycaemic targets of less than 53 mmol/mol (87–92% vs. 20%) and 48 mmol/mol or less (81–86% vs. 10%), and 31–52% of patients on tirzepatide versus only 1% on the placebo reached an HbA1c level of less than 39 mmol/mol. Furthermore, there were no episodes of severe hypoglycaemia reported, while dose-dependent gastrointestinal events were the most frequent side effects [23]. In a post hoc analysis of SURPASS-1, tirzepatide monotherapy at doses 5, 10 and 15 mg was shown to induce significant improvements in several fasting biomarkers of pancreatic β-cell function and insulin sensitivity, effects which were only partially attributable to the observed weight loss, shedding more light into the underlying pathophysiological mechanisms explaining the improved glycaemic control of patients with T2D under tirzepatide treatment [24].

In SURPASS-2, participants with T2DM were randomized to receive tirzepatide (5, 10 or 15 mg) or semaglutide, 1 mg, once weekly for 40 weeks. The data showed that tirzepatide was non-inferior and even superior to semaglutide concerning the mean change in HbA1c from baseline to 40 weeks. The estimated differences between the 5 mg, 10 mg and 15 mg tirzepatide groups and the semaglutide group were −0.15 percentage points ($p = 0.02$), −0.39 percentage points ($p < 0.001$) and −0.45 percentage points ($p < 0.001$), respectively [25].

The SURPASS-3 trial evaluated the efficacy and safety of once-weekly tirzepatide versus once-daily titrated insulin degludec for 52 weeks in T2D individuals inadequately controlled with metformin, with or without sodium–glucose cotransporter 2 (SGLT2) inhibitors. From a mean baseline HbA1c of 8.17%, the estimated treatment difference versus degludec ranged from −0.59% to −1.04% for tirzepatide ($p < 0.0001$ for all tirzepatide doses), and the percentage of patients achieving HbA1c less than 7.0% (<53 mmol/mol) was greater ($p < 0.0001$) in all three tirzepatide dose groups (82–93%) compared to insulin degludec (61%) at week 52. In addition, fewer episodes of hypoglycaemia were reported in tirzepatide groups compared to degludec. The authors concluded that tirzepatide treatment can achieve better glycaemic control with a lower risk of hypoglycaemia in diabetic patients who are suboptimally controlled with oral glucose-lowering drugs compared to insulin degludec [26]. A substudy of the SURPASS-3 trial was designed (“SURPASS-3 CGM”), aiming to assess the efficacy of once-weekly tirzepatide versus once-daily degludec on glycaemic control measured by continuous glucose monitoring (CGM) in adults with T2D. The primary endpoint was the proportion of time spent in the tight target range (71–140 mg/dL) at 52 weeks in individuals treated with tirzepatide (10 and 15 mg) compared to degludec. The data showed that the participants receiving tirzepatide (pooled 10 and 15 mg groups) had a greater proportion of time in the target range compared with the subjects receiving degludec (estimated treatment difference, 25% ($p < 0.0001$)). These results provided further solid proof of the beneficial impact of tirzepatide on achieving glycaemic targets without an increase in hypoglycaemia risk when compared to basal insulin treatment [27].

In the SURPASS-4 trial, tirzepatide was compared with a different basal insulin, glargine, regarding the achievement of glycaemic control in people with T2D and increased cardiovascular risk being treated with

metformin, a sulfonylurea or an SGLT-2 inhibitor. After 52 weeks of treatment, tirzepatide at all tested doses significantly reduced HbA1c compared with glargine. The investigators found that the estimated treatment difference versus glargine was −0.99% for tirzepatide, 10 mg, and −1.14% for 15 mg, and the non-inferiority criterion of 0.3% was met for both doses. Fewer hypoglycaemic episodes were also observed in the tirzepatide groups, and most importantly, all these outcomes were achieved with no excess cardiovascular risk [28].

SURPASS-5 was designed to assess the effect of once-weekly tirzepatide (5, 10 or 15 mg) compared with the placebo when added to titrated insulin glargine on glycaemic control in patients with T2D. After 40 weeks, the mean HbA1c change from baseline was −2.11% with 5 mg, −2.40% with 10 mg and −2.34% with 15 mg of tirzepatide vs. −0.86% with the placebo ($p < 0.001$ for all doses). These data further supported the evidence that tirzepatide is associated with a dose-dependent reduction in HbA1c in diabetic patients [29].

To understand the pathophysiological mechanisms underlying the action of tirzepatide in patients with T2D, Heise et al. conducted a randomized, double-blind, parallel-arm, phase 1 study in individuals with T2D treated with lifestyle measures and metformin, with or without one additional glucose-lowering drug. The participants were assigned to receive either tirzepatide (15 mg), semaglutide (1 mg) or the placebo once weekly for 28 weeks and the primary endpoint was the effect of tirzepatide vs. the placebo on the change in the clamp-derived disposition index (a composite outcome of insulin secretion and sensitivity). The authors found that the glycaemic benefits of tirzepatide in T2D resulted from concurrent improvements in key components of the diabetes pathophysiology, namely β-cell function, insulin sensitivity and glucagon secretion [30]. These effects could explain the remarkable glucose-lowering potential of tirzepatide observed in all phase 3 studies.

Lastly, the difference in T2D pathophysiology between Japanese and Caucasian individuals has been described previously in the literature [31]. To examine whether the glycaemic benefits of tirzepatide can also be implemented in Japanese patients with T2D, two phase 3 RCTs (SURPASS J-mono and SURPASS J-combo) were conducted. These studies have shown that tirzepatide is well tolerated and may significantly improve HbA1c when compared with dulaglutide, 0.75 mg, or the placebo, and demonstrated the applicability of tirzepatide to such patients regarding improvement in glycaemic control [32][33].

Taking all the above data into consideration, it becomes evident that tirzepatide displays a remarkable ability to lower blood glucose levels and even achieve normoglycaemia in patients with T2D, which allowed tirzepatide to be officially approved for the treatment of T2D in addition to diet and exercise in the USA and Europe [14].

2.2. Impact of Tirzepatide on Obesity and Weight Loss

Several animal studies have described the beneficial effects of twincretins on weight loss. A study of Irwin et al. showed that the combined administration of a GIP and GLP-1 receptor agonist in high-fat-fed (HFF) mice led to superior weight loss compared to GLP-1 RA alone [16]. This finding was further supported by Gault et al., who showed that both liraglutide and Lira-AcGIP could significantly reduce food intake in obese diabetic mice, but only Lira-AcGIP resulted in a significant decrease in body weight [17]. Other studies have also demonstrated that

incretins combined together are able to reduce food intake and increase energy consumption in mice [16][34]. Pathak et al. assessed the metabolic effects of chronic treatment (twice daily for 28 days) with N-ac(D-Ala2) GIP/GLP-1-exe and exendin-4 alone, and in combination with (D-Ala2)GIP, in HFF mice. The investigators reported a significant decrease in body weight, which was mainly driven by a loss of the total body fat mass, while the lean body mass remained unchanged and was thus preserved [18].

Multiple clinical trials have robustly confirmed the powerful beneficial impact of twincretins in general and particularly tirzepatide on weight loss outcomes in humans [8][15][21][35]. A recent systematic review and meta-analysis, which included seven RCTs and a total of 6609 adults with T2D irrespective of their background glucose-lowering treatment, demonstrated a dose-dependent superiority of tirzepatide in reducing body weight compared to long-acting GLP-1 RAs, insulin or a placebo. Specifically, when compared to long-acting GLP-1 RAs (dulaglutide (1.5 mg) or semaglutide (1 mg) once weekly), tirzepatide resulted in larger reductions in body weight ranging from 1.68 kg with tirzepatide, 5 mg, to 7.16 kg with tirzepatide, 15 mg. Nevertheless, the authors acknowledged a series of study limitations, which mainly comprise the presence of statistical heterogeneity in the meta-analyses for change in HbA1c and body weight, the assessment of the risk of bias solely for the primary outcome (defined as change in HbA1c from baseline) and the limited generalization of the results mainly to individuals who are overweight/obese and already on metformin-based background treatment [8]. It should be also noted that weight loss was a secondary outcome in all these trials and results should therefore be interpreted with caution.

To date, there is only one RCT that investigated the effect of tirzepatide on weight loss as the primary outcome as summarized in [36]. SURMOUNT-1 was a phase 3 double-blinded RCT, in which adults with a body mass index (BMI) of 30 or more, or more than 27 with at least one obesity-related complication excluding diabetes, were assigned to receive either once-weekly subcutaneous tirzepatide (at doses 5, 10 or 15 mg) or the placebo for a total duration of 72 weeks, including a 20-week dose-escalation period. The primary endpoints included the percentage change in body weight from baseline and a weight reduction of 5% or more, which is considered to be clinically significant. At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0 kg/m^2 and 94.5% of participants had a BMI of 30 or higher. The data showed that, at week 72, the mean percentage change in body weight was −15.0% (95% CI, −15.9 to −14.2) with 5 mg of tirzepatide, −19.5% (95% CI, −20.4 to −18.5) with 10 mg and −20.9% (95% CI, −21.8 to −19.9) with 15 mg, whereas the respective weight change was only −3.1% (95% CI, −4.3 to −1.9) in the placebo group ($p < 0.001$ for all comparisons vs. placebo). The proportion of participants having a weight reduction of at least 5% was 85%, 89% and 91% with 5 mg, 10 mg and 15 mg of tirzepatide, respectively, and only 35% with the placebo. Interestingly, a substantial reduction in body weight of 20% or more was achieved in 50% and 57% of participants in the 10 and 15 mg of tirzepatide groups, respectively, compared with only 3% in the placebo group ($p < 0.001$ for all comparisons vs. placebo). As expected, the most common side effects were gastrointestinal adverse events mainly occurring during dose escalation [36].

Based on the clinical data described above, once-weekly subcutaneous tirzepatide can achieve substantial and sustained weight loss in obese patients with or without T2D and could thus represent a promising and powerful treatment for obesity in the near future.

2.3. Impact of Tirzepatide on NAFLD Outcomes

The association of NAFLD with clinically relevant extra-hepatic manifestations has been well described in the literature [6][37]. Younossi et al. have demonstrated a strong link between NAFLD and several cardiometabolic comorbidities including obesity, T2D, hyperlipidaemia, hypertension and metabolic syndrome as a constellation of risk factors [5]. These associations seem to be related either to the secondary effects of obesity or the direct pathophysiological effects of insulin resistance in NAFLD [6].

A recent systematic review and meta-analysis evaluating the global prevalence of NAFLD and non-alcoholic steatohepatitis (NASH) in the overweight and obese population has provided important data for improving understanding of the global NAFLD burden and optimizing disease management in this high-risk cohort of patients. In more detail, in the aforementioned analysis consisting of 101,028 individuals, the prevalence of NAFLD and NASH in the overweight population was found to be 70% and 33.5%, respectively. Similar prevalence estimates were reported in the obese population (75.3% for NAFLD and 33.7% for NASH, respectively). Clinically significant fibrosis (stages F2–4) was present in 20.3% of the overweight and 21.6% of the obese patients with NAFLD, while 6.7% of the overweight and 6.9% of the obese individuals with NAFLD presented with advanced stages of fibrosis (stages F3–4) [38]. Similarly, Ciardullo et al. showed that people with diabetes, and particularly T2D, not only have a higher prevalence of steatosis but also of significant liver fibrosis, as suggested by fibroscan results [39].

An additional meta-analysis has been performed to assess the global epidemiology of NAFLD/NASH in patients with T2D. According to this meta-analysis, the global prevalence of NAFLD and NASH in individuals with T2D was found to be 55.5% and 37.3%, respectively. The incidence of advanced fibrosis in patients with NAFLD and T2D was estimated to be 17.0% [40]. These figures indicate the clinical and economic burden of NASH in patients with T2D around the world and highlight the urgent need for optimal therapeutic options.

To address the need for NAFLD treatment in T2D patients, Hartman et al. performed post hoc analyses in a phase 2 trial exploring the effect of tirzepatide on biomarkers of NASH and liver fibrosis in T2D individuals receiving either once-weekly tirzepatide (1, 5, 10 or 15 mg), dulaglutide (1.5 mg) or the placebo for 26 weeks. Changes from baseline in aspartate aminotransferase (AST), alanine aminotransferase (ALT), procollagen III (Pro-C3), cytokeratin-18 (CK-18) and adiponectin levels were measured. The authors demonstrated a statistically significant decrease from baseline in AST (all groups except for tirzepatide, 10 mg), ALT (all groups), Pro-C3 (tirzepatide, 15 mg) and CK-18 (tirzepatide 5, 10, 15 mg) at 26 weeks. Tirzepatide at doses of 10 and 15 mg resulted in a significant reduction in CK-18, Pro-C3 and ALT levels when compared to the placebo and dulaglutide, respectively. In addition, tirzepatide at doses of 10 and 15 mg significantly increased adiponectin levels from baseline compared to the placebo. According to these data, higher doses of tirzepatide could significantly reduce NASH-related biomarkers and increase adiponectin in individuals with T2D [41]. Of note, there are currently no published data regarding the potential effects of tirzepatide on histological features assessed with liver biopsy such as hepatic inflammation and fibrosis in humans with NASH. To address this issue, there is an ongoing randomized, placebo-controlled, phase 2 clinical trial (SYNERGY-NASH; NCT04166773), which is expected to be completed within

February 2024 and will likely provide strong evidence as to whether tirzepatide can reverse NASH and improve hepatic outcomes for patients with NAFLD.

Gastaldelli et al. have recently presented their findings from the SURPASS-3MRI trial, which was a substudy of the randomized, open-label, parallel-group, phase 3 SURPASS-3 trial [42]. To date, this has been the only study that investigated the impact of a 52-week treatment with once-weekly subcutaneous tirzepatide versus once-daily subcutaneous insulin degludec on liver fat content (LFC) in adults with inadequately controlled T2D and a fatty liver index of at least 60. A total of 296 participants without a history of significant alcohol consumption were randomly assigned to receive active treatment (tirzepatide (5 mg), n = 71; tirzepatide (10 mg), n = 79; tirzepatide (15 mg), n = 72; insulin degludec, n = 74). The primary outcome was the change from baseline in LFC as evaluated with the MRI–proton density fat fraction (MRI-PDFF) at week 52, using pooled data from tirzepatide, 10 and 15 mg, vs. insulin degludec. The secondary outcomes included changes in the volume of visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT). From an overall mean baseline LFC of 15.7%, at week 52, the absolute decrease in LFC was significantly greater for the pooled 10 and 15 mg of tirzepatide groups versus the insulin degludec group (−8.1% vs. −3.4%). The estimated treatment difference versus insulin degludec was −4.7% ($p < 0.0001$). Compared to baseline, after 52 weeks of treatment with tirzepatide, the mean LFC was reduced from 14.86 to 10.11 (tirzepatide, 5 mg), from 14.78 to 8.16 (tirzepatide, 10 mg) and from 16.65 to 8.59 (tirzepatide, 15 mg). The reduction in LFC was significantly correlated with baseline LFC, reductions in VAT, reductions in ASAT and reductions in body weight in the tirzepatide groups. The authors concluded that these results provide further evidence supporting the beneficial metabolic effects of this novel dual GIP/GLP-1 RA [42].

Considering all data presented above, tirzepatide appears to be a promising agent to reduce hepatic steatosis and may provide NAFLD patients with a novel therapeutic option as previously reported for selective GLP-1 Ras [43][44]. It is yet unknown how much of this benefit is attributable to weight loss per se, or whether there are any additional independent effects related to adipose tissue insulin sensitivity or whole-body systemic metabolism. Future research is required to address this question and elucidate the pathophysiological mechanisms underlying these effects, especially focusing on liver histology and a potential tirzepatide-induced improvement or reversal of histological features of NAFLD (inflammation, fibrosis).

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