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Tirzepatide – a new hope for type 2 diabetes mellitus and obesity management. A literature review.

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ABSTRACT

INTRODUCTION AND PURPOSE. While obesity and type 2 diabetes mellitus (T2DM) are defined (according to WHO) as civilization diseases we are still searching for the ideal tool to fight them. Recently, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved tirzepatide subcutaneous injections as monotherapy or combination therapy, with diet and physical exercise, to achieve better glycemic blood levels in patients with diabetes and weight reduction among obese and overweighted patients. This review evaluates the efficacy and safety of using tirzepatide based on GIP/GLP-1 agonists clinical trials.

MATERAILS AND METHODS. Literature available in the PubMeb Database and Google Scholar Databases was reviewed using keywords.

RESULTS AND CONCLUSIONS. Tirzepatide is a novel medicine which stands against type 2 diabetes and obesity pandemic. Combining two agonists of GIP and GLP-1 receptors helps decrease glycemic blood levels, HbA1c levels and reducing body weight in more efficient way than the GLP-1 receptor agonists. All these effects have also resulted in minimizing cardiovascular risk which is observed as an improvement in heart failure, hyperlipidemia and hypertension. Beyond that, the recent data present possible positive long-term effect of tirzepatide in such diseases as MAFLD (metabolic associated fatty liver disease) and OSA (obstructive sleep apnea). However, triagonists, achieving a concurrent activation of GLP-1, GIP, and glucagon receptors, normalize body weight in a manner superior to that of monoagonists and dual agonists. Therefore, the triple agonism or other than GIP/GLP-1 combinations could soon represent a new standard for pharmaceutical interventions.

KEYWORDS: tirzepatide; obesity; type 2 diabetes; weight reduction; GIP; GLP-1.

INTRODUCTION

Tirzepatide is a brand new organic compound, a first-in-class twincretin which combines two agonist actions of GIP and GLP-1 receptors, injected subcutaneous once a week (1). Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) are incretin hormones (1). The nutrient intake results in their release in the intestine (1). Combining GIP/GLP-1 with their receptors on pancreatic beta cells provokes secretion of insulin which decreases glycemic blood levels (1). Incretins have also many other metabolic functions (12). GLP-1 reduces food intake and appetite without direct changes in energy expenditure, delays gastric emptying and inhibits glucagon secretion (12). On the other hand, GIP increases lipogenesis, reduces nausea and inhibits bone resorption (12). Although the therapeutic implications of the lipogenic actions of GIP are debated, its ability to improve lipid and glucose metabolism is especially evident when paired with the anorexigenic mechanism of GLP-1 (32). Tirzepatide efficacy and safety has been well evaluated in many clinical trials. Even though it is still a novelty to the pharmaceutical world, the research data have already shown tirzepatide to decrease high blood pressure, low-density lipoprotein cholesterol and triglycerides levels (15, 24). Tirzepatide may become a holy grail among other medications in the fight against two great enemies of our times: type 2 diabetes mellitus and obesity (16). This review evaluates the efficacy and safety of using tirzepatide and its possible use in other diseases.

A BRIEF DESCRIPTION OF STATE OF KNOWLEDGE

PATHOGENESIS AND EPIDEMIOLOGY

Type 2 diabetes is a very complex metabolic disease with pathophysiology of both genetic predispositions and environmental triggers with multiple associated comorbidities (4). It primarily occurs as a result of obesity and lack of exercise, however some people are genetically more at risk than the others (4). Skeletal muscle, adipose tissue and liver cells become resistant to insulin because of hyperglycemia which promotes pancreatic islets failure (4). On the other hand beta cells apoptosis causes even greater systemic resistance for insulin (4) which closes the vicious circle. Exactly why these two problems appear is not known but for certain obesity

or overweight together with staying inactive are key contributing factors (4). Storing fat mainly in the abdomen, rather than the hips and thighs, indicates a greater risk (5).

As the scientific understanding of T2DM pathophysiology deepens, new treatment options become possible, expanding the potential for improved control of this complex disorder (4). Rates of patients suffering from T2DM have increased markedly since the second half of the 20th century in parallel with excess weight spreading in the society (4). In the 21th century we observe around 400 million people diagnosed with the disease (4).

Obesity is at present considered a disease (with a defined ICD-10 code) with excess body fat accumulated to such an extent that it can contribute to negative effects on health (5). It increases a risk of developing various metabolic diseases, cardiovascular disease, stroke, neurodegenerative diseases (Alzheimer's disease), osteoarthritis, depression and certain types of cancers (endometrial, breast, ovary, prostate, liver, gallbladder, kidney and colon) (5). T2DM is a perfect example of a metabolic complication due to systemic lipid surplus (5). Depending on the degree and the presence of comorbidities, obesity is related to 2-20 year shorter life expectancy (5). Patients are classified as obese with their Body Mass Index (BMI) over 30 kg/m2, the range of 25 - 30 kg/m2 is defined as overweight BMI is assessed based on a ratio of patient's weight in kilograms to the square of patient's height in meters (5). However, this measure ignores variations between individuals in the amounts of lean body mass, particularly muscle mass (5). The preferred metrics in these cases are body fat percentage or waist and hip circumference so as not to overdiagnose patients (5). Currently over 2 billion people are obese worldwide (5).

PREVIOUS PHARMACOLOGICAL TREATMENT

As it became sure that excess weight can cause T2DM, the pharmaceutical companies took a closer insight into the pathology of obesity and attempt to create the most effective medicine for both conditions. Over the last few years, GLP-1 receptor analogs have helped with the management of diabetes by combining effective reductions in glycemia with clinically important weight loss and weight maintenance (2). Due to efficacy of semaglutide or liraglutide (the most often used GLP-1 receptor agonists), they have been repurposed and approved at higher doses as treatment for obesity (23). Liraglutide 3 mg once-a-week injections in combination with a moderate intensity lifestyle interventions led to 5,8% to 8,0% weight decrease continued by weight maintenance (23). Semaglutide 2,4 mg once-a-week injections resulted in 14,9% to 17,4% weight loss in people without diabetes (23). Unfortunately these outcomes are limited among patients with T2DM (2). The most common adverse effects of GLP-1 receptor agonists treatment are those regarding digestive system (nausea and vomiting) and turned out to be dose-dependent (23). In the end the monoagonists have not quite met the expectations, however they have paved the way for further research concerning other intestine hormones (including GIP, amylin and glucagon) (2). That is why dual and triple agonists have been trialed to enhance the metabolic effects of GLP-1 by addressing various mechanisms of actions (2).

GLYCEMIC CONTROL

Phase 1 and 2 clinical trials compared changes in glycemic parameters and weight loss to placebo and dulaglutide (3). Safety and good tolerability in doses up to 15 mg once a week was proved both in healthy people and those with T2DM, with gastrointestinal side effects being the most commonly reported (3).

The results of phase 2 led to the SURPASS program which was composed of multiple phase 3 clinical trials (3). The SURPASS assessed the safety and efficacy of tirzepatide in people with T2DM (18). Participants were given subcutaneous tirzepatide 5, 10 and 15 mg once weekly either in monotherapy or in combination with other glucose-lowering medications supported by lifestyle changes (18). The effect of tirzepatide was assessed against placebo, basal insulins (glargine and degludec), GLP-1 receptor agonists (dulaglutide 0,75 mg and semaglutide 1 mg) (18). The key endpoint was to compare the change in HbA1c levels from baseline (20). The twincretin reduced HbA1c in a dose-dependent manner far more than other competitors or placebo (20). In patients with T2DM treated only with diet and exercise (SURPASS-1), tirzepatide 5 to 15 mg improved glycosylated hemoglobin levels by 1,87% to 2,07% against 0,04% increase in the placebo group (7). In SURPASS-2 tirzepatide 5 to 15 mg was compared to semaglutide 1 mg which resulted in 2,09% to 2,46% versus 1,86% HbA1c reduction (7). This study has also shown significant improvements in insulin sensitivity, beta-cell function as well as reduction in glucagon secretion among patients on dual agonist (28). In SURPASS-3 tirzepatide resulted in 1,93% to 2,37% versus 1,34% decrease in HbA1c with insulin degludec (7). SURPASS-4 was constructed for people with advanced T2DM and elevated cardiovascular risk, compared compound was insulin glargine (14). In this trial GLP-1/GIP receptor agonist reduced HbA1c by 2,24% to 2,58% against 1,44% for insulin (14). In SURPASS-5 tirzepatide was added in patients who were already taking insulin glargine – decrease in HbA1c level by 2,23% to 2,58% dependent on the dose versus 0,93% with placebo (10). A solid glycemic reduction resulted in a decrease in insulin use (10). This data was also confirmed by another two programs conducted in Japanese population (3). Regardless of used comparator, in every trial tirzepatide led to better HbA1c control (11). However for fasting serum glucose in SURPASS-3, the FSG reduction was comparable with insulin degludec, when in SURPASS-4 only the 15 mg dose tirzepatide resulted in significant FSG reduction compared to insulin glargine (8). Therefore, it seems that both patients and doctors need to wait for the final glycemic control results as the HbA1c parameter evaluates glucose levels in more long-term manner than FSG (8).

WEIGHT CONTROL

Weight loss was observed in all tirzepatide groups during SURPASS program and was greater than for other assessed molecules (33). In SURPASS-1 trial injecting tirzepatide 5 to 15 mg once a week was associated with 7 to 9,5 kg weight loss compared to 0,7 kg with placebo (31). SURPASS-2 has shown that GLP-1/GIP receptor analog in any evaluated dose was more efficient than monoagonist of GLP-1 (-7,8, -10,3 and -12,4 kg for 5, 10 and 15 mg tirzepatide versus -6,2 kg for 1 mg semaglutide) (31). However, the reduction in energy intake between mono- and biagonists did not differ significantly which may suggest that mechanisms other than reduced food intake are contributed more to lower the weight (9). Insulin degludec in SURPASS-3 initiated a weight gain of 2,3 kg in the opposition to tirzepatide which reduced

weight by 7,5 to 12,9 kg dependently on the used dose (31). A subgroup of patients in this program went through magnetic resonance imaging proton density fat fraction assessment which showed decrease by 29,78% to 47,11% in visceral abdominal and abdominal subcutaneous adipose tissue regardless of the dose of the twincretin (19).
Liver fat content was also reduced which results in improvement in liver histology suggesting that tirzepatide may be a treatment option for MAFLD (19). In SURPASS-4 using insulin glargine led to 1,9 kg weight gain in comparison to 7,1 to 11,7 kg weight loss for tirzepatide (31). Patients injecting only basal insulin glargine gained weight in the amount of 1,7 kg compared to 6,2 to 10,9 kg weight loss when adding tirzepatide (31).
SURMOUNT-1 trial was prepared to assess patients with obesity or overweight without T2DM (13). Study group on tirzepatide 5, 10 and 15 mg obtained a greater weight loss of 16% to 22,5% compared to 2,4% in the placebo group (only with a moderate intensity lifestyle) (13). Almost every patient with prediabetes converted on tirzepatide to normoglycemia (HbA1c <5,7%) versus only 62% of people in the control group (13). SURMOUNT-4 was dedicated to adults with a body mass index greater than or equal to 30 or greater than or equal to 27 and a weight-related complication, excluding diabetes, to assess the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction (13). Overall, participants receiving tirzepatide maintained at least 80% of the weight loss during the lead-in period compared with 16.6% receiving placebo (13). In participants with obesity or overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction (13).

CARDIOVASCULAR RISK CONTROL

The SURPASS trials have shown that some of the cardiovascular risk factors can be tamed using tirzepatide and the effect is dose-dependent (17). Systolic and diastolic blood pressure decreased by 2,8 to 12,6 mmHg and 1 to 5,5 mmHg respectively and waist circumference was reduced by 3,8 to 10,9 cm (24). Total cholesterol, LDL cholesterol fraction, HDL cholesterol fraction and triglycerides improved and hepatic enzymes (ALT, AST) levels tended to normalize (31). However, pulse rate was found to increase by 0,7 to 8,3 beats per minute which was also observed during trials on GLP-1 receptor analogs (17).
In SURMOUNT trails the same cardiovascular risk factors were assessed and administration of tirzepatide had a positive and significant effect on all of them compared to placebo and active comparators groups (13).

LIVER FUNCTION CONTROL

Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease associated with liver-related complications and death (34). The SYNERGY-NASH clinical trial involved participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis (34). Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks (34). The primary end point was resolution of MASH without worsening of fibrosis (34). The percentage of participants who met the criteria was 10% in the placebo group, 44% in the 5-mg tirzepatide group, 56% in the 10-mg tirzepatide group, and 62% in the 15-mg tirzepatide group which indicated that treatment

with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis (34).

BREATHING CONTROL

Obstructive sleep apnea is described as disordered breathing during sleep and is associated with major cardiovascular complications, for example hypertension or stroke (37). Excess adiposity is an etiologic risk factor, thus tirzepatide may be a potential treatment (37). The SURMOUNT-OSA clinical trial involved adults with moderate-to-severe obstructive sleep apnea and obesity (37). The participants were assigned to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks (37). The primary endpoint was the change in the apnea-hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline (37). Also in this case significant improvements in the measurements were observed with tirzepatide as compared with placebo (37).

SAFETY

Safety of using tirzepatide was mostly assessed in SURPASS-4 compared to insulin glargine among patients with T2DM and high cardiovascular risk (14). The endpoint of MACE-4 consisting of: cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina was not increased in tirzepatide groups (14). This matter was also taken into consideration while creating cardiovascular metanalysis that covered seven clinical trials with a 26-week follow up (14). The time to first occurrence of MACE-4 did not significantly differ between tirzepatide and control group (14). What is more tirzepatide seemed to have a positive impact on renal function by delaying the estimated glomerular filtration rate (eGFR) decline (-1,4 mL/min/1,73 m2/year at the tirzepatide groups versus -3,6 mL/min/1,73 m2/year at the insulin group) and reduced the urine albumin to creatinine ratio (UACR) (-6,8% at the tirzepatide group versus +36,9% at the insulin group) (3).

TOLERABILITY

Clinical trials have shown that tirzepatide is a well-tolerated medicine and number or magnitude of adverse events were comparable with placebo and active comparators (21). The amount of reported side effects varied depending on the severity and duration of T2DM (21). In the SURPASS program serious adverse events were observed among 1% to 8% of patients with early diabetes, when in 6% to 17% of people with advanced diabetes (21). The vast majority of side effects were gastrointestinal (nausea, vomiting, diarrhoea, constipation, decreased appetite, dyspepsia) with magnitude of mild-moderate, occurring in a dose-dependent manner (22). In few patients acute pancreatitis and cholelithiasis was observed (25). Injection site reactions were also very rare (25). Clinically important or serious hypoglycemia happened in few cases, mostly in participants that were on another glucose-lowering substance such as insulin or sulfonylureas (25).

In SURMOUNT studies the most reported adverse events were similar to those observed at SURPASS program (25). Cholelithiasis was observed more often which is probably associated with considerable weight reduction with tirzepatide (25).
However, in six randomized controlled trials with a total of almost 5000 patients adverse events were reported more frequently than previous studies showed (30). The comparators were placebo, GLP-1 receptor agonists drugs and insulin degludec (30).

The incidence rate of nausea, vomiting, constipation, decreased appetite, diarrhoea in patients who received tirzepatide was 20.43%, 9,05%, 2,54%, 9,64%, 16,24% respectively while the incidence rate in the comparators was 10.47%, 4,86%, 0,856%, 2,88%, 8,63% respectively and it was significantly higher in the tirzepatide arm than in the comparators (30). These findings may influence clinical decision-making and patient counseling on the use of tirzepatide but more research is required (30).

FUTURE

GIP and GLP-1 are not the only incretin hormones being evaluated as a potential treatment for type 2 diabetes and obesity (35). Glucagon is another possible molecule integrated together with GLP-1/GIP receptor agonism to create a triple-acting medicine (35). Concurrent activation of the glucagon-like peptide-1, glucose-dependent insulinotropic peptide, and glucagon receptors, combines the anorectic and insulinotropic activities of GLP-1 and GIP with the energy expenditure effect of glucagon (35). Currently, some preclinical studies and early phase clinical trials are being held assessing such combinations on safety, tolerability and efficacy (36). Triagonists normalize body weight in mice and enhance energy expenditure in a manner superior to that of GLP-1R monoagonists and GLP-1R/GIPR coagonists (36). These data suggest unimolecular polypharmacology as an effective means to target multiple mechanisms contributing to obesity (36). Amylin is another promising gut hormone, included in the Cagri-Sema (2,4 mg/2,4 mg) with semaglutide (36). Amylin agonism reduces appetite, food intake and decreases glucose levels by slowing the gastric emptying and suppressing glucagon secretion (36). It is clear that future may bring even greater success in treatment for type 2 diabetes and obesity (36).

CONCLUSION

Undoubtedly, the approval of the first GLP-1 receptor agonist in 2005 has revolutionized the pharmacological treatment of obesity and T2DM. Prior to that, the treatment of obesity has been predominantly limited to lifestyle interventions and bariatric surgery. Tirzepatide is a novel "twincretin" that was recently approved by the Food and Drug Administration and European Medicine Agency for the management of type 2 diabetes mellitus, obesity and overweight. Similar to previously approved GLP-1 receptor agonists, weight loss is a common positive side effect of tirzepatide which prompted research focused on its use as a primary weight loss therapy. The pharmaceutical world was already expecting this compound to be useful in lowering glycemic blood levels especially for diabetic patients, even before the research evaluating its efficacy started, yet the magnitude exceeded the expectations. The exact molecular mechanism leading to more significant effects of tirzepatide in glycemic control and

weight loss comparing to the monoagonists is still under investigation. Some studies have shown possible GIP/GLP-1 receptor agonist use in such diseases as nonalcoholic steatohepatitis, obstructive sleep apnea and heart failure, other trials are still under evaluation. This drug has been approved as an antiobesity and antidiabetic medication based on several clinical trials that have demonstrated superior weight-reducing and glucose-decreasing efficacy and similar safety and tolerability compared with placebo and previously approved medications.

Overall, evidence mainly from five SURPASS clinical trials has demonstrated that tirzepatide is determining the path to the new era in T2DM and/or obesity management through dual agonism of gut hormones. The further synergistic combination approach with other gastrointestinal hormones and creation of GLP-1/GIP/glucagon receptor triagonist has shown unprecedented pharmacologically achieved weight loss and glucose levels decrease with further cardiometabolic benefits in both obesity and T2DM.

AUTHOR'S CONTRIBUTIONS

The authors confirm contribution to the paper as follows:
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