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# ONE DRUG TO FIX IT ALL? THE ROLE OF TIRZEPATIDE IN TREATING COMPONENTS OF METABOLIC SYNDROME

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## ABSTRACT

Metabolic syndrome is a growing global health concern, driven largely by lifestyle-related factors such as poor diet, physical inactivity, and obesity. It is defined as a cluster of risk factors - including abdominal obesity, insulin resistance, hypertension, and dyslipidemia - that significantly increase the risk of developing cardiovascular disease, stroke, and type 2 diabetes. With its prevalence rising worldwide and substantial impact on morbidity and mortality, there is an urgent need for effective, multifactorial treatment strategies. Tirzepatide, a dual GIP and GLP-1 receptor agonist, has recently emerged as a promising therapeutic agent. The aim of this article is to review the current state of knowledge regarding tirzepatide's potential in addressing key components of metabolic syndrome. Evidence from the SURPASS clinical program and the SURMOUNT-1 trial demonstrates tirzepatide's robust effects on several metabolic parameters. It has been shown to significantly reduce HbA1c levels, promote substantial and dose-dependent weight loss, improve lipid profiles, and lower blood pressure. Notably, in a post hoc analysis of the SURPASS trials, tirzepatide led to normalization of blood glucose in a large proportion of patients and reduced the prevalence of individuals meeting the criteria for metabolic syndrome. Although metabolic syndrome was not a primary endpoint in these studies, the improvements seen across its components support tirzepatide's potential as a comprehensive treatment. These findings suggest that tirzepatide may represent a significant advancement in the management of metabolic syndrome and offer new hope for patients burdened by multiple cardiometabolic risk factors.

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## KEYWORDS

Tirzepatide, Metabolic Syndrome, Obesity, Type 2 Diabetes Mellitus

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### Introduction, Purpose and Methodology

Among the leading risk factors driving the global burden of disease, half of the top ten were related to metabolic risk. These included high blood pressure, elevated fasting plasma glucose, high body mass index (BMI), and increased levels of LDL cholesterol. Between 2000 and 2021, the disease burden linked to metabolic factors rose significantly, with age-standardized Disability-Adjusted Life Years (DALYs) increasing by 15.7% for high BMI and 7.9% for high Fasting Plasma Glucose (FPG) [1, 2].

According to statistical data, metabolic risk in the population is continuously increasing, significantly impacting both the quality and longevity of life. Lifestyle changes, including sedentary work, high consumption of processed foods, and lack of physical activity, are key contributors to the development of metabolic syndrome. Its consequences are far from negligible, leading to severe cardiovascular complications, which are among the leading causes of death worldwide [3, 4]. This issue is both significant and costly, underscoring the urgent need for innovative therapies, medications, and treatment strategies. In 2022, the U.S. Food and Drug Administration (FDA) approved tirzepatide for the treatment of type 2 diabetes, and by the end of 2023, it was also approved for obesity, offering hope for improving the health of patients affected by metabolic syndrome [5]. This article aims to present the current evidence on the use of tirzepatide in managing the components of metabolic syndrome, with a focus on its effectiveness in reducing the health burden among patients affected by these risk factors.

The literature review was conducted using the following keywords in the PubMed and Google Scholar databases: "tirzepatide", "metabolic syndrome", "components of metabolic syndrome" and "tirzepatide metabolic syndrome".

## Description of The State of Knowledge

### Metabolic syndrome

Metabolic syndrome is considered a 21st-century epidemic and is increasingly referred to as a lifestyle-related disease, with its prevalence continuing to rise globally [6]. According to the World Health Organization (WHO), it is a pathological condition characterized by abdominal obesity, insulin resistance, hypertension, and dyslipidemia. Metabolic syndrome is a cluster of risk factors that increase the likelihood of developing cardiovascular disease, stroke, and type 2 diabetes [7, 8]. The scale of the problem is alarming - among U.S. adults aged 18 and older, the prevalence of metabolic syndrome increased by more than 35% between 1988–1994 and 2007–2012, rising from 25.3% to 34.2% [9].

### Diagnostic Criteria

To diagnose metabolic syndrome according to the International Diabetes Federation (IDF) 2006 guidelines, the following criteria must be met:

Waist circumference > 94 cm (men) or > 80 cm (women), along with the presence of at least two of the following:

1. Blood glucose greater than 5.6 mmol/L (100 mg/dl) or diagnosed diabetes;
2. HDL cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or drug treatment for low HDL-C;
3. Blood triglycerides > 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides;
4. Blood pressure > 130/85 mmHg or drug treatment for hypertension [10].

### Pathogenesis

The pathogenesis of metabolic syndrome is complex and not yet fully understood. Its clinical manifestations are closely linked to an unhealthy lifestyle - insufficient physical activity, chronic stress, and poor dietary habits, particularly the excessive intake of highly processed foods. However, beyond lifestyle-related factors, cellular processes, disruptions in metabolic pathways, and genetic predisposition also play a significant role.

Below is a summary of the key risk factors contributing to the development of metabolic syndrome [11].

- Insulin Resistance
- Pancreatic  $\beta$ -Cell Dysfunction
- Cellular Dysfunction by Protein Kinases and Phosphatases
- Suppression of IRS1 and IRS2 Gene Expression and Function
- Obesity and Lipid Toxicity
- Oxidative Stress and Glucose Toxicity
- Chronic Inflammation
- Circadian Disruption
- Genetics and Epigenetics
- Gut Microbiota
- Dietary Effects

The consequences of metabolic syndrome are severe and pose a significant threat to health and life. The increased risk of cardiovascular events, such as stroke, coronary heart disease, heart failure, myocardial infarction, and sudden deaths, has been widely documented in scientific studies [12].

Prevention is both crucial and achievable. Physical activity and the Mediterranean diet play key roles in preventing diabetes and metabolic syndrome. Studies show that regular physical activity and adherence to the Mediterranean diet have a significant impact on reducing the risk of these conditions, including improving insulin sensitivity and reducing body weight [13,14].

### Metabolic syndrome treatment

The goal of treating metabolic syndrome is to reduce cardiovascular risk and effectively manage associated conditions, such as obesity, type 2 diabetes, hypercholesterolemia, and hypertension. Therefore, a multidisciplinary therapeutic strategy is recommended, which includes both lifestyle modifications and pharmacological treatment. It is also crucial to adopt a holistic approach to the patient, addressing their individual health needs and supporting changes in dietary habits and physical activity, with the aim of improving overall health and quality of life [15,16].

The International Diabetes Federation recommends lifestyle modifications as the primary management strategy for metabolic syndrome. These modifications include caloric restriction (aiming for a 5–10% reduction in body weight during the first year), increases in physical activity, and dietary adjustments [17]. Should these measures prove insufficient, pharmacological and surgical interventions are recommended.

In pharmacological treatment, in addition to traditional medications used for treating atherogenic dyslipidemia, elevated blood pressure, insulin resistance, and hyperglycemia, multi-target drugs are emerging. An encouraging drug in this context is tirzepatide, which has been registered for the treatment of obesity and type 2 diabetes, two conditions closely associated with metabolic syndrome [18].

### Mechanism of action of tirzepatide

Tirzepatide is a long-acting, selective dual agonist of the incretin receptors GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1). By stimulating these receptors, tirzepatide plays a crucial role in regulating insulin secretion, glucose metabolism, and appetite control, thereby influencing multiple metabolic processes [19].

- Structure

The structure of the tirzepatide molecule consists of 39 amino acids arranged in a sequence similar to the native GIP hormone, with an attached 20-carbon fatty acid chain, which enables albumin binding and prolongs half-life. Tirzepatide has a high affinity for plasma albumin (99%). The primary routes of excretion for tirzepatide metabolites are through the kidneys and the gastrointestinal tract [20].

- Receptors

Both GIP and GLP-1 receptors are expressed in various tissues, including pancreatic  $\alpha$  and  $\beta$  cells, heart, vasculature, immune cells (leukocytes), gut, kidneys, and brain regions involved in appetite regulation. Additionally, GIP receptors are found on adipocytes, highlighting their role in the regulation of fat metabolism [21].

- Mechanism of Action

Tirzepatide reaches neurons in brain regions responsible for regulating appetite and food intake, activating these areas to help control appetite. Through the GIP receptor, tirzepatide can modulate fat utilization. In human adipocytes, tirzepatide acts on GIP receptors to regulate glucose uptake and modulate lipid metabolism and lipolysis [22].

Tirzepatide increases the sensitivity of pancreatic  $\beta$ -cells to glucose, facilitating insulin release in response to hyperglycemia, thereby improving glycemic control in individuals with type 2 diabetes [19].

- Adverse Events

The most commonly reported adverse events associated with tirzepatide are gastrointestinal problems, including nausea, diarrhea, abdominal pain, vomiting, and constipation. These side effects are generally mild and tend to decrease over time with continued treatment [19].

### A post hoc analysis from the SURPASS Clinical Program

Tirzepatide has gained well-established indications for the treatment of type 2 diabetes and obesity. The SURPASS clinical trial program has provided robust and consistent evidence supporting its high efficacy and favorable safety profile in managing these conditions. The trials within the program aimed to assess the effects of tirzepatide in various doses on key health parameters, including blood glucose levels, weight reduction, and the overall impact on metabolic syndrome components [23].

The primary focus of the phase 3 trials in the SURPASS program was to evaluate the effectiveness and safety of tirzepatide in doses of 5, 10, and 15 mg in participants with type 2 diabetes. The individual studies within the program assessed the following:

- **SURPASS-1:** Tirzepatide monotherapy versus placebo over 40 weeks.
- **SURPASS-2:** Tirzepatide in combination with metformin versus once-weekly GLP-1 receptor agonist semaglutide 1 mg for 40 weeks.
- **SURPASS-3:** Tirzepatide in combination with metformin, with or without a sodium-glucose cotransporter-2 inhibitor (SGLT-2i), versus once-daily insulin degludec for 52 weeks.
- **SURPASS-4:** Tirzepatide in combination with metformin, sulfonylurea, and an SGLT-2 inhibitor versus once-daily insulin glargine 100 units/mL for 52 weeks, with an optional additional treatment period of up to 52 weeks.
- **SURPASS-5:** Tirzepatide in combination with insulin glargine, with or without metformin, versus placebo for 40 weeks.

In all five SURPASS trials, a significant decrease in HbA1c levels and body weight reduction were observed in patients treated with tirzepatide [24-28].

In the context of the clinical diagnosis of metabolic syndrome, it is important to recognize that both type 2 diabetes and obesity are closely linked to other components of the syndrome, such as dyslipidemia and hypertension. While the primary focus of the SURPASS trials was on the management of type 2 diabetes and obesity, the components of metabolic syndrome were also examined, given their strong association with these conditions.

### **Effects of tirzepatide**

In the study titled *"Reduction of Prevalence of Patients Meeting the Criteria for Metabolic Syndrome with Tirzepatide: A Post-Hoc Analysis from the SURPASS Clinical Trial Program"*, the effects of tirzepatide on various metabolic syndrome components were evaluated [29].

- **Blood Glucose Control**

One of the main signs of metabolic syndrome is hyperglycemia, which can lead to insulin resistance and, over time, type 2 diabetes. Tirzepatide has been shown to reduce blood glucose levels and HbA1c levels in all five SURPASS studies. In the SURPASS-4 study, tirzepatide led to large drops in HbA1c. In the SURPASS-1 trial, more than half of the patients achieved normoglycemia (HbA1c < 5.7%) without an increased incidence of hypoglycemic events. These results show that tirzepatide not only helps control blood glucose level but can also bring it back to normal in people with metabolic syndrome.

- **Weight Reduction**

Obesity represents a fundamental component of metabolic syndrome, and weight reduction is a critical therapeutic target for improving metabolic health and reducing cardiovascular risk. Tirzepatide has demonstrated robust, dose-dependent effects on body weight reduction. These findings were further supported by the SURMOUNT-1 trial, which specifically evaluated tirzepatide in individuals with overweight or obesity. Although the SURPASS trials primarily focused on glycemic control in patients with type 2 diabetes, they consistently reported significant reductions in body weight and waist circumference among participants receiving tirzepatide. In SURMOUNT-1, administration of the 15 mg dose resulted in a mean decrease in waist circumference of 18.5 cm, with some individuals achieving weight loss exceeding 20% of initial body weight - an effect comparable to that observed following bariatric surgery.

- **Lipid Profile**

Participants treated with tirzepatide experienced reductions in triglycerides and LDL cholesterol levels, as well as an increase in HDL cholesterol levels or an improvement in the triglyceride/HDL ratio. These lipid improvements are crucial for reducing the risk of cardiovascular diseases, which are more prevalent in individuals with metabolic syndrome.

- **Blood Pressure**

Hypertension is a common component of metabolic syndrome, and its management is essential for reducing the risk of cardiovascular events. In SURPASS-5, patients treated with tirzepatide experienced a mean reduction in systolic blood pressure ranging from 6.1 to 12.6 mmHg. Notably, greater reductions in blood pressure were observed in patients with more significant weight loss, highlighting the close relationship between weight reduction and blood pressure regulation.

The data show that tirzepatide not only improves blood glucose control and promotes significant weight loss, but it also positively impacts lipid profiles and blood pressure, all of which are critical elements of metabolic syndrome.

### **Conclusions**

The results of the SURPASS clinical trials underscore the clinical efficacy of tirzepatide in the management of type 2 diabetes and obesity - two major components of metabolic syndrome. Tirzepatide demonstrated consistent improvements across multiple metabolic parameters, including glycemic control (HbA1c), body weight, lipid profile, and blood pressure, supporting its potential as a comprehensive therapeutic agent for patients with metabolic syndrome. Although metabolic syndrome was not designated as a primary endpoint in these trials, the favorable outcomes observed across its individual components provide important insights into tirzepatide's broader therapeutic utility. Collectively, these findings position tirzepatide as a significant advancement in the pharmacologic management of metabolic syndrome and a promising option for reducing cardiometabolic risk in affected individuals.

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