International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
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ARTICLE TITLE	OBESITY AS A CHRONIC INFLAMMATORY DISEASE: ADIPOSE TISSUE PATHOPHYSIOLOGY, PHARMACOLOGICAL REVOLUTION, AND MULTIDISCIPLINARY TREATMENT STRATEGIES
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4512
RECEIVED	15 November 2025
ACCEPTED	26 December 2025
PUBLISHED	30 December 2025
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OBESITY AS A CHRONIC INFLAMMATORY DISEASE: ADIPOSE TISSUE PATHOPHYSIOLOGY, PHARMACOLOGICAL REVOLUTION, AND MULTIDISCIPLINARY TREATMENT STRATEGIES

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ABSTRACT

Obesity is a global epidemic and a complex chronic neurohormonal disease, which is the main cause of lifestyle diseases. The aim of this review is to thoroughly collect and critically evaluate the latest information on the pathophysiology of obesity, including the importance of low-grade inflammation (meta-inflammation), as well as to analyze the effectiveness of breakthrough, multidirectional treatment methods. We conducted a narrative review of scientific literature from major medical databases, focusing on studies published between 2015 and 2025 that addressed pathogenesis, clinical consequences (cardiovascular disease, oncology), modern pharmacotherapy (GLP-1/GIP agonists), and bariatric surgery.
Obesity is driven by adipose tissue (endocrine organ) dysfunction and chronic inflammation (metaflammation), leading to insulin resistance and gut-brain axis dysregulation. Modern pharmacotherapy, in particular GLP-1/GIP agonists, achieves weight loss of 15-22% (in STEP/SURMOUNT studies), which is comparable to the effects of early bariatric surgery. Surgery remains the most effective method of weight reduction and remission of metabolic complications. Effective treatment of obesity requires a personalized approach in which new pharmacology, lifestyle modification, and bariatric surgery must be integrated. The need for continuous, long-term treatment is crucial for maintaining weight and combating weight regain.

KEYWORDS

Obesity, Metaflammation, GLP-1 Agonists, Tirzepatide, Bariatric Surgery, Pharmacological Treatment

CITATION

Lucjan Kocemba, Piotr Rachwał, Idalia Myszor, Michał Madej, Maria Kubacka, Gabriela Mroczka, Sylwia Nycz-Jucha, Paulina Łobaza, Brygida Pinkowicz, Barbara Nowak-Misiąg. (2025). Obesity as a Chronic Inflammatory Disease: Adipose Tissue Pathophysiology, Pharmacological Revolution, and Multidisciplinary Treatment Strategies. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4512

1. Introduction

Obesity (defined as a body mass index – BMI ≥ 30 kg/m²) is recognized by the World Health Organization (WHO) as a global epidemic and one of the most serious health challenges of the 21st century [1]. The prevalence of obesity worldwide has nearly tripled since 1975, and the scale of the problem translates into dramatic economic and social costs resulting from the development of numerous coexisting diseases [2]. Obesity is no longer seen solely as a matter of energy balance, but as a chronic, progressive neurohormonal disease characterized by excessive or abnormal accumulation of adipose tissue that can impair health [3].

A key change in the understanding of the pathogenesis of obesity is the recognition of adipose tissue as an active endocrine organ capable of secreting a wide range of adipokines and cytokines that lead to the development of chronic low-grade inflammation (metaflammation) [4, 5]. This inflammation is directly responsible for the development of insulin resistance, dyslipidemia, hypertension, and an increased risk of cardiovascular disease (CVD) and certain cancers [6].

1.1. Research Problem and Justification

The complex pathophysiological picture of obesity absolutely requires the implementation of a multidirectional treatment plan. For many decades, traditional methods—involving only behavioral interventions, diet, and older-generation pharmacotherapy—have proven ineffective in providing patients with long-term and clinically significant weight loss [7].

The recent revolution in obesity pharmacology, in particular the introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual agonists (GLP-1/GIP), has fundamentally changed the therapeutic landscape [8]. These drugs, which achieve weight loss comparable to bariatric surgery, require urgent and comprehensive synthesis of their mechanisms of action, clinical efficacy (in light of studies such as the STEP and SURMOUNT series), and their integration with other treatment strategies [9, 10].

There is therefore an urgent need to collect and critically analyze the latest scientific evidence that: (1) describes in detail the role of adipose tissue as a generator of inflammation; (2) evaluates the place and

effectiveness of new pharmacotherapies in terms of outcomes and safety profile; and (3) compares these data with traditional strategies, including lifestyle modification and bariatric surgery, to create optimal, personalized treatment algorithms.

1.2. Research Objectives

The main objective of this review is to provide a comprehensive synthesis and critical analysis of the scientific literature on modern approaches to the treatment of obesity. Specific objectives include:

- An in-depth description of the pathophysiological mechanisms of obesity, with an emphasis on the role of adipose tissue as an active endocrine organ and generator of inflammation (metaflammation).
- A detailed analysis of the mechanisms of action and clinical efficacy of modern pharmacological therapies for weight loss, with particular emphasis on GLP-1 and GIP agonists.
- A comparison of pharmacotherapy with bariatric surgery and lifestyle modification to develop integrated strategies for long-term obesity management.

2. Methodology

2.1. Research Design and Search Strategy

This paper is a comprehensive narrative review of the scientific literature. Our goal is to critically gather evidence on the pathophysiology, clinical consequences, and modern pharmacological and surgical strategies used in the treatment of obesity.

The relevant literature was searched in the most important electronic medical databases, such as:

-PubMed/MEDLINE

-Embase

-Cochrane Library

-Google Scholar

The search covered publications from 2015 to 2025, with a particular focus on recent groundbreaking clinical trials of new pharmacotherapies for obesity.

2.2. Inclusion and Exclusion Criteria

Only publications with high scientific credibility that provided key information for the purposes of the study were included in the review:

- Inclusion: Systematic Reviews and Meta-analyses, Randomized Controlled Trials (RCTs), large Observational and Registry Studies (Real-World Data) on the efficacy and safety of pharmacotherapy, and review articles on pathophysiology. Publications in English and Polish.
- Exclusion: Case reports, letters to the editor, works without full text, and works concerning only obesity in animals (unless they concerned molecular mechanisms with a direct translation to human pathophysiology).

2.3. Data Extraction and Synthesis Process

The identified articles underwent a two-stage selection process: evaluation of the title and abstract, followed by evaluation of the full text. Key variables were extracted and categorized from the included articles, including:

- Pathophysiology: We gathered information on the role of adipokines and proinflammatory cytokines (such as TNF-α and IL-6), as well as the mechanisms leading to insulin resistance.
- Pharmacological efficacy: We analyzed the average percentage of weight loss, the results of the landmark STEP and SURMOUNT clinical trials, and the impact of new drugs on cardiovascular complications (CVD).
- Surgical Treatment: We compared the mechanisms of action and long-term effectiveness of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy procedures.
- Safety: Adverse event profile, especially in terms of gastrointestinal tolerance and potential rare events (e.g., pancreatitis).

3. Pathophysiology of Obesity as a Chronic Inflammatory Disease

Understanding obesity as a chronic inflammatory and neurohormonal disease is key to effective treatment. The classic definition of obesity, based on simple energy accumulation, has been replaced by a model in which adipose tissue is an active endocrine organ that regulates metabolic homeostasis and generates systemic inflammation [11].

3.1. Adipose Tissue as an Active Endocrine Organ

Adipose tissue (AT) is a complex organ consisting not only of adipocytes, but also of stem cells, preadipocytes, fibroblasts, endothelial cells, and immune system cells [12]. The latter fraction, called the stromal vascular fraction (SVF), plays a key role in the development of obesity. Adipocytes secrete numerous adipokines (or adipocytokines) that act autocrinally, paracrinally, and endocrinally, affecting insulin sensitivity, lipid metabolism, and inflammatory processes [13].

In healthy adipose tissue, a balance is maintained between pro- and anti-inflammatory adipokines:

Adiponectin: This is a hormone with anti-inflammatory and insulin-sensitizing effects [14]. In obesity and insulin resistance, adiponectin levels are significantly reduced, which is an indicator of adipose tissue dysfunction. Low adiponectin concentrations are associated with a higher cardiovascular risk [15].

Leptin: It regulates appetite and energy expenditure by acting on satiety centers in the hypothalamus [16]. In obesity, leptin levels are elevated, but leptin resistance develops (a condition similar to insulin resistance), leading to a vicious cycle of increased food intake and fat accumulation [16].

Resistin and Wisfatin: These are other adipokines that correlate with insulin resistance and inflammation, although their exact role in the pathogenesis of human obesity is still the subject of intensive research [17].

3.2. Obesity as Low-Grade Inflammation (Metaflammation)

The most important pathophysiological feature of obesity is the development of chronic low-grade inflammation, known as metaflammation (metabolic inflammation) [4].

As adipocytes expand and hypertrophy (increase in size), adipose tissue becomes hypoxic and ischemic. Adipocytes undergo necrosis, releasing lipids and sending an alarm signal to the immune system [18]. This process results in:

-Macrophage infiltration: Adipose tissue in obese patients is heavily infiltrated by macrophages. These cells change their phenotype from protective (M2) to pro-inflammatory (M1)[18]. M1 macrophages accumulate around dead adipocytes, forming characteristic crown-like structures (CLS). They are the main source of pro-inflammatory cytokines [19].

-Secretion of pro-inflammatory cytokines: M1 macrophages and other immune cells, including T lymphocytes, secrete key pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) [4]. These cytokines are released into the bloodstream, acting on distant tissues, including the liver and muscles, which is a direct cause of insulin resistance and endothelial damage [20].

The state of metaflammation disrupts insulin signaling pathways. TNF-α and IL-6 interfere with the action of insulin receptors, leading to a decrease in the sensitivity of peripheral tissues to insulin [20]. As a result, the pancreas must produce more insulin (hyperinsulinemia) to maintain normal blood glucose levels, which ultimately leads to β-cell exhaustion and the development of type 2 diabetes [21].

3.3. Gut-Brain Axis and Appetite Regulation

The regulation of appetite and satiety, although controlled by centers in the hypothalamus, is closely modulated by peptides secreted in the small intestine in response to food intake. Obesity is largely a disease of dysregulation of this neurohormonal axis [22].

Incretin hormones play a key role:

- Glucagon-like peptide 1 (GLP-1): Secreted by L cells in the large intestine and ileum. GLP-1 increases glucose-dependent insulin secretion, inhibits glucagon secretion, and, most importantly in the context of obesity, delays gastric emptying and induces a feeling of satiety through receptors in the brain (arcuate nucleus, hypothalamus) [23]. In patients with obesity and diabetes, GLP-1 function is often impaired [24].

- Glucose-dependent insulinotropic peptide (GIP): Secreted by K cells in the duodenum and jejunum. Traditionally associated mainly with the insulinotropic effect, it has also been found to be a key regulator of fat metabolism. In obese patients, although GIP levels may be elevated, its action is often impaired [25].

There is growing evidence that the composition of the gut microbiota in obese patients is different from that in lean individuals (reduced diversity and altered proportions of Bacteroidetes to Firmicutes) [26]. This microbiota may influence metabolism through the production of short-chain fatty acids (SCFAs), which act on intestinal cells, modifying the secretion of GLP-1 and PYY, thereby influencing appetite and energy storage [27].

In summary, the pathophysiology of obesity goes far beyond the calorie equation, encompassing chronic adipose tissue dysfunction, a state of metaflammation, global insulin resistance, and neurohormonal dysregulation of the gut-brain axis. Understanding these mechanisms is fundamental to evaluating the effectiveness of modern pharmacotherapy targeting these specific pathways.

4. Clinical Consequences and Complications of Obesity

Pathophysiological dysfunction of adipose tissue, combined with chronic low-grade inflammation (metaflammation) and insulin resistance, triggers a cascade of negative clinical effects. Obesity is a risk factor for almost all serious lifestyle diseases, which clearly emphasizes its status as a systemic disease and not just a cosmetic problem [28].

4.1. Metabolic Syndrome and Cardiovascular Risk

Obesity, especially visceral obesity, is a key component of metabolic syndrome, which in turn is the most important predictor of cardiovascular morbidity and mortality[29].

-Atherogenic Dyslipidemia: The classic triad of dyslipidemia is often observed in obese patients. This includes elevated triglyceride levels, reduced high-density lipoprotein (HDL-C) levels, and the presence of small, dense low-density lipoprotein (sdLDL) particles, which are highly atherogenic [30].

- Endothelial dysfunction: The release of pro-inflammatory adipokines (TNF-α, IL-6) and free fatty acids leads to chronic vascular endothelial dysfunction and increased oxidative stress. This condition promotes the migration and accumulation of macrophages in the vessel walls, which is the first stage in the development of atherosclerotic plaques [31]. Obesity not only accelerates the formation of plaques, but also destabilizes existing plaques, increasing the risk of acute coronary events [32].

Obesity is closely linked to the development of hypertension through several mechanisms [33]:

- Activation of the RAA System: Adipose tissue produces components of the renin-angiotensin-aldosterone (RAA) system, leading to increased sodium and water retention and vasoconstriction.

- Activation of the sympathetic nervous system: Hyperinsulinemia and leptin resistance increase the activity of the sympathetic nervous system.

Chronic volume and hormonal overload leads to obesity cardiomyopathy and left ventricular remodeling (hypertrophy), increasing the risk of heart failure with preserved ejection fraction (HFpEF), which is increasingly recognized as a metabolic complication [34].

4.2. Oncological Risk and Hormonal Impact

Obesity is a recognized risk factor for at least 13 types of cancer, including breast cancer (in postmenopausal women), colon cancer, esophageal cancer, pancreatic cancer, liver cancer, and kidney cancer [35].

The carcinogenic effects of obesity stem from three main axes [36]:

- Chronic Inflammation: Pro-inflammatory cytokines (IL-6, TNF-α) generated by adipose tissue create a microenvironment that promotes the survival and proliferation of cancer cells and inhibits apoptosis.

- Hyperinsulinemia and IGF-1: Insulin resistance leads to chronic elevated levels of insulin and insulin-like growth factor 1 (IGF-1), which are potent mitogens and promote tumor growth.

- Sex Hormone Dysregulation: Adipose tissue is the main site of conversion of androgens to estrogens (via the enzyme aromatase). In postmenopausal women, this excess estrogen increases the risk of hormone-dependent cancers such as breast and endometrial cancer [36].

4.3. Obesity and Other Systems

The consequences of obesity affect almost every system in the body.

Digestive System and Liver

- Fatty Liver Disease (NAFLD): Accumulation of lipids in hepatocytes resulting from insulin resistance and excessive flow of free fatty acids. NAFLD is currently the most common cause of chronic liver disease and can lead to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma [37].

- Gallstones: Increased secretion of cholesterol into bile increases the risk of gallstone formation.

- Gastroesophageal Reflux Disease (GERD): Increased abdominal pressure (intra-abdominal pressure) promotes gastroesophageal reflux.

Respiratory and Musculoskeletal Systems

- Obstructive Sleep Apnea (OSA): Excessive accumulation of fat tissue around the throat (neck) leads to collapse of the airways during sleep, causing episodes of hypoxemia and increasing the risk of pulmonary hypertension and arrhythmias.

- Osteoarthritis (OA): Mechanical overload of the knee and hip joints is the main cause of OA development. However, obesity also contributes to cartilage destruction through metabolic and inflammatory mechanisms (e.g., through the release of adipokines, which have a catabolic effect on cartilage) [38].

Mental Health and Quality of Life

Obesity is associated with an increased incidence of depression, anxiety, and lower self-esteem. Social and professional stigmatization, as well as chronic physical discomfort, significantly reduce quality of life (QoL) and contribute to social isolation, which is an important clinical factor that should be taken into account when planning treatment [39].

5. Pharmacological Revolution in the Treatment of Obesity

Given the limited long-term effectiveness of behavioral interventions and older pharmacotherapy, recent years have seen a revolution in the pharmacological treatment of obesity. New classes of drugs targeting the neurohormonal pathways that regulate appetite and satiety (described in Chapter 2) have enabled clinically significant and sustained weight loss, often comparable to the effects of early bariatric surgery [40].

5.1. GLP-1 Receptor Agonists (GLP-1 RAs)

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of drugs originally developed for the treatment of type 2 diabetes. Their ability to induce weight loss, resulting from central action and delayed gastric emptying, quickly made them key drugs in the treatment of obesity [41].

GLP-1 RAs work through the following synergistic mechanisms [42]:

- Central Action: Activation of GLP-1 receptors in the arcuate nucleus (ARC) of the hypothalamus leads to increased satiety and reduced appetite (reduction in hedonic appetite), which limits calorie intake.

- Peripheral Action: Delayed gastric emptying (gastric effect) prolongs the feeling of fullness after a meal.

The efficacy of GLP-1 RAs in obesity has been comprehensively documented in the STEP (Semaglutide Treatment Effect in People with Obesity) series of Phase III studies.

- Semaglutide: A weekly GLP-1 agonist, it has proven to be the most groundbreaking. In the STEP 1 study (involving patients without diabetes), semaglutide at a dose of 2.4 mg (compared to placebo) resulted in an average weight loss of 14.9%, with more than one-third of patients achieving a weight reduction of 20% or more [8]. This was a level unprecedented in conventional obesity pharmacotherapy.

- Liraglutide: Another GLP-1 agonist, administered once daily, showed an average weight loss of approximately 8% compared to placebo in clinical trials, which was also a clinically significant advance [43].

5.2. Dual Agonists (GLP-1 and GIP)

The next step in the evolution of pharmacotherapy was the introduction of drugs that simultaneously activate two key incretin receptors: GLP-1 and GIP (Glucose-dependent Insulinotropic Polypeptide).

Tirzepatide, the first approved dual GLP-1/GIP agonist, works synergistically to maximize the potential of the gut-brain axis. It is believed that activation of the GIP receptor enhances sensitivity to GLP-1 and additionally affects fat metabolism, which translates into greater and more sustained weight loss [44].

The unique efficacy of dual agonists has been demonstrated in the SURMOUNT clinical trial series.

- Tirzepatide: In the SURMOUNT-1 study (involving patients without diabetes), the highest dose of tirzepatide (15 mg) resulted in an average weight loss of 22.5% [10]. This result is comparable to the effects observed after sleeve gastrectomy, which clearly highlights the groundbreaking nature of this class of drugs.

- Clinical implications: Such significant weight loss not only improves aesthetics, but above all achieves remission or significant improvement in obesity-related complications, including type 2 diabetes, dyslipidemia and hypertension.

5.3. Older Pharmacotherapy and Combination Strategies

Although the new generation of incretin drugs dominates the market, older drugs still have their place in therapy, especially in the context of combination therapy.

Lipase Inhibitors (Orlistat)

Orlistat works by inhibiting pancreatic lipase, which leads to reduced fat absorption from the gastrointestinal tract. Although the weight loss effect is moderate (body weight reduction of approximately 3-5%), it is useful as an adjunct to dietary interventions. Its main limitation is its tolerance profile (gastrointestinal side effects) [45].

Central Nervous System (CNS) Drugs

- Phentermine/Topiramate: This is a combination drug with mechanisms of action affecting appetite (phentermine - a noradrenergic agonist) and satiety (topiramate). This combination is more effective than monotherapy (average weight loss of approximately 8-10%) and is an option for patients who are not eligible for or cannot tolerate incretin therapy [46]. Potential limitations of this therapy include possible adverse effects on the central nervous system (such as insomnia or paresthesia) and the risk of teratogenicity.

-Naltrexone/Bupropion: This combination acts on the reward system in the brain, effectively reducing appetite and compulsive eating behaviors (cravings). Although its effectiveness is moderate (weight reduction is approximately 5%), the use of this combination is sometimes limited due to contraindications such as hypertension or addiction [47].

6. Multidisciplinary Strategies and Bariatric Surgery in the Treatment of Obesity

Effective treatment of obesity requires the integration of pharmacological, behavioral, and, when necessary, surgical therapies. No single method guarantees long-term success, which highlights the absolute need for a multidimensional approach involving dietitians, psychologists, physical therapists, and surgeons [48].

6.1. Bariatric Surgery: Mechanisms and Effectiveness

Bariatric and metabolic surgery is widely recognized as the most effective form of treatment for morbid obesity (BMI $\geq$ 40 kg/m² or $\geq$ 35 kg/m² with complications). It provides the highest and most sustainable weight loss and long-term remission of metabolic diseases [49]. It is crucial to understand that the metabolic benefits of surgery go far beyond restriction (reduction of stomach volume) alone.

Main Procedures and Their Mechanisms

-Sleeve Gastrectomy (SG): This involves removing most of the stomach (approximately 75-80%), resulting in the creation of a narrow sleeve. The mechanism of action is twofold: limiting food intake and eliminating the fundus of the stomach – the main site of ghrelin (hunger hormone) production [50]. Reducing ghrelin levels contributes to a decrease in appetite and a change in the satiety point.

-Gastrointestinal bypass (Roux-en-Y Gastric Bypass, RYGB): This is a more complex procedure. In addition to creating a small, restrictive gastric pouch, the procedure involves bypassing a significant portion of the duodenum and jejunum. The metabolic mechanism is stronger here and includes: 1) Enhanced Incretin Effect: Faster delivery of undigested food to the distal sections of the intestine results in a rapid and significant increase in GLP-1 and PYY secretion [51]. This powerful incretin signal is the main cause of rapid and sustained remission of type 2 diabetes, often independent of weight loss. 2) Restriction and Change in Food Preferences: RYGB is more effective than SG in treating the most severe metabolic complications, although it is associated with a higher risk of nutritional deficiencies and long-term complications [52].

Long-term studies, such as SOS (Swedish Obese Subjects), confirm that bariatric surgery leads to a permanent reduction in overall and cardiovascular mortality [53]. However, long-term monitoring of patients for micronutrient deficiencies (vitamin B12, iron, folic acid) and the risk of postoperative hypoglycemia is essential.

6.2. Lifestyle Interventions: Behavioral and Dietary Role

Despite the pharmacological revolution and the effectiveness of surgery, lifestyle change remains the foundation of any obesity treatment program. These interventions focus on caloric deficit, optimizing diet composition, and increasing energy expenditure.

Behavioral and Motivational Therapy

High-quality obesity treatment programs are based on intensive behavioral modification [54]. This process is multifaceted and involves techniques aimed at permanently changing habits and relationships with food. The key elements of this therapy are:

-Self-observation and monitoring: regularly keeping food and activity diaries, which allow the patient and therapist to identify problematic patterns.

-Stimulus Control Techniques: working to identify and eliminate triggers that lead to uncontrolled food consumption.

-Social and psychological support: it is essential to involve loved ones (family and friends) in the treatment process and to address co-occurring problems such as eating disorders (e.g., binge eating disorder) or mood disorders.

Dietary Strategies

Weight loss is most effective when a negative energy balance is achieved. The choice of a specific diet (low-carbohydrate, low-fat, Mediterranean) should be personalized [55].

- Total Meal Replacement Diets (VLCD/LCD): Very low-calorie diets (VLCD, < 800 kcal/day) can lead to rapid weight loss, but require close medical supervision and are mainly effective as a starting phase of treatment.

- Role of Physical Activity: Physical activity (e.g., 150 minutes of moderate exercise per week) is crucial not so much for initiating significant weight loss as for maintaining weight loss and improving insulin sensitivity [56].

6.3. Personalization of Therapy and Decision Algorithms

The era of modern pharmacotherapy requires a shift from universal recommendations to personalized treatment.

- Criteria for Weight Loss: Treatment goals should be set based on the desired effect:1) A reduction of 5-10% is clinically significant and improves metabolic markers.2) A reduction of >15-20%, achievable only with new-generation drugs or surgery, can lead to remission of diabetes and other metabolic diseases.

- Choice of Therapy: The decision algorithm must take into account (see Table 1):

1. Degree of Obesity (BMI) and Complications: Severe cardiovascular complications or a BMI > 35 kg/m² indicate bariatric surgery or the most effective medications (GLP-1/GIP agonists).

2. Presence of Type 2 Diabetes: Drugs with proven cardiovascular and renal benefits (e.g., GLP-1 RAs, SGLT2i – in the case of diabetes) are preferred.

3. Tolerance and costs: The side effect profile (especially gastrointestinal) and economic accessibility are crucial for long-term retention of therapy.

Table 1. Comparison of the effectiveness and mechanisms of the main strategies for treating obesity

Strategy	Average Body Weight Reduction (1 Year)	Main Mechanism of Action	Long-term Effect on Comorbidities
Lifestyle	3–5%	Negative calorie balance, energy expenditure	Moderate improvement in insulin sensitivity
GLP-1 RAs (Semaglutide 2.4 mg)	15–17%	Increased satiety, delayed gastric emptying	Significant reduction in cardiovascular risk and diabetes
GLP-1/GIP RAs (Tirzepatide 15 mg)	20–22%	Synergistic regulation of the gut-brain axis	Highest rates of diabetes remission
Bariatric Surgery (RYGB)	25–35%	Restriction, strong incretin effect (bypass of the intestine)	Highest and most sustained metabolic and cardiovascular improvement

7. Discussion

This review confirms that obesity is a chronic systemic disease driven by complex pathophysiology (metaflammation, neurohormonal axis dysfunction). The results of clinical trials, particularly in the field of modern pharmacotherapy, mark a historic moment in which weight loss of more than 15% is routinely achievable without surgical intervention. However, effectively combating the epidemic requires the integration of these breakthrough drugs with behavioral and surgical interventions as part of a personalized, long-term plan [57].

7.1. Integration of Pharmacotherapy with Surgery: Competition or Complementarity?

The introduction of GLP-1/GIP agonists, which achieve weight loss similar to that of sleeve gastrectomy (SG), has sparked debate about the future place of bariatric surgery [58].

Despite impressive pharmacological results (20-22% weight loss for tirzepatide), bariatric surgery, especially RYGB, still provides the highest and most durable weight loss (25-35%) and the strongest metabolic effect, as measured by remission of type 2 diabetes [59].

From a clinical point of view, new-generation drugs are becoming a therapeutic bridge for patients who:

- Are not eligible for bariatric surgery (e.g., due to high anesthesia risk).
- Are afraid of surgery but require immediate, intensive weight loss due to complications.
- Experience weight regain after bariatric surgery – in this case, incretin agonists are a valuable adjunctive tool.

Pharmacotherapy should therefore not be seen as competition, but as a complement to the treatment algorithm that increases the number of patients in whom clinical goals can be achieved [60].

The benefits of modern pharmacotherapy go beyond body weight alone:

- Cardiovascular Risk: Studies have shown that GLP-1 agonists, in addition to their effect on body weight, offer independent cardioprotective benefits (MACE reduction) in patients with diabetes and cardiovascular disease [61]. This highlights the need to treat them as metabolic-cardioprotective drugs.
- Liver: Intensive weight loss, made possible by GLP-1/GIP agonists, plays a key role in reversing fatty liver disease (NAFLD) and improving inflammation markers in non-alcoholic steatohepatitis (NASH) [62].

7.2. Clinical Challenges and Barriers to Therapy

Pharmacological success brings new challenges that must be addressed in clinical practice and further research.

The main barrier to long-term use of incretin-based drugs remains their tolerance profile, especially with regard to gastrointestinal side effects (nausea, vomiting, diarrhea/constipation) [63]. Although these are usually mild to moderate and transient, they can lead to discontinuation of the drug.

Serious Adverse Events: Continuous monitoring of rare but serious events is required, such as the risk of acute pancreatitis or a potential association with thyroid C-cell tumors (although the latter is mainly observed in rodent models) [64].

The treatment of obesity is chronic. Studies have shown that discontinuation of GLP-1 RAs leads to rapid and almost complete regain of lost weight [65]. This is because obesity is a neurohormonal disease, and drugs only modify the pathological regulation of hunger centers rather than treating the underlying cause. The need for continuous medication is a major challenge in terms of: 1) Cost and Availability: The high cost of new-generation drugs poses a serious barrier in healthcare systems. 2) Adherence (Cooperation): Patients must be educated about the need for continuous treatment, as is the case with hypertension or diabetes.

Knowledge Gaps and Need for Further Research

Key gaps include:

- Long-Term Complications: Lack of long-term data (> 5-10 years) on safety and oncological risk for dual agonists (GLP-1/GIP).
- Response Biomarkers: Lack of predictive markers that could determine which patients (e.g., those with high GIP levels, low GLP-1 levels, or a predominance of hedonic appetite) will respond best to a given combination of drugs.
- Children and Adolescents: Limited data on the long-term safety of these drugs in the pediatric population.

8. Conclusions

Obesity should be treated as a chronic, inflammatory metabolic disease that requires a multidisciplinary and long-term approach to treatment. The pharmacological revolution, represented by GLP-1 and GIP agonists, has provided tools capable of achieving clinically significant weight loss.

The main conclusions of this review are presented below:

- Pathophysiology: The central therapeutic targets are the gut-brain axis and adipose tissue inflammation, referred to as metaflammation.

-Therapy Efficacy: Modern incretin-based drugs (GLP-1/GIP RAs) provide weight reduction and metabolic improvement comparable to the results of bariatric surgery.

- Treatment Algorithm: Optimal obesity management requires personalized therapy that takes into account BMI, comorbidities (especially cardiometabolic), and safety profile. However, bariatric surgery remains the gold standard for patients with morbid obesity and its severe complications.

- Long-Term Challenges: The main challenge remains maintaining the achieved body weight and ensuring that patients continue chronic therapy, which is necessary due to the chronic nature of the disease.

Further research must focus on therapy integration, biomarker identification, and ensuring access to treatment in order to effectively address the global obesity pandemic.

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