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REVIEW ARTICLE

The Intricate Relationship between Obesity and Type 2 Diabetes

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Abstract: The rising prevalence of obesity and Type 2 Diabetes Mellitus (T2DM) has emerged as one of the most pressing global public health challenges, profoundly impacting various demographic groups worldwide. This review synthesizes recent epidemiological data and explores the intricate biochemical mechanisms linking obesity to T2DM. We highlight the multifactorial nature of obesity, characterized by excessive adipose tissue, systemic inflammation, and hormonal dysregulation, which collectively contribute to insulin resistance a defining feature of T2DM. Moreover, we delve into the roles of brown and beige adipose tissues in energy metabolism and their potential dysfunction in these metabolic disorders. Current therapeutic strategies, including lifestyle changes, pharmacotherapy, and bariatric surgery, are examined for their comparative effects on managing both conditions. While lifestyle intervention remains foundational, advancing pharmacological options and the efficacy of surgical interventions offer promising avenues for treatment. Understanding the reciprocal relationship between obesity and T2DM is critical for developing comprehensive management strategies and addressing their shared pathophysiological underpinnings, ultimately aiming to mitigate the health burden associated with these diseases.

Keywords: Type 2 Diabetes Mellitus, Obesity, Insulin Resistance, Adipose Tissue, Metabolic Syndrome, Chronic Inflammation, Bariatric Surgery, Pharmacotherapy

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Introduction

The second half of the 20th century brought unprecedented improvements in quality of life in both developed and developing countries. However, this progress inadvertently created an environment in which physical inactivity and excess calories became the norm rather than the exception. As a result, obesity has transformed from a local health problem into a global epidemic, now ranking among the most serious Noncommunicable Diseases (NCDs) [1-3]. Alarmingly, the

epidemiological curve shows no signs of stabilizing; projections indicate that this trend will intensify in the coming years across virtually all demographic groups. This trajectory compels the medical community to go beyond descriptive statistics and urgently improve both preventive measures and therapeutic protocols. Critically, the consequences of rising obesity extend far beyond weight gain itself, triggering a parallel surge in comorbidities primarily Type 2 Diabetes Mellitus (T2DM), reflecting the widespread global prevalence of obesity [4,5].

Studying the relationship between obesity and type 2 diabetes has become a central focus of metabolic research. The rationale is compelling: the dramatic increase in the incidence of type 2 diabetes over recent decades cannot be fully explained by genetic drift alone, pointing instead to modifiable environmental and behavioral factors that intersect with genetic predisposition. To decipher this interaction, a significant body of research spanning molecular biology, clinical endocrinology, and large-scale population genetics has been deployed to analyze the mechanisms linking these two diseases [6–9].

A particularly fertile area of research is the shared genomic and epigenomic landscapes underlying both conditions. The advent of multi-omics profiling and computational systems biology has enabled researchers to move beyond simple gene-disease associations to a more dynamic understanding of convergent pathophysiological cascades. Specifically, when genetically predisposed individuals experience obesity under certain conditions, adipose tissue abnormally expands, triggering a cascade of metabolic disturbances. This state of nutrient excess leads to peripheral insulin resistance, disrupts autophagic clearance mechanisms, and impairs bidirectional communication along the gut-microbiome-brain axis. The cumulative effect is a state of chronic, low-grade immunometabolic inflammation, which directly accelerates pancreatic β-cell decompensation. Over time, this progressive disruption of glycemic homeostasis crystallizes into the clinical phenotype of type 2 diabetes [10–12].

Given their interrelated pathophysiologies, it is not surprising that therapeutic paradigms for obesity and type 2 diabetes often converge. Current clinical algorithms integrate a spectrum of methods, ranging from first-line behavioral modifications to pharmacotherapy, novel device-based interventions, and metabolic/bariatric surgery [13,14]. Lifestyle modification remains a cornerstone of disease management, given its robust evidence base and favorable risk-benefit ratio; indeed, sustained weight loss is one of the most effective preventive measures against the development of type 2 diabetes. However, the pharmacological situation is controversial: although some anti-obesity drugs have additional glucose-lowering properties, a number of antidiabetic drugs, particularly insulin-containing ones, are paradoxically associated with unwanted weight gain. Regarding surgical treatment, bariatric surgery has demonstrated remarkable efficacy in achieving sustained remission of both diseases. However, these procedures are not without their inherent risks, including perioperative morbidity and specific postoperative metabolic complications, emphasizing the need for careful patient selection [15–17].

Although the existing literature contains fragmented reports addressing specific aspects of this dyad, a notable gap remains in the form of an integrated synthesis encompassing the epidemiological codynamics, the overall pathogenetic architecture, and the bidirectional impact of different treatment regimens. To address this gap, this review is structured as follows: we begin with a critical assessment of recent epidemiological trajectories to determine how changing prevalence rates of one disease impact the other. We then analyze the key molecular links linking their etiologies, followed by a systematic comparative evaluation of current therapeutics, with a particular focus on their combined use in patients with a dual diagnosis [18–21].

Table 1: Comparison of Obesity and Type 2 Diabetes Mellitus (T2DM)

Parameter	Obesity	Type 2 Diabetes Mellitus (T2DM)
Definition	Excessive body fat accumulation (BMI ≥ 30)	Chronic hyperglycemia due to insulin resistance
Global Prevalence	Over 650 million adults; increasing globally	~537 million adults; projected to reach 783 million by 2045
Contributing Factors	Sedentary lifestyle, unhealthy diet	Insulin resistance, β-cell dysfunction
Associated Health Risks	Cardiovascular disease, kidney disease	Cardiovascular disease, nerve damage, kidney issues
Mechanisms	Inflammation, dysregulated adipokines	Impaired insulin signaling, inflammation, glucotoxicity
Prevalence Rates in Specific Regions	42.4% adults (U.S.); 14% men, 20% women (by 2030)	High rates in U.S., China (88.5 million), India (65.9 million)

Scoping the Problem: Epidemiological Features of Obesity and Type 2 Diabetes

In clinical obesity, the Body Mass Index (BMI) is defined as ≥30 kg/m², with the standard diagnostic threshold being ≥30 kg/m². However, this anthropometric indicator only scratches the surface of the extremely complex pathophysiology. The disorder is based on chronic positive energy balance, but the underlying factors are highly diverse, ranging from polygenic predisposition and neuroendocrine dysregulation to the corresponding impact of environmental factors that promote increased calorie intake and physical activity [22-24]. At the biochemical level, changes in fat depots, particularly in the visceral region, are transformed from passive storage tissue into an active endocrine organ. This transition alters the profile of adipokine secretion: leptin levels are disproportionately increased, while adiponectin levels, a key hormone that increases insulin sensitivity, decrease. Simultaneously, resident adipose tissue macrophages infiltrate hypertrophied adipocytes and release a cascade of proinflammatory mediators, primarily Tumor Necrosis Factor-alpha (TNF-α) and interleukin-6 (IL-6). This local inflammatory environment ultimately spreads systemically, creating a state of chronic, low-grade stress that directly antagonizes insulin receptor signaling in classic target tissues the liver, skeletal muscle, and the body's own adipocytes [25-29].

Concurrently, the pathophysiology of type 2 diabetes mellitus (T2DM) is based on a dual defect: peripheral insulin resistance, exacerbated by the progressive inability of pancreatic β-cells to maintain compensatory hyperinsulinemia. The molecular basis involves aberrant post-receptor signaling, in which serine phosphorylation in insulin receptor substrate (IRS) proteins mediates the canonical phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This results in a dual effect: impaired GLUT4-mediated glucose influx into myocytes and uncontrolled hepatic gluconeogenesis, which leads to increased blood glucose [30–33]. At the same time, persistent metabolic stress on β-cell layers, so-called glucolipotoxicity, perpetuates a vicious cycle of oxidative stress, Endoplasmic Reticulum (ER) stress, and ultimately cell apoptosis. This degenerative process is further enhanced by inflammatory signals originating from adipose tissue and obesity, in particular through the activation of stress-sensitive kinases such as JNK and NF-κB, which provide a direct molecular bridge between obesity and β-cell decompensation [34–37].

From an epidemiological perspective, the coincidence of these two conditions is not simply coincidental, but reflects a synchronized global health crisis. According to recent estimates, there are currently over 650 million obese adults worldwide—a figure that has nearly tripled since the mid-1970s [38–41]. Although historically, the epicenter of this epidemic was concentrated in wealthy, industrialized countries, it is now shifting decisively toward low- and middle-income regions, driven by rapid urbanization, sedentary workplaces, and the widespread availability of high-calorie, ultra-processed foods.

The United States provides a prime example: data from the 2017–2020 National Health and Nutrition Examination Survey (NHANES) show that 42.4% of adults met the BMI criteria for obesity, and another 9.2% fell into the severely obese category (BMI ≥40 kg/m²). Alarmingly, this trend is now clearly visible among younger age groups: 20.9% of children and adolescents suffer from this disease [42-44]. Extrapolating these trends to 2030, modeling studies project an alarming global picture: approximately 14% of men and 20% of women will be clinically obese, and the prevalence of BMI >30 kg/m², >35 kg/m², and >40 kg/m² will reach 18%, 6%, and 2% of the global population, respectively [45-47].

The epidemiological dynamics of type 2 diabetes mellitus reflect this upward trend with striking accuracy. According to current data, 537 million adults worldwide have diabetes, and this number is projected to increase to 783 million by 2045. The overlap between the two epidemics is particularly evident: epidemiological studies consistently show that more than 80% of people with type 2 diabetes are overweight or obese [48–50]. Regional hotspots further illustrate this connection. For example, Pacific island nations, including Fiji and American Samoa, have some of the highest age-standardized rates of type 2 diabetes in the world, while countries in Southeast Asia have seen a sharp increase in incidence over the past two decades. In absolute terms, the largest number of cases is concentrated in the world's most populous countries: China (88.5 million), India (65.9 million), and the United States (28.9 million) together account for a significant share of the global population with diabetes [50,51].

This bidirectional epidemiological synergy has significant implications for public health infrastructure. The combined burden of these two metabolic disorders is a major cause of the increasing incidence of macrovascular complications (coronary heart disease, cerebrovascular events) and microvascular sequelae (nephropathy, neuropathy, retinopathy), creating a huge and growing burden on healthcare systems worldwide [52–54]. Taken together, these data highlight the need for comprehensive screening, prevention, and treatment strategies that address obesity and type 2 diabetes not as isolated phenomena, but as interrelated manifestations of an overall metabolic syndrome.

Thermogenic Adipose Depots

Mammalian evolution has equipped certain adipose depots with a remarkable capacity to dissipate chemical energy as heat—a function that, in the context of modern caloric abundance, positions brown adipose tissue (BAT) and its inducible counterpart, beige (or "brite") fat, as compelling therapeutic targets against obesity and type 2 diabetes mellitus (T2DM). Unlike classical white adipocytes, which specialize in energy storage, brown adipocytes are densely packed with mitochondria and express high levels of uncoupling protein 1 (UCP1). This transmembrane protein creates a proton leak across the inner mitochondrial membrane, short-circuiting the electrochemical gradient that normally drives ATP synthesis and diverting the liberated energy toward thermogenesis [55-58]. Beige adipocytes, which emerge within white adipose tissue (WAT) depots in response to specific environmental or pharmacological cues most notably cold exposure and β-adrenergic stimulation can undergo a phenotypic transformation known as “browning.” This adaptive process entails a dramatic upregulation of UCP1, expansion of mitochondrial mass, and acquisition of a thermogenic molecular signature that mirrors that of classical brown fat [59-62].

At the molecular level, the thermogenic mechanism is primarily regulated by the sympathetic nervous system (SNS). Cold stress triggers central thermoregulatory circuits, which in turn increase the local release of norepinephrine. This catecholamine activates β3-adrenergic receptors on the surface of adipocytes, initiating the canonical cAMP/protein kinase A (PKA) signaling axis. Once activated, PKA phosphorylates hormone-sensitive lipase and perilipin, releasing lipolysis of intracellular triglyceride stores. The resulting free fatty acids serve a dual function: they act as oxidative substrates for mitochondrial β-oxidation, fueling the heat-generating cycle, and simultaneously function as allosteric activators of UCP1 itself. Beyond this acute response, PKA signaling also triggers a transcriptional cascade that amplifies a thermogenic program involving key regulators such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and PR domain-containing protein 16 (PRDM16), which together orchestrate mitochondrial biogenesis and maintain the expression of UCP1 and associated effector genes [63-72].

In the context of obesity, this finely tuned system is severely disrupted. A substantial body of evidence suggests that brown adipose tissue mass and resting metabolic rate are significantly reduced in obese individuals, and that brown adipose tissue capacity is also reduced. This functional decline is not simply a passive consequence of excess adiposity, but is actively driven by the inflammatory environment that accompanies weight gain. Adipose tissue macrophages and hypertrophic adipocytes themselves secrete a variety of proinflammatory cytokines, including TNF-α and IL-6, which suppress transcriptional networks required for brown adipogenesis and directly impair mitochondrial oxidative capacity in thermogenic adipocytes [73–76]. Concomitantly, the state of insulin resistance characteristic of both obesity and type 2 diabetes exacerbates this defect. Insulin normally facilitates glucose uptake by brown and beige adipocytes via GLUT4 translocation, providing a critical carbon source for both thermogenesis and de novo lipogenesis required to maintain the thermogenic cycle. When this signaling is disrupted, glucose supply to these tissues is reduced, depriving them of fuel and further reducing their thermogenic activity [77–80]. This metabolic impairment triggers a detrimental positive feedback loop: reduced energy dissipation promotes further fat accumulation, which exacerbates inflammatory and insulin-resistant states, which in turn further suppress brown adipose tissue activity. Therefore, disrupting this cycle has become a major research priority. Pharmacological or physiological interventions that activate the thermogenic program, such as chronic cold exposure, β3-adrenergic receptor agonists, or small-molecule activators of PGC-1α, consistently demonstrate beneficial metabolic effects in preclinical models, including increased energy expenditure, improved glycemic control, and increased insulin sensitivity [81–84]. These findings highlight the therapeutic potential of targeting thermogenic adipocytes, although translation into clinical practice remains an active area of research.

When considering type 2 diabetes mellitus (T2DM) specifically, the interplay between insulin resistance and brown adipose tissue (BAT) dysfunction reveals additional layers of complexity. In healthy individuals, insulin not only serves as a glucose-lowering hormone but also as a positive modulator of BAT function, upregulating UCP1 expression and maintaining mitochondrial activity. However, in the setting of insulin resistance in T2DM, this anabolic effect is lost. The reduced capacity of brown adipocytes to uptake glucose directly contributes to postprandial hyperglycemia, a hallmark of the disease, while the concomitant reduction in thermogenesis reduces 24-hour energy expenditure, further promoting weight gain and a worsening metabolic phenotype [85–87]. Furthermore, the sympathetic nervous system, which is required for BAT activation, exhibits diminished responsiveness in T2DM. This may result from downregulation of β3-adrenergic receptors on the adipocyte surface, defective intracellular signaling downstream of the receptor, or both. Regardless of the precise mechanism, the end

result is a reduced capacity for thermogenic responses to cold or food stimuli, effectively rendering brown adipose tissue metabolically "deaf" to its primary activating signals [88-92].

Parallel to these signaling defects, obesity and type 2 diabetes mellitus cause severe disturbances in lipid metabolism in thermogenic adipocytes. Brown and beige cells utilize fatty acids released from their own triglyceride stores as the primary substrate for thermogenesis. However, the systemic lipotoxic environment characteristic of these metabolic disorders marked by elevated levels of circulating free fatty acids leads to ectopic lipid accumulation in lean tissues and, critically, to the infiltration of lipid metabolic intermediates into brown adipocytes themselves. This lipid overload induces mitochondrial damage via oxidative stress and disrupts the electron transport chain, directly compromising the integrity of the thermogenic apparatus. The resulting “mitochondrial dysfunction” is the hallmark of metabolic inflexibility: an impaired ability to switch between carbohydrate and lipid oxidation, characteristic of obesity and type 2 diabetes. Furthermore, brown adipose tissue activation by cold exposure is significantly attenuated in affected individuals, partly due to impaired mitochondrial biogenesis and partly due to deficits in upstream signaling pathways that normally regulate the adaptive thermogenic response [93–99]. Taken together, these data allow us to view brown adipose tissue and beige adipose tissue not as passive observers, but as active determinants of metabolic fate. Their dysfunction is both a consequence and a contributing factor to the development of metabolic syndrome, and restoring their thermogenic capacity represents a conceptually attractive, albeit technically challenging, therapeutic intervention.

Links between Obesity and Hyperglycemia

Metabolic Storm

The transition from uncomplicated obesity to overt type 2 diabetes mellitus (T2DM) is not a linear process, but rather a convergence of multiple, interconnected biochemical abnormalities. At the core of this pathological cascade is the transformation of excess adipose tissue particularly visceral adipose tissue from a passive energy reservoir into an aggressively active endocrine and paracrine organ. This hypertrophied tissue mass secretes a complex cocktail of bioactive mediators: Adipokines, Free Fatty Acids (FFA), inflammatory cytokines, and chemotactic factors, which collectively alter the systemic metabolic landscape [100–102]. Among the most significant changes is a profound shift in the adipokine secretion profile. In adipose tissue, obesity significantly increases leptin production. However, this increase is paradoxically accompanied by central leptin resistance, rendering the hormone ineffective in suppressing appetite and maintaining positive energy balance. Conversely, the secretion of adiponectin a pleiotropic adipokine with potent insulin-sensitizing and anti-inflammatory effects is sharply reduced. This dual imbalance creates a favorable environment for the development of insulin resistance, which serves as the fundamental fulcrum around which the relationship between obesity and type 2 diabetes revolves [103–105].

Lipotoxicity and Impaired Insulin Signaling

The concept of lipotoxicity describes the detrimental effects of chronic excess free fatty acids (FFA) on lean tissues. In obesity, uncontrolled lipolysis from increased fat stores floods the circulation with FFA, which is then actively taken up by the liver and skeletal muscle—tissues not evolutionarily adapted to such lipid loads. In hepatocytes, this FFA load stimulates de novo triglyceride synthesis and accumulation, leading to hepatic steatosis. This fatty infiltration reduces the liver's ability to adequately regulate gluconeogenesis, contributing to fasting hyperglycemia [106–108]. In myocytes, the picture is even more complex. FFA are converted into bioactive lipid intermediates, primarily diacylglycerol (DAG) and ceramides. These metabolites directly activate new isoforms of protein kinase C (PKC), which in turn phosphorylate key serine residues on Insulin Receptor Substrate (IRS) proteins. This serine phosphorylation sterically interferes with canonical tyrosine phosphorylation of IRS, effectively uncoupling the insulin receptor from its downstream effectors. The subsequent disruption of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling axis prevents GLUT4 translocation to the plasma membrane, dramatically reducing insulin-stimulated glucose uptake by muscle. This results in a state of severe peripheral insulin resistance, leading to compensatory hyperinsulinemia—a characteristic feature of the early stage of metabolic decompensation [109–111].

Inflammation as a Self-Sustaining Mechanism for the Development of Insulin Resistance

The inflammatory aspect of obesity is no less important. Hypertrophied adipocytes, under conditions of hypoxia and mechanical stress, attract and activate adipose tissue macrophages (ATM), which switch to a proinflammatory M1 phenotype.

Together with the adipocytes themselves, these cells become abundant sources of TNF-α, IL-6, and resistin—cytokines that act as molecular antagonists of insulin action [112–114]. These inflammatory mediators interact with their corresponding receptors on target cells and trigger two converging stress signaling cascades: the c-Jun N-terminal kinase (JNK) pathway and the nuclear factor kappa B (NF-κB) pathway. JNK directly phosphorylates IRS proteins at serine residues, reproducing the inhibitory effect observed with lipid intermediates and further attenuating insulin signaling. NF-κB, on the other hand, acts as a master transcriptional regulator, stimulating the expression of additional proinflammatory genes and perpetuating a vicious cycle of increasing inflammation. This vicious cycle is exacerbated by endoplasmic reticulum (ER) stress, a condition that occurs when the ER's protein-folding capacity is overwhelmed by excess nutrients and lipids characteristic of obesity. ER stress activates the unfolded protein response (UPR), which in turn enhances JNK and NF-κB signaling, creating a three-way intersection lipotoxicity, inflammation, and ER stress—that collectively maintains insulin resistance [115,116].

Enteroendocrine and Microbial Aspects

Beyond these classical mechanisms, the association between obesity and type 2 diabetes extends to the gut, where enteroendocrine and microbial factors modulate systemic metabolism. Incretin hormones, particularly glucagon-like peptide-1 (GLP-1), play a key role in postprandial glucose homeostasis by enhancing glucose-stimulated insulin secretion and suppressing glucagon release. However, the effect of incretins is significantly attenuated in many obese individuals, representing an early defect that exacerbates hyperglycemia and promotes β-cell depletion. The mechanisms underlying this impairment are multifactorial and include decreased L-cell secretion, accelerated enzymatic degradation by dipeptidyl peptidase-4 (DPP-4), and decreased receptor sensitivity on pancreatic β-cells [117–119]. Concurrently, obesity-induced changes in the gut microbiome—so-called dysbiosis—have emerged as a significant factor contributing to metabolic endotoxinemia. Dysbiosis disrupts the integrity of the intestinal barrier, facilitating the translocation of bacterial lipopolysaccharides (LPS) into the portal circulation. This LPS load activates Toll-like receptor 4 (TLR4) on immune cells and hepatocytes, triggering a strong inflammatory response that further exacerbates systemic insulin resistance. This intestinal-derived inflammatory process synergizes with adipose-induced inflammation, creating a dual attack on insulin sensitivity [120–122].

Mitochondrial Overload and Oxidative Stress

Finally, mitochondrial dysfunction represents a unifying downstream mechanism that perpetuates the cycle of metabolic deterioration. In obesity, chronic excess lipid delivery to oxidative tissues skeletal muscle and the liver—overwhelms the capacity of the electron transport chain to handle the electron flow. This imbalance triggers excessive formation of reactive oxygen species (ROS), which cause oxidative damage to mitochondrial DNA, proteins, and lipid membranes. The resulting mitochondrial inefficiency not only reduces fatty acid oxidation but also amplifies intracellular stress signals, which converge on the same JNK and NF-κB pathways discussed above, exacerbating insulin resistance. In adipose tissue itself, mitochondrial dysfunction impairs adipocyte differentiation and lipid storage capacity, promoting ectopic lipid deposition in muscle tissue and further increasing the lipotoxic load [123–125]. Thus, mitochondrial dysfunction is both a consequence and a contributing factor to the development of metabolic syndrome, linking various mechanisms into a self-sustaining network that leads to the progression of obesity to type 2 diabetes.

Therapeutic Interactions: How Treatments for One Disease Alter the Treatment of Another

The clinical management of obesity and type 2 diabetes mellitus (T2DM) is characterized by a remarkable degree of therapeutic overlap, yet the bidirectional effects of specific interventions often produce outcomes that are either synergistic or unexpectedly antagonistic. The available armamentarium spans three broad tiers lifestyle modification, pharmacotherapy, and metabolic/bariatric surgery each operating through distinct mechanisms, with differential impacts on weight, glycemic control, and the interconnected pathophysiology that binds these two disorders [126,127].

Lifestyle Change as a Fundamental Principle

Diet and physical activity modification remain the cornerstone of first-line therapy for both conditions, not only because of their effectiveness but also because they address the underlying behavioral drivers of obesity. Evidence-based dietary protocols typically include calorie restriction, reduced intake of refined carbohydrates and saturated fats, and increased intake of fiber-rich vegetables, whole grains, and lean proteins. Comparative studies have shown that both low-carbohydrate (including ketogenic) and low-fat regimens result in significant weight loss and metabolic improvements, although long-term success is often determined by individual adherence. Notably, diets such as the Mediterranean or DASH (Dietary Approaches

to Stop Hypertension) diets provide additional cardiovascular protection beyond blood glucose control, making them particularly attractive for patients at high risk of metabolic disorders [128–130]. Physical activity complements dietary efforts; Aerobic exercise walking, running, cycling enhances insulin-stimulated glucose uptake and promotes fat oxidation, while resistance training offsets the loss of muscle mass that accompanies calorie restriction, thereby preserving resting energy expenditure. Despite these well-documented benefits, lifestyle interventions face a fundamental reality: consistent adherence is extremely difficult to maintain, and the achieved weight loss is often modest, typically insufficient for patients with severe obesity or long-standing type 2 diabetes. Consequently, lifestyle interventions alone are rarely sufficient for this subgroup, necessitating the use of pharmacological or surgical strategies [131–133].

Pharmacotherapy: Two Sides of the Same Coin

When lifestyle modification measures prove insufficient, pharmacotherapy becomes a critical adjunct. The current pharmacopoeia for the treatment of obesity and type 2 diabetes includes drugs that affect appetite regulation, nutrient absorption, insulin secretion, and renal glucose handling each with its own advantages and disadvantages.

In obesity, the lipase inhibitor orlistat reduces fat absorption from food by approximately 30%, providing modest but clinically significant weight loss. However, its gastrointestinal side effect profile limits tolerability. More significantly, the class of GLP-1 receptor agonists, including liraglutide and high-dose semaglutide, has changed the landscape of obesity treatment. These drugs mimic the action of endogenous GLP-1, exerting pleiotropic effects: glucose-dependent enhancement of insulin secretion, delayed gastric emptying, increased central nervous system-mediated satiety, and, in some cases, decreased hedonic eating behavior. In the SUSTAIN and STEP trials, semaglutide was found to be the most effective weight loss agent among non-surgical methods, achieving 15-17% body weight loss in some groups [134-136]. The extended-release combination of phentermine and topiramate represents another mechanistic approach, combining noradrenergic appetite suppression (phentermine) with topiramate-mediated GABA-glutamate modulation, although its use is limited by potential cognitive and cardiovascular side effects [137-139].

The pharmacopoeia for type 2 diabetes mellitus is also diverse. Metformin remains the drug of choice, primarily reducing hepatic gluconeogenesis and modestly improving peripheral insulin sensitivity. Sulfonylureas and meglitinides stimulate pancreatic insulin secretion but carry risks of hypoglycemia and weight gain. Thiazolidinediones (TZDs), such as pioglitazone, activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), promoting fatty acid sequestration in adipose tissue, reducing circulating lipid load, and attenuating lipotoxic inhibition of insulin signaling. However, the use of TZDs is complicated by fluid retention, weight gain, and an increased risk of heart failure, limiting their use in vulnerable populations [140–142]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors empagliflozin, canagliflozin, and dapagliflozin offer a mechanistically orthogonal approach: they block renal glucose reabsorption, inducing glycosuria, lowering plasma glucose levels, and leading to modest weight loss. Importantly, the EMPA-REG and CANVAS trials have established cardiovascular and renoprotective effects beyond glycemic control, making this class of drugs a preferred option for patients with existing cardiovascular disease. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, preserve endogenous incretin activity by preventing GLP-1 degradation, but their potency is relatively low and they lack the weight loss benefits of GLP-1 receptor agonists [143–145]. Insulin therapy, although universally effective for glycemic control, is usually delayed until later stages of the disease because of the need for dose titration, monitoring for hypoglycemia, and the paradoxical weight gain that often accompanies improvement in glycemia a particularly undesirable effect in patients who are already obese [146,147].

Bariatric Surgery

In patients with severe obesity and poorly controlled type 2 diabetes, bariatric surgery consistently provides superior and more sustainable results compared to medical therapy alone. The three most common procedures Roux-en-Y gastric bypass (RYGB), Sleeve Gastrectomy (SG), and Adjustable Gastric Banding (AGB) are fundamentally different in their anatomical effects and metabolic consequences.

RYGB is widely considered the gold standard and involves creating a small gastric pouch that reroutes the proximal small intestine. This procedure restricts caloric intake while simultaneously altering neurohumoral signaling from the gut. The resulting increase in postprandial secretion of GLP-1 and peptide YY (PYY), coupled with decreased ghrelin levels, leads to significant appetite suppression and sustained weight loss. Notably, some studies report type 2 diabetes remission rates of up to 70–80% after RYGB, often occurring within days or weeks of surgery before significant weight loss—emphasizing the primary role of enteroendocrine mechanisms in glycemic restoration [148–150].

Sleeve gastrectomy, currently the most commonly performed bariatric procedure worldwide, involves resection of approximately 80% of the fundus and body of the stomach, leaving a narrow gastric tube. In addition to mechanical restriction, sleeve gastrectomy reduces ghrelin (the "hunger hormone") production and enhances postprandial GLP-1 and PYY responses. Weight loss and metabolic benefits are comparable to RYGB, although sleeve gastrectomy may be associated with slightly lower type 2 diabetes remission rates and a higher risk of gastroesophageal reflux [151,152]. Adjustable gastric banding (AGB) the placement of an inflatable silicone ring around the gastric cardia offers a less invasive, reversible, and adjustable alternative. It restricts food intake by slowing gastric emptying and inducing early satiety. However, its metabolic efficiency is significantly lower: weight loss is more modest, remission rates for type 2 diabetes are significantly lower, and long-term complications (band dislodgment, erosion, and port-site infections) have led to a decline in its use in favor of RYGB and SG [153-155].

The metabolic benefits of bariatric surgery extend beyond weight loss. Improved insulin sensitivity, reduced levels of circulating proinflammatory cytokines, and improved β-cell function collectively contribute to impressive clinical outcomes. However, surgical interventions are associated with risks perioperative complications, nutritional deficiencies, and, in the case of RYGB, dumping syndrome and the potential for prolonged hypoglycemia requiring careful patient selection and lifelong follow-up [156–158].

Synthesis of the Therapeutic Spectrum

In practice, these three therapeutic levels should not be viewed as mutually exclusive, but rather as sequential or complementary elements of an integrated treatment pathway. Lifestyle interventions form the foundation of all treatment plans, providing basic health benefits that enhance the effectiveness of subsequent pharmacological or surgical approaches. Pharmacotherapy fills a gap for patients who do not respond adequately to lifestyle modifications alone, with GLP-1 receptor agonists offering a particularly attractive option due to their dual effects on weight and glycemia. Bariatric surgery remains the definitive treatment for patients with more advanced disease, providing results that currently exceed those achievable with any pharmacological regimen. The optimal strategy ultimately depends on patient-specific factors: BMI, diabetes duration, cardiovascular risk profile, and individual preferences. Growing evidence supports the 'step-by-step treatment' approach, although emerging evidence suggests that early surgical intervention in selected patients may provide more effective long-term metabolic protection [159-162].

Table 2: Therapeutic Strategies for Managing Obesity and T2DM

Therapeutic Approach	Description	Target Conditions	Strengths	Limitations
Lifestyle Interventions	Dietary changes, physical activity	Obesity, T2DM	Foundation of treatment; broad health benefits	Requires long-term commitment; modest weight loss for some
Pharmacotherapy	Medications (e.g., GLP-1 agonists, metformin)	Obesity, T2DM	Effective for some patients; enhances weight loss and glucose control	Possible side effects; not suitable for all patients
Bariatric Surgery	Procedures like RYGB and sleeve gastrectomy	Severe obesity, T2DM	Most effective for weight loss and T2DM remission	Risks and complications; reserved for severe cases

Conclusion

In conclusion, the interrelationship between obesity and type 2 diabetes mellitus (T2DM) underscores the complexity of these prevalent metabolic disorders and their significant public health implications. The escalating prevalence of both conditions necessitates a multifaceted approach to prevention and treatment, emphasizing the importance of early intervention and comprehensive management strategies. We have highlighted the pivotal role of insulin resistance, chronic low-grade inflammation, and metabolic dysregulation as central mechanisms linking obesity and T2DM.

The current therapeutic landscape encompasses lifestyle modifications, pharmacotherapy, and surgical options, each with its strengths and limitations. Lifestyle interventions remain crucial as the first line of treatment, promoting not only weight loss but also improved metabolic health. Pharmacological advancements offer additional support for individuals struggling to achieve their health goals. Meanwhile, bariatric surgery has emerged as a highly effective option for patients with severe obesity and T2DM, though it is not without risks and considerations.

Future research should continue to explore the biochemical pathways connecting these disorders and the potential for novel therapeutic interventions. A better understanding of the genetic, metabolic, and environmental factors at play will inform

personalized treatment approaches and ultimately enhance patient outcomes. By addressing the shared pathogenesis of obesity and T2DM, healthcare providers can develop innovative strategies to reduce the burden of these interconnected non-communicable diseases, paving the way for improved global health.

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Ethics

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Conflicts of Interest

The authors declare no conflict of interest.

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