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Review

Obesity: Genetic Insights, Therapeutic Strategies, Pharmacoeconomic Impact, and Psychosocial Dimensions

Gladious Naguib El-hadidy [1], Youssef Basem [2], Mahmoud M. Mokhtar [3], Salma A. Hamed [3], Sara M. Abdelstar [4], Abdelrhman R. Nasef [5] and Rehab Abdelmonem [3,*]

[1] Department of Pharmaceutics, College of Pharmaceutical Sciences and Drug Manufacturing, Misr University for Science and Technology (MUST), Giza 12566, Egypt; gladuos.nageeb@must.edu.eg
[2] Medical and Pharmaceutical Industrial Biotechnology Department, College of Biotechnology, Misr University for Science and Technology (MUST), Giza 12566, Egypt; 200025117@must.edu.eg
[3] Industrial Pharmacy Department, College of Pharmaceutical Sciences and Drug Manufacturing, Misr University for Science and Technology (MUST), Giza 12566, Egypt; 59054@must.edu.eg (M.M.M.); 200052241@must.edu.eg (S.A.H.)
[4] Faculty of Pharmacy, Zagazig University, Zagazig 44519, Egypt; 20612022200211@pharmacy.zu.edu.eg
[5] Faculty of Pharmacy, Al-Azhar University, Assiut 71524, Egypt; abdalrhmanredanasef@gmail.com
* Correspondence: rehab.abdelmonem@must.edu.eg

Abstract

Obesity has emerged as one of the most complex and urgent public health challenges of the twenty-first century, driven by genetic, environmental, metabolic, and psychosocial determinants that collectively disturb energy homeostasis and systemic health. It is characterized by adipose tissue dysfunction, insulin resistance, chronic low-grade inflammation, and gut microbiota dysbiosis, all of which interact to perpetuate metabolic and cardiovascular diseases. Beyond the biological dimension, obesity profoundly affects mental health, being closely linked to depression, anxiety, body-image dissatisfaction, and stigma, which further reduce adherence to treatment. Current therapeutic strategies rely on a stepped-care approach, beginning with lifestyle interventions encompassing dietary modification, physical activity, and behavioral therapy. Pharmacologic treatments, particularly incretin-based agents such as semaglutide, liraglutide, and tirzepatide have transformed medical management through substantial and sustained weight loss, while bariatric surgery remains the most effective long-term option for severe obesity. Emerging approaches, including gene therapy, microbiome modulation, and nanomedicine, offer mechanistically targeted and potentially safer alternatives, though they remain largely experimental. Pharmacoeconomic analyses support the cost-effectiveness of combining behavioral, pharmacological, and surgical modalities, highlighting the economic advantage of integrated care models. Meanwhile, artificial intelligence and machine learning are redefining obesity research and management, enhancing cancer risk prediction, personalizing pharmacotherapy, optimizing resource allocation, and enabling precision medicine through multi-omics and imaging integration. Collectively, these insights support a shift toward a learning health-system paradigm that unites mechanistically anchored therapies with digital and AI-driven personalization to achieve sustainable weight reduction, reduce cardiometabolic and cancer burden, and improve global health outcomes.

Keywords: obesity; incretin-based pharmacotherapy; bariatric surgery; gut microbiota; gene therapy; nanomedicine; pharmacoeconomics; artificial intelligence; machine learning; precision medicine

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1. Introduction

Globally, obesity has become one of the most pressing public health challenges of the 21st century. The prevalence of obesity has nearly tripled since 1975, and recent analyses indicate that more than one billion people worldwide are now living with obesity, including approximately 880 million adults and 160 million children and adolescents [1]. According to the NCD Risk Factor Collaboration, global obesity prevalence increased across nearly all regions between 1990 and 2022, with particularly rapid growth in low- and middle-income countries undergoing nutrition transition [1]. Environmental, behavioral, and socioeconomic factors including urbanization, ultra-processed food consumption, sedentary lifestyles, and reduced sleep have all contributed to this alarming rise [2,3].

Obesity is a multifactorial, chronic disease characterized by abnormal or excessive accumulation of body fat that presents a risk to health. It is typically defined using body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg/m^2). The World Health Organization (WHO) defines overweight as a BMI $\geq$ 25 kg/m^2 and obesity as a BMI $\geq$ 30 kg/m^2, though some regions, particularly in Asia, use lower cut-offs due to higher cardiometabolic risk at lower BMI levels. For children and adolescents, the International Society for Pediatric and Adolescent Diabetes (ISPAD/ISDS) defines overweight and obesity based on age- and sex-specific BMI percentiles, with overweight typically classified as BMI $\geq$85th percentile and obesity as BMI $\geq$ 95th percentile [4]. Beyond BMI, emerging approaches emphasize waist circumference, visceral adiposity, and body composition to better capture metabolic risk [4].

The health consequences of obesity are extensive. It is a leading risk factor for type 2 diabetes, cardiovascular diseases, hypertension, stroke, non-alcoholic fatty liver disease (NAFLD), osteoarthritis, certain cancers, and mental health disorders [5]. High BMI ranks among the top global causes of premature death and disability, accounting for over 5 million deaths and more than 160 million disability-adjusted life years (DALYs) in 2019 [6]. Moreover, obesity exacerbates vulnerability to infectious diseases, as evidenced during the COVID-19 pandemic where individuals with obesity had higher rates of hospitalization and mortality [7].

In addition to its public health burden, obesity poses a substantial economic challenge worldwide. The total global economic impact of overweight and obesity was estimated at US$2 trillion annually in 2022, equivalent to about 2.4% of global GDP [8]. The economic costs include direct healthcare expenses (diagnosis, treatment, and management of obesity-related comorbidities) and indirect costs such as productivity loss, absenteeism, and premature mortality [9]. Without effective interventions, these costs are projected to rise dramatically, placing additional strain on healthcare systems, particularly in developing countries [10].

Addressing obesity thus requires a comprehensive and multisectoral approach that encompasses prevention, early detection, clinical management, and policy interventions aimed at promoting healthy food environments and physical activity. The subsequent sections of this review discuss the definition, global prevalence trends, health impacts, and economic implications of obesity, highlighting the need for evidence-based strategies to mitigate this growing epidemic.

2. Pathophysiology and Mechanisms of Obesity

Obesity is a multifactorial disorder characterized not merely by excess fat accumulation but by profound disturbances in metabolic, hormonal, and inflammatory homeostasis. It arises from a complex interplay between adipose tissue dysfunction, insulin resistance, chronic low-grade inflammation, and gut microbiota imbalance. These interconnected mechanisms create a self-perpetuating cycle that exacerbates metabolic stress and increases

the risk of cardiometabolic diseases. The following sections outline the key molecular and physiological pathways underlying the pathogenesis of obesity.

2.1. Insulin Resistance and Metabolic Stress

Insulin resistance is one of the earliest and most critical pathophysiological features of obesity. Expansion of adipose tissue promotes lipolysis and the release of free fatty acids (FFAs), which disrupt insulin signaling in skeletal muscle and liver, impairing glucose uptake and promoting hepatic gluconeogenesis [11,12]. In parallel, oxidative stress and endoplasmic reticulum (ER) stress in hypertrophic adipocytes activate stress kinases such as JNK and IKKβ, which phosphorylate IRS1 on inhibitory serine residues, blocking PI3K/Akt signaling [13,14]. Chronic hyperinsulinemia contributes further to de novo lipogenesis and ectopic fat deposition, sustaining a vicious metabolic cycle [15,16].

2.2. Adipokines and Hormonal Regulation

Adipose tissue acts as an endocrine organ, secreting adipokines that regulate systemic energy homeostasis. Leptin, secreted in proportion to fat mass, should suppress appetite and increase energy expenditure, but obesity induces leptin resistance through impaired transport across the blood–brain barrier and SOCS3-mediated hypothalamic signaling blockade [17,18]. Adiponectin, normally protective via AMPK activation and anti-inflammatory effects, is markedly reduced in obesity, exacerbating insulin resistance [19]. Pro-inflammatory adipokines such as resistin, chemerin, MCP-1, and visfatin amplify metabolic dysfunction by recruiting macrophages and enhancing local inflammation [20,21]. Novel adipokines like WISP1 and SFRP5 have also been implicated in adipose fibrosis and systemic insulin resistance, expanding the therapeutic landscape [22,23].

2.3. Ghrelin and Appetite Dysregulation

Ghrelin, the "hunger hormone" secreted mainly by the stomach, is critical for appetite stimulation and energy storage. Normally, ghrelin levels rise pre-prandially and fall after meals; however, in obese individuals, postprandial suppression is blunted, sustaining hunger and caloric intake [24,25]. Moreover, central nervous system sensitivity to ghrelin appears diminished, reducing the efficiency of appetite feedback regulation [26]. Ghrelin also interacts with AMPK and other metabolic sensors, linking appetite control to systemic energy balance [27].

2.4. Hypothalamic Inflammation and Disruption of Satiety Signaling

Emerging evidence indicates that high-fat diets (HFDs) elicit hypothalamic inflammation, which plays a pivotal role in the dysregulation of energy homeostasis and appetite control. Chronic exposure to dietary saturated fats triggers activation of microglia and astrocytes within the arcuate nucleus of the hypothalamus, leading to the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [28]. These mediators interfere with the leptin–melanocortin pathway by impairing leptin receptor signaling and suppressing pro-opiomelanocortin (POMC) neuron activity, thereby diminishing satiety responses [29]. Consequently, the brain becomes resistant to leptin's anorexigenic effects, promoting hyperphagia, positive energy balance, and progressive weight gain. Furthermore, hypothalamic endoplasmic reticulum stress and activation of stress-responsive kinases such as JNK and IKKβ amplify neuronal injury and sustain the inflammatory state. Collectively, diet-induced hypothalamic inflammation represents a crucial mechanistic link between nutrient excess and central leptin resistance, offering a potential therapeutic target for obesity prevention and treatment [28,29].

2.5. Hypothalamic Inflammation as a Link Between Obesity and Mental Health Disorders

Recent insights highlight hypothalamic inflammation as a critical neurobiological bridge connecting obesity with mental health disturbances such as depression, anxiety, and cognitive decline. Chronic activation of microglia and astrocytes in response to high-fat diet–induced metabolic stress alters hypothalamic–pituitary–adrenal (HPA) axis activity, promoting hypercortisolemia and emotional dysregulation [28]. Inflammatory mediators, including TNF-α, IL-6, and IL-1β, can cross the blood–brain barrier or signal through vagal afferents, disrupting monoaminergic neurotransmission and neuroplasticity in mood-regulating regions such as the hippocampus and prefrontal cortex [30]. Moreover, leptin resistance secondary to hypothalamic injury impairs leptin's neuromodulator functions normally exerting antidepressant and anxiolytic effects thereby contributing to mood vulnerability [31]. This neuroinflammatory–metabolic axis underscores how obesity is not merely a peripheral metabolic disorder but a systemic and neuropsychiatric condition, highlighting the need for integrative therapeutic strategies that target both metabolic and neuroinflammatory pathways [28,30,31].

2.6. Role of Satiety Signals and Reward Pathways in the Brain

Energy intake and feeding behavior are tightly regulated by a complex interplay between homeostatic satiety signals and hedonic reward pathways. Hypothalamic neurons, particularly those expressing pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP), integrate peripheral signals such as leptin, insulin, ghrelin, and peptide YY to maintain energy balance [32]. Dysregulation of these pathways in obesity, including leptin and insulin resistance, impairs satiety signaling and promotes overconsumption.

Concurrently, mesolimbic dopaminergic circuits, encompassing the ventral tegmental area (VTA) and nucleus accumbens (NAc), mediate the hedonic aspects of feeding by encoding the rewarding properties of palatable food [33]. High-fat and high-sugar diets enhance dopamine release in these regions, increasing the motivational drive for food consumption, even in the absence of energy deficit. Furthermore, crosstalk between hypothalamic satiety neurons and reward circuits modulates both the pleasure derived from eating and homeostatic regulation, creating a feedback loop that reinforces overeating [33]. Disruption of this balance underlies compulsive-like feeding behaviors observed in obesity and suggests potential targets for neuromodulatory or pharmacological interventions aimed at normalizing reward processing and restoring satiety responsiveness.

2.7. Chronic Low-Grade Inflammation ("Meta Inflammation")

Obesity is associated with chronic low-grade inflammation, or "meta inflammation" characterized by infiltration of adipose tissue by immune cells such as M1 macrophages and activated T cells. These immune populations secrete TNF-α, IL-6, IL-1β, and MCP-1, which impair insulin signaling and propagate systemic inflammation [34,35]. Adipose hypoxia due to inadequate vascularization induces HIF-1α activation, stimulating fibrotic remodeling and perpetuating local inflammation [36,37]. Concurrently, oxidative stress and ER stress activate NF-κB and JNK pathways, linking metabolic overload to immune dysregulation [38,39].

2.8. Gut Microbiota Dysbiosis

The gut microbiota plays a pivotal role in modulating host immunity and metabolism. Obesity often correlates with dysbiosis, reflected in reduced microbial diversity and altered Firmicutes/Bacteroidetes ratios [40,41]. Dysbiosis compromises epithelial integrity, increasing intestinal permeability and allowing translocation of lipopolysaccharide (LPS) into circulation, which activates TLR4 signaling in adipose and hepatic tissue [27]. Mi-

crobial metabolites such as short-chain fatty acids (SCFAs) normally exert protective anti-inflammatory and insulin-sensitizing effects, but are altered in obesity [9]. Similarly, bile acid metabolism is disrupted, impairing FXR and TGR5 signaling [42]. Beneficial species such as *Akkermansia muciniphila* are often depleted, reducing mucosal protection and exacerbating inflammation [27,43].

2.9. Integration and Therapeutic Implications

Obesity's pathophysiology represents a synergistic loop in which adipokine imbalance, insulin resistance, chronic inflammation, and gut microbiota dysbiosis reinforce one another [35,38]. Animal models show that transplantation of microbiota from obese donors induces obesity and insulin resistance in germ-free mice, underscoring causality [26,27]. In humans, interventions such as probiotics, prebiotics, high-fiber diets, and fecal microbiota transplantation have shown promise, though results remain variable [41]. Breaking the vicious cycle may require multi-targeted approaches that combine metabolic modulation, anti-inflammatory therapies, and microbiome remodeling [11,16].

3. Psychological and Mental Health Aspects

Obesity is not just a physical health condition; it also has psychological and mental health aspects. This section explores the highly prevalent mental health disorders that coexist with obesity, such as depression, anxiety, and eating disorders, showing the bidirectional relation between these disorders and obesity. It also discusses the relation between elevated levels of stigma and body concerns and lower quality of life. Finally, the section addresses the way that these psychological barriers and comorbidities have a significant impact on adhering to treatment plans.

3.1. Psychological Comorbidities of Obesity

There is a bidirectional relationship between depression and body weight across both males and females, as individuals experiencing depression tend to have higher body weight than those without depression. Conversely, individuals with elevated body weight face an increased likelihood of developing depression [44]. The same correlation applies to children as well. A recent study, which evaluated symptoms of depression and anxiety in a total of 4098 children aged 6–9, demonstrated that childhood obesity or overweight is independently associated with more than a twofold increased probability of exhibiting depression and anxiety [45]. Correspondingly, a prospective study examining a comprehensive lifestyle intervention across multiple disciplines showed a notable decrease in both depression and anxiety scores, especially among children with obesity [46].

Another link between depression and obesity can be attributed to limited daily functioning, including insufficient physical activity, relationship problems, increased susceptibility to emotional and physical abuse, and the strain of obesity-related medical complications. These factors collectively generate persistent frustration and chronic stress [47].

Obesity is also associated with a significantly higher risk of developing eating disorders (EDs). A recent study that included 3504 participants has found that nearly 20% of those considered overweight or obese exhibit this increased risk, wherein obese individuals demonstrate significantly higher ED scores compared with normal-weight individuals [48]. Typical psychological factors, such as low self-esteem, negative self-evaluation, and, notably, strong body dissatisfaction, may predispose both obesity and eating disorders. This complex mental health comorbidity is often described as a bidirectional relationship [49].

From a biological perspective, a mechanism explaining the connection between obesity and depression is the pro-inflammatory cytokines produced by adipocytes and related

inflammatory conditions. These cytokines have the capacity to impact brain physiology directly and can contribute to the onset of depression [44].

3.2. Stigma, Body Image, and Quality of Life

Health-related quality of life (HRQoL) declines as body mass index (BMI) increases; however, this decline is negligible when comparing individuals with a normal weight to those who are overweight. The substantial reduction in HRQoL becomes apparent at higher levels of obesity. Studies show that people who are obese, even without chronic diseases or long-term conditions (LTCs), are more likely to have an unhealthy future, as their high BMI is already affecting their quality of life and making them vulnerable to developing future LTCs [50].

In a recent study, researchers evaluated 2350 participants aged between 4 and 18 years. Regarding HRQoL, they noted deteriorating scores in physical well-being and psychological well-being as body mass index standard deviation scores (BMI-SDS) increased [51]. Multiple studies have documented that people living with obesity frequently encounter ongoing discrimination across various contexts, including workplaces, schools, and even medical facilities. Those with obesity have been found to receive lower initial wages, be perceived as less competent, and work longer hours compared to their thinner colleagues [52].

The effects of stigma based on weight have deep repercussions on physical and mental health, particularly in youth with overweight or obesity who regularly experience bullying, teasing, and rejection. Studies show that stigma itself regardless of actual body weight is strongly associated with psychological difficulties such as depression, anxiety, low self-esteem, and substance use, in addition to promoting unhealthy eating behaviors such as binge eating. Moreover, the experience of weight stigma relates to adverse physical health practices, such as decreased exercise, unhealthy diets, and sedentary habits, which, paradoxically, lead to further weight increase and elevate the long-term risk of developing conditions like type 2 diabetes and cardiovascular disease [53].

3.3. Impact on Adherence to Treatment

Studies have found that psychological barriers such as depression and anxiety lead to a lack of interest, confidence, motivation, and self-discipline, which in turn leads to difficulty with adherence to long-term treatments that involve more physical activity and a healthy diet and lifestyle [54,55]. Depressive and anxiety disorders are also found to have an impact on the selection of the type of treatment (surgical or nonsurgical) in obese patients, In one study, it was found that obese patients with severe anxiety favored the surgical intervention and selected bariatric surgery as a more rapid solution to eliminate factors that trigger and intensify their anxiety, rather than addressing the anxiety appropriately.

Therefore, psychiatric evaluation and intervention must occur before and after management of obesity to optimize outcomes. Lack of these psychosocial interventions in the management of obesity may be responsible for some of the observed adverse outcomes, highlighting the need for increased patient-focused interventions [50].

3.4. Maternal Health and Pregnancy Outcomes

Obesity exerts a profound impact on maternal health, significantly increasing the risk of gestational diabetes mellitus (GDM), preeclampsia, and cesarean delivery, as well as postpartum complications such as infections and hemorrhage [56]. Excess maternal adiposity alters placental function and endocrine signaling, promoting insulin resistance and chronic low-grade inflammation that may impair fetal growth and development [57]. Moreover, intrauterine exposure to maternal obesity is associated with long-term metabolic programming in offspring, predisposing them to obesity, type 2 diabetes, and cardiovascular disease

later in life [58]. Addressing obesity in women of reproductive age is therefore essential to mitigate these intergenerational risks and improve both maternal and neonatal outcomes.

4. Current Therapeutic Approaches

Obesity management requires a multifaceted approach that addresses its genetic, metabolic, and behavioral roots. Current strategies integrate lifestyle modification, pharmacotherapy, and bariatric surgery, aiming not only for weight reduction but also for improvement in metabolic health. Lifestyle intervention remains the cornerstone of treatment, while pharmacological and surgical options are reserved for cases where lifestyle measures alone are insufficient. Emerging approaches such as gene therapy, microbiome modulation, and nanotechnology are also showing promise for more personalized and effective obesity care.

4.1. Lifestyle Intervention

Lifestyle intervention is the first-line treatment for obesity, combining diet, exercise, and behavioral changes over at least six months. It typically leads to about 8 kg (or 8%) weight loss, improving overall health and quality of life [59]. Four major dietary regimens are commonly employed in the management of overweight and obesity: low-calorie diets (LCDs), low-fat diets, low-carbohydrate diets, and very low-calorie diets (VLCDs). The first three typically provide 800–1500 kcal/day, yielding a mean weight reduction of about 10% within 3–12 months for LCDs and approximately 5% within 2–12 months for both low-fat and low-carbohydrate diets. In contrast, VLCDs provide <800 kcal/day and can induce >10% weight loss within only 2–8 weeks [60]. Most adults with overweight or obesity initially turn to exercise as a weight-loss strategy; however, in isolation, it produces only limited reductions of about 0.1 kg per week, making it insufficient without concurrent calorie restrictions. Evidence indicates that aerobic training yields greater effects, resulting in 2–3 kg more weight loss than no training and approximately 1 kg more than resistance training alone, regardless of intervention duration [61]. Resistance training, in contrast, contributes less to total weight reduction but plays a crucial role during calorie restriction by preserving lean body mass, a benefit not achieved with aerobic exercise [61]. Nevertheless, because physical activity provides benefits beyond weight loss, current guidelines recommend 150–180 min of moderate-intensity aerobic activity per week, such as brisk walking [59]. In addition to modest improvements in body weight and composition, aerobic exercise lowers blood pressure, improves lipid profiles, reduces visceral fat, and enhances cardiorespiratory fitness collectively helping to mitigate obesity-related mortality risk [59]. Behavioral therapy is a central component of lifestyle interventions for obesity, aiming to modify diet and physical activity through structured strategies. Self-monitoring of food intake, calories, activity, and weight remains the most effective technique, complemented by goal setting, problem-solving, and stimulus control [59]. To address challenges such as emotional eating, programs may also incorporate motivational interviewing, mindfulness, and cognitive strategies, with Cognitive Behavioral Therapy (CBT) showing particular benefits for psychological triggers [62]. Evidence from the AHA/ACC/TOS'S guidelines indicates that intensive, face-to-face programs lasting at least 14 sessions over six months with continued follow-up achieve an average weight loss of about 8 kg at one year, leading to significant cardiometabolic improvements and reduced diabetes risk [63].

4.2. Pharmacological Treatments

When lifestyle interventions fail to achieve adequate or sustained weight reduction, pharmacological therapy becomes the next line of management. Anti-obesity medications act through various mechanisms, including appetite suppression, delayed gastric emptying,

enhanced satiety, or reduced fat absorption. These agents aim to complement lifestyle modification rather than replace it, providing additional weight loss and metabolic benefits. Current pharmacotherapies include incretin-based agents such as GLP-1 receptor agonists and dual GIP/GLP-1 agonists, as well as non-incretin drugs like orlistat, phentermine/topiramate, and naltrexone/bupropionneach differing in efficacy, tolerability, and mechanisms of action.

4.2.1. Incretin-Based Therapies (GLP-1 Receptor Agonists and Dual Agonists)

Semaglutide

Semaglutide, a GLP-1 receptor agonist, works through several complementary actions. It boosts insulin release in response to glucose, suppresses glucagon to lower liver glucose production, and slows gastric emptying to reduce post-meal glucose spikes. By acting on the brain's appetite centers, it also decreases hunger and food intake, leading to meaningful weight loss. These effects occur with a low risk of hypoglycemia and may help preserve β-cell function over time [64]. After 68 weeks, semaglutide led to an average weight loss compared to 2.4% with placebo ($p < 0.001$), with 32% achieving ≥20% loss. Significant improvements were also seen in metabolic and quality-of-life measures [65].

Liraglutide

Liraglutide shares the same mechanism of action as semaglutide but is less potent, requires daily administration, and achieves comparatively lower weight loss outcomes [64]. In the SCALE Obesity and Prediabetes trial ($n = 3731$), liraglutide 3 mg plus lifestyle changes led to greater weight loss (-8.4 ± 7.3 kg) than placebo (-2.8 ± 6.5 kg; $p < 0.001$) after 56 weeks [66]. Additionally, when comparing in a randomized clinical trial once-weekly semaglutide with once-daily liraglutide in adults with overweight or obesity (without diabetes), we found that semaglutide was more effective in reducing body weight. At 68 weeks, semaglutide resulted in significantly greater weight loss, with a higher proportion of participants achieving clinically meaningful reductions of 5–15%, as well as greater improvements in several cardiometabolic risk factors [53]. Both agents promote weight loss primarily through decreased energy intake; however, the effect was more pronounced with semaglutide compared with liraglutide (around 16%) [67].

Adverse events were predominantly gastrointestinal in both drugs, though treatment discontinuation rates were higher with liraglutide, likely due to its shorter half-life, more frequent dosing, and dose-escalation tolerability issues. These findings align with prior evidence from the STEP 1 (semaglutide) and SCALE (liraglutide) trials [68].

Tirzepatide (Dual GIP/GLP-1 Receptor Agonist)

Tirzepatide is a novel dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. It binds to the GIP receptor with an affinity like native GIP, while its affinity for the GLP-1 receptor is approximately fivefold lower than that of native GLP-1. This dual receptor activity is thought to produce complementary effects on glycemic control, appetite regulation, and energy balance, contributing to the potent weight- and fat-reducing properties observed in clinical trials [69]. In 2022, the FDA and EMA approved tirzepatide (Mounjaro) for type 2 diabetes. In November 2023, its indication was expanded to include treatment of overweight and obesity in adults with BMI $\geq$ 27 kg/m^2 plus comorbidities, or BMI $\geq$ 30 kg/m^2, similar to prior approvals for liraglutide and semaglutide [70]. In a large, multicenter RCT, 2539 persons with overweight or obesity were randomized to receive tirzepatide (5, 10, or 15 mg) or a placebo for a duration of 72 weeks. Significantly larger waist circumference reductions were achieved with tirzepatide (-14.0 to -18.5 cm vs. -4.0 cm with placebo). In a DXA substudy ($n = 160$), tirzepatide decreased total fat mass by 33.9%, while a placebo decreased it by 8.2%. The

fall in fat-free mass was less pronounced but nevertheless significant (−10.9% vs. −2.6%). Overall, tirzepatide produced a greater improvement in the fat mass-to-fat-free mass ratio than a placebo [71].

4.3. Non-Incretin-Based Therapies

4.3.1. Phentermine/Topiramate

Phentermine/topiramate promotes weight loss mainly by suppressing appetite, though the exact mechanisms are unclear. Phentermine enhances central norepinephrine, dopamine, and serotonin activity, while topiramate, originally an antiepileptic, may contribute through neurostabilization and increased thermogenesis [72]. Phentermine/topiramate ER (Qsymia®, Campbell, CA, USA) was approved by the FDA in 2012 as the first long-term combination therapy for obesity, but the EMA withheld approval due to concerns about phentermine's cardiovascular and addictive potential and topiramate's cognitive side effects. Because it contains phentermine, the drug is classified as a DEA schedule IV-controlled substance [72]. In a randomized clinical trial including 1267 individuals with a body mass index (BMI) of 35 or higher, participants were allocated to receive either phentermine–topiramate 3.75/23 mg per day, phentermine–topiramate 15/92 mg per day, or placebo. At 56 weeks, mean weight reduction was 5.1% with the lower dose, 10.9% with the higher dose, and 1.6% with placebo [73]. In a secondary analysis of 222 adolescents with obesity, no baseline demographic or clinical characteristics including age, sex, race/ethnicity, pubertal stage, or baseline BMI were significantly associated with BMI reduction. These findings indicate that both mid and top dose phentermine/topiramate are effective for weight reduction irrespective of patient subgroups [35].

4.3.2. Orlistat

Orlistat is a weight-loss medication that works by blocking gastric and pancreatic lipases, preventing the breakdown and absorption of about 30% of dietary fat, which is then excreted in the feces, thereby reducing caloric intake. In addition to supporting weight loss, orlistat improves lipid profiles by lowering LDL cholesterol. Because it is minimally absorbed into the bloodstream, its effects are confined to the gastrointestinal tract, which limits the risk of systemic side effects [74]. The meta-analysis conducted in children and adolescents found that orlistat produced significant improvements in waist circumference and insulin levels, while its effects on body weight, BMI, blood glucose, and lipid profile, though positive, were not statistically significant. The authors further noted that, in contrast, studies in adults have reported a mean weight loss of nearly 2.9 kg over 12 months, with additional evidence supporting the long-term efficacy of Orlistat as an anti-obesity agent in overweight and obese adults [75]. In addition, a meta-analysis of 16 randomized controlled trials including 10,631 participants found that treatment with 120 mg orlistat three times daily resulted in a placebo-adjusted mean weight reduction of −2.9% (95% CI, −3.4% to −2.5%) after one year [76]. Steatorrhea, oily spotting, fecal urgency/incontinence are characteristic and frequently cited as reasons for discontinuation [77].

4.3.3. Naltrexone/Bupropion

Bupropion, a norepinephrine and dopamine reuptake inhibitor used to treat depression, activates pro-opiomelanocortin (POMC) neurons and suppresses appetite through melanocortin-4 receptor signaling. It produces clinically meaningful weight loss in individuals with obesity. When paired with the opioid antagonist naltrexone, which blocks beta-endorphin activity and reduces food cravings, the combination synergistically enhances POMC activation, strengthens appetite suppression, and helps reduce overeating [60]. The clinical studies demonstrated that naltrexone/bupropion reduces body fat by approximately 14% and visceral fat by 15%, while largely preserving lean mass (−3%).

In contrast, the current 6-month real-world study identified naltrexone/bupropion as the least effective of the assessed anti-obesity medications (AOMs), both in overall weight reduction and fat mass loss. Fewer participants in this group achieved a ≥5% weight loss compared with those receiving phentermine, liraglutide, or lorcaserin, and its ranking for fat mass reduction placed it last among the evaluated agents, indicating comparatively limited efficacy in this setting [78].

4.4. Bariatric Surgery

4.4.1. Indications

Bariatric and metabolic surgery (MBS) is typically the option for patients who have failed at non-surgical weight loss or who have attempted to lose weight through non-surgical methods but failed. It is not a first step; it is more like a last resort when lifestyle changes and medical treatments have not worked long-term. The 1991 NIH BMI guidelines remain the main reference point. They suggest that surgery is suitable for people with a BMI of 40 kg/m^2 or higher, or at least 35 kg/m^2 if there are serious obesity-related health issues involved. But more recent studies have shown that some people with T2DM and a BMI between 30 and 35 kg/m^2 can also benefit, especially when their blood sugar stays high despite strong medical treatment [79]. Adolescents and young adults may achieve similar weight-loss and metabolic benefits as adults but require pediatric/adolescent multidisciplinary care and long-term follow-up. The American Academy of Pediatrics and the American Society for Metabolic and Bariatric Surgery (ASMBS) now recommend that metabolic and bariatric surgery (MBS) be considered for children and adolescents with a BMI greater than 120% of the 95th percentile (classified as Class II obesity) when accompanied by major comorbidities, or a BMI greater than 140% of the 95th percentile (Class III obesity). Importantly, research indicates that MBS does not interfere with pubertal development or normal growth. As a result, specific Tanner stages or bone age milestones are no longer viewed as mandatory prerequisites for surgical eligibility [80]. Preoperative assessment Comprehensive evaluation (nutrition, psychiatric and medical optimization, informed consent about lifelong follow-up and micronutrient supplementation) is essential; many programs require documented failure of sustained non-surgical therapy before operation [81].

4.4.2. Outcomes

Recent research clearly shows that bariatric surgery is one of the most effective treatments for obesity and its related metabolic diseases. Among the most widely used procedures, laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric byAOMspass (LRYGB) consistently deliver impressive short- and long-term outcomes.

Comparative studies show that bariatric surgery leads to far greater weight loss and BMI reduction than medical therapy, especially in patients with severe obesity (BMI > 40 kg/m^2) [82]. The effectiveness varies by surgical type: duodenal switch (DS) and biliopancreatic diversion (BPD) produce the most dramatic and long-lasting results, while gastric banding (LAGB) is less effective but carries fewer risks [82]. Data from Siriraj Hospital confirms these trends after one year, patients lost an average of 56.8% of their excess weight with LSG and 67% with LRYGB. Metabolic improvements were also striking fasting glucose dropped from 127 to 99 mg/dL, HbA1c decreased from 6.6% to 5.5%, and 67% of patients with diabetes achieved complete remission. Hypertension resolved in 58% of cases, and 73% of patients with dyslipidemia saw normalization of LDL and triglyceride levels [83]. Long-term studies show that both sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) maintain significant weight loss over time, with RYGB showing a slight but not statistically significant advantage. On average, patients maintained about

35% total weight loss at two years, 28% at six years, and 27% at twelve years after RYGB. For individuals with very high BMI or limited success after SG, biliopancreatic diversion with duodenal switch (BPD/DS) achieves the most substantial weight reduction, around 70–80% of excess weight loss within two years [84]. A large meta-analysis of 17 studies involving 174,772 participants further demonstrated that metabolic–bariatric surgery reduces all-cause mortality by about 49% and extends life expectancy by an average of six years. Patients with diabetes benefited the most, gaining approximately nine additional years of life compared with about five years in non-diabetic patients. These benefits appeared consistent across different surgical types, highlighting the overall survival advantage associated with bariatric surgery [15].

The pharmacological treatment of acquired hypothalamic obesity (HO), a rare and challenging condition, has long yielded disappointing results, with limited long-term efficacy [85]. HO typically develops after damage to the hypothalamus, most often due to tumors such as craniopharyngioma, or because of surgery or radiotherapy in this region. In recent years, setmelanotide, a synthetic agonist of the melanocortin-4 receptor (MC4R), has emerged as a promising novel therapy for this disorder [86].

4.4.3. Mechanism and Rationale

Setmelanotide has been approved by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of genetic forms of obesity caused by monogenic mutations in the leptin–melanocortin pathway, such as POMC, LEPR, and PCSK1 deficiencies [86].

The rationale for its use in acquired hypothalamic obesity (HO) lies in its ability to reestablish signaling within the disrupted leptin–melanocortin pathway [86]. Although hypothalamic injury can impair the neuronal circuits responsible for appetite regulation, the hypothalamus is rarely completely destroyed [87]. This allows setmelanotide to stimulate the remaining functional neurons, helping to restore energy balance and satiety signaling [87].

Setmelanotide has demonstrated encouraging early clinical outcomes in individuals with HO resulting from hypothalamic injury.

Phase 2 Interim Findings (NCT04725240)

A Phase 2, open-label, multicenter trial evaluated the effects of setmelanotide over a 16-week treatment period in 18 patients aged 6–40 years diagnosed with acquired HO.

The results were notably positive 89% of participants achieved at least a 5% reduction in BMI, with an average decrease of 15% across the group [86]. Additionally, 72.2% of patients experienced a BMI reduction of 10% or more within the 16-week period [85]. Among participants older than 12 years, there was a 45% average reduction in hunger scores, indicating significant control over hyperphagia [85]. Beyond the measurable outcomes, patients and families reported remarkable improvements in daily life, with one parent expressing, "We have our family life back." Such feedback underscores the meaningful psychological and social benefits of treatment [87]. Setmelanotide was generally well tolerated, with most side effects described as mild and manageable. The most reported adverse events were nausea, vomiting, and hyperpigmentation, the latter attributed to off-target activation of melanocortin-1 receptors (MC1R), which are involved in skin pigmentation [86].

4.4.4. Emerging Therapy

Gene Therapy

Obesity has a significant genetic basis, ranging from rare monogenic forms caused by single-gene mutations (e.g., LEP, LEPR, MC4R, POMC, PCSK1, BDNF), which often lead to severe early-onset obesity, to more common polygenic forms driven by the cumulative

effect of multiple small-risk variants such as those in the FTO locus. Understanding these genetic mechanisms has not only clarified the biology of appetite and energy balance but also opened new opportunities for gene-targeted therapeutic strategies. There are many targets for gene therapy in treating obesity. Some of them are still in the preclinical phase [88]. Other approaches look at boosting thermogenesis with genes like UCP1 or ADRB3 [89] or even changing how fat cells behave by using things like miR-130b or PPAR regulation [90]. There is also work on targeting inflammation, such as with nanovesicles that can reprogram macrophages [91]. On the other hand, scientists are also pointing to bigger, more general pathways that might be good targets in the future. These include circadian clock genes that affect energy balance, the FTO gene linked to appetite and fat metabolism, LDL receptor genes that help clear lipids, and glucocorticoid receptor genes that are tied to visceral fat expansion [92]. Researchers are trying out several delivery methods for obesity gene therapy, and each one comes with certain benefits. AAV vectors are one of the most promising because the newer adipose-specific versions can keep gene expression going for a long time without much risk of DNA integration. For instance, the V7 AAV carrying the human leptin gene was able to bring back leptin levels and lead to long-term weight loss in *ob/ob* mic [9]. Driving UCP1 expression in fat to increase thermogenesis is one proposed use for plasmid DNA delivery, which is significantly easier because it is non-viral and permits recurrent dosing [68]. Lipid nanoparticles and nanovesicles also show potential since they deliver RNA very efficiently and can be adjusted to target fat or the liver. A good example is dendritic RNAi nanovesicles with miR-130b, which reduced weight and improved metabolic health in mice [93]. There are also cell-based strategies where adipose-derived stem cells (ADMSCs) are modified outside the body and then transplanted back to help change the fat tissue environment [94]. Lastly, some advanced nanomedicine systems with targeting molecules are being tested for more precise delivery to fat, stimulating browning, or even mixing metabolic and immune effects in one treatment [95]. In short, gene therapy for obesity is still experimental, and the early promising results have so far been observed primarily in preclinical models, using different targets and delivery methods, highlighting potential avenues for future treatments.

Microbiome Modulation

Microbiome modulation has emerged as a promising therapeutic strategy for obesity management, encompassing several distinct but complementary approaches that target the gut–adipose axis through restoration of microbial balance and metabolic function [96]. Probiotics are the most common approach and have been studied the most. Their effect is not massive, but it is consistent. For example, meta-analyses of clinical trials show small drops in body weight (−0.73 kg), fat mass (−0.61 kg), and waist size (−0.53 cm) when probiotics are added to normal weight loss programs. Synbiotics, which mix probiotics with prebiotics, seem to perform a bit better. In fact, they are linked with bigger reductions in fat mass (−1.53 kg) and waist circumference (−1.31 cm). This probably happens because the prebiotics help feed the beneficial microbes, which then increase short-chain fatty acid (SCFA) production [97]. Early studies suggest it can successfully change the gut microbiota and improve metabolic health in people with obesity or metabolic syndrome, though the weight loss results are not always consistent across studies [98]. Diet also matters a lot. Diets that are high in fiber, polyphenols, or follow a Mediterranean style seem promising since they support good microbes and increase SCFA production. Actually, some recent work even points toward personalized diets based on someone's microbiome [99]. Even though these strategies are different, they seem to work through similar mechanisms: they strengthen the gut barrier, lower inflammation, improve glucose regulation through SCFA effects on incretin hormones, and influence bile acid metabolism [10]. Overall, microbiome-

based therapies look promising as extra tools to support obesity management. But at the same time, there are still challenges. We need standardized treatment protocols, better strain selection, and more long-term safety data before these strategies can be fully relied on in clinical practice.

4.5. Nanotechnology and Obesity Management

Nanotechnology utilizes the unique size and structure dependent properties of matter predominantly in the nanoscale (≈1 to 100 nm, as defined in ISO 80004-1:2023) [100], where quantum effects and increased surface to volume ratios make interdisciplinary transformative applications possible.

Its integration into medicine termed nanomedicine has advanced rapidly, encompassing therapeutic, diagnostic, and imaging purposes [101]. Nanomedicine refers to the application of nanoscience and nanotechnology in medical sciences, for treatment, diagnosis and imaging purposes [102].

Several studies have shown the potential of nanomedicine in obesity management by enhancing patient compliance and overcoming limitations of commercially available anti-obesity drugs [100–102].

The application of nanomedicines in the treatment of obesity addresses various pathological processes, including abnormalities in adipose tissue, oxidative stress and inflammation, endocrine metabolic disorders and imbalances in gut flora. The three strategies were effective for reversal of obesity at lower doses and reduction in bystander effects and normalization of metabolic activities. These nanosystems delivered non-specific and poorly soluble drugs to the target and confined their effects directly on the diseased cells while sparing surrounding tissues [103].

Currently, the main nanomaterials and their functions used for the treatment of obesity include the following: (1) Inorganic nanomaterials (e.g., gold nanoparticles, zinc oxide nanoparticles) directly intervene in fat metabolism through photothermal conversion, antioxidation, and other physicochemical properties. (2) Organic nanomaterials (e.g., cationic dendrimer polymers, polyphenol-based nanomaterials) possess both drug-targeted delivery and intrinsic biological activities (e.g., anti-inflammation, intestinal flora regulation). (3) Biomimetic nanomaterials (e.g., cell membrane-coated nanoparticles, exosomes) utilize natural bio-interfacial properties to achieve efficient targeting and immune escape [104].

For instance, Fucoxanthin, a lipophilic compound with notable anti-obesity potential, faces limitations due to poor solubility and bioavailability. The development of solid lipid nanoparticles (SLNs) enhanced its therapeutic efficacy, particularly in high-fat diet–induced obese mice. Researchers found that the tested formulations containing dispersed SLNs (D-SLN) achieved the greatest reductions in body weight gain (29.94%) and fat mass gain (61.80%), and they significantly improved metabolic parameters, liver function, lipid profile, and inflammatory markers. Histopathological analyses further confirmed reduced hepatic lipid accumulation and improved tissue morphology, supporting the potential of SLN-based fucoxanthin formulations as effective anti-obesity agents [105].

Moreover, functional snacks of nano-encapsulated resveratrol were created and studied to overcome its poor physiochemical properties. These nano-encapsulated resveratrol snacks had 43–53% resveratrol content present after formulation compared to snacks containing free resveratrol (5.24%). Additionally, these snacks exhibited greater antioxidant, anti-diabetic, and anti-obesity effects compared to those containing free resveratrol. These approaches highlight the potential of nano-encapsulation to enhance the efficacy of resveratrol while minimizing its toxic effects.

In the following table we summarized the most studied anti-obesity nanodrugs, as well as their route of administration and implementation. The main nanocarrier systems and their potential applications in obesity management are summarized in Table 1.

Table 1. Comparative Summary of Nanocarrier Systems and Their Potential Applications in Obesity Management.

Nanoformulation Type	Route of Administration	Advantages	Reference
Sclareol solid lipid nanoparticles	Intraperitoneal injection	Reduce adiposity, increasing brown adipose tissue weight, increasing HDL levels and improving glycemic profile	[106]
Curcumin liposomes	Oral	Reduced inflammation, promoted fat metabolism, and positively affected the gut microbiome.	[107]
Quercetin and curcumin nanoemulsion	Oral	Reduced fat accumulation, improved glucose metabolism, and reduced inflammation.	[107]
Apigenin encapsulated in poly lactic-co-glycolide nanoparticles	Oral	Reduced body weight, fat accumulation, and inflammation through several mechanisms, including inhibiting adipocyte differentiation and improving the gut microbiome.	[39]
Reservatrol Nanostructured Lipid Carrier	Microneedle patch	Improved metabolic factors like insulin sensitivity and glucose control, promoted "browning" of white fat tissue, and reduced fat accumulation.	[108]
Lipase nanoparticles of Orlistat	Oral	Helps manage obesity by inhibiting digestive enzymes (lipases) in the gut, which reduces the absorption of dietary fat by about 30%. This leads to a caloric deficit and weight loss.	[109]
Superparamagnetic iron oxide nanoparticles	Oral	Improve metabolic markers, promote fat browning, and increase mitochondrial function. Lower body weight and improve lipid profiles, while also acting as an antioxidant and improve glucose metabolism.	[110]
Fucoxanthin Solid lipid nanoparticles	Oral	Reduce body weight, visceral fat, and fat accumulation by increasing fat burning, increase energy expenditure, inhibits the enzymes involved in fat synthesis, improve insulin resistance, and can positively impact gut microbiota.	[111]
Liralutide liposomes	Oral	Causes weight loss, reduces fat mass, and improves related health markers like blood pressure, blood glucose, and triglycerides. It works by suppressing appetite and increasing feelings of fullness.	[112]

Therefore, the implementation of nanotechnology in treatment of obesity offers opportunities that promotes weight loss and prevent metabolic disorders in patients.

5. Pharmacoeconomics of Obesity Treatment

Obesity is a chronic condition that imposes significant health and economic burdens globally, and pharmacoeconomic assays help to obtain the most suitable treatment strategy by comparing costs against health benefits [113].

Direct costs include both medical expenses related to treatment delivery to patients and management of obesity, such as physician visits, lab tests, medications, interventions, or surgery [113]. Direct non-medical costs refer to expenses related to patient care, not treatment, such as costs of transportation to and from the clinics, home care if needed, costs of complementary medicine, and any objects the patient may need due to illness [114]. In addition, indirect costs result from productivity loss, such as disabilities, absenteeism from work or school, and premature mortality, which affect the country's economy and income [115]. Overall, these costs are an important consideration, as they affect patient comfort and health impact in general [114].

Cost-effectiveness of interventions is another crucial pharmacoeconomic aspect. Lifestyle interventions are considered the first-line approach recommended for obesity treatment, as they are the most cost-effective and more applicable compared to other interventions, including diet improvement, increasing movement and activities, and behavior modification, which, in general, improve quality-adjusted life years (QALYs) [116]. Pharmacotherapy is also an option for obesity treatment and is often used together with lifestyle modifications. Some studies explained that phentermine–topiramate is cost-effective for both adults and adolescents with obesity and is economically acceptable in incremental cost-effectiveness ratios (ICERs) [117–119]. Newer classes such as GLP-1 receptor agonists like semaglutide are highly effective but not agreeable with cost-effectiveness due to their high price [119,120]. A more invasive method is bariatric surgery, but it is highly cost-effective in the long term. It has been shown to increase QALYs and reduce healthcare costs associated with obesity-related complications [121–123], proven by studies showing an average 22.6% reduction in healthcare costs within two years after the procedure, especially among patients with obesity and type 2 diabetes [124].

Economic evaluations in healthcare systems play a crucial role in decision-making not only about the value of anti-obesity intervention methods but also about costs and healthcare spending [125]. They rely on simulation models to help overcome gaps in real-world long-term evidence by projecting quality-adjusted life years (QALYs) gained and incremental cost-effectiveness ratios (ICERs) for various interventions to help authorities make decisions about obesity management strategies [125]. This ensures continuous updating of clinical guidelines and shaping of reimbursement policies [76].

6. Artificial Intelligence in Obesity-Related Cancer Research

Across many different studies, a strong correlation exists between obesity and cancer, where carcinogenesis and tumor progression are mainly driven by the tissue-microenvironment interactions, which are significantly altered by metabolic conditions [126]. This link is exemplified across a spectrum of malignancies, including breast cancer, where high body mass index (BMI) is associated with distinct mutational patterns (e.g., in CDH1, TBX3, and PIK3CA) [126], and endometrial cancer, which has one of the strongest established epidemiological and biological links to obesity [127]; ovarian cancer, ranked highest in its connection to obesity [128]; prostate cancer, where obesity is linked to higher incidence and mortality [129]. Additionally, hepatocellular carcinoma (HCC) is often preceded by obesity-driven non-alcoholic fatty liver disease (NAFLD) [130]; papillary thyroid cancer, which shares inflammatory pathways with obese adipose tissue [131]. However, there are various gaps that pose a challenge for clinical transition, such as the mechanistic opacity, with gaps in understanding the specific biological pathways connecting adiposity and carcinogenesis in humans [128,130,132]. Furthermore, the reliance on imperfect risk tools could be problematic. For example, different studies have supported the inaccuracy of body mass index (BMI) as an indicator for metabolic homeostasis affected by adiposity, thereby highlighting the need for more accurate measurement tools

to define obesity and identify cancer development [126,133]. Medical imaging, such as magnetic resonance imaging (MRI), shows limitations in the diagnostic process [127], as well as the weight-adjusted waist index (WWI) [130]. The suboptimal therapy selection is another limitation, which encompasses the failure of the traditional cancer treatment without killing all tumors, such as radiation therapy, which leads to damage to the surrounding tissues. Using a single drug for a single target disease could lead to undesirable repercussions. A prime example is bicalutamide, which is a selective androgen receptor (AR) antagonist, implicated in gynecomastia for men as monotherapy, and may trigger the occurrence of late-stage prostatic cancer [129]. Artificial intelligence (AI) and machine learning (ML) bridge these gaps across multiple data layers. These methods can decode obesity-cancer pathways from multi-omics data [134], identify epigenetic biomarkers like HSD17B8 hypermethylation [135], and extract prognostic signals from medical imaging and radiomics [127]. Therefore, we synthesize evidence across four pillars: (1) mechanistic understanding, (2) early detection and risk stratification, (3) therapeutic personalization, and (4) pharmacoeconomic insights.

6.1. Mechanistic Understanding

Adiposity is mediated by metabolic and inflammatory alterations in adipose tissues and regulated by different signaling pathways. Thus, it is crucial to identify these pathways and design personalized strategies for early prophylaxis and prevention. Obesity-cancer related pathways encompass the insulin resistance, dysregulation in insulin-like growth factor-1(IGF-1) system signaling, and altered sex hormone biosynthesis, chronic low-grade inflammation and oxidative stress, alterations in adipokine pathophysiology, microenvironment, and cellular perturbations [128].

6.1.1. Insulin/IGF Axis and Metabolic Rewiring

The insulin/insulin-like growth factor-1 (IGF-1) signaling is a significant pathway linking obesity and the risk of many different cancers, such as pancreatic, colorectal, and prostate cancer [128]. Ceylan et al. underscored that the deregulation of IGF1 is directly linked with hepatocellular carcinoma development, and this growth factor may activate the phosphoinositide 3-kinase (PI3K)/AKT (protein kinase B) and MAPK (mitogen-activated protein kinase) pathways, which are the major signaling pathways in cancer [130]. A breast cancer (ER+/HER2−) study highlighted that high BMI is associated with increased somatic mutations in *CDH1* and *TBX3* and decreased PIK3CA via regulators such as leptin induction and adiponectin attenuation, which enhance the insulin/IGF pathway [126]. These findings support the notion that tumor cells may shift toward other non-canonical proliferative mechanisms. Furthermore, in the hepatocellular carcinoma (HCC) study, multiomics integration identified *IGF1*, along with ACADL, CYP2C9, and G6PD, as key genes associated with obesity-driven HCC [130]. These findings highlight potential molecular links between metabolic dysregulation and liver tumorigenesis in obese individuals.

6.1.2. Adipokines and Low-Grade Inflammation

Adipokines are bioactive hormones that are produced by adipose tissue to regulate metabolism, angiogenesis, and cell proliferation, and they are key mediators that link obesity to cancer. Leptin is a type of adipokine that is responsible for regulating energy balance. In a breast cancer model discussed the role of leptin in enhancing the tumor growth of MCF-7 cells through activation of STAT3 (Signal Transducer and Activator of Transcription 3) and the MAP kinase (*MAPK*) pathway [136]. Moreover, pro-inflammatory cytokines such as Interleukin-6 (IL-6) and tumor necrosis factor (TNF-α), elevated in obesity, can stimulate the PI3K pathway activity in breast cancer; similarly, inflammatory cytokines are implicated in clear-cell renal cell carcinoma (ccRCC) [126,136]. These signals are multi-

layered and patient-specific; thus, AI can integrate multi-omics, imaging, and clinical data to map mechanisms, stratify, and guide precision therapy.

6.1.3. Immune Remodeling and Cytokine Signaling

Several lines of evidence reveal that obesity-induced cytokine regulates stromal and vascular alterations in the ovarian microenvironment that generate conditions that trigger malignant growth. Single-cell RNA-seq data of the human ovarian cortex model showed that with the rise in BMI, there is a decrease in stromal cells (SCs) and an increase in blood vascular endothelial cells (BECs) [132]. This shift suggests that the remodeling of the ovarian microenvironment, where reduced SCs may impair tissue stability and immune surveillance, while increased BECs may enhance angiogenesis and support malignant transformation. Notably, hock protein family D member 1 (HSPD1) deficiency was correlated with poor prognosis and impaired stress response [126,132]. These observations support deconvolution assisted by AI of bulk tumor RNA to single-cell references, as bulk profiles might not be robust for the transcriptomic profile of tumor microenvironment (TME) [126].

6.1.4. Hypoxia/Angiogenesis and ECM Remodeling

In obesity, hypertrophic adipose tissue creates a hypoxic (low oxygen) microenvironment. This hypoxia, which relies on chronic inflammation, enhances expression of the key mediator angiopoietin-like 4 (ANGPTL4). ANGPTL4 promotes breast carcinogenesis by stimulating angiogenesis (new blood vessel formation) and remodeling the extracellular matrix (ECM), thereby facilitating tumor growth and metastasis [137]. The obese microenvironment induces oncogenic ECM remodeling, increasing stiffness and composition changes to amplify tumor development and progression [138]. The integration of AI and radiogenomics enables a deeper understanding of these mechanisms. Machine learning models can decode medical images, linking specific radiographic features to the activity of these pro-angiogenic and ECM-remodeling pathways, thus providing a non-invasive window into the tumor's biological drivers [139].

6.1.5. Sex Hormones

Many different studies underscore the importance of sex hormone concentrations as the key link between obesity and cancer, in particular, breast and endometrial cancers [128]. Obesity is accompanied by dysregulated hormone levels, and high levels of estrogen are highlighted as the leading cause of hormone-sensitive breast cancer, which represents nearly 70% of breast cancer cases. To illustrate, elevated estrogen concentrations, alongside persistent activation of breast epithelial cells, may foster malignant transformation and breast carcinogenesis by altering the metabolic balance [136]. Therefore, at the gene level, HSD17B8 metabolic gene responsible for the regulation of the concentration of estrogens and androgens, could be a potential biomarker [136].

6.2. Early Detection and Risk Stratification

6.2.1. Population/EHR Models

Machine learning applied to population datasets and electronic health records (EHRs) systematically evaluates adiposity measures beyond BMI for cancer risk prediction. An analysis of NHANES data from 2005 to 2018 evaluated breast cancer prevalence using the weight-adjusted waist index (WWI) as a predictor, comparing the performance of regression, least absolute shrinkage and selection operator (LASSO), and random forest models [133]. The random forest model identifies WWI as a top predictor with a minimal depth of 3.04, indicating strong variable importance. Both random forest and LASSO models achieved an area under the curve (AUC) value (0.79–0.797), which reflects strong

predictive performance [133], illustrating that ML can detect useful features that help with prediction, even if those features do not show a clear link in traditional statistical analysis.

For predicting the risk of sarcopenic obesity (SO). created an online web calculator based on the gradient boosting machine (GBM) model. First, they assessed six ML methods: classification and regression trees (CART), gradient boosting machine, K-nearest neighbors (KNN), linear regression (LR), neural network (NNet), and extreme gradient boosting (XGboost). Among all these tested algorithms, the GBM-based model demonstrated the highest predictive performance [140]. It is based on phenotypes such as age, race, and BMI as input features, and it achieved AUC values of 0.820 and 0.832 in the training and validation sets, respectively. The model also exhibited good calibration, clinical utility, and robustness across internal evaluations [140]. Similarly, another study developed ML models to predict low muscle mass (LMM), a key component of SO. Utilizing algorithms like random forest, CatBoost, and XGBoost with LASSO-based feature selection, the random forest accomplished the best performance by scoring in AUROC = 0.994 and strong calibration [141]. SHAP (Shapley Additive exPlanations) analysis highlighted the body roundness index (BRI), age, and metabolic markers as predictors, as well as creating an online calculator to support clinical use [141]. Together, the findings demonstrate that compound risk phenotypes through ML offer enhanced screening opportunities for sarcopenic obesity in clinical practice. Among seven models, CatBoost, which is a novel ML algorithm, showed significant prediction ability by achieving an AUC of 0.87, predicting the overweight-to-obesity transition in 5236 adults. This model was visualized and explained by SHAP values to analyze waist/hip circumference, female sex, and systolic blood pressure as important features [142].

Collectively, these findings illustrate that ML can use alternative obesity measures beyond BMI while accomplishing robust predictive performance across different conditions. Thus, these approaches support the notion of translating complex phenotypic data into clinically accessible tools for screening, prognosis, and may reduce cancer incidence.

6.2.2. Imaging and Radiomics: Deep Learning Classifiers and Obesity-Aware Thresholds

Medical imaging, specifically magnetic resonance imaging (MRI), provides quantitative, organ-specific phenotypes that are vital for cancer and obesity management. Therefore, enhancing the efficiency and interpretation of MRI is essential to ameliorate phenotype-driven screening and risk stratification. For instance, in obesity-linked endometrial cancer (EC), MRI is considered a viable tool for assessing EC and identifying the metastatic spread, but there is a diagnostic limitation related to MRI, such as moderate sensitivity (43%) and specificity (73%) in the detection of metastatic lymph nodes [127]. Hence, radiomics and AI offer solutions by converting images into quantitative data, which can improve risk stratification, prognosis prediction, and treatment decision-making [127]. Recent advances in deep learning (DL)-based MRI reconstruction enhance the utility of T2-weighted imaging by reducing the acquisition time and improving image quality [143]. This can be exemplified that DL-reconstructed sequences achieved up to 36% faster acquisition and demonstrated a sharpness and diagnostic agreement, which may indicate an improvement in radiomics feature extraction and interpretation [143]. Therefore, this technical approach could be a viable solution to the obesity-linked EC diagnostic issue [127].

In the radiomics model, a drop in performance has been noticed from training to validation set in AUC from 0.85 to 0.68, and accuracy from 78% to 69% associated with the small sample size (n = 73), which suggests overfitting and reduced validity, as well as variations in imaging technology. Consequently, these findings highlight the necessity of data harmonization and multi-site validation to ensure clinical applicability of radiomics models [127], indicating the importance of introducing robust models such as the T2-weighted

radiomics model, which has a high diagnostic performance (AUC 0.82) with a sensitivity of 80.0%, offering promising potential for clinically meaningful generalization across imaging environments [127,144]. However, there are some constraints that were reported as to develop these radiomics models, which require large and varied datasets and a standardized protocol [127]. Moreover, a deep learning framework applied to whole-body MRI identified muscle volume and fat infiltration as independent mortality predictors in obese cancer patients, outperforming BMI and conventional L3 slice metrics. These phenotypes reflect metabolic dysfunction more accurately than crude adiposity, supporting their integration into AI-driven risk stratification pipelines [145]. In endometrial cancer, a phenotype-based model revealed that non-obese patients were 2.5 times more likely to have microsatellite instability (MSI) than obese patients, challenging the conventional link between obesity and this cancer type. The model, which also incorporated tumor grade, achieved moderate accuracy (AUROC = 0.683), underscoring the potential of clinical variables for initial MSI risk stratification. These findings underscore the predictive relevance of compound phenotypes and support the integration of histological and metabolic features into AI-driven stratification pipelines. By proposing a function that estimates MSI probability based on obesity and tumor grade, this approach aligns with the broader goal of enhancing precision screening and immunotherapy eligibility through phenotype-aware modeling [146].

6.3. Therapeutic Personalization

AI can enhance and support cancer treatment selection and dosing strategies. Obesity alters drug pharmacokinetics and pharmacodynamics through changes in body composition, distribution, volume of distribution, clearance, and metabolism. A review related to anticancer dosing in obesity highlighted that obese patients receive insufficient chemotherapy doses, which reduces the efficacy [147]. In the thyroid cancer study, machine learning has shown promising success in dose prediction; a support vector regression model (SVM) achieved validation for levothyroxine dosing and improved the percentages of patients reaching therapeutic targets from 10.5% to 52.1% by relying on phenotypes such as BMI, weight, and body surface area [148]. However, the study focused on endocrine rather than oncology and did not discuss details about body composition parameters such as visceral adiposity or sarcopenic obesity. Several AI models have been developed for response prediction in targeted therapy. DrugCell is an interpretable deep learning model of human cancer cells trained on responses of 1235 tumor cell lines to 684 drugs. In ER-positive metastatic breast cancer, DrugCell successfully stratified overall survival for patients on mTOR/CDK4-6 inhibitors by linking tumor genomic profiles to biological subsystems [149]. For immunotherapy, network-guided machine learning (NetBio) successfully predicted responses to immune checkpoint inhibitors across three cancer types, achieving AUCs between 0.72 and 0.79, outperforming programmed death-ligand 1 (PD-L1) and identifying resistance pathways [150]. In gastric cancer, SVM was trained on multiplex features (DUOX2, HSPB1, S100A14, C1QA, TGFB1, LTF) predicted resistance to anti-PD1 and chemotherapy with an AUC of 0.85, mechanistically linking TGFB1-HSPB1 signaling and ferroptosis suppression to therapeutic failure [151]. Furthermore, a slide-based approach called ENLIGHT-DeepPT consists of DeepPT, a deep learning framework that predicts genome tumor mRNA expressions from slides, and ENLIGHT, which predicts the response to targeted and immune therapies. It achieved response prediction across five cohorts, imputing transcriptomes from H&E images [152], while metabolomics-based random forests stratified gastric cancer prognosis (C-index 0.83), superior to clinical factors [153].

Dynamic optimization using reinforcement learning has shown potential for personalized treatment scheduling. For instance, this study underscored that adaptive therapy using deep reinforcement learning significantly extended progression time in prostate cancer

models by identifying dosing holidays. The approach relied on interpretable, threshold-based policies that remained robust across diverse patient profiles [154].

6.4. AI-Driven Economic Evaluation and Resource Optimization in Obesity-Associated Oncology

6.4.1. Enhancing Cost-Effective Models: AI-Predicted Outcome

Traditional cost-effectiveness analyses (CEAs) in oncology mainly depend on population-average data, which may overlook the clinical pathways and economic burden of obese patients.

AI can enhance these models by providing granular risk prediction for obese patient subgroups. For instance, a protocol for weight-loss intervention uses a reinforcement learning algorithm (RL), like upper confidence bound (UCB1), and multi-armed bandits can optimize resource allocation under capacity constraints, achieving non-inferior weight loss at lower cost [155]. This could be suitable for oncology: by substituting weight loss with oncology-specific endpoints like progression-free survival (PFS), overall survival (OS), or objective response rate (ORR) predicted by AI, we can generate more accurate incremental cost-effectiveness ratios (ICERs) and quality-adjusted life years (QALYs) for obese cohorts. Several studies establish robust economic frameworks, such as the Cost of Obesity Model (COM), a validated Markov cohort model that links BMI and cardiometabolic factors to events such as postmenopausal breast, endometrial, and colorectal cancers [156]. For colorectal cancer screening, another study modeled AI-assisted colonoscopy via microsimulation and showed per-person cost savings [157].

Collectively, there are no studies that have incorporated AI to predict the obesity-stratified oncology outcomes in their ICER calculations. Therefore, the immediate next step is to feed AI-generated predictions of therapy response, toxicity, or survival of obese subgroups into these economic models to determine if AI-personalized care for obese cancer patients is cost-effective.

6.4.2. AI for Budget Impact and Capacity Planning

Health systems require realistic forecasts of the financial and operational impacts of new technologies. AI models show the capability for dynamic capacity planning beyond static budgets. Population-level microsimulation models demonstrate that targeting obesity can yield substantial budget savings. One study projected that policies like a minimum unit price (MUP) for alcohol could reduce the liver cancer incidence and yield cumulative healthcare cost savings of over €600 million in France alone by 2030 [158]. Similarly, a model of calorie labeling for obesity-associated cancers in the US incorporated expenditures, productivity losses, patient time costs, and policy compliance expenses and projected net healthcare savings of $1.46 billion [159]. These studies provide a roadmap, but when combined with AI tools that manage clinic-level resources, they offer the complete potential to plan obesity-aware cancer care over the years.

6.4.3. Predicting Real-World Cost Drivers

A significant part of cancer care costs is driven by dose management, toxicity, and unplanned hospitalizations. AI models can predict these events for obese patients, allowing for proactive cost management. For example, a study on ventral hernia repair used regression models to identify operation time, device price, and BMI as significant factors in financial loss [160]. While in cancer applications, an interpretable ML model (logistic regression with SHAP analysis) was developed to predict radiation-induced hepatotoxicity (RIHT) in hepatocellular carcinoma (HCC) patients by identifying BMI, liver irradiation volume (V5), and pre-treatment Child-Pugh score as key risk factors [161]. Hence, by training AI models on oncology datasets to predict toxicities, dose reductions, and hospital admissions in obese patients, as well as attaching micro costs (e.g., growth factors, ED

visits, ICU stays) to these predicted events, this reflects the real-world economic burden and the potential savings from AI-guided, proactive interventions.

6.4.4. Informing Policy via AI-Driven Scenario Simulations

Ultimately, economic models must inform policy. AI facilitates this by running complex simulations to test different policy scenarios. The decision tree analysis from the bariatric surgery study showed that the cost-effectiveness threshold at which a more expensive robotic technique became preferable [162]. This approach can be directly applied to oncology policy.

6.5. Implementation, Reporting and Ethics

The translation of AI models into clinical practice for obese cancer patients faces many hurdles. Studies highlight real-world constraints such as the absence of key data (e.g., BMI) due to weak computing infrastructure, and workflow integration challenges like variable appointment durations [155]. Furthermore, the generalizability of these models is also a concern, as performance can be restricted by imaging variability, variable reimbursement structures, and potential implementation barriers across different healthcare systems [155,160]. Therefore, to promote rigorous, transparent, and high-quality reporting of artificial intelligence interventions in healthcare, it is essential to follow established guidelines such as the Consolidated Standards of Reporting Trials-AI (CONSORT-AI) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis-AI (TRIPOD-AI). The adherence to these standards will facilitate transparency, reproducibility, and accountability, which help to address potential biases and enhance the equitable implementation of AI systems [163,164].

7. Future Directions and Perspectives

7.1. Personalized/Precision Medicine in Obesity Management

Precision medicine is reframing obesity care from a one-size-fits-all paradigm to stratified, mechanism-anchored therapy. Multi-omics patient "fingerprints" (genome, epigenome, proteome, metabolome, microbiome) now enable data-driven subtyping that predicts disease trajectory and differential treatment response [162,163]. Polygenic scores and large-scale genetic mapping improve risk prediction and could guide early, targeted prevention and pharmacotherapy, including GLP-1/GIP–based agents [59,71,164]. Concurrently, multi-omics integration reveals adiposity subtypes with distinct cardio-metabolic risks, underscoring why identical BMIs can mask heterogeneous biology [165,166].

Epigenetic mechanisms appear pivotal for "memory of obesity," explaining persistent metabolic risk after weight loss and pointing to epigenome-targeted strategies [90,165,167]. Tissue-specific DNA methylation patterns in adipocytes are increasingly linked to adiposity variation and comorbidity clustering [166,168]. At the phenome level, consensus roadmaps emphasize closing translational gaps standardizing evidence thresholds, addressing equity and cost-effectiveness, and embedding precision strategies into real-world workflows [84].

Microbiome-host modeling promises personalized nutrition and post-bariatric care, as gut community signatures predict glycemic/lipid responses to diets and surgery [169]. Clinically, precision obesity clinics are piloting multi-omics case conferences and algorithmic treatment selection, supported by practice frameworks in adults and pediatrics [170–172].

7.2. Integration of Digital Health and AI in Obesity Prevention and Treatment

Digital health is shifting obesity care toward continuous, personalized, and scalable support. Wearables and phones generate dense behavioral and physiologic streams, while AI converts them into dynamic risk scores and just-in-time adaptive interventions [173].

In hospitals and communities, device-supported programs improve activity and weight outcomes, with meta-analytic evidence for benefit and growing implementation beyond face-to-face care [169,174,175].

Continuous glucose monitoring and digital phenotyping now inform precision nutrition by predicting glycemic responses and tailoring meal timing/macros [64]. AI-ECG can even estimate BMI as a proxy for adiposity to flag risk at scale [176]. On population platforms, telehealth and remote monitoring enable rapid medication titration and longitudinal follow-up; real-world analyses of GLP-1-centered, telemedicine-delivered programs report double-digit weight losses at 12 months [177], complementing pragmatic RCTs of digital weight-gain prevention and structured remote behavioral treatment [176,178].

Conversational agents, virtual coaches, VR/gamified programs, and image-assisted diet logging are expanding reach and engagement, though high-quality trials with longer follow-up are still needed [179]. Looking ahead, digital twins virtual patient avatars integrating multi-omics and behavioral data could simulate responses to dietary, pharmacologic, or surgical interventions before clinical deployment [105].

7.3. Research Gaps and Opportunities

Three translation gaps dominate. First, generalizability and equity: most training datasets for PRS and AI models remain Eurocentric, limiting transferability; multi-ancestry consortia and fairness metrics are priorities [59,81]. Second, long-term effectiveness and cost: we need multi-year comparative-effectiveness and cost-utility analyses for precision/digital care especially in low -and middle -income countries (LMICs) and safety-net settings [165]. Third, infrastructure and governance: standards for data interoperability, privacy-preserving analytics, and auditing of black-box models are essential [179–182].

Mechanistically anchored anti-obesity pharmacotherapy (e.g., semaglutide, tirzepatide) sets new efficacy benchmarks, and the next wave of triple agonists will likely further raise the bar [6,62]. The opportunity now is to couple these agents with individualized digital behavioral supports, AI-guided dose/adjunct selection, and multi-omics monitoring to maximize durable weight loss and cardiometabolic risk reduction [183]. Emerging epigenetic and inflammatory signatures may help identify "responders," while microbiome-informed nutrition and post-bariatric precision follow-up could reduce relapse [167]. Together, these avenues chart a path to a learning health system for obesity closed-loop, equitable, and mechanistically precise.

8. Conclusions

Obesity is not merely a metabolic imbalance but a complex, chronic condition that interlaces physiological, psychological, and social suffering. Beyond metabolic disruption, individuals with obesity often endure emotional distress, stigma, and diminished quality of life, which amplify disease persistence and hinder adherence to therapy. Emerging mechanistic insights spanning insulin resistance, adipokine dysregulation, and microbiome alterations have paved the way for a paradigm shift from generalized treatment to precision and AI-integrated medicine. Artificial intelligence now enables early risk prediction, phenotype stratification, and real-time treatment optimization by integrating multi-omics, clinical, imaging, and behavioral data. Through these models, obesity management can become dynamically adaptive tailoring nutrition, pharmacotherapy, and behavioral interventions to each patient's molecular and psychosocial profile.

Furthermore, the impact of obesity extends into maternal health, where excessive gestational weight gain and metabolic inflammation impair placental function and fetal development, predisposing offspring to lifelong metabolic risk. Personalized medicine combined with AI-guided monitoring during pregnancy could predict complications

such as gestational diabetes, preeclampsia, and impaired fetal growth, allowing for early, individualized intervention. Integrating maternal fetal data streams from continuous glucose monitoring to ultrasound-derived radiomics into AI models can refine our understanding of how maternal obesity shapes fetal metabolic programming and long-term health trajectories.

Ultimately, tackling obesity requires a holistic and compassionate framework that merges mechanistically anchored pharmacotherapy with digital precision care, addressing both the biological roots and the human suffering it causes. AI-enhanced personalized medicine, when ethically implemented and equitably accessible, has the potential to transform obesity and pregnancy outcomes like supporting healthier mothers, resilient offspring, and sustainable public health progress across generations.

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