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Original Article

Obesity & Innovative Anti-Obesity Drugs

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ABSTRACT

Obesity, which refers to the state of excessive body fat accumulation owing to an imbalance between energy intake and expenditure, is a major risk factor for non-communicable diseases, such as type 2, diabetes mellitus, dyslipidaemia, cardiovascular diseases, stroke, and some cancers. the world health organization(who)defined obesity is major public health problem in 1997. Lifestyle modification such as diet and exercise intervention is essential both prevention and management of obesity, and pharmacotherapy may be considered if the interventions are ineffective for individuals with a body mass index [bmi] ≥30 kg/M OR FOR THOSE WITH bmi ≥27kg/m when co-morbidities, such as hypertension or type 2 diabetes mellitus are present. However, anti-obesity drugs are a frequent adjunct because these interventions have limited long term success and the weight is regained when treatment is discontinued. Many modifications have been used to manage obesity over the years. However, most of the anti-obesity drugs that were approved and marketed have now been withdrawn due to serious adverse effects. In the 1990s, fenfluramine and dexfenfluramine were withdrawn from the market because of heart valve damage. In 2000, the European medicines agency recommended the market withdrawal of several anti-obesity drugs including phentermine, diethylpropion, and mazindol, due to an unfavourable risk to benefit ratio. The first selective CB1 receptor blocker, rimonabant, was available in 56 countries from 2006 but was never approved by the us. food and drug administration (FDA) due to an increased risk of psychiatric adverse events, including depression, anxiety, and suicidal ideation. Subsequently, rimonabant was withdrawn from the European market in 2009.

Keywords: Obesity, Anti-Obesity Drugs

INTRODUCTION

Definition of Obesity (WHO Criteria) World Health Organization defines obesity as an abnormal or excessive accumulation of body fat that presents a risk to health. In clinical and epidemiological practice, obesity is most assessed using Body Mass Index (BMI), calculated as weight in kilograms divided by the square of height in meters (kg/m²). According to WHO criteria, BMI 18.5–24.9 kg/m² is considered normal, 25.0–29.9 kg/m² as overweight, and ≥30 kg/m² as obesity. Obesity is further subclassified into Class I (30.0–34.9 kg/m²), Class II (35.0–39.9 kg/m²), and Class III (≥40 kg/m²), reflecting increasing health risk. Although BMI does not directly measure body fat percentage, it is strongly correlated with adiposity and is widely used due to its simplicity and reproducibility in large populations [1,4].

Difference Between Overweight and Obesity

Overweight and obesity are distinct categories based on BMI and associated health risks. Overweight (BMI 25.0–29.9 kg/m²) indicates excess body weight relative to height but does not necessarily imply excessive body fat or metabolic dysfunction. Obesity (BMI ≥30 kg/m²), however, represents a pathological excess of adipose tissue associated with increased morbidity and mortality. Research demonstrates that the risk of type 2 diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular disease rises progressively with increasing BMI, particularly beyond 30 kg/m². Additionally, fat distribution—

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especially central (abdominal) obesity measured by waist circumference—is more strongly associated with metabolic complications than total body weight alone [7,8].

Obesity as a Chronic Metabolic Disease

Obesity is now recognized as a chronic, relapsing, multifactorial metabolic disease rather than merely a lifestyle condition. It results from complex interactions among genetic predisposition, environmental influences, neuroendocrine regulation, and behavioural factors. Excess adipose tissue acts as an active endocrine organ, secreting adipokines and inflammatory mediators that contribute to insulin resistance, chronic low-grade inflammation, and metabolic syndrome. The genetic contribution to obesity is estimated to account for 25–40% of variability in BMI, though polygenic influences predominate in most individuals. Given its chronic and progressive nature, obesity requires long-term management strategies including lifestyle modification, pharmacotherapy, and, in selected cases, bariatric surgery [9,7].

Global Prevalence and Epidemiological Trends

Obesity has reached epidemic proportions globally. According to the World Health Organization, worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults were overweight, of whom over 650 million were obese. The prevalence is rising not only in high-income countries but also in low- and middle-income nations, particularly in urban settings. Childhood obesity is also increasing at an alarming rate, predisposing younger populations to early onset of metabolic diseases. Epidemiological studies consistently show a strong association between increasing BMI and higher risks of cardiovascular disease, type 2 diabetes, certain cancers, and all-cause mortality [2,10].

Economic and Social Burden of Obesity

The economic and social burden of obesity is substantial and multifaceted. Direct medical costs include expenses related to the management of diabetes, cardiovascular disease, orthopaedic complications, and obesity-related cancers. Indirect costs arise from reduced productivity, absenteeism, disability, and premature mortality. In many countries, obesity-related healthcare expenditures account for a considerable proportion of total healthcare spending. Beyond economic implications, obesity contributes to social stigma, discrimination, psychological distress, and reduced quality of life. The increasing prevalence of obesity places considerable strain on healthcare systems and underscores the need for comprehensive public health strategies focusing on prevention, early intervention, and long-term management [11,9].

2. Body Mass Index (BMI) Classification (WHO & Asian Criteria)

World Health Organization classifies Body Mass Index (BMI) as a practical anthropometric index to categorize nutritional status in adults. BMI is calculated as weight in kilograms divided by height in meters squared (kg/m^2). According to WHO international criteria, BMI 18.5–24.9 kg/m^2 is considered normal, 25.0–29.9 kg/m^2 as overweight, and ≥30 kg/m^2 as obesity. Obesity is further divided into subclasses based on severity. However, because Asian populations develop metabolic complications at lower BMI levels, WHO and expert consultation groups proposed lower cut-off values for Asian populations: normal BMI 18.5–22.9 kg/m^2, overweight 23.0–24.9 kg/m^2, and obesity ≥25 kg/m^2. These modified thresholds improve early identification of cardiometabolic risk in Asian individuals [1,3].

Class I, II and III Obesity (Morbid Obesity)

Obesity is further categorized based on severity to estimate health risk. According to WHO and the National Institutes of Health classification, Class I obesity is defined as BMI 30.0–34.9 kg/m^2, Class II obesity as BMI 35.0–39.9 kg/m^2, and Class III obesity as BMI ≥40 kg/m^2. Class III obesity is often termed "morbid obesity" because it is associated with markedly increased risk of cardiovascular disease, type 2 diabetes mellitus, obstructive sleep apnea, osteoarthritis, and premature mortality. Epidemiological studies demonstrate a progressive rise in morbidity and mortality with increasing BMI categories, particularly beyond 35 kg/m^2. This classification helps guide clinical decisions regarding pharmacotherapy and bariatric surgery [4,7].

Central vs General Obesity

Obesity may be classified not only by total body fat (general obesity) but also by fat distribution. General obesity refers to overall excess adiposity measured primarily by BMI. In contrast, central obesity (also called abdominal or android obesity) refers to excess fat accumulation in the abdominal region, particularly visceral adipose tissue. Studies have shown that central obesity is more strongly associated with insulin resistance, dyslipidaemia, hypertension, and cardiovascular disease than general obesity. Waist circumference is a simple and reliable measure of central obesity, with cut-off values of >102 cm in men and >88 cm in women indicating increased metabolic risk. Imaging techniques such as computed tomography and magnetic resonance imaging provide accurate assessment of visceral fat but are not practical for routine clinical use. [12,7].

Health Risk Levels Based on BMI and Waist Circumference

Health risk increases progressively with both BMI and waist circumference. Individuals with overweight and obesity have elevated risks of type 2 diabetes, coronary heart disease, stroke, certain cancers, and all-cause mortality. Importantly, individuals with normal BMI but increased waist circumference may still carry high cardiometabolic risk due to excess visceral fat. Clinical guidelines therefore recommend combining BMI with waist circumference to better stratify health risk. For example, a person with BMI 25–29.9 kg/m² and elevated waist circumference has a substantially higher risk than someone with the same BMI but normal waist measurement. This combined assessment improves identification of individuals requiring early intervention and intensive lifestyle modification [8,3].

3. High-Calorie Diet and Processed Foods

Consumption of high-calorie diets rich in saturated fats, refined carbohydrates, and ultra-processed foods is a major contributor to obesity. Energy-dense foods promote positive energy balance when caloric intake exceeds expenditure, leading to triglyceride accumulation in adipose tissue. Diets high in sugar-sweetened beverages and processed snacks are associated with increased visceral fat deposition and insulin resistance. Research indicates that chronic overnutrition alters hypothalamic appetite regulation and promotes adipocyte hypertrophy and hyperplasia. Additionally, excessive intake of refined carbohydrates contributes to hyperinsulinemia, which favours lipogenesis and inhibits lipolysis. Thus, dietary overload is not merely a caloric issue but also a metabolic driver of adiposity and related complications [13,14].

Sedentary Lifestyle and Reduced Physical Activity

Physical inactivity is a critical etiological factor in obesity. Modern lifestyles characterized by prolonged sitting, reduced occupational physical labour, and increased screen time significantly reduce total daily energy expenditure. When energy expenditure declines without a proportional reduction in caloric intake, fat accumulation ensues. Sedentary behaviour also impairs lipid oxidation, decreases insulin sensitivity, and contributes to chronic low-grade inflammation. Studies show that regular physical activity improves glucose utilization, enhances mitochondrial function, and reduces central adiposity. Therefore, insufficient physical activity not only promotes weight gain but also accelerates metabolic dysfunction [13,14].

Genetic and Familial Factors

Genetic predisposition significantly influences susceptibility to obesity. Twin and family studies demonstrate that 25–40% of BMI variability can be attributed to genetic factors. Genes regulate appetite, satiety, energy expenditure, and adipocyte differentiation. Mutations affecting leptin signalling, melanocortin receptors, and neuropeptide pathways may lead to hyperphagia and reduced thermogenesis. Furthermore, familial clustering of obesity reflects both shared genetic makeup and environmental influences such as dietary habits and physical activity patterns. Although genetics alone rarely causes obesity, it increases vulnerability when combined with obesogenic environmental factors [13].

Endocrine Disorders (Hypothyroidism, PCOS, Cushing's Syndrome)

Certain endocrine disorders contribute to secondary obesity. Hypothyroidism reduces basal metabolic rate, leading to weight gain and fluid retention. Polycystic Ovary Syndrome (PCOS) is associated with insulin resistance, hyperandrogenism, and central obesity, creating a vicious cycle that promotes further metabolic disturbance. Cushing's syndrome, characterized by chronic glucocorticoid excess, leads to truncal obesity, muscle wasting, and impaired glucose tolerance. Hormonal imbalances in these disorders disrupt normal metabolic regulation and favour fat deposition, particularly in the abdominal region. Early diagnosis and appropriate hormonal therapy are essential to prevent progressive weight gain and metabolic complications [14,13].

Stress, Emotional Eating and Psychological Factors

Psychological stress plays a substantial role in obesity through neuroendocrine and behavioural pathways. Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis, increasing cortisol secretion, which promotes visceral fat accumulation and insulin resistance. Emotional eating, characterized by consumption of high-calorie comfort foods in response to stress or negative emotions, further contributes to weight gain. Additionally, depression and anxiety are frequently associated with dysregulated appetite and reduced motivation for physical activity. These psychological factors create a feedback loop that sustains obesity and complicates its management [13].

Sleep Deprivation and Circadian Rhythm Disturbance

Inadequate sleep and disruption of circadian rhythms are increasingly recognized as contributors to obesity. Sleep deprivation alters appetite-regulating hormones, decreasing leptin levels and increasing ghrelin secretion, thereby stimulating hunger and preference for calorie-dense foods. It also impairs glucose metabolism and increases insulin resistance. Chronic circadian misalignment, such as that seen in shift workers, disrupts metabolic homeostasis and promotes adiposity. Epidemiological evidence suggests that individuals sleeping fewer than 6 hours per night have a significantly higher risk of developing obesity compared to those with adequate sleep duration [13].

Environmental and Socioeconomic Influences

Environmental and socioeconomic factors strongly influence obesity prevalence. Urbanization, easy availability of inexpensive processed foods, reduced opportunities for physical activity, and marketing of energy-dense foods contribute to an obesogenic environment. Lower socioeconomic status is associated with limited access to healthy foods, inadequate healthcare, and reduced awareness of lifestyle modification strategies. Cultural practices and social norms also affect dietary patterns and body weight perception. Therefore, obesity is not solely an individual problem, but a complex public health issue shaped by environmental, social, and economic determinants [14].

4. Energy Imbalance Theory

The Energy Imbalance Theory is the fundamental concept underlying the pathogenesis of obesity. It states that obesity develops when energy intake chronically exceeds energy expenditure, resulting in a positive energy balance. Excess calories are stored primarily as triglycerides in adipose tissue. Modern lifestyles characterized by high-calorie diets, processed foods, and reduced physical activity contribute significantly to sustained energy surplus. Although simple in principle, energy balance is tightly regulated by neuroendocrine mechanisms, and even small daily imbalances over time can lead to substantial weight gain. Genetic susceptibility and environmental factors further influence energy storage efficiency and metabolic adaptation, thereby promoting obesity development [15].

Adipose Tissue Expansion and Hypertrophy

Adipose tissue plays a central role in obesity by serving as the primary storage site for excess energy. During positive energy balance, adipose tissue expands through two mechanisms: hypertrophy (increase in adipocyte size) and hyperplasia (increase in adipocyte number). In early obesity, hypertrophy predominates, leading to enlarged adipocytes that become metabolically dysfunctional. Hypertrophic adipocytes exhibit impaired lipid storage capacity, increased lipolysis, and secretion of pro-inflammatory cytokines. As adipose tissue expands beyond its vascular supply, local hypoxia develops, triggering macrophage infiltration and inflammatory signalling pathways. This dysfunctional adipose tissue contributes to metabolic complications associated with obesity [16].

Role of Hypothalamus in Appetite Regulation

The hypothalamus is the primary brain region responsible for regulating appetite and energy homeostasis. Within the hypothalamus, the arcuate nucleus contains two key neuronal populations: orexigenic neurons (NPY/AgRP) that stimulate appetite and anorexigenic neurons (POMC/CART) that suppress food intake. These neurons respond to peripheral hormonal and nutrient signals to maintain energy balance. When regulatory signalling is disrupted, as seen in obesity, hypothalamic inflammation and leptin resistance impair satiety signalling, leading to increased food intake and reduced energy expenditure. Thus, dysfunction of hypothalamic pathways contributes significantly to sustained weight gain [17].

Hormonal Regulation (Leptin, Ghrelin, GLP-1, Insulin)

Hormones play a crucial role in appetite control and metabolic regulation. Leptin, produced by adipocytes, signals satiety to the hypothalamus and reduces food intake; however, in obesity, elevated leptin levels lead to leptin resistance, diminishing its anorexigenic effect. Ghrelin, secreted by the stomach, stimulates hunger and increases before meals, promoting food intake. GLP-1 (glucagon-like peptide-1), released from intestinal L-cells, enhances insulin secretion and promotes satiety, thereby reducing caloric intake. Insulin, beyond its metabolic role in glucose uptake, also acts centrally to suppress appetite. Dysregulation of these hormonal pathways contributes to overeating, weight gain, and metabolic disturbances in obesity [18].

Development of Insulin Resistance

Insulin resistance is a hallmark metabolic complication of obesity. It develops when peripheral tissues such as skeletal muscle, liver, and adipose tissue become less responsive to insulin signalling. Enlarged adipocytes release excessive free fatty acids into circulation, leading to ectopic fat deposition in liver and muscle. Accumulation of intracellular lipid metabolites interferes with insulin receptor signalling pathways. Additionally, pro-inflammatory cytokines such as TNF-α and IL-6 further impair insulin action. As a result, higher insulin levels are required to maintain glucose homeostasis, eventually contributing to hyperinsulinemia and type 2 diabetes mellitus [19].

Chronic Low-Grade Inflammation

Obesity is characterized by chronic low-grade systemic inflammation. Expanded adipose tissue recruits immune cells, particularly macrophages, which shift toward a pro-inflammatory phenotype. These immune cells release inflammatory mediators including TNF-α, IL-6, and C-reactive protein. Persistent inflammatory signalling disrupts insulin signalling pathways and promotes metabolic dysfunction. Unlike acute inflammation, this low-grade inflammation is sustained over prolonged periods and contributes to the development of insulin resistance, cardiovascular disease, and other obesity-related complications. Therefore, obesity is now recognized not only as a metabolic disorder but also as a chronic inflammatory condition [20].

5. Obesity-Related Diseases

Obesity is a chronic, relapsing metabolic disorder characterized by excessive accumulation of adipose tissue that impairs health and predisposes individuals to multiple systemic diseases. It results from a long-term imbalance between energy intake and energy expenditure, influenced by genetic, environmental, hormonal, and behavioural factors. The World Health Organization defines obesity as a body mass index (BMI) ≥ 30 kg/m², although lower BMI thresholds are recommended for certain Asian populations because of higher cardiometabolic risk at comparatively lower body weights. The global rise in obesity prevalence has made it a major contributor to morbidity, mortality, and healthcare burden worldwide [13].

Cardiovascular disease

Cardiovascular disease is the most significant and life-threatening complication of obesity. Numerous epidemiological studies, including long-term population analyses, have demonstrated a positive association between obesity and coronary artery disease, myocardial infarction, cerebrovascular disease, and congestive heart failure. Although adiposity alone may not directly cause atherosclerosis, obesity contributes indirectly through associated risk factors such as hypertension, diabetes mellitus, dyslipidaemia, and reduced high-density lipoprotein (HDL) cholesterol levels. These metabolic abnormalities accelerate endothelial dysfunction and plaque formation, increasing the risk of thrombotic events and premature cardiovascular mortality [14].

Hypertension

Hypertension is strongly linked with obesity and is one of its most common comorbid conditions. Increased adipose tissue leads to expanded plasma volume, elevated cardiac output, and activation of the renin–angiotensin–aldosterone system, resulting in increased blood pressure. Sodium retention and sympathetic nervous system stimulation further aggravate hypertension in obese individuals. Obesity-related hypertension significantly increases the risk of stroke, heart failure, and kidney disease. Importantly, clinical evidence shows that even moderate weight reduction can produce substantial reductions in blood pressure, emphasizing the importance of lifestyle intervention in management [14].

Type 2 diabetes mellitus

Type 2 diabetes mellitus is a major metabolic consequence of obesity. Excess adipose tissue, particularly visceral fat, releases pro-inflammatory cytokines and adipokines that interfere with insulin signalling pathways. This leads to insulin resistance, reduced glucose uptake by peripheral tissues, and persistent hyperglycaemia. Chronic insulin resistance places increased demand on pancreatic beta cells, eventually resulting in beta-cell dysfunction and overt diabetes. The inflammatory state associated with obesity, often termed “meta inflammation,” further exacerbates glucose intolerance. Therefore, obesity is considered the most important modifiable risk factor for the development of type 2 diabetes mellitus [13].

Dyslipidaemia

Dyslipidaemia frequently accompanies obesity and plays a significant role in cardiovascular complications. Obese individuals commonly exhibit elevated levels of low-density lipoprotein (LDL) cholesterol and triglycerides along with decreased HDL cholesterol. These lipid abnormalities contribute to the formation of atherosclerotic plaques within arterial walls. Altered lipid metabolism in obesity increases hepatic synthesis of very-low-density lipoproteins and impairs lipid clearance, thereby enhancing the risk of coronary heart disease and stroke [14].

Metabolic syndrome

Metabolic syndrome represents a clustering of obesity-related metabolic abnormalities, including central obesity, hyperglycaemia, hypertension, hypertriglyceridemia, and reduced HDL cholesterol. Central adiposity is considered a key pathogenic component because visceral fat is metabolically active and strongly associated with insulin resistance. Individuals with metabolic syndrome have a markedly increased risk of developing cardiovascular disease and type 2 diabetes. The syndrome reflects the interconnected pathophysiological processes of inflammation, hormonal imbalance, and metabolic dysregulation seen in obesity [13].

Gallbladder disease

Gallbladder disease, particularly cholelithiasis, is more prevalent among obese individuals. Obesity alters cholesterol metabolism, leading to supersaturation of bile with cholesterol and promoting gallstone formation. Increased hepatic secretion of cholesterol into bile and reduced gallbladder motility contribute to stone formation. Rapid weight loss, especially following very-low-calorie diets, may further increase the risk of gallstone development [14]. Obesity is increasingly recognized as a chronic low-grade inflammatory condition. Adipose tissue acts as an endocrine organ and secretes various pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukins, and C-reactive protein, while decreasing anti-inflammatory adipokines like adiponectin. Macrophage infiltration into adipose tissue enhances this inflammatory environment. This persistent inflammation contributes to insulin resistance, endothelial dysfunction, atherosclerosis, and progression of metabolic diseases [13]. Certain cancers have also been linked to obesity. Chronic hyperinsulinemia, increased levels of insulin-like growth factors, sex hormone alterations, and systemic inflammation create a favourable environment for carcinogenesis. Epidemiological data suggest increased risk of breast, colorectal, endometrial, and other hormone-related cancers in obese individuals. Thus, obesity not only affects metabolic health but also contributes to oncological risk [13]. In addition to metabolic and cardiovascular disorders, obesity causes mechanical and functional complications. Excess body weight places increased stress on weight-bearing joints, leading to osteoarthritis and chronic musculoskeletal pain. Accumulation of adipose tissue in the thoracic and abdominal regions impairs respiratory mechanics, predisposing individuals to reduced pulmonary function and sleep-disordered breathing. These complications significantly reduce quality of life and functional capacity.14 Diagnosis and Clinical Evaluation of Obesity [1].

6. Body Mass Index (BMI)

Calculation and Clinical Use Body Mass Index (BMI) is the most widely used and practical method for diagnosing obesity in clinical and epidemiological settings. It is calculated using the formula: BMI = Weight (kg) / Height (m^2). According to international guidelines, BMI values are classified as follows: normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥30 kg/m^2). Obesity is further subclassified into Grade I (30–34.9 kg/m^2), Grade II (35–39.9 kg/m^2), and Grade III (≥40 kg/m^2). Although BMI correlates well with body fat at the population level, it does not differentiate between fat mass and lean body mass. Therefore, muscular individuals may be misclassified as overweight or obese. Despite this limitation, BMI remains the primary screening tool due to its simplicity, reproducibility, and strong association with morbidity and mortality risk [7].

Waist Circumference and Waist–Hip Ratio

Assessment of fat distribution is a vital component of clinical evaluation because central (abdominal) obesity is more strongly associated with metabolic and cardiovascular complications than overall obesity. Waist circumference (WC) is measured midway between the lower rib margin and the iliac crest. Abnormal values are ≥102 cm in men and ≥88 cm in women. Waist–hip ratio (WHR) is calculated by dividing waist circumference by hip circumference. Elevated WC and WHR indicate visceral fat accumulation, which is linked to insulin resistance, type 2 diabetes mellitus, dyslipidaemia, and cardiovascular disease. Studies suggest that waist circumference is a better predictor of metabolic risk than BMI alone. Hence, combining BMI with waist measurements improves clinical risk stratification.

Body Fat Percentage Assessment Body fat percentage

provides a more accurate representation of adiposity than BMI because it distinguishes fat mass from lean mass. Obesity is defined as body fat ≥25% in men and ≥35% in women. Methods for assessment include skinfold thickness measurement, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), underwater weighing, and fat mass index (FMI). Among these, BIA is commonly used in clinical practice due to its convenience and non-invasive nature. However, it requires population-specific predictive equations for accuracy. Studies have shown that BMI may misclassify individuals when compared with percentage body fat and FMI, highlighting the importance of body composition analysis in selected patients [21].

Laboratory Investigations

Laboratory evaluation is essential to detect obesity-related metabolic complications. The standard investigations include fasting blood glucose, HbA1c, lipid profile (total cholesterol, LDL, HDL, triglycerides), and sometimes liver function tests. Elevated fasting glucose and HbA1c indicate impaired glucose tolerance or type 2 diabetes mellitus. Dyslipidaemia in obesity typically presents as elevated triglycerides, increased LDL cholesterol, and reduced HDL cholesterol. These metabolic abnormalities significantly increase cardiovascular risk. Therefore, laboratory screening is crucial not only for diagnosis but also for risk assessment and therapeutic monitoring in obese patients [22].

Metabolic Syndrome

Criteria Metabolic syndrome is a cluster of metabolic abnormalities commonly associated with obesity, particularly central obesity. Diagnostic criteria include abdominal obesity, elevated triglycerides (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), elevated blood pressure (≥130/85 mmHg), and fasting glucose ≥100 mg/dL. The presence of three or more of these criteria confirms the diagnosis. Central adiposity plays a key role in the pathogenesis of insulin resistance, systemic inflammation, and atherogenesis. Identification of metabolic syndrome is important because it significantly increases the risk of cardiovascular disease and type 2 diabetes [7].

Table: Clinical Evaluation Parameters in Obesity

Parameter	Method of Assessment	Diagnostic Criteria	Clinical Significance
BMI	Weight (kg) / Height (m²)	≥30 kg/m² = Obesity	General obesity classification
Waist Circumference	Measuring tape	≥102 cm (men), ≥88 cm (women)	Central obesity, metabolic risk
Waist–Hip Ratio	WC / HC	>0.90 (men), >0.85 (women)	Visceral fat risk
Body Fat %	BIA, DEXA, skinfold	≥25% (men), ≥35% (women)	Accurate adiposity measure
Fasting Glucose	Blood test	≥100 mg/dL	Diabetes risk
HbA1c	Blood test	≥6.5% (diabetes)	Long-term glycemic control
Lipid Profile	Blood test	TG ≥150 mg/dL, Low HDL	Cardiovascular risk
Blood Pressure	Sphygmomanometer	≥130/85 mmHg	Hypertension risk

7. Non-Pharmacological Management of Obesity

Medical Nutrition Therapy (Calorie Restriction and Balanced Diet) Medical nutrition therapy (MNT)

MNT is the cornerstone of obesity management and is based on the principle of creating a sustained negative energy balance. A daily caloric deficit of 500–1000 kcal is recommended to achieve gradual weight loss of 0.5–1 kg per week. Balanced diets typically include 45–65% carbohydrates, 20–35% fats, and 10–20% proteins, with emphasis on fibre-rich foods, fruits, vegetables, whole grains, and lean protein sources. Clinical evidence demonstrates that structured dietary counselling significantly improves weight reduction and reduces obesity-related comorbidities such as hypertension, dyslipidaemia, and type 2 diabetes. Importantly, dietary intervention must be individualized according to age, sex, cultural preference, metabolic risk, and comorbid conditions to ensure long-term adherence and effectiveness [22].

Low-Carbohydrate and Ketogenic Diet

Low-carbohydrate diets restrict carbohydrate intake to less than 130 g/day, while ketogenic diets further reduce intake to less than 50 g/day, inducing a metabolic state of ketosis. In ketosis, the body shifts from glucose metabolism to fat oxidation, producing ketone bodies for energy. Studies show that these diets promote rapid short-term weight loss, improved insulin sensitivity, and reduced triglyceride levels. The mechanisms include appetite suppression, increased satiety from protein intake, and enhanced fat metabolism. However, long-term sustainability remains a concern, and potential risks such as micronutrient deficiency and lipid abnormalities require monitoring. Therefore, these diets should be medically supervised, especially in patients with metabolic syndrome or diabetes [23].

Mediterranean Diet

The Mediterranean diet emphasizes high consumption of fruits, vegetables, legumes, nuts, olive oil, and whole grains, moderate intake of fish and poultry, and low intake of red meat and processed foods. This dietary pattern is rich in monounsaturated fats and antioxidants, which contribute to cardiometabolic protection. Evidence indicates that the Mediterranean diet improves lipid profile, reduces inflammatory markers, enhances insulin sensitivity, and lowers cardiovascular risk in obese individuals. Unlike restrictive diets, it promotes sustainable eating habits and is associated with long-term weight maintenance [7].

Intermittent Fasting Intermittent fasting (IF):

IF involves structured periods of fasting and eating, such as the 16:8 method or alternate-day fasting. IF promotes weight loss primarily through caloric restriction and metabolic switching from glucose to fat utilization. It has been shown to improve insulin sensitivity, reduce visceral fat accumulation, and decrease systemic inflammation. Some studies suggest that intermittent fasting may enhance metabolic flexibility and mitochondrial function. However, adherence varies among individuals, and IF may not be suitable for pregnant women, elderly individuals, or patients with eating disorders. Therefore, patient selection and counselling are essential [23].

Physical Activity (Aerobic and Resistance Training)

Physical activity plays a critical role in both weight reduction and long-term weight maintenance. Aerobic exercises such as brisk walking, cycling, or swimming increase energy expenditure and improve cardiovascular fitness. Resistance training enhances lean body mass, increases resting metabolic rate, and prevents sarcopenia during weight loss. Current recommendations suggest at least 150–300 minutes of moderate-intensity aerobic activity per week, combined with resistance training two to three times weekly. Exercise also improves insulin sensitivity, reduces blood pressure, enhances lipid metabolism, and lowers chronic inflammation. Regular physical activity is strongly associated with sustained weight loss and reduced obesity-related complications [23].

Behavioural Modification Therapy

Behavioural therapy addresses psychological and environmental factors contributing to obesity. Core components include self-monitoring of food intake and physical activity, stimulus control, goal setting, cognitive restructuring, and relapse prevention. Structured behavioural programs delivered over at least 6 months significantly enhance weight loss outcomes compared to minimal counselling. Long-term follow-up and maintenance therapy are essential to prevent weight regain, as obesity is a chronic relapsing condition. Behavioural interventions improve self-efficacy, motivation, and treatment adherence, making them fundamental to comprehensive obesity management [22].

Digital Health and Lifestyle Monitoring:

Digital health technologies, including mobile applications, wearable devices, and telehealth counselling, have emerged as innovative tools in obesity management. These platforms facilitate self-monitoring of calorie intake, step count, heart rate, and sleep patterns. Digital interventions increase patient engagement, provide real-time feedback, and improve adherence to lifestyle modifications. Studies demonstrate that technology-supported behavioural programs achieve clinically meaningful weight loss comparable to traditional in-person programs. Digital health also improves accessibility, particularly in primary care and remote settings [23].

Summary Table: Non-Pharmacological Interventions in Obesity

Intervention	Mechanism	Benefits	Limitations
Calorie Restriction	Creates energy deficit	Gradual weight loss, improved metabolic profile	Requires long-term adherence
Low-Carbohydrate/ Ketogenic Diet	Fat oxidation and ketosis	Rapid weight loss, improved insulin sensitivity	Sustainability concerns
Mediterranean Diet	Anti-inflammatory, cardioprotective	Improved lipid profile, heart protection	Slower weight loss
Intermittent Fasting	Metabolic switching	Reduced visceral fat, improved insulin sensitivity	Not suitable for all populations
Physical Activity	Increased energy expenditure	Improves cardiovascular health, maintains lean mass	Requires motivation and consistency
Behavioral Therapy	Cognitive restructuring and monitoring	Enhances adherence and relapse prevention	Requires structured programs

Digital Health	Self-monitoring and feedback	Improved engagement and accessibility	Technology dependence

8. Pharmacological Management of Obesity

Indications for Drug Therapy (BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities)

Pharmacological therapy is recommended as an adjunct to lifestyle modification in patients who fail to achieve adequate weight reduction with diet and physical activity alone. According to major clinical guidelines, anti-obesity drugs should be considered in adults with a body mass index (BMI) ≥30 kg/m² or ≥27 kg/m² in the presence of obesity-related comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidaemia, or obstructive sleep apnea. Drug therapy is not intended as monotherapy but should always accompany structured lifestyle intervention. The rationale is that biological adaptations following weight loss (reduced energy expenditure and increased appetite) often lead to weight regain, and pharmacotherapy helps counteract these compensatory mechanisms [24]. Long-term pharmacotherapy is especially indicated in patients with persistent obesity despite structured lifestyle programs. The UK National Institute for Health and Care Excellence (NICE) recommends initiating pharmacological treatment only after dietary, exercise, and behavioural approaches have been attempted and evaluated. Similarly, US guidelines emphasize individualized treatment decisions based on BMI, comorbid conditions, and risk–benefit assessment [24].

Treatment Goals (5–15% Weight Reduction

The primary goal of pharmacological therapy is clinically meaningful weight loss, typically defined as a 5–15% reduction in baseline body weight. A weight reduction of at least 5% is associated with significant improvements in glycaemic control, blood pressure, lipid profile, and inflammatory markers. Greater weight loss (10–15%) provides additional metabolic and cardiovascular benefits, including improved insulin sensitivity and reduction in cardiovascular risk factors [13]. Regulatory authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require anti-obesity medications to demonstrate either a placebo-subtracted weight loss of ≥5% at one year or that at least 35% of treated patients achieve ≥5% weight loss compared with placebo. These criteria ensure that approved medications provide clinically meaningful benefits beyond lifestyle intervention alone [24].

Duration of Therapy

Obesity is now recognized as a chronic, relapsing disease; therefore, pharmacotherapy often requires long-term or even lifelong use. Anti-obesity drugs are effective only while they are being taken, and discontinuation frequently results in weight regain due to persistent biological drivers of weight gain. Clinical guidelines recommend evaluating the response after 3–4 months at the maximum tolerated dose. If at least 4–5% weight loss is not achieved, the medication should be discontinued and alternative options considered. [1]. Some older agents such as phentermine were initially approved for short-term use (<12 weeks), but newer agents including GLP-1 receptor agonists are approved for long-term therapy. The decision regarding duration depends on efficacy, tolerability, safety profile, and patient adherence [24].

Monitoring and Safety Considerations

Careful monitoring is essential to ensure safety and therapeutic effectiveness. Baseline assessment should include BMI, waist circumference, blood pressure, fasting glucose, HbA1c, and lipid profile. During therapy, periodic monitoring of weight, cardiovascular parameters, glycaemic status, and adverse effects is recommended. Some medications may increase heart rate or blood pressure, while others may cause gastrointestinal disturbances or neuropsychiatric effects [24]. All anti-obesity medications are contraindicated during pregnancy. Caution is required in patients with cardiovascular disease, psychiatric disorders, or renal impairment depending on the drug used. Regular evaluation ensures early identification of adverse events and appropriate dose adjustments or discontinuation if necessary [25].

9. Classification of Anti-Obesity Drugs Anti-obesity drugs (AODs)

Drugs Anti-obesity drugs (AODs) are pharmacological agents used as adjuncts to lifestyle modification for the management of obesity. They act through various mechanisms, including appetite suppression, reduction of nutrient absorption, and modulation of gut–brain hormonal pathways. Based on their mechanism of action, anti-obesity drugs are broadly classified into appetite suppressants, lipase inhibitors, GLP-1 receptor agonists, dual and triple incretin agonists, and combination therapies. The evolution of these drugs reflects advances in understanding the neuroendocrine regulation of body weight and energy balance (13).

Appetite Suppressants

Appetite suppressants primarily act on the central nervous system, particularly the hypothalamus, to reduce hunger and increase satiety. Earlier agents such as phentermine stimulate the release of norepinephrine, thereby decreasing appetite through activation of the sympathetic nervous system. Other centrally acting drugs like sibutramine (withdrawn due to cardiovascular risk) worked by inhibiting the reuptake of serotonin and norepinephrine. More recent agents such as lorcaserin selectively stimulated 5-HT2C receptors to enhance satiety, although it was later withdrawn due to safety concerns. These drugs generally produce modest weight loss (5–10%) and are indicated for patients with BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities. However, their use is limited by adverse effects such as insomnia, increased heart rate, hypertension, and potential for abuse (2).

Lipase Inhibitors

Lipase inhibitors reduce dietary fat absorption by inhibiting gastric and pancreatic lipases in the gastrointestinal tract. Orlistat is the only approved drug in this class and acts locally within the intestine to block approximately 30% of fat absorption. Because of its minimal systemic absorption, orlistat has a favourable systemic safety profile. However, gastrointestinal side effects such as steatorrhea, flatulence, and faecal urgency are common, particularly when patients consume high-fat meals. Orlistat has also shown modest benefits in improving lipid profiles and reducing the incidence of type 2 diabetes in obese patients. Its efficacy typically results in 5–8% weight reduction over one year when combined with dietary modification (7).

GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists represent a major advancement in obesity pharmacotherapy. Drugs such as liraglutide and semaglutide mimic endogenous GLP-1, enhancing glucose-dependent insulin secretion, delaying gastric emptying, and increasing satiety via central mechanisms. Clinical trials have demonstrated significant weight loss ranging from 10–15% or more, particularly with higher-dose semaglutide formulations. These agents also provide cardiovascular and glycaemic benefits, making them especially valuable in patients with obesity and type 2 diabetes. Common adverse effects include nausea, vomiting, and gastrointestinal discomfort, which are usually dose-dependent and transient (4).

Dual and Triple Incretin Agonist

Recent research has focused on multi-agonist therapies targeting multiple gut hormones simultaneously. Dual incretin agonists such as tirzepatide act on both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, leading to enhanced weight reduction and glycaemic control. Clinical trials have reported weight loss exceeding 15–20%, approaching results seen with bariatric surgery. Emerging triple agonists targeting GLP-1, GIP, and glucagon receptors are currently under investigation and show promising early results in enhancing energy expenditure and fat oxidation. These novel agents represent the future direction of pharmacological obesity management.

Combination Therapy

Combination therapy involves the use of two drugs with complementary mechanisms to enhance efficacy and reduce individual drug doses. Examples include phentermine/topiramate extended release and naltrexone/bupropion sustained release. Phentermine/topiramate combines appetite suppression with modulation of gamma-aminobutyric acid (GABA) receptors to reduce food intake, producing weight loss of 8–12%. Naltrexone/bupropion acts on hypothalamic appetite pathways and the mesolimbic reward system to decrease food cravings. Combination therapies often provide superior weight reduction compared to monotherapy but require careful monitoring for neuropsychiatric and cardiovascular adverse effects [9].

10. Mechanism of Action of Anti-Obesity Drugs

Anti-obesity drugs exert their therapeutic effects through multiple physiological pathways involved in appetite regulation, energy balance, nutrient absorption, and metabolic control. The mechanisms primarily target central nervous system pathways, gut-derived hormonal signalling, gastrointestinal motility, lipid digestion, and thermogenesis. Understanding these mechanisms is essential for rational drug selection and safe clinical use.

Appetite Suppression via Central Nervous System (CNS)

Appetite suppression is mainly mediated through hypothalamic pathways that regulate hunger and satiety. Several anti-obesity drugs act on the arcuate nucleus of the hypothalamus, influencing pro-opiomelanocortin (POMC) neurons and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons. Sympathomimetic agents increase norepinephrine release, thereby stimulating POMC neurons and reducing appetite. Serotonergic agents act on 5-HT2C receptors to promote satiety, while combination therapies such as naltrexone–bupropion enhance POMC activation and reduce reward-driven eating behaviour. These centrally acting drugs decrease caloric intake by modulating neurotransmitters involved in feeding behaviour and reward pathways. However, they may also produce CNS-related adverse effects such as insomnia, anxiety, and increased heart rate [24].

Satiety Enhancement via Gut Hormones

Recent advances in obesity pharmacotherapy focus on incretin-based therapies that mimic endogenous gut hormones. GLP-1 receptor agonists (e.g., liraglutide, semaglutide) enhance glucose-dependent insulin secretion, suppress glucagon release, and increase satiety by acting on both central and peripheral GLP-1 receptors. Dual and triple incretin agonists target GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors, producing synergistic effects on appetite regulation and energy balance. These agents reduce hunger signals, prolong satiety after meals, and significantly reduce caloric intake. Clinical trials demonstrate substantial weight reduction with these agents compared to lifestyle modification alone. Gastrointestinal side effects such as nausea and vomiting are common but often transient [24].

Delay in Gastric Emptying Certain anti-obesity drugs

particularly GLP-1 receptor agonists, slow gastric emptying. By delaying the transit of food from the stomach to the small intestine, these agents prolong gastric distension and enhance postprandial fullness. The delayed gastric emptying contributes to reduced meal size and decreased frequency of eating. This mechanism also improves postprandial glycaemic control, which is particularly beneficial in patients with type 2 diabetes and obesity. Although effective, excessive delay in gastric emptying may lead to gastrointestinal discomfort, nausea, or bloating [13].

Reduction of Fat Absorption

Orlistat is a pancreatic and gastric lipase inhibitor that reduces dietary fat absorption. It acts locally within the gastrointestinal tract by inhibiting lipase enzymes required for triglyceride hydrolysis. As a result, approximately 30% of ingested fat is excreted undigested in the faces, leading to reduced caloric absorption and gradual weight loss. Because its action is peripheral rather than central, systemic side effects are minimal. However, gastrointestinal adverse effects such as steatorrhea, flatulence, and fat-soluble vitamin deficiencies may occur, necessitating dietary counselling and supplementation when required [24].

Increased Energy Expenditure

Some anti-obesity agents promote weight loss by increasing energy expenditure. Agents with sympathomimetic activity stimulate β-adrenergic receptors, leading to enhanced thermogenesis and lipolysis. Experimental agents targeting glucagon receptors and mitochondrial uncoupling pathways are designed to increase metabolic rate and fat oxidation. Although increased energy expenditure contributes to weight reduction, the magnitude of this effect is generally smaller compared to appetite suppression mechanisms. Safety concerns such as cardiovascular stimulation limit the widespread use of thermogenic agents. Emerging dual and triple incretin agonists may also influence energy expenditure through glucagon receptor activation, representing a promising future direction in obesity pharmacotherapy [24].

11. Innovative Anti-Obesity Drugs

Obesity is a chronic, relapsing metabolic disease characterized by excess adiposity and associated with type 2 diabetes, cardiovascular disease, dyslipidaemia, and certain cancers. Lifestyle modification remains the foundation of management; however, long-term weight loss through diet and exercise alone is often modest and difficult to sustain due to physiological adaptations such as reduced energy expenditure and increased hunger signalling. Therefore, pharmacotherapy has emerged as an important adjunct in obesity management, especially with the advent of newer gut hormone–based therapies that target central appetite regulation pathways [24,23].

GLP-1 Receptor Agonists (Semaglutide, Liraglutide)

Glucagon-like peptide-1 (GLP-1) receptor agonists represent a breakthrough in anti-obesity pharmacotherapy. GLP-1 is an incretin hormone secreted from intestinal L-cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and increases satiety via hypothalamic appetite centers. Liraglutide (3.0 mg daily) and semaglutide (2.4 mg weekly) are synthetic GLP-1 analogues resistant to DPP-4 degradation. Clinical trials have shown that semaglutide produces approximately 15% mean weight loss at 68 weeks, which is nearly double that achieved by intensive lifestyle modification alone. These agents significantly reduce hunger, energy intake, and preference for energy-dense foods [23,29].

Dual Incretin Agonists (Tirzepatide)

Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. By activating both incretin pathways, it enhances insulin secretion, improves glycaemic control, and exerts potent appetite-suppressing effects. Clinical trials have demonstrated mean weight reductions up to 20.9%, making it one of the most effective pharmacological therapies currently available. Tirzepatide reduces caloric intake primarily by increasing satiety and reducing hunger, like GLP-1 agonists but with greater magnitude. Its dual mechanism may provide synergistic metabolic benefits, including improved insulin sensitivity and lipid profiles [23,24].

Oral GLP-1 Preparations

The development of oral GLP-1 receptor agonists represents a significant advancement aimed at improving patient adherence. Traditionally, GLP-1 analogues required subcutaneous administration due to peptide degradation in the gastrointestinal tract. However, novel absorption enhancers have enabled oral semaglutide formulations. These preparations demonstrate clinically meaningful weight reduction and glycaemic control while eliminating injection-related barriers. Although weight loss with oral formulations may be slightly less than injectable high-dose semaglutide, they expand accessibility and acceptance of incretin-based therapies in obesity management [24,29].

Amylin Analogues

Amylin is a pancreatic hormone co-secreted with insulin that regulates postprandial glucose levels and promotes satiety by slowing gastric emptying and acting on the area postrema in the brainstem. Synthetic amylin analogues, such as pramlintide, have demonstrated modest weight loss effects and improved glycaemic control. Emerging research suggests that combining amylin analogues with GLP-1 receptor agonists may produce additive or synergistic effects on appetite suppression and energy intake reduction. This combination strategy reflects a broader trend toward polytherapeutic approaches targeting multiple appetite-regulating pathways to enhance efficacy while maintaining safety [29,24].

Future Triple Agonists (GLP-1/GIP/Glucagon)

Future pharmacotherapy is moving toward triple agonist molecules that simultaneously activate GLP-1, GIP, and glucagon receptors. While GLP-1 and GIP reduce appetite and enhance insulin secretion, glucagon receptor activation increases energy expenditure and promotes lipolysis. The rationale behind triple agonists is to mimic the metabolic effects of bariatric surgery by targeting multiple hormonal pathways involved in energy balance. Preclinical and early clinical studies suggest that these multi-agonists may produce greater and more sustained weight loss than single or dual agents. However, safety, tolerability, and long-term cardiovascular outcomes remain areas of ongoing investigation [29].

12. Drug Development and Recent Advances in Obesity Management

Drug Development in Obesity

Obesity is a chronic, relapsing metabolic disease characterized by excessive adiposity resulting from an imbalance between energy intake and expenditure. It is associated with significant morbidity and mortality, including type 2 diabetes mellitus, cardiovascular disease, dyslipidaemia, and certain cancers. Because lifestyle modification alone typically produces only modest and unstained weight loss (3–10%), pharmacological intervention has become an essential adjunct in long-term obesity management. Early anti-obesity drugs primarily targeted central monoaminergic pathways but were limited by modest efficacy and significant adverse effects. The evolution of obesity pharmacotherapy reflects improved understanding of neuroendocrine regulation of appetite and energy homeostasis, particularly gut–brain axis signalling mechanisms [29,22]. Recent advances in drug development focus on targeting hormonal regulators of satiety and hunger, including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and other incretin pathways. These newer agents demonstrate substantially greater efficacy compared to first-generation medications such as orlistat and sibutramine. Importantly, regulatory agencies such as the FDA and EMA now require at least 5% placebo-subtracted weight loss or ≥35% of treated patients achieving ≥5% weight loss at one year to establish clinical efficacy, thereby raising the standard for approval of new agents [24].

Advances in Incretin-Based Therapy

Incretin-based therapies represent a change in thinking in obesity pharmacotherapy. GLP-1 receptor agonists were initially developed for type 2 diabetes but demonstrated significant weight-reducing effects due to appetite suppression, delayed gastric emptying, and enhanced satiety. Semaglutide 2.4 mg has shown mean weight reductions of approximately 15% at 68 weeks, which is nearly double. that achieved with intensive lifestyle intervention alone. Tirzepatide, a dual GIP and GLP-1 receptor agonist, has demonstrated even greater mean weight reductions, reaching up to 20% in clinical trials. These findings mark a significant advancement toward pharmacological outcomes [23,24]. Mechanistically, incretin therapies act on hypothalamic appetite-regulating centres and peripheral metabolic tissues, improving glycaemic control while reducing caloric intake. Unlike earlier appetite suppressants that acted primarily through central monoamine pathways, incretin-based drugs align more closely with physiological hormone signalling, contributing to improved safety profiles. Ongoing research is evaluating triple agonists (GLP-1/GIP/glucagon) and combination therapies to further enhance efficacy and durability of weight loss [23].

Clinical Trial Phases (Phase I–III)

The development of anti-obesity drugs follows a rigorous multi-phase clinical trial pathway. Phase I trials primarily assess safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy volunteers. These studies determine appropriate dosing ranges and identify early adverse effects. Phase II trials evaluate preliminary efficacy in individuals with obesity and refine optimal dose selection while continuing safety assessments [24]. Phase III trials are large-scale randomized controlled trials designed to confirm efficacy and monitor long-term safety in diverse patient populations. Regulatory authorities require demonstration of clinically meaningful weight loss sustained for at least one year. Additionally, improvement in obesity-related comorbidities such as hypertension, dyslipidaemia, and type 2 diabetes is considered an important secondary outcome. Post-marketing surveillance (Phase IV) continues safety monitoring due to historical concerns regarding cardiovascular and psychiatric adverse events associated with earlier anti-obesity drugs [24].

Role of Pharmaceutical Innovations

Pharmaceutical innovation has significantly transformed obesity treatment by shifting from centrally acting sympathomimetic agents to hormone-based and multi-target therapies. Advances in peptide engineering, extended-release formulations, and injectable delivery systems have improved drug stability and patient adherence. The integration of molecular biology and receptor pharmacology has enabled the development of receptor-specific agonists with improved selectivity and reduced off-target effects [22]. Furthermore, combination therapies targeting multiple pathways simultaneously are emerging as a promising strategy. Like treatment approaches in diabetes and hypertension, combining agents at lower doses may enhance efficacy while minimizing adverse effects. This multi-mechanistic approach addresses the redundancy and complexity of energy homeostasis pathways, which historically limited single-agent therapies [24].

Contribution of Novo Nordisk and Eli Lilly

Pharmaceutical companies have played a crucial role in advancing incretin-based obesity therapies. Novo Nordisk pioneered GLP-1 receptor agonists, including liraglutide and semaglutide, significantly expanding the therapeutic landscape for obesity management. Semaglutide 2.4 mg (Wegovy) demonstrated unprecedented weight reduction outcomes, establishing a new benchmark in pharmacotherapy [23]. Eli Lilly further advanced the field with tirzepatide, a dual GIP and GLP-1 receptor agonist, demonstrating superior weight reduction compared to GLP-1 monotherapy. Clinical trials reported mean weight loss exceeding 20% in some participants, positioning tirzepatide as one of the most effective pharmacological options currently available. These contributions have reshaped clinical practice and renewed interest in obesity as a biologically treatable chronic disease rather than solely a lifestyle condition [23,29].

Precision Medicine Approach in Obesity

The future of obesity pharmacotherapy lies in precision medicine, which aims to tailor treatment based on genetic, metabolic, and phenotypic characteristics. Individual responses to anti-obesity drugs vary significantly; some patients achieve substantial weight loss, while others show minimal response. Understanding genetic polymorphisms, hormonal profiles, gut microbiota composition, and metabolic phenotypes may enable clinicians to select the most appropriate therapy for each patient [23,24]. Precision medicine also involves early identification of responders and non-responders within 3–4 months of therapy initiation, as recommended by regulatory guidelines. Discontinuation of ineffective treatment prevents unnecessary exposure to adverse effects and improves cost-effectiveness. Integrating pharmacogenomics, biomarkers, and digital health monitoring may further optimize long-term outcomes and reduce obesity-related complications [24].

13.Surgical Management of Obesity

Indications for Bariatric Surgery (BMI Criteria)

Bariatric surgery is indicated for individuals with severe obesity who have not achieved adequate weight reduction through lifestyle modification and pharmacotherapy. According to the World Health Organization and the National Institutes of Health guidelines, surgery is recommended for patients with a Body Mass Index (BMI) ≥40 kg/m² or ≥35 kg/m² with significant obesity-related comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidaemia, or obstructive sleep apnea. These BMI thresholds are based on strong evidence linking severe obesity with increased morbidity and mortality risk. Recent updates also consider metabolic surgery for patients with BMI 30–34.9 kg/m² when uncontrolled type 2 diabetes persists despite optimal medical therapy,5 BMI classification defines obesity as ≥30 kg/m², with further subclassification into Class I (30–34.9), Class II (35–39.9), and Class III (≥40), which is often termed severe or morbid obesity. These criteria are widely adopted in surgical decision-making to stratify risk and determine eligibility for bariatric procedures [2]. The presence of central obesity, assessed through waist circumference, further increases cardiometabolic risk and strengthens surgical indication [7].

Patient Selection Guidelines

Appropriate patient selection is critical to ensure optimal surgical outcomes. Candidates must demonstrate a history of unsuccessful structured weight loss attempts, adequate understanding of the procedure, and willingness to adhere to long-term dietary and lifestyle modifications. Comprehensive evaluation includes assessment of obesity-related comorbidities, psychological readiness, and absence of contraindications such as untreated major psychiatric disorders or active substance abuse.6,1 Age, severity of obesity, metabolic profile, and overall functional status are also considered. Patients should be motivated and capable of engaging in long-term follow-up care. Current evidence emphasizes individualized risk–benefit assessment, balancing surgical risks against potential improvements in quality of life and reduction in obesity-related complications [4]. Preoperative Evaluation [4].

Preoperative evaluation

aims to optimize patient safety and minimize perioperative complications. A thorough medical assessment includes complete history taking, physical examination, laboratory investigations (complete blood count, liver function tests, lipid profile, fasting glucose), and screening for micronutrient deficiencies. Cardiovascular and pulmonary evaluation is particularly important due to the increased anaesthetic risk associated with severe obesity [27]. Additional investigations such as upper gastrointestinal endoscopy, abdominal ultrasound, or sleep studies may be performed depending on clinical indications. Nutritional assessment and counselling are mandatory to correct deficiencies and prepare patients for postoperative dietary changes. Psychological evaluation is also conducted to identify behavioural or emotional factors that may affect postoperative adherence and outcomes [1].

Multidisciplinary Approach

The success of bariatric surgery depends on a coordinated multidisciplinary approach involving surgeons, physicians, dietitians, psychologists, anaesthesiologists, and nursing staff. Each team member plays a crucial role in preoperative preparation, intraoperative management, and long-term follow-up. This collaborative model enhances patient education, reduces complications, and improves adherence to lifestyle modifications.1 Long-term follow-up is essential to monitor weight loss progress, nutritional status, and resolution of comorbidities. Regular assessment helps detect potential complications such as micronutrient deficiencies, dumping syndrome, or weight regain. Multidisciplinary care has been shown to significantly improve both clinical outcomes and patient satisfaction following bariatric surgery [27].

Expected Weight Loss Outcomes

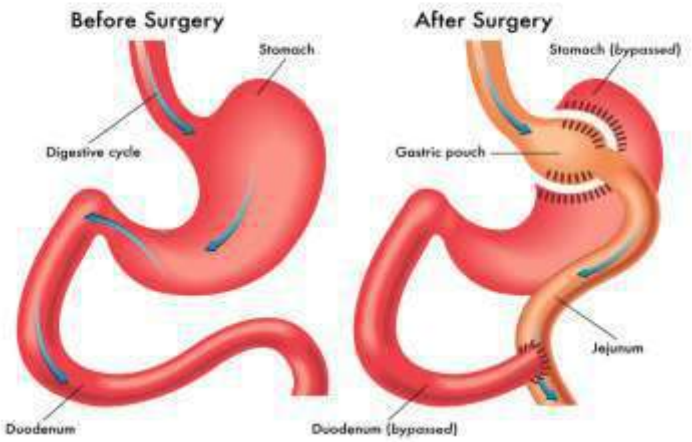
Bariatric surgery results in substantial and sustained weight reduction compared to non-surgical interventions. On average, patients lose 50–70% of excess body weight within 1–2 years following procedures such as gastric bypass or sleeve gastrectomy. Significant improvements are observed in type 2 diabetes, hypertension, dyslipidaemia, and obstructive sleep apnea, with many patients achieving remission of diabetes [27]. Long-term studies demonstrate durable weight loss and reduce overall mortality among surgically treated patients compared to non-surgical controls. The degree of weight loss varies depending on the type of procedure, patient adherence, and baseline characteristics. Overall, bariatric surgery is considered the most effective intervention for sustained weight reduction in severe obesity [27].

14. Types of Bariatric Surgery Basic Principles

Restrictive vs Malabsorptive Procedures

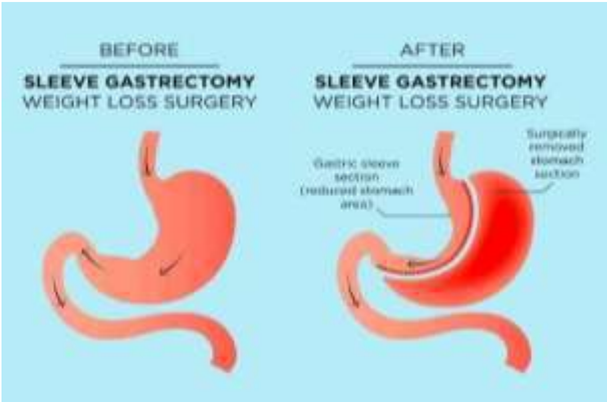
Bariatric procedures are broadly classified into restrictive, malabsorptive, and combined techniques based on their mechanism of action. Restrictive procedures reduce stomach capacity, thereby limiting food intake and promoting early satiety. Malabsorptive procedures bypass a segment of the small intestine, decreasing nutrient and calorie absorption. Combined procedures, such as gastric bypass, incorporate both restriction and malabsorption to enhance weight reduction and metabolic improvement. These mechanisms contribute not only to weight loss but also to favourable hormonal changes affecting insulin sensitivity and lipid metabolism [1]. The reduction in obesity-related comorbidities, including diabetes and dyslipidaemia, further highlights the metabolic impact of these surgical interventions [27,14].

Roux-en-Y Gastric Bypass (RYGB)



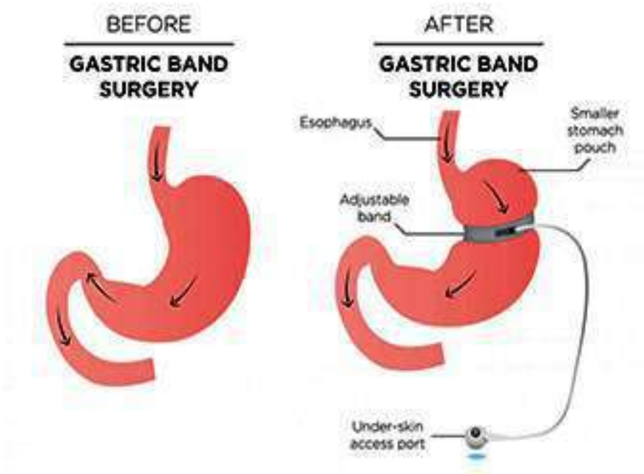
Roux-en-Y gastric bypass is a combined restrictive and malabsorptive procedure and is considered the gold standard of bariatric surgery. In this technique, a small gastric pouch (approximately 15–30 mL) is created from the proximal stomach and connected directly to the jejunum, bypassing a large portion of the stomach and the duodenum. This reduces caloric intake and limits nutrient absorption. Additionally, alterations in gut hormones such as GLP-1 improve glycaemic control, making it particularly effective in patients with type 2 diabetes mellitus [1]. RYGB typically results in 60–70% excess weight loss within 12–18 months postoperatively. It has demonstrated significant remission rates of diabetes, hypertension, and dyslipidaemia. However, potential complications include dumping syndrome, micronutrient deficiencies (iron, vitamin B12, calcium), and anastomotic leaks [27].

Sleeve Gastrectomy



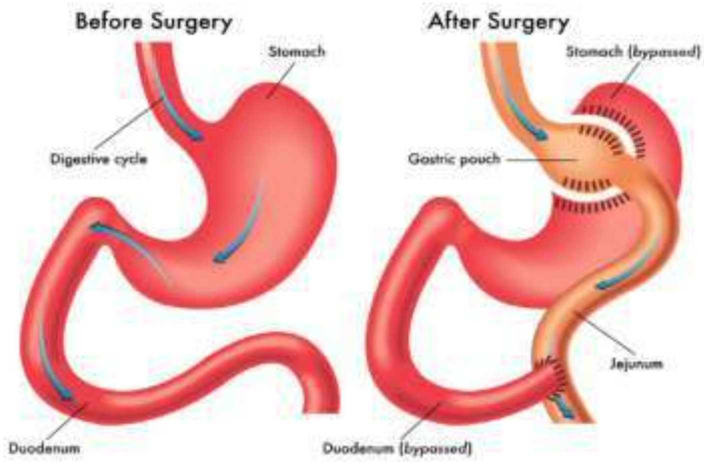
Sleeve gastrectomy is primarily a restrictive procedure involving removal of approximately 70–80% of the stomach, leaving a tubular gastric remnant. This significantly reduces gastric volume and decreases ghrelin production, thereby reducing appetite. Unlike RYGB, there is no intestinal bypass, making it technically simpler and associated with fewer malabsorptive complications [1]. Patients undergoing sleeve gastrectomy typically achieve 50–60% excess weight loss within the first year. Improvements in metabolic parameters, including insulin sensitivity and lipid profile, are well documented. Complications may include staple line leaks, gastroesophageal reflux disease, and long-term nutritional deficiencies if dietary adherence is poor [27,14].

Adjustable Gastric Banding

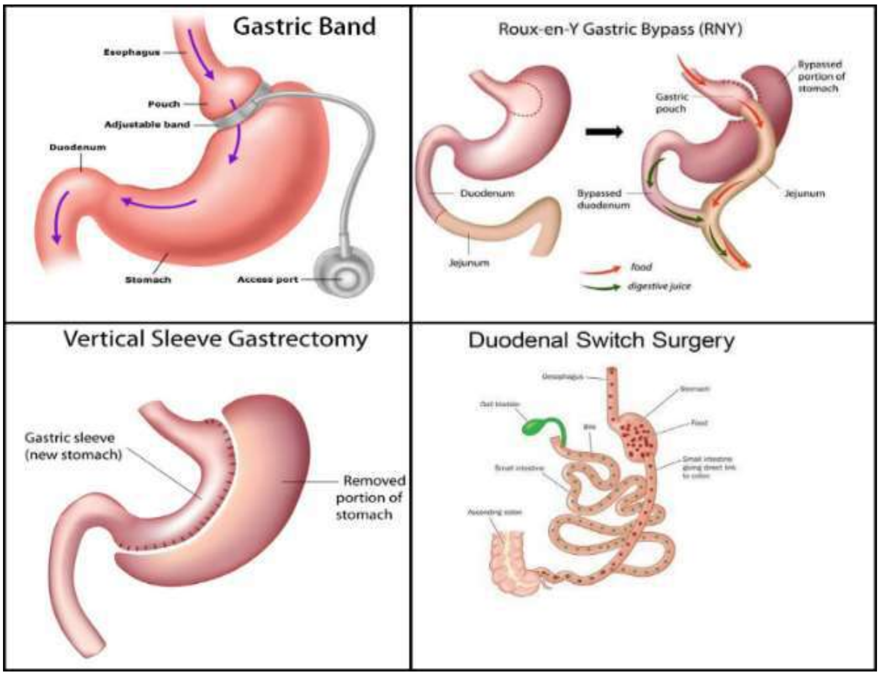


Adjustable gastric banding is a purely restrictive procedure in which an inflatable silicone band is placed around the upper portion of the stomach, creating a small pouch. The band is connected to a subcutaneous port that allows adjustment of tightness by saline injection. This restricts food intake and promotes early satiety without altering intestinal anatomy [14]. Although adjustable gastric banding is less invasive and reversible, weight loss outcomes are generally modest, averaging 40–50% excess weight loss over 2–3 years. Long-term complications include band slippage, erosion, port infection, and need for revision surgery. Due to these concerns and comparatively lower efficacy, its popularity has declined in recent years [27].

Biliopancreatic Diversion (BPD)



Biliopancreatic diversion is predominantly a malabsorptive procedure and includes variants such as the duodenal switch. It involves partial gastrectomy combined with extensive bypass of the small intestine, significantly limiting calorie and fat absorption. The common channel where bile and pancreatic enzymes mix with food is shortened, reducing nutrient assimilation [27]. BPD produces the greatest weight loss among bariatric procedures, with 70–80% excess weight loss. It is highly effective in resolving severe obesity and metabolic syndrome. However, due to significant risks of protein malnutrition, fat-soluble vitamin deficiencies, anaemia, and diarrhoea, it requires strict lifelong nutritional monitoring and supplementation [27,14].



15. Nutritional Deficiencies (Iron, Vitamin B12, Calcium)

Nutritional deficiencies are among the most common long-term complications following bariatric surgery, particularly after malabsorptive procedures such as Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD). Iron deficiency occurs due to reduced gastric acid production, bypass of the duodenum (primary site of iron absorption), and decreased intake of iron-rich foods. Vitamin B12 deficiency results from reduced intrinsic factor secretion and limited gastric surface area, impairing cobalamin absorption in the terminal ileum. Calcium deficiency is mainly due to bypass of the duodenum and proximal jejunum, leading to secondary hyperparathyroidism and increased risk of osteoporosis. If not identified early, these deficiencies may result in anaemia, neuropathy, and metabolic bone disease; therefore, routine biochemical monitoring and lifelong supplementation are essential components of postoperative care [28,13].

Dumping Syndrome

Dumping syndrome is a frequent complication following gastric bypass procedures and is characterized by rapid gastric emptying of hyperosmolar contents into the small intestine. It is classified into early dumping (occurring within 30 minutes after meals) and late dumping (1–3 hours postprandial). Early dumping results from fluid shifts into the intestinal lumen causing abdominal pain, diarrhoea, tachycardia, and hypotension. Late dumping is related to exaggerated insulin release and subsequent hypoglycaemia. The syndrome is more common after Roux-en-Y gastric bypass due to alteration in pyloric function. Dietary modification—such as consuming small, frequent meals with reduced simple carbohydrates—is the cornerstone of management. Severe cases may require pharmacological therapy such as acarbose or octreotide [2].

Infection and Surgical Risks

As with any major surgical intervention, bariatric procedures carry perioperative and postoperative risks including wound infection, anastomotic leak, haemorrhage, pulmonary embolism, and deep vein thrombosis. The risk profile varies depending on the type of surgery, patient comorbidities, and surgeon experience. Laparoscopic approaches have significantly reduced morbidity compared to open procedures. Obese patients often present with comorbid conditions such as type 2 diabetes mellitus, hypertension, and obstructive sleep apnea, which may increase perioperative complications. Despite these risks, bariatric surgery has been shown to reduce long-term mortality and obesity-related complications when performed in appropriate candidates under multidisciplinary supervision [2].

Weight Regain

Although bariatric surgery produces significant initial weight loss, a proportion of patients experience partial weight regain over time. Causes include behavioural factors (non-adherence to dietary guidelines), psychological issues, anatomical changes such as gastric pouch dilation, and metabolic adaptation. Hormonal changes involving ghrelin, leptin, and other gut peptides may also influence appetite regulation post-surgery. Long-term success depends heavily on sustained lifestyle modification, dietary compliance, and regular physical activity. Multidisciplinary follow-up helps identify early weight regain and implement corrective interventions such as nutritional counselling, pharmacotherapy, or revisional surgery when necessary [28,13].

Lifelong Follow-Up and Supplementation

Lifelong follow-up is mandatory after bariatric surgery to monitor nutritional status, metabolic parameters, and psychological well-being. Regular laboratory evaluation includes haemoglobin, ferritin, vitamin B12, folate, calcium, vitamin D, and parathyroid hormone levels. Standard supplementation typically includes multivitamins, iron, calcium with vitamin D, and vitamin B12 (oral or parenteral). Long-term follow-up also addresses weight maintenance, management of comorbidities, and prevention of complications such as osteoporosis and protein-energy malnutrition. Structured postoperative care significantly enhances surgical outcomes and reduces long-term morbidity, reinforcing that bariatric surgery is not merely a procedure but a lifelong therapeutic commitment [28].

16. Prevention Strategies for Obesity

Obesity is a major global public health challenge characterized by excessive accumulation of body fat and associated with increased morbidity and mortality. The prevalence of obesity has risen dramatically worldwide, affecting both adults and children, and is strongly linked to comorbidities such as type 2 diabetes, cardiovascular disease, and certain cancers. Given the limited long-term success of lifestyle treatment alone and the high cost of pharmacological and surgical interventions, prevention strategies remain the cornerstone of obesity control at the population level. Preventive approaches must address behavioural, environmental, and socio-economic determinants that contribute to positive energy balance and weight gain [29]. Early prevention is particularly important because childhood obesity frequently persists into adulthood and increases the risk of chronic metabolic diseases later in life. Evidence suggests that the prevalence of obesity in children and adolescents is rising globally, with projections indicating a substantial increase if effective preventive measures are not implemented. Preventive strategies during early life stages can therefore significantly reduce long-term health burdens and healthcare costs [29].

Early Childhood Obesity Prevention

Early childhood represents a critical window for obesity prevention, as dietary habits, physical activity patterns, and metabolic programming are established during this period. Parental feeding practices, breastfeeding, timing of complementary feeding, and exposure to energy-dense foods significantly influence weight trajectories in infancy and early childhood. Studies indicate that early rapid weight gain is associated with a higher risk of obesity in later life, highlighting the importance of monitoring growth patterns and promoting healthy feeding behaviours from infancy [29]. Family-based interventions are essential in early childhood prevention programs. Educating parents about balanced nutrition, limiting sugar-sweetened beverages, reducing screen time, and encouraging active play can help establish lifelong healthy habits. Since children are highly influenced by their home environment, strategies targeting parental modelling and household food availability have shown positive outcomes in preventing excessive weight gain. Furthermore, early intervention may counteract genetic predispositions by modifying environmental risk factors [24]. Community health services, including maternal and child health clinics, can play a vital role in identifying children at risk through anthropometric assessments such as BMI-for-age percentiles. BMI remains a practical and widely used screening tool to classify overweight and obesity in both adults and children, despite limitations in assessing body fat distribution [3]. Early identification enables timely counselling and behavioural interventions to prevent progression to obesity [7].

School-Based Nutrition Programs

Schools provide an ideal setting for large-scale obesity prevention initiatives because they reach children during formative years. School-based nutrition programs aim to improve dietary habits by providing balanced meals, restricting access to high-calorie snacks, and incorporating nutrition education into the curriculum. Evidence suggests that structured school interventions combining healthy food policies with physical activity promotion can significantly reduce the incidence of childhood obesity [29]. Nutritional standards for school meals, removal of vending machines selling sugar-rich beverages, and inclusion of fruits and vegetables in daily menus contribute to healthier dietary intake. Educational sessions that teach children about portion control, reading food labels, and the importance of physical activity further reinforce healthy behaviours. Although lifestyle modification alone often produces modest weight reduction, consistent environmental support in schools enhances sustainability of behavioural change [24]. Physical education programs are equally important components of school-based prevention. Regular moderate-to-vigorous physical activity improves energy expenditure, insulin sensitivity, and overall metabolic health. Integrating daily exercise sessions and encouraging active transportation (walking or cycling to school) can reduce sedentary behaviour and help maintain healthy body weight. Such comprehensive approaches align with recommendations that lifestyle modification remains the foundation of obesity management and prevention [24].

Community Health Awareness

Community-level interventions address broader environmental and societal factors that contribute to obesity. Public health campaigns that promote awareness about healthy eating, physical activity, and the risks associated with obesity can influence social norms and individual behaviours. Media campaigns, community fitness events, and public policies such as taxation of sugar-sweetened beverages are examples of population-based strategies designed to reduce obesogenic exposures [29]. Urban planning initiatives that create safe walking paths, parks, and recreational facilities encourage physical activity among community members. Access to affordable healthy foods through farmers' markets and regulation of fast-food outlets in residential areas also supports healthier lifestyle choices. Since obesity results from complex interactions between biological, behavioural, and environmental factors, community-based strategies must adopt a multisectoral approach involving healthcare providers, policymakers, educators, and local organizations [29]. Healthcare professionals play an important role in community awareness by providing counselling, screening, and early intervention. Routine measurement of BMI and waist circumference in primary care settings allows identification of individuals at increased metabolic risk. Central obesity, assessed through waist circumference, is particularly associated with insulin resistance and cardiovascular disease risk [7]. Community screening programs can thus facilitate early detection and preventive guidance [7].

Workplace Wellness Programs

Workplace wellness programs are increasingly recognized as effective platforms for obesity prevention among adults. Since a significant proportion of adults spend much of their day at work, interventions targeting occupational settings can substantially influence dietary and physical activity behaviours. Programs may include healthy cafeteria options, scheduled physical activity breaks, weight management counselling, and incentives for participation in wellness activities [29]. Evidence suggests that combined lifestyle interventions in structured environments produce better outcomes than individual efforts alone. Behavioural counselling, peer support groups, and regular health monitoring at workplaces can improve adherence to weight management strategies. Although lifestyle changes typically result in modest weight loss, consistent reinforcement and supportive policies in occupational settings can enhance long-term sustainability [24] Employers also benefit from workplace wellness programs through reduced absenteeism, improved productivity, and lower healthcare expenditures. Given that obesity is associated with increased healthcare costs and economic burden, preventive interventions in workplaces serve both public health and economic interests [1]. Integrating health promotion into corporate policies reflects a comprehensive strategy to combat obesity at the societal level.

17.Future Perspectives in Obesity Management

Obesity is now recognized as a chronic, relapsing disease requiring long-term and multidisciplinary management. Despite advances in pharmacotherapy and bariatric surgery, long-term weight maintenance remains challenging due to adaptive physiological mechanisms that promote weight regain. Emerging strategies focus on understanding genetic, molecular, microbial, and digital determinants of energy balance to provide more effective and individualized therapies. These innovations aim to overcome the biological redundancy of appetite and metabolic regulation while minimizing adverse effects [24].

Personalized and Genomic-Based Therapy

Personalized medicine in obesity management involves tailoring interventions based on genetic susceptibility, metabolic phenotype, hormonal profile, and behavioural characteristics. Genetic studies indicate that 25–40% of BMI variability is heritable, involving multiple genes regulating appetite, adipogenesis, and energy expenditure. Advances in genomics and pharmacogenomics may help predict individual responses to anti-obesity medications such as GLP-1 receptor agonists or centrally acting agents. Identification of polymorphisms affecting leptin signalling, melanocortin pathways, or insulin sensitivity could guide targeted therapy, improve efficacy, and reduce adverse effects [7]. Furthermore, precision medicine incorporates metabolic phenotyping—distinguishing between individuals with predominant hyperphagia, low energy expenditure, or emotional eating patterns—to select optimal therapeutic combinations. As genomic profiling becomes more accessible, obesity classification may shift from BMI-based systems to molecular subtyping, allowing clinicians to design individualized intervention plans integrating diet, pharmacotherapy, and behavioural therapy [29]

Microbiome-Based Treatment

The gut microbiome plays a crucial role in energy harvest, fat storage, and systemic inflammation. Alterations in gut microbial composition (dysbiosis) have been associated with increased adiposity and metabolic dysfunction. Emerging research suggests that modulation of gut microbiota through probiotics, prebiotics, dietary fibre, faecal microbiota transplantation, or microbiome-targeted drugs may influence weight regulation and metabolic health [10]. Microbial metabolites such as short-chain fatty acids affect satiety hormones (GLP-1, PYY) and insulin sensitivity, highlighting the therapeutic potential of microbiome manipulation. Future treatments may involve personalized microbial profiling to identify dysbiosis patterns and tailor microbiome-correcting interventions, thereby complementing pharmacological or surgical approaches in obesity management [10].

Gene Editing and Hormonal Modulation

Gene-editing technologies such as CRISPR-Cas9 present future possibilities for correcting monogenic forms of obesity, particularly those involving leptin deficiency or melanocortin receptor mutations. Although still in experimental stages, such approaches could provide long-term correction of specific genetic defects contributing to severe obesity. Ethical and safety concerns, however, require careful evaluation before clinical implementation [29]. Hormonal modulation remains a promising strategy. Recent advances focus on multi-agonist therapies targeting combinations of gut hormones such as GLP-1, glucagon, and gastric inhibitory peptide (GIP). These co-agonists enhance satiety, improve glycaemic control, and increase energy expenditure more effectively than single-hormone agents. Novel peptide analogues and dual/triple receptor agonists currently under investigation demonstrate superior weight-loss outcomes compared with earlier pharmacotherapies [5].

AI and Digital Therapeutics Artificial intelligence (AI)

and digital health technologies are transforming obesity management by enabling continuous monitoring, behavioural tracking, and predictive analytics. Smartphone applications, wearable devices, and telemedicine platforms allow real-time assessment of dietary intake, physical activity, glucose levels, and sleep patterns. AI-driven algorithms can analyse these data to provide personalized feedback, optimize treatment adherence, and predict relapse risk [24]. Digital therapeutics also facilitate remote behavioural therapy, cognitive behavioural interventions, and medication monitoring. Integration of machine learning models with genomic and metabolic data may enhance individualized treatment planning, bridging the gap between lifestyle interventions and medical therapy. Such technology-based approaches are expected to improve long-term adherence and sustainability of weight loss outcomes [24].

Emerging Anti-Obesity Drug Pipeline

The anti-obesity drug pipeline is increasingly focused on gut-brain axis modulation and combination peptide therapies. Current research emphasizes multi-receptor agonists targeting GLP-1, GIP, and glucagon pathways to produce greater and more sustained weight reduction. These agents not only reduce appetite but also enhance energy expenditure and improve metabolic parameters [24]. Additionally, novel centrally acting agents, amylin analogues, and combination pharmacotherapies are under development to overcome compensatory biological mechanisms that limit weight loss. The ideal anti-obesity drug should produce sustained weight reduction, minimal adverse effects, non-addictive properties, and long-term safety. Although past drug development has been marked by withdrawals due to safety concerns, improved understanding of neurohormonal regulation of appetite offers optimism for safer and more effective therapies in the future [22].

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