EXPERT OPINION

Obesity: Pathophysiology, Interventions, and Policy

Reviewed by:

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Introduction

Definition and Classification of Obesity

According to WHO, obesity is excessive fat accumulation that harms health and is recognized as a chronic metabolic disease resulting from genetic, physiological, and environmental factors.[1] A Body Mass Index (BMI) above 25 is classified as overweight, while a BMI above 30 indicates obesity. The issue is a global health concern impacting quality of life across populations, with at least 2.8 million deaths annually attributed to overweight and obesity.[2] An ideal obesity classification system should rely on practical, widely accessible measurements, accurately predict health risk, and guide treatment strategies and goals.[3]

Global Epidemiology

Overweight and obesity rates continue to rise rapidly. Among children and adolescents aged 5–19 years, obesity increased fourfold from 2% in 1990 to 8% in 2022. In adults aged 18 and older, prevalence more than doubled, rising from 7% to 16%. In 2020, 2.6 billion people were affected by obesity, and global rates are projected to increase from 38% in 2020 to over 50% by 2035. Obesity alone is expected to rise from 14% to 24%, impacting nearly 2 billion individuals across all age groups by 2035.[2]

Public Health Significance

Obesity is a major global public health challenge with profound effects on health, life expectancy, quality of life, and socioeconomic outcomes. It causes serious illness, reduces life span, and significantly impairs both physical and psychosocial well-being, particularly in individuals with class 3 obesity. Childhood obesity often persists into adulthood and predisposes to Obesity-Related Non-Communicable Diseases (OR-NCDs) such as type 2 diabetes, Coronary Artery Disease (CAD), stroke, cancer, asthma, and chronic obstructive pulmonary disease. The stigma surrounding obesity discourages healthcare utilization, leading to lower rates of preventive measures such as cancer screening, with women especially delaying gynecological screening due to social barriers.[5]

Table 1: Criteria for Using BMI as a Measure of Obesity in Children and Adults[3,4]

Category	BMI (kg/m^2)	Obesity Class	Disease Risk* (Relative to Normal Weight and Waist Circumference)
			Men ≤ 40 inches (≤ 102 cm), Women ≤ 35 inches (≤ 88 cm)
Underweight	<18.5	-	-
Normal†	18.5–22.9	-	-
Overweight	23.0–24.9	-	Increased
Obesity	25.0–29.9	1	High
	30.0–34.9	2	Very High
Extreme Obesity	>35	3	Extremely High

*Disease risk for type 2 diabetes, hypertension, and cardiovascular disease
†Increased waist circumference can also indicate higher risk even in individuals with normal weight[3]

Pathophysiology of Obesity[6]

The Imbalance of Energy Homeostasis and Metabolic Adaptation

Obesity arises from an imbalance in energy homeostasis, where intake exceeds expenditure, leading to storage of excess energy as triacylglycerol in adipocytes. These adipocytes are distributed in subcutaneous, visceral, pelvic, retroperitoneal, pericardial, and intramuscular depots.

Hormonal Regulation

Adipocytes secrete cytokines such as leptin, adiponectin, IL-6, TNF-α, resistin, and others that regulate appetite, satiety, and fat content. Disruption of these mechanisms contributes to insulin resistance and obesity.

Neural Control

The arcuate nucleus (ARC) of the hypothalamus regulates feeding behavior and systemic energy balance through POMC and NPY/AgRP neurons, which integrate central and peripheral inputs.

Genetics and Epigenetics

Genetic and epigenetic factors significantly influence obesity risk, with twin and family studies attributing 40–70% of variability to hereditary factors. These genetic causes include both polygenic and monogenic mutations.

Risk Factors and Determinants[2]

Socio–Cultural Factors

Socio-demographic, economic status, family structure, peer influence, and cultural norms significantly shape dietary habits and physical activity. Social inequality, stigma, and globalization further drive obesity risk across different populations.

Technological Factors

Digital media, online food delivery, and automation promote sedentary lifestyles and poor food choices. Increased screen time, targeted marketing, and remote learning reduce physical activity and encourage weight gain.

Economic Factors

Income levels, food prices, poverty, and unemployment directly affect access to nutritious foods. Financial stress, inequality, and rising costs push people toward high-calorie, low-nutrient diets, worsening obesity prevalence.

Environmental Factors

Urbanization, unsafe neighborhoods, and limited access to green spaces reduce opportunities for physical activity. Food environments dominated by fast-food outlets and limited healthy options further promote obesity risk.

Comorbidities Associated with Obesity[6]

The recently published definition of clinical obesity, released by the Lancet Commission (2025), lists 18 conditions in adults, and 13 in adolescent, which may complicate obesity. These include Type 2 Diabetes Mellitus (T2DM), Cardiovascular Diseases (CVD), Non-Alcoholic Fatty Liver Disease (NAFLD), respiratory disorders, Obesity-Related Nephropathy (ORN), musculoskeletal disorders, cancers, and psychological conditions. Associated conditions encompass CAD, Sudden Cardiac Death (SCD), Metabolic Dysfunction-Associated Steatohepatitis (MASH), Hepatocellular Carcinoma (HCC), Obstructive Sleep Apnea (OSA), Polycystic Ovary Syndrome (PCOS), Multiple Myeloma (MM), Temporomandibular Joint Osteoarthritis (TMJ OA), and Acute Pancreatitis (AP), along with factors such as Low-Density Lipoprotein (LDL), Vascular Endothelial Growth Factor-B (VEGF-B), and Reactive Oxygen Species (ROS).

Diagnosis and Evaluation[1]

Anthropometric Methods

BMI, neck circumference, waist circumference, waist-to-hip ratio, and waist-to-height ratio are commonly used to assess body fat status.

Lipidomics, demographic factors (age and sex), and anthropometric measures such as waist circumference are used in indicators such as Lipid Accumulation Product (LAP), Visceral Adiposity Index (VAI), Chinese Visceral Adiposity Index (CVAI), and metabolic Body Mass Index (mBMI) to evaluate visceral fat.

Imaging Techniques

Although various indicators exist, 3D-CT and MRI remain the gold standards for quantifying visceral fat.

Due to radiation risks with CT and the high cost of MRI, ultrasound and bioelectrical impedance analysis are widely applied in clinical practice. Body fat percentage helps to diagnose adiposity, and monitor the effects of treatment.

Management Strategies[6,7]

Current evidence-based guidelines recommend lifestyle modifications, pharmacotherapy, and bariatric surgery as primary strategies for obesity management.

Lifestyle Modifications

Comprehensive lifestyle interventions—including dietary regulation (ADF, Ramadan diet, anti-inflammatory diet), physical activity optimization (aerobic exercise, HIIT, reduced screen time), and behavioral adaptation—form the foundation of weight management and cardiovascular risk reduction in obesity.

Pharmacological Treatments

FDA and Indian regulator–approved anti-obesity medications for chronic weight management include Orlistat, Phentermine/Topiramate ER, Naltrexone SR/Bupropion SR, Liraglutide, Semaglutide, and Tirzepatide, while Phentermine alone is approved only for short-term use.[6,7]

Bariatric Surgery

It is recommended for patients with severe obesity (BMI ≥37.5 kg/m^2) or those unresponsive to lifestyle and pharmacological interventions. Procedures such as sleeve gastrectomy, Roux-en-Y gastric bypass, adjustable gastric banding, and biliopancreatic diversion with duodenal switch modify gut anatomy, reduce food intake and nutrient absorption, promote sustained weight loss, improve metabolic comorbidities including T2DM, enhance quality of life, and increase survival.

Emerging Therapies

Emerging obesity therapies target multiple metabolic pathways. Low-dose IL-2 and 11β-HSD1 inhibitors help restore metabolic balance, while marine fish oil and porcine cerebral peptide reduce weight, improve BMI, and alleviate hyperglycemia. MD-2 inhibitors mitigate obesity-related cognitive impairment, and DSG limits harmful ectopic lipid accumulation.

Prebiotics and probiotics demonstrate potential anti-obesity effects by modulating the gut microbiota; prebiotics, as non-digestible fibers, selectively nourish beneficial bacteria such as *Bifidobacteria* and *Lactobacilli*, thereby supporting a healthier microbial balance.[8]

Device-Based Therapies

Device-based interventions, including mobile smart devices, pharmacogenomics-based devices, and localized delivery systems, improve obesity-related outcomes such as body weight, insulin resistance, cholesterol, and inflammatory markers. They can be used to support therapies.

Genetic Therapies

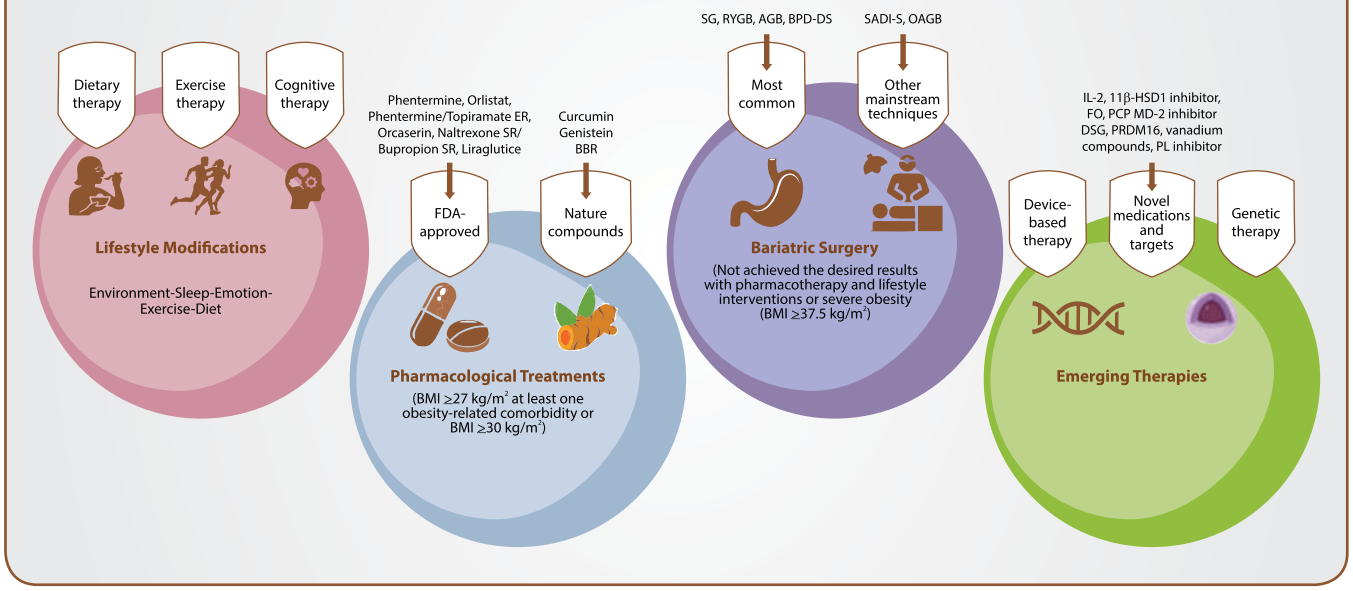
Genetic approaches using AAV, miRNAs, and genes like *LEP*, *MC4R*, and *POMC*, delivered via adipose-derived mesenchymal stem cells or fecal microbiota transplants, effectively address obesity-associated comorbidities, including metabolic dysfunction, cellular senescence, osteoarthritis progression, oxidative DNA damage, and epigenetic hypermethylation.

Prevention of Obesity

School-Based Interventions

Programs combining nutritional education and physical activity effectively reduce BMI and improve weight status in children. Regular physical education, extracurricular sports, and parental involvement enhance outcomes by supporting healthy weight and energy balance. These multifaceted strategies are vital for combating childhood obesity and promoting long-term health.[9]

Figure 1: The Interventions of Obesity



Policy and Population Interventions

Guidelines recommend increasing vegetables, whole grains, lean proteins, fruits, and water, while limiting processed foods high in sodium, saturated fats, and sugar to prevent obesity. SSB taxation effectively reduces sugar intake and lowers obesity rates, while low-calorie diets support weight loss. For children, policies should promote active playgrounds, more physical activity, and non-competitive activities.[10]

Healthcare Provider Role

A team-based approach to obesity management involves collaboration among physicians, nurses, dietitians, psychologists, exercise specialists, and pharmacists, with active participation from patients and families. This model emphasizes individualized care, lifestyle modification, behavioral support, and pharmacological or surgical interventions where appropriate, to achieve sustained weight loss, prevent complications, and improve quality of life.[11]

Conclusion

Obesity is a complex, multifactorial disease with rising global prevalence and significant health, social, and economic consequences. Effective management requires integrated strategies, including lifestyle modifications, pharmacotherapy, bariatric surgery, and emerging therapies. Preventive measures through school-based programs, policy interventions, and healthcare provider involvement are essential to curb obesity rates.

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Abbreviations: 3D-CT – Three-Dimensional Computed Tomography, MRI – Magnetic Resonance Imaging, CT – Computed Tomography, ADF – Alternate-Day Fasting, HIIT – High-Intensity Interval Training, FDA – U.S. Food and Drug Administration, ER – Extended Release, SR – Sustained Release, IL-2 – Interleukin-2, 11β-HSD1 – 11 Beta-Hydroxysteroid Dehydrogenase Type 1, MD-2 – Myeloid Differentiation Factor 2, DSG – Desmoglein, AAV – Adeno-Associated Virus, miRNAs – MicroRNAs, Lep – Leptin gene, MC4R – Melanocortin 4 Receptor, POMC – Proopiomelanocortin, SSB – Sugar-Sweetened Beverages; TNF-α - Tumor Necrosis Factor alpha, NPY/AgRP - Neuropeptide Y/Agouti-related Peptide neurons.