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Review Article

Overview: Obesity

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Abstract:

Obesity is a chronic, multifactorial disease driven by complex interactions between genetic, environmental, and behavioral factors. This paper reviews the underlying pathophysiological mechanisms, including dysregulation in hypothalamic appetite control and hormonal imbalances such as leptin resistance. The global rise in obesity is associated with a spectrum of comorbidities, including cardiovascular disease, type 2 diabetes mellitus, obstructive sleep apnea, and certain cancers. This review also explores contemporary and emerging management options, from lifestyle modifications to pharmacological agents such as GLP-1 receptor agonists, minimally invasive endoscopic procedures, bariatric surgery, and future innovations like microbiome modulation and gene therapy. A comprehensive understanding of these mechanisms and treatment strategies is essential for improving patient outcomes in the ongoing battle against obesity.

Key words: obesity; pathophysiology; leptin resistance; glp-1 receptor agonists; bariatric surgery; metabolic syndrome; gut microbiome

Introduction

Obesity has reached epidemic proportions globally, affecting over 650 million adults worldwide [1]. Defined as excessive fat accumulation that poses a risk to health, obesity is not merely a cosmetic concern but a major risk factor for chronic diseases and mortality. The multifactorial nature of obesity demands an integrative approach to understanding its pathogenesis and devising effective treatment strategies.

Pathophysiology of Obesity

Obesity arises from sustained positive energy balance, where caloric intake exceeds energy expenditure. At the core of this imbalance lies a disruption in homeostatic mechanisms regulated by neural and hormonal pathways [2]. The hypothalamus, particularly the arcuate nucleus, plays a central role in appetite regulation. Two key neuronal populations are involved:

• Neuropeptide Y (NPY)/Agouti-related peptide (AgRP) neurons promote hunger.

• Pro-opiomelanocortin (POMC)/Cocaine- and amphetamine-regulated transcript (CART) neurons suppress appetite [3]. Leptin, a hormone produced by adipose tissue, modulates these pathways by inhibiting NPY/AgRP and activating POMC/CART neurons. However, in obesity, leptin resistance diminishes this effect, promoting excessive food intake [4]. The endocannabinoid system also contributes to dysregulated eating behaviors through its effects on reward pathways and executive control [5].Health Consequences of Obesity

Obesity significantly increases the risk of numerous medical conditions:

• Cardiovascular diseases: Hypertension, coronary artery disease, stroke [6].

• Metabolic disorders: Type 2 diabetes mellitus, insulin resistance, dyslipidemia [7].

• Respiratory issues: Obstructive sleep apnea, obesity hypoventilation syndrome [8].

• Musculoskeletal complications: Osteoarthritis, lower back pain [9].

• Cancers: Breast, colon, endometrial cancers [10].

• Metabolic syndrome: A cluster of conditions raising the risk for cardiovascular disease and diabetes [11].

Classification of Obesity

1. By fat distribution

• Central (android): Linked with higher cardiometabolic risk [12].

• Peripheral (gynoid): More common in women; mechanical stress-related issues prevail [13].

2. By etiology

• Primary obesity: Due to lifestyle and environmental factors [14].

• Secondary obesity: From medical conditions like hypothyroidism, Cushing's syndrome, PCOS, or genetic syndromes such as Prader-Willi [15].

3. By BMI (WHO classification)

• Overweight: 25–29.9 kg/m²

• Class I: 30–34.9 kg/m²

• Class II: 35–39.9 kg/m²

• Class III: ≥40 kg/m² [16].

4. By metabolic health

• Metabolically Healthy Obesity (MHO): Obese without metabolic abnormalities.

• Metabolically Unhealthy Obesity (MUO): Associated with insulin resistance, dyslipidemia, hypertension [17].

5. By adipocyte characteristics

• Hypertrophic obesity: Enlarged fat cells, commonly seen in adults.

• Hyperplastic obesity: Increased fat cell number, typically from childhood obesity [18].

1. Genetic and Biological Factors

• Family history: A strong predictor; obesity tends to run in families.

• Genetic syndromes: Prader-Willi syndrome, Bardet-Biedl syndrome.

• Hormonal imbalances: Hypothyroidism, Cushing's syndrome, PCOS.

• Age: Metabolic rate tends to slow down with age, promoting fat accumulation.

• Sex: Females are more prone to fat deposition, especially after menopause.

2. Lifestyle and Behavioral Factors

• Excessive calorie intake: Diets high in sugar, fat, and ultra-processed foods.

• Physical inactivity: Sedentary lifestyles contribute significantly to weight gain.

• Sleep deprivation: Alters hunger hormones like ghrelin and leptin.

• Emotional eating: Eating in response to stress, depression, or boredom.

3. Environmental Factors

• Urbanization: Limited space for physical activity, increased availability of fast food.

• Food marketing: Aggressive marketing of unhealthy food, especially to children.

• Socioeconomic status: Limited access to healthy foods or safe places for exercise.

• Work environment: Long hours, desk jobs, and lack of physical engagement.

4. Medications

Certain drugs can promote weight gain:

• Antidepressants (e.g., SSRIs, tricyclics)

• Antipsychotics (e.g., olanzapine, risperidone)

• Corticosteroids

• Antidiabetic agents (e.g., insulin, sulfonylureas)

5. Psychological and Social Factors

• Low self-esteem and body dissatisfaction

• History of trauma or abuse

• Social isolation or lack of support networks

Management Strategies

1. Lifestyle modifications

• Diet: Calorie-restricted, nutrient-dense diets [19].

• Exercise: Minimum 150 minutes/week of moderate activity [20].

2. Behavioral therapy

• Cognitive-behavioral therapy improves adherence and addresses emotional eating [21]

3. Pharmacological therapy

• GLP-1 Receptor Agonists

• Semaglutide: Reduces appetite and body weight by up to 15% [22].

• Tirzepatide: Dual GLP-1/GIP agonist; up to 22% weight reduction [23].

• Liraglutide: Older agent with moderate efficacy [24].

• Sympathomimetic agents

• Phentermine-topiramate, Bupropion-naltrexone: Target CNS pathways to reduce hunger [25].

• Lipase inhibitor

• Orlistat: Reduces fat absorption; limited by gastrointestinal side effects [26].

4. Minimally Invasive Endoscopic Procedures

• Endoscopic sleeve gastroplasty: Stomach volume reduction via suturing [27].

• Intragastric balloons: Temporary space-occupying devices [28].

• Aspiration therapy: Allows post-meal gastric emptying [29].

5. Bariatric Surgery

• Laparoscopic sleeve gastrectomy (LSG): Removes 75% of the stomach; reduces ghrelin [30].

• Roux-en-Y gastric bypass (RYGB): Bypasses part of the intestine; gold standard for T2DM with obesity [31].

• Adjustable gastric banding: Less effective and less commonly used today [32].

6. Emerging and Future Treatments

• Gene therapy: CRISPR and gene editing may personalize treatments [33].

• Gut microbiome modulation: FMT and probiotics under research [34].

• Brown fat activation: Investigational drugs targeting brown adipose tissue [35].

• Anti-obesity vaccines: Trials underway targeting appetite-regulating hormones [36].

Conclusion

Obesity is a multifactorial disease with complex pathophysiology and serious health consequences. A personalized, multidisciplinary approach encompassing lifestyle changes, pharmacotherapy, endoscopic and surgical interventions, and innovative therapies holds promise in curbing the obesity epidemic.

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