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FROM MOLECULAR MECHANISMS TO INNOVATIVE THERAPIES: A COMPREHENSIVE REVIEW OF CONTEMPORARY APPROACHES TO OBESITY

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ABSTRACT

Obesity is a chronic, multifactorial disease resulting from complex interactions between genetic predisposition, environmental influences, lifestyle factors, and the gut microbiota. The objective of this review is to provide a concise summary of the current evidence on the molecular and epigenetic mechanisms that underpin obesity, the role of the gut microbiota, and the emerging therapeutic strategies that are available. The reviewed data indicate that numerous genetic variants, including those in the FTO, MC4R, and LEP/LEPR genes, modulate appetite and metabolism, thereby increasing susceptibility to obesity. Epigenetic modifications, including DNA methylation and histone modifications, have been demonstrated to play a crucial role in the regulation of metabolic genes. These modifications are significantly influenced by factors such as diet, physical activity, and circadian rhythm disruptions. The gut microbiota has been shown to play a pivotal role in the regulation of energy homeostasis, with its composition being significantly influenced by dietary habits, physical activity levels, and bariatric surgery interventions. Contemporary therapeutic methodologies, including microbiome modulation, the activation of brown adipose tissue, and epigenetic interventions, hold considerable promise for the treatment of obesity. The findings emphasise the necessity for personalised therapeutic strategies that incorporate behavioural, pharmacological, and microbiota-targeted approaches, with the potential to significantly enhance future clinical outcomes.

KEYWORDS

Obesity, Genetics, Epigenetics, Microbiota, Lifestyle, And Innovative Therapies

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1. Introduction

Obesity is defined as a chronic, multifactorial, and systemic disease characterised by excessive or abnormal accumulation of adipose tissue. This may arise from intrinsic adipose tissue dysfunction and, in turn, contribute to organ damage. The condition has been demonstrated to increase the risk of developing diabetes, cardiovascular diseases, cancers, and metabolic disorders. Moreover, it has a detrimental effect on quality of life and socioeconomic productivity. Obesity represents a significant contemporary public health concern. In 2022, the global adult population was found to include more than one billion adults who were classified as obese (BMI $\geq$ 30 kg/m^2), accounting for approximately one-eighth of the global adult population. Meanwhile, it was found that nearly half of all adults had overweight or obesity (1, 2). Since 1990, the prevalence of obesity has increased significantly, leading to its recognition as a global epidemic (3). Of particular concern is the increasing prevalence of severe obesity (BMI $\geq$ 40 kg/m^2), which affects approximately 8% of adults in the United States and is increasingly observed in middle-income countries (4). These trends unequivocally demonstrate that obesity is an escalating global health problem (5). It is evident that dietary interventions, physical activity, and time-restricted eating remain fundamental components of weight management (6). Contemporary therapeutic strategies encompass pharmacotherapy, gut microbiota modulation, and gene-based interventions, facilitating a personalised approach to treatment. This review summarises current evidence on genetic determinants, lifestyle influences, and innovative therapeutic strategies in obesity, emphasising the need for comprehensive and individualised management.

2. Methodology

This literature review is based on a systematic search of publications in PubMed, Web of Science, and Google Scholar using the following keywords: “obesity,” “BMI,” “genetics,” “epigenetics,” “bariatric surgery,” “microbiota,” “lifestyle,” and “innovative therapies.” Articles published between 2010 and 2025 were included, with particular emphasis on studies involving human participants. Both original research papers and systematic reviews, as well as WHO reports, were considered. The selection of publications was limited to articles in English, published within the last 15 years, and available in full-text online. The analysis involved a critical appraisal of methodological quality, study outcomes, and limitations. The conclusions were synthesized by integrating data from multiple research domains, including epidemiology, genetics, molecular mechanisms, lifestyle influences, gut microbiota, and novel therapeutic interventions.

3. Results

3.1. Genetic and Molecular Determinants of Obesity

Genetic and molecular factors play a pivotal role in the pathogenesis of obesity by influencing appetite regulation, metabolism, and individual susceptibility to excessive weight gain. Obesity is a complex, polygenic trait, defined as a predisposition towards excess body weight, shaped by a multitude of genetic variants. Each variant exerts a small but cumulative effect, contributing to the overall predisposition. A substantial body of research has demonstrated an association between variants in genes such as FTO, MC4R, and LEP, and elevated BMI, as well as a heightened propensity for adipose tissue accumulation (7). For instance, genetic variants in the FTO (Fat Mass and Obesity-Associated) gene are considered to be among the strongest genetic predictors of obesity risk, due to their impact on appetite regulation (8). The MC4R gene, which is responsible for encoding the melanocortin-4 receptor, plays a pivotal role in the regulation of energy balance. Mutations that result in the loss of function of this gene are the most prevalent cause of monogenic obesity, a condition that is characterised by the development of hyperphagia and subsequent increase in body weight (9, 10). The LEP gene, which is responsible for encoding the hormone leptin (a hormone that regulates satiety) and its receptor gene LEPR, also play essential roles (11). Alterations in leptin signalling are a common mechanism underlying obesity through the development of leptin resistance. A summary of genetic determinants is provided in Table 1.

Table 1. Genetic determinants of obesity: types of changes, molecular mechanisms, and their phenotypic consequences.

Gene	Type of Variant	Molecular Mechanism	Functional Effect	Phenotypic Consequence	Source
FTO	Intronic SNPs (e.g., rs9939609)	Altered regulation of IRX3/IRX5 expression; disruption of appetite control pathways	Increased energy intake and preference for high-calorie foods	Higher BMI, increased adiposity	(12)
MC4R	Loss-of-function mutations (missense, nonsense, deletions)	Impaired melanocortin signaling; reduced anorexigenic response	Hyperphagia, impaired satiety	Early-onset monogenic obesity	(13)
LEP	Missense/nonsense mutations or variants reducing leptin production	Decreased leptin secretion or loss of function	Absent satiety signaling	Severe childhood obesity, sometimes immunological abnormalities	(14)
LEPR	Mutations affecting receptor structure or signaling domains	Impaired leptin signaling via JAK2/STAT3 pathway	Leptin resistance	Increased appetite, progressive weight gain	(15)

In addition to DNA sequence, epigenetic modifications, encompassing DNA methylation and histone modifications, influence the expression of genes implicated in energy homeostasis. These modifications are modulated by dietary influences, physical activity, and other environmental factors (16). In adipocytes, changes in DNA methylation have been observed in genes essential for metabolic regulation, such as IRS1 (insulin receptor substrate 1) and PIK3R1, both participating in the insulin signalling pathway. Increased methylation of these loci may reduce their expression and promote the development of insulin resistance (17, 18). Furthermore, obesity has been demonstrated to be associated with distinct alterations in histone modifications, such as elevated trimethylation of H3K4 (H3K4me3) in adipocytes, which correlates with BMI and insulin resistance (19). It has been demonstrated by other studies that a high-fat diet has the capacity to reduce H3K27 acetylation (H3K27ac) in adipose-derived cells, which may result in a limitation of their proliferation and differentiation capacity (20). The development of obesity is the result of a complex interplay of molecular and genetic processes, including gene variants such as FTO, MC4R, and LEP, as well as epigenetic modifications of DNA and histones that regulate metabolism, appetite, and adipocyte function. These mechanisms are collectively influenced by dietary intake, levels of physical activity, and exposure to the environment. Collectively, these factors shape individual susceptibility to excessive fat accumulation and disturbances in energy homeostasis.

3.2. Lifestyle and Gut Microbiota in Obesity Development

Lifestyle factors, encompassing dietary habits, levels of physical activity, and circadian rhythm disruption, have been identified as pivotal in the development of obesity. This phenomenon is primarily attributed to the modulation of gut microbiota and its subsequent impact on host metabolism. High-fat diets and irregular meal timing disrupt natural diurnal oscillations of the microbiota, leading to reduced production of short-chain fatty acids (SCFAs). SCFAs normally signal to the liver and other tissues to regulate clock gene expression and lipid metabolism (21). In a similar manner, circadian misalignment – such as shift work or simulated jet lag, has been demonstrated to induce "chronodisruption" of the gut microbiota. In mice lacking the core clock gene Bmal1, rhythmicity of bacteria responsible for SCFA fermentation and lipid metabolism is lost, which correlates with increased body weight and impaired glucose tolerance. Concurrently, microbial metabolites, such as SCFAs, modulate clock gene expression in the liver and gut, thereby demonstrating bidirectional communication between the microbiome and the host circadian system (22-24). It is evident that physical inactivity has a significant impact on the composition of the gut microbiota. Regular exercise has been shown to be associated with increased microbial diversity and the enrichment of metabolically beneficial bacteria (25). In a randomised clinical trial involving individuals with obesity, a 12-week calorie-restricted diet combined with resistance training and high-intensity interval training (HIIT) increased the abundance of Akkermansia muciniphila and Parabacteroides merdae, while reducing the proportion of SCFA-producing bacteria (e.g., Butyrivibrio, Coprococcus, Blautia). These changes were associated with alterations in body weight and metabolic markers (26). Finally, dietary interventions and probiotics that modulate the composition of the microbiota (e.g., enhancing SCFA-producing populations) may exert therapeutic effects through restoration of favourable epigenetic profiles in host cells, opening new avenues for microbiome-targeted obesity treatments (27).

3.3. Innovative Therapies in Obesity Management

Contemporary obesity therapies encompass a range of approaches, including the administration of medications that suppress appetite, in addition to the utilisation of emerging strategies that target the epigenetics and microbiota of the individual. The utilisation of small molecules that stimulate brown or beige adipose tissue, through the activation of AMPK, nuclear receptors, or GPCRs, is a promising approach to increasing energy expenditure (28). Class I histone deacetylase (HDAC) inhibitors, such as MS-275, have been demonstrated in high-fat-diet mouse models to reduce adiposity, enhance glucose homeostasis, and promote browning of white adipose tissue through increased UCP1 expression (29). From the microbiota perspective, bariatric surgeries (e.g., Roux-en-Y gastric bypass) have been shown to significantly reshape gut microbial composition and SCFA profiles, which has been linked to enhanced brown adipose tissue activity post-procedure (30). In the context of animal studies, the transplantation of post-bariatric surgery microbiota into germ-free mice has been demonstrated to restore brown adipose tissue (BAT) thermogenesis and enhance metabolism through bile-acid–mediated pathways. The activation of intestinal Farnesoid X receptor (FXR) and systemic TGR5 by taurine-conjugated bile acids has been shown to stimulate thermogenic responses (31). Notably, microbiota-based therapies, including fecal microbiota transplantation (FMT), have demonstrated

that beneficial post-bariatric microbiota can independently enhance glucose metabolism, indicating the potential for novel therapeutic targets focused on microbiome modulation (32). Table 2 provides a synopsis of innovative therapeutic methods and their metabolic effects in obesity management. Contemporary trends in the treatment of obesity emphasise individualised approaches that integrate lifestyle modification, pharmacological therapy, and, when indicated, surgical procedures, accounting for metabolic, behavioural and genetic differences among patients.

Table 2. Innovative therapeutic methods and their metabolic effects in obesity management.

Therapeutic Strategy	Mechanism	Metabolic Effects	Source
Class I HDAC Inhibitor (e.g. MS-275)	Inhibition of histone deacetylases leads to epigenetic modulation in adipose tissue	- **Browning** of white adipose tissue (↑ UCP1) - Improved glucose tolerance - Enhanced insulin secretion (when combined with GLP-1R agonists)	(29, 33)
Histone deacetylase 1 (HDAC1) inhibition	Epigenetic reprogramming via histone modifications	- Increased transcription of thermogenesis genes (PGC1α, UCP1) in beige fat - Elevated energy expenditure, reduced obesity, better glucose metabolism	(34, 35)
Bariatric surgery - shaped microbiota	Alteration of gut microbiome leads to increase in taurine-conjugated bile acids, which activates activation of bile acid receptors (FXR, TGR5)	- Reactivation of brown adipose tissue (BAT) thermogenesis - Improved glucose homeostasis, lipid metabolism, liver health	(31, 36)
Fecal microbiota transplantation (FMT) post-bariatric surgery	Transfer of "post-surgery" microbiota	- Improved insulin sensitivity - Increased energy expenditure via BAT activation	(32)

4. Conclusions and Future Directions

The findings presented illustrate that obesity is a disease of complex etiology, in which genetic, epigenetic, environmental, and gut microbiota–related factors interact. The interpretation of the evidence suggests that genetic variants (including FTO, MC4R, LEP/LEPR) and epigenetic modifications influence the regulation of metabolism and appetite, thereby underscoring the biological foundations of obesity. Concurrently, lifestyle factors and circadian rhythms modulate gut microbiota composition, which plays a pivotal role in energy homeostasis. These insights underscore the necessity for personalised treatment strategies that encompass genetic profiling, lifestyle assessment, and microbiome characteristics. It is recommended that future research efforts concentrate on the integration of clinical data, the development of precise microbiota-targeted therapies, the identification of effective epigenetic interventions, and the investigation of the long-term impact of lifestyle modifications on the epigenome and gut microbiota. A comprehensive, multidimensional approach is imperative for the advancement of modern obesity management.

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