Review

Molecular Mechanisms of Obesity in Children

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Review

Molecular Mechanisms of Obesity in Children

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Abstract

Childhood obesity is a globally pervasive condition driven not only by lifestyle and environmental factors but also by complex molecular mechanisms. These mechanisms involve genetic predisposition, epigenetic regulation, hormonal signaling pathways, adipose tissue biology, immuno-inflammatory responses, and interactions with environmental endocrine disruptors. This review synthesizes current evidence from scientific articles, systematic reviews, and mechanistic studies to elucidate how molecular processes shape the development, onset, and progression of obesity in children. Understanding these pathways is critical for developing precise prevention strategies and targeted interventions.

Keywords: childhood obesity; genetic; epigenetic; adipose tissue; adipocitokynes; molecular pathways

1. Introduction

Childhood obesity has escalated over recent decades to epidemic proportions worldwide, carrying profound implications for long-term health outcomes. International surveys indicate significant increases in overweight and obesity prevalence among children aged 5–19, estimated to have risen from ~2% to ~8% between 1990 and 2022 alone [1]. Approximately 19.7% of children and adolescents (14.7 million) are affected all over the world [2]. Childhood obesity rates have significantly increased and have rising trends, with notable disparities based on socioeconomic and racial factors. The WHO reported 41 million children under five had overweight or obesity in 2016. The prevalence of obesity among children aged 5-19 rose from 4% in 1975 to over 18% in 2016. In the U.S., obesity rates in children aged 2-19 increased from 17.7% in 2011-12 to 21.5% in 2017-20. Higher obesity rates are observed among Hispanic and non-Hispanic Black children compared to their White and Asian counterparts [3].

Childhood obesity is a multifaceted issue with significant health implications. Obesity is a complex disorder of multifactorial nature influenced by genetic, environmental, and biological factors, not merely an energy imbalance. Obesity arises from an energy imbalance between calories consumed and expended. Genetic components significantly contribute to obesity risk. Emerging factors include epigenetics, neurotrophic factors, and microRNAs. Monogenic obesity has identifiable genetic causes, while polygenic obesity involves multiple genes and mutations [4].

Development of obesity cannot be entirely explained by changes in calorie intake and physical activity. Molecular biology plays a central role. Genetic predispositions, epigenetic programming, hormonal regulation, adipokine networks, immune signaling, and environmental factors interact to drive obesity susceptibility early in life [1]. The simplistic view of obesity as solely a positive energy balance is misleading and overlooks complex biological mechanisms. Obesity often misinterpreted as a direct result of increased energy intake or decreased expenditure. The relationship between energy balance and body mass is descriptive, not causal. Changes in fat dynamics and regulation are crucial to understanding obesity development. The minute daily fat accumulation is difficult to measure, complicating research [4]. There are behavioral misconceptions regarding obesity. Common assumptions about overeating and inactivity as primary causes of obesity are often flawed and

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oversimplified. Increased energy intake and decreased physical activity are often seen as direct causes of obesity. The argument that obesity results from voluntary overeating is misleading; many struggle to maintain weight loss. Individuals with obesity may eat more to meet increased energy needs, not necessarily due to overeating. Understanding the biological mechanisms behind obesity is essential for effective prevention and treatment strategies [4].

The obesogenic environment contributes to the global obesity epidemic through the availability of energy-dense foods and reduced physical activity. The obesogenic environment is characterized by cheap, energy-dense foods and limited opportunities for physical activity. It remains unclear whether this environment drives obesity or merely permits its development. Genetic predisposition plays a role in obesity, with some individuals more susceptible in an obesogenic environment. Early life environmental influences may create additional predispositions to obesity. There is significant heterogeneity in obesity prevalence across different populations and over time [4].

Various psychosocial factors influence obesity development. Psychosocial challenges significantly influence obesity risk, particularly in environments with abundant food. Key determinants of obesity include age, sex, and various psychosocial factors. Individuals facing psychosocial challenges are at a higher risk of developing obesity in food-abundant environments. The relationship between psychosocial factors and obesity development is well established, unlike the connection between food intake and physical activity. Hypotheses suggest a direct link between mental states induced by psychosocial challenges and fat dynamics in adipose tissue. A broader, cross-disciplinary approach is necessary to understand the molecular mechanisms of obesity [4].

A growing body of research highlights that these mechanisms operate even before birth, shaping metabolic trajectories into childhood and beyond. For example, maternal obesity and gestational diabetes can reprogram gene expression in offspring through epigenetic alterations, with measurable DNA methylation changes observable in the first year of life [1,5]. Molecular mechanisms and dysfunctions in childhood obesity are summarized in Table 1.

Childhood obesity is a global challenge and a leading cause of malnutrition worldwide, necessitating a comprehensive understanding and effective prevention strategies. The prevalence of childhood obesity remains high despite public health interventions. A multifaceted approach is required, including research, intervention strategies, and policy formulation [3].

Table 1. Molecular mechanisms and dysfunctions in childhood obesity.

Modification	Impaired mechanism
Genetic modifications	Monogenic (syndromic, non-syndromic), polygenic
Mitochondrial dysfunction	Reduced mitochondrial density, impaired oxidative capacity, increased reactive oxygen species (ROS)
Epigenetic modifications	DNA methylation, microRNAs, noncoding RNAs, histone modifications, nutritional factors, multi-omics, prenatal programming, intergenerational and transgenerational inheritance, sex-specific molecular modifications,
Adipose tissue and adipogenesis modifications	differentiation of preadipocytes into mature adipocytes, proliferator-activated receptor gamma (PPARγ), Inflammatory cytokines, retinoid X receptor (RXR), liver X receptor (LXR), farnesoid X receptor (FXR), aryl hydrocarbon receptor (AhR), extracellular matrix (ECM)
Hormonal and metabolic modifications	Leptin (LEP), leptin receptor (LEPR), leptin resistance, adiponectin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), resistin, visfatin, angiotensin, insulin signaling, insulin resistance,
Immune and inflammatory modifications	Inflammatory cytokines - TNF-α, IL-6, Monocyte Chemoattractant Protein-1 (MCP-1), chronic inflammation, macrophages, dendritic cells, natural killer (NK), cells B cells, T cells, neutrophils, ROS, monoamine Oxidase (MAO)

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Neurobiological modifications	Mutations in the leptin-melanocortin pathway (LEP, LEPR, melanocortin-4 Receptor - MC4R), mutations of the regulatory factors (melanocortin-2 receptor accessory protein 2 - MRAP2, adenylate cyclase 3 - ADCY3), pro-opiomelanocortin (POMC) and agouti-related protein (AGRP), brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), class 3 semaphorins (SEMA3A–G), orexigenic neuropeptides (neuropeptide Y / agouti-related protein - NPY/AgRP), anorexigenic neuropeptides (pro-opiomelanocortin/cocaine / amphetamine-regulated transcript - POMC/CART, alpha-melanocyte-stimulating hormone α - α-MSH), hypothalamus and eating behavior, hypothalamic-pituitary-adrenal (HPA) in response to chronic stress, leptin signaling, central leptin and insulin resistance, Janus kinases/ signal transducers and activators of transcription (JAK/STAT) pathway,
Gut microbiota	Dysbiosis, ghrelin, Glucagon-Like Peptide-1 (GLP-1), Glucose-Dependent Insulinotropic Polypeptide (GIP), microbial metabolites and host signaling, metabolic endotoxemia, epigenetic and immune interactions
Environmental influences	Nutrition (cholecystokinin (CCK), peptide YY, leptin, insulin, dietary patterns), obesogenic environment, physical activity / sedentary behavior, endocrine-disrupting chemicals (EDCs, obesogens)
Vitamins, minerals, other factors	Vitamin A deficiency, retinol-binding protein 4 (RBP4), vitamin D deficiency, ion channels (K^+, G protein-gated inwardly rectifying K+ channels – GIRK, transient Receptor Potential channels - TRP - Ca^{2+}, Mg^{2+}, Na^+), metabotrophic factors (neurotrophins: nerve growth factor – NGF, brain-derived neurotrophic factor - BDNF; adipokines: leptin, adiponectin, and resistin; myokines: irisin and fibroblast growth factor-21), adipose tissue hypoxia, viral infections, zinc: deficiency or excess, Zinc-α2-Glycoprotein (ZAG)
Obesity-associated comorbidities	Impairments from metabolic dysfunction-associated steatotic liver disease (MASLD), cardiometabolic risk and atherosclerosis and cardiovascular diseases; disruptions of sleep and circadian rhythm

DNA - deoxyribonucleic acid, RNA - ribonucleic acid.

2. Genetic Basis of Childhood Obesity

Both genetic and environmental factors play significant roles in susceptibility and development of childhood obesity, influencing susceptibility and disease progression. Obesity heritability ranges from 40% to 75%, with various genetic forms contributing to its development and over 300 genes linked to obesity. Genetic obesity forms include Mendelian syndromic, Mendelian non-syndromic, and polygenic obesity. Mendelian obesity results from rare chromosomal abnormalities and gene variants affecting energy balance. Polygenic obesity is influenced by multiple common genetic variants, with FTO being a prominent contributor. Genome-wide association studies (GWAS) have identified numerous loci linked to obesity, but specific mechanisms remain under investigation [2,5,6]. Genetics significantly influence obesity, but environmental factors play a larger role. Twin studies suggest 40-70% of obesity may be genetic. Polygenic obesity accounts for only 3-5% of individual variation in obesity risk. Environmental factors explain 85% of metabolic syndrome risk [5,7,8]. Parental obesity significantly increases the risk of childhood obesity, with maternal obesity having a stronger effect. Genetic susceptibility to obesity is mediated through various homeostatic

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mechanisms. The prevalence of obesity has tripled since the 1980s, indicating a complex interplay of genetics and environment [4].

Genetic and epigenetic factors play a crucial role in the development of childhood obesity, influencing susceptibility and disease progression. Genetic causes of obesity come in many forms [3]. Genetic mutations play a significant role in childhood obesity, particularly in specific genes. Approximately 2% to 5% of children with obesity have heterozygous mutations in the MC4R gene. A follow-up study showed skinfold thickness was associated with lower gene variants in children with the MC4R TT genotype and LEP AG genotype. Studies indicate that genes linked to severe obesity in animals are also relevant in humans, often without developmental delay. The set point theory and thrifty gene theory explain genetic influences on body weight regulation. More research with larger sample sizes is needed to understand genetic contributions to childhood obesity [5,9].

2.1. Obesity genes. Numerous genetic mutations that cause obesity have been described. Genetic studies have evaluated the following obesity-related genes: (1) single genes including LEP, LEPR, POMC, MC4R, SIM1, NTRK2, KSR2, CPE, PCSK1, BDNF, SH2B1, and SH2B1; (2) syndromic obesity genes including NIPBL, SH2B1, GNAS, and ALMS1; (3) genes related to overgrowth syndrome, including PTEN, ICR1/H19/KCNQ1OT1/CDKN1, and RASA1; and (4) miscellaneous genes including MYTL1. In addition, epigenetic changes, which are reversible chemical modifications to DNA with no changes in DNA sequences, are involved in obesity development through the following mechanisms: (1) DNA methylation (the circadian clock genes CLOCK, clock circadian regulator; BMAL1, aryl hydrocarbon receptor nuclear translocator-like; PER2, period circadian 2); (2) histone modification (preadipocyte factor-1 (Pref-1), CCAAT-enhancer-binding protein β (C/EBPβ), C/EBPα, peroxisome proliferator-activated receptor gamma (PPAR-γ), and adipocyte protein 2 (aP2)); and (3) microRNAs (miRNA: miR- 148a, miR-26b, miR-30, and miR-199a) [10]. Methods used in research included chromosomal microarray analysis (CMA), whole-exome sequencing (WES), genome sequencing, next-generation sequencing (NGS), exome array data, and new long-read sequencing platforms [8,11].

Obesity is categorized into monogenic (rare, severe, single gene defects) and polygenic (common, multifactorial, multiple genetic variants) forms, based on genetic inheritance [2,3,8,12].

2.2. Monogenic obesity is a rare, severe, early-onset form of obesity, caused by a single-gene mutation, with little or no influence of the environment, that provides insights into specific genes and pathways [3]. Monogenic obesity is caused by pathogenic variants in genes involved in the leptin-melanocortin pathway. Mutations in genes regulating central appetite pathways (e.g., LEP, LEPR, POMC, PCSK1) result in severe early-onset obesity, hyperphagia, and endocrine irregularities. Key genes include LEP (leptin), LEPR (leptin receptor), POMC (proopiomelanocortin), MC4R (melanocortin 4 receptor), and PCSK1 (proprotein convertase subilisin/kexin 1) [12]. Congenital leptin deficiency is rare, with an estimated prevalence of 1 in 15 million, leading to severe obesity and hyperphagia. POMC deficiency leads to obesity, adrenal insufficiency, and hyperphagia, with fewer than 50 reported cases. MC4R mutations are the most common form of monogenic obesity, affecting 1.7–5.8% of individuals with obesity [4,13].

The leptin-melanocortin pathway is crucial for regulating appetite and body weight, with many monogenic obesity cases linked to defects in this pathway. Clinical features of monogenic obesity include rapid weight gain from infancy, hyperphagia, and potential endocrine defects. Key disorders include: MC4R Deficiency - most common, causing severe obesity and hyperinsulinemia, Leptin Deficiency - rare, leading to severe hyperphagia and obesity, with additional endocrine issues, Leptin Receptor Deficiency - Similar to leptin deficiency but with elevated leptin levels, POMC Deficiency - results in obesity, red hair, and adrenal insufficiency, PCSK1 Deficiency - causes early-onset obesity with gastrointestinal and endocrine complications [4,14].

Genetic testing is crucial for diagnosing rare variants of monogenic obesity, particularly in cases with severe early-onset obesity and endocrine anomalies. Genetic testing techniques enhance the diagnosis of monogenic and syndromic obesity. Whole-exome sequencing has identified new monogenic obesity cases and improved understanding of obesity mechanisms. Array techniques,

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including single nucleotide polymorphisms (SNPs) and copy number variants (CNVs), are now standard for diagnosing developmental disorders associated with obesity. Advancements in next-generation sequencing (NGS) have expanded genetic testing capabilities and have facilitated the discovery of causative genetic variations in patients with severe early-onset obesity [4,14].

Ongoing research aims to clarify genotype-phenotype correlations in obesity-related genetic disorders. Understanding the relationship between genetic variants and their phenotypic effects is crucial for identifying the causes of obesity and other genomic disorders. Continuous aggregation of genotype and phenotype data is essential for clinical testing. Improved phenotypic data can aid in developing profiles for genomic disorders like obesity. Identification of candidate genomic regions can lead to targeted diagnostic tools for obesity. Targeted clinical arrays can detect genetic variations that contribute to obesity risk [4].

Challenges in Genetic Variant Detection. Detecting genetic variants associated with obesity presents significant challenges due to the limitations of current methodologies. GWAS face issues with copy number variants (CNV) calling algorithms, particularly for small and common CNVs. Sparse SNP distribution in low-copy repeat regions complicates variant detection. High-resolution SNP array platforms have been developed to improve detection in gene-poor regions. Errors in CNV detection algorithms can impact association analyses, necessitating further research [4].

Monogenic obesity is classified as either syndromic (associated with additional clinical features) or non-syndromic (obesity as the sole feature). The distinction is becoming blurred as more genes are linked to both obesity and neurodevelopmental disorders, indicating a spectrum of symptoms rather than strict categories. Examples include Bardet-Biedl syndrome and Prader-Willi syndrome, which exhibit obesity alongside cognitive and behavioral challenges [12].

Syndromic obesity is characterized by various co-morbidities and presents diagnostic challenges. Over 80 obesity syndromes have been identified, with only a few fully characterized. Phenotypic heterogeneity complicates diagnosis and treatment. Genetic and environmental factors contribute to the variability in clinical presentations. Advances in genetic testing are improving the understanding and classification of syndromic obesity [12]. Syndromic obesity includes conditions with excessive adiposity and other features like endocrine dysfunction and dysmorphisms. Notable syndromes include Bardet–Biedl syndrome, Alstrom syndrome, and Prader–Willi syndrome, each with complex genetic bases [13]. Currently known forms of syndromic obesity are detailed in Table 2. [11,14,15].

Table 2. Syndromic obesity forms and genetic defects.

Syndrome	Defects
Prader–Willi Syndrome (PWS)	Loss of paternal 15q11–q13 - SNORD116 microdeletion or imprinting defect
Bardet–Biedl Syndrome (BBS)	Mutations in >20 BBS genes - e.g., BBS1, BBS2, BBS10
Alström Syndrome (ALMS)	ALMS1 mutations
WAGR Syndrome	Deletion at 11p13, including WT1 and PAX6
Cohen Syndrome	VPS13B gene mutations
Carpenter Syndrome	RAB23 mutations
Fragile X Syndrome	FMR1 CGG trinucleotide expansion
Borjeson–Forssman–Lehmann Syndrome (BFLS)	PHF6 mutations
Albright Hereditary Osteodystrophy (AHO)	GNAS mutations affecting imprinting pattern
Simpson–Golabi–Behmel Syndrome	GPC3 mutations
Beckwith–Wiedemann Syndrome (BWS)	Epigenetic abnormalities or paternal uniparental disomy at 11p15.5
Alazami Syndrome	LARP7 gene mutations

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Craniopharyngioma-associated Hypothalamic obesity	Secondary to hypothalamic damage
Leptin (LEP) Deficiency/gene mutations	Gene ID: 3952, rs10487505
Leptin receptor (LEPR) deficiency/gene mutations	Gene ID: 3953, rs11208659
Melanocortin 4 receptor (MC4R) deficiency/gene mutations	Gene ID: 4160, rs17782313
Pro-opiomelanocortin (POMC) deficiency/gene mutations	Gene ID: 5443POMC, rs6545975
Adenylate cyclase type 3 (ADCY3) mutations	Gene ID: 109, rs6545814
Agouti-related protein (AGRP) mutations	Gene ID: 181
Brain-derived neurotrophic factor (BDNF)	Gene ID: 627, rs925946
Kinase suppressor of Ras2 (KSR2)	Gene ID: 283455, rs56214831
Melanocortin receptor accessory protein 2 (MRAP2)	Gene ID: 112609
Neurotrophic receptor tyrosine kinase 2 (NTRK2)	Gene ID: 4915, rs10868215
Proprotein convertase subtilisin/ kexin type 1 (PCSK1)	Gene ID: 5122, rs6235
Pleckstrin homology domain interacting protein (PHIP)	Gene ID: 55023
SH2B adaptor protein 1 (SH2B1)	Gene ID: 25970, rs7498665
Single-minded homologue (SIM) bHLH (basic helix–loop–helix) transcription factor 1 (SIM1)	Gene ID: 6492, rs6907240
Other gene mutations	SEMA3A-G, MC3R deficiency/mutations, DYRK1B, RAI1

SNORD116 - Small Nucleolar RNA, C/D Box 116, WT1 - Wilms tumor 1, PAX6 - Paired box 6, VPS13B - vacuolar protein sorting-associated 13B, RAB23 - Ras-related protein Rab-23, FMR1 CGG - Fragile X Messenger Ribonucleoprotein 1 Cytosine-Guanine-Guanine, PHF6 - Plant Homeodomain Finger Protein 6, GNAS - Guanine nucleotide binding protein alpha stimulating activity polypeptide, GPC3 - Glypican-3, LARP7 - La-related protein 7, SEMA3A-G - Semaphorin 3A–G, MC3R - Melanocortin 3 receptor, DYRK1B - Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1B, RAI1 - Retinoic acid induced 1.

Despite that molecular diagnostics have made progress in identifying pathogenic variants, between 30 and 40 percent of syndromic obesity cases remain genetically unexplained. The variation in phenotype across people with the same mutation suggests the influence of epigenetic and environmental factors. Limited resources and differences in access to genetic testing decrease or prevent the diagnostic [11].

2.3. Polygenic Obesity involves multiple genetic variations, each contributing modestly to obesity risk. Unlike monogenic obesity, which primarily affects hypothalamic circuits, polygenic obesity involves brain regions associated with addiction and reward, suggesting different underlying mechanisms. Polygenic risk can influence the severity of monogenic obesity, indicating that genetic susceptibility plays a role in the expression of obesity phenotypes [12].

The genetic influence on childhood obesity is complex and primarily polygenic. More than 1,100 independent genetic loci have been identified in genome-wide association studies (GWAS) as associated with body mass index (BMI) and related traits. These loci include genes involved in

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appetite regulation, energy balance, adipose tissue function, glucose and lipid metabolism, and neural signaling pathways [16].

Polygenic obesity is a common multifactorial form of obesity, resulting from an interaction between the obesogenic environment and hundreds of genetic variants and involves numerous common genetic variants, each contributing modestly to obesity risk, with hundreds of genes identified through genome-wide association studies (GWAS). The FTO gene is notably linked to obesity and body mass index (BMI), with variants such as rs9939609 associated with increased fat mass and BMI in children [3,4,14].

Genome-wide association studies (GWAS) have explored the genetic basis of childhood obesity, revealing consistent genetic associations across different life stages and have significantly advanced the understanding of genetic factors contributing to obesity. GWAS have identified over 1,100 loci associated with BMI and obesity traits, primarily expressed in the central nervous system, explaining approximately 5% of BMI variability. The Early Growth Genetics (EGG) consortium studied birth weight and pediatric BMI, finding loci also linked to adult obesity. Over 20 genes linked to severe early-onset monogenic obesity and approximately 1,000 loci associated with common polygenic obesity have been identified, many of which are expressed in the brain. A distinct genetic signature for peak BMI during infancy has been identified. The first GWAS for BMI (2007) identified the FTO locus as a key association with obesity across multiple ancestries, with variants explaining 1-3% of BMI variance. Subsequent waves of GWAS have identified additional loci, including MC4R and others, contributing to obesity susceptibility. The cumulative effect of identified loci explains a small percentage of the overall heritability of obesity, indicating the complexity of its genetic basis [2,4,12,14].

Common variants in the *fat mass and obesity-associated gene (FTO)* are among the most strongly implicated. FTO polymorphisms influence eating behavior, energy intake, and adiposity, likely by modulating neuronal and adipocyte gene networks [17]. FTO is highly expressed in adipose tissues and is implicated in obesity-related metabolic disorders [18]. FTO is highly polymorphic, with variants categorized into promoter, exonic, and intronic polymorphisms. FTO polymorphisms may influence metabolic processes through various biological mechanisms: aberrant expression of FTO and its target genes; increased expression of FTO mRNA is observed in A allele carriers of rs9939609; the rs1421085 polymorphism affects the expression of adjacent genes involved in adipocyte differentiation. FTO polymorphisms are linked to higher levels of key metabolic enzymes and hormones, such as stearoyl-CoA desaturase and ghrelin. Regarding FTO variants and appetite regulation, A allele carriers show increased food intake. FTO encodes an RNA demethylase that regulates RNA stability and functions. FTO polymorphisms, such as rs9939609 and rs9930506, are associated with increased adipogenesis, appetite, and decreased energy expenditure, while the rs9939609 polymorphism shows a strong relationship with MetS components. Minor allele A frequency varies and studies indicate that AA or AT genotypes are associated with higher body weight and adiposity [18].

FTO gene polymorphisms are significantly associated with increased waist circumference in children and adolescents. The rs9939609 polymorphism (A allele) is associated with increased WC in children and adolescents, while A allele carriers have a higher risk of developing abdominal obesity. WC is associated increased with TT, TA, and AA genotypes (Han Chinese children). Polymorphisms such as rs17817449, rs1421085, and rs8050136, rs1861868, rs1558902, rs7206790, and rs11644943 show significant associations with higher mean WC in children and adolescents. The CT genotype of the rs1421085 polymorphism is linked to a higher mean WC compared to the TT genotype. Studies indicate that specific genotypes are linked to variations in physical activity and obesity indexes among children. Variations in waist circumference are also influenced by non-genetic factors like gender and lifestyle. FTO Polymorphisms influence also blood pressure, glucose and lipid regulation [18].

The FTO Gene and Obesity Susceptibility. FTO is the first gene identified with common variants that influence obesity risk in the general population. FTO locus contains BMI-associated SNPs,

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particularly in its first intron. Initial GWAS identified SNPs rs9939609 and rs9930506 as significantly associated with BMI. Subsequent studies confirmed multiple FTO SNPs linked to obesity traits across various populations. The SNP cluster spans approximately 46 kb in the FTO gene's first intron. Replication studies show FTO's effects are consistent across European, Asian, and some Hispanic populations, but results in African populations are inconsistent. FTO's effect on BMI is similar across ancestries, but the minor allele frequency is lower in African populations (12%). FTO SNPs do not influence birth weight but affect body weight from early childhood, peaking in young adulthood. FTO variants have the largest effect size among obesity susceptibility loci identified to date. Each additional risk allele correlates with a 0.39 kg/m^2 increase in BMI and a 1.20-fold increased risk of obesity. Approximately 43% of the population carries one risk allele, and 20% carries two. FTO explains only 0.34% of inter-individual BMI variation, making obesity risk prediction based on FTO genotype poor [4].

Lifestyle Factors and FTO's Role in Obesity. FTO's association with obesity is influenced by lifestyle factors, particularly food intake and physical activity. FTO SNPs are linked to increased energy intake, appetite, and reduced satiety. Studies show no significant association between FTO SNPs and physical activity levels. Physical activity reduces the impact of FTO on BMI by approximately 30% in adults, while increase of physical activity or a healthy diet can attenuate the effect of the FTO locus on obesity risk by 30–40%. Environmental factors, including exercise, can influence the genetic burden of FTO risk alleles [4,8].

FTO's Role in Energy Homeostasis. FTO is implicated in energy homeostasis and growth regulation through its expression and activity. FTO expression is highest in the brain, particularly in the hypothalamus, which regulates food intake. Nutritional status influences FTO levels, with downregulation during fasting and upregulation with high-fat diets [4].

FTO as a Nutrient Sensor. FTO may act as a sensor for essential amino acid availability, linking nutrient status to growth and metabolism. FTO expression decreases with essential amino acid deprivation, suggesting a role in sensing nutrient availability. FTO deficiency leads to reduced mTORC1 signaling and increased autophagy, contributing to growth retardation [4].

FTO and m6A Methylation. FTO's demethylation activity on 6meA is crucial for regulating gene expression and cellular processes. 6meA is enriched in mRNA and plays a role in gene expression regulation. FTO's ability to demethylate specific mRNA subsets may influence dopamine signaling and ghrelin levels [4].

The Role of IRX3 in Obesity. Recent findings suggest that iroquois homeobox 3 (IRX3), rather than FTO, may be responsible for obesity-associated SNP effects. FTO intron 1 SNPs are linked to IRX3 expression, indicating a regulatory relationship. IRX3-deficient mice exhibit reduced fat mass and increased metabolic rate, supporting its role in body weight regulation [4].

Variants of the *melanocortin-4 receptor (MC4R) gene*, essential for hypothalamic appetite control, also significantly affect weight regulation [17]. These genetic associations partly explain why some children are more susceptible to weight gain under similar environmental exposures. While individual variants exert small effects, the cumulative burden of risk alleles helps determine overall obesity susceptibility and may influence responses to lifestyle interventions [16].

Next-generation sequencing (NGS) technology allows for the simultaneous analysis of multiple genes, improving mutation detection. New genetic analysis techniques, such as whole genome sequencing, may identify rare polymorphisms associated with obesity [4].

Genetic Risk Scores for Obesity (GRS). Combining information from multiple obesity-related loci into GRS can enhance the prediction of obesity susceptibility. GRS can summarize risk-associated genetic variations across the genome. The use of GRS is more effective in identifying susceptibility to common traits than individual loci. Differences in allele frequencies across populations can affect the predictive power of GRS [4].

2.4. Monogenic versus Polygenic Obesity Genetics. Monogenic and polygenic obesity are interconnected, sharing biological pathways, particularly the leptin-melanocortin pathway.

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Monogenic and polygenic forms of obesity are not discrete entities, belong to a spectrum and determine partially overlapping metabolic dysfunctions [8,14].

Recent GWAS have identified loci associated with both monogenic and polygenic forms of obesity, highlighting overlapping genetic pathways. Genes like MC4R and POMC, linked to extreme obesity, also show associations with common obesity. Disruptions in BDNF–TrkB and leptin–melanocortin signaling pathways are implicated in severe obesity [2].

Monogenic obesity is a rare, early-onset, and severe form of obesity from mutations in specific genes that has a Mendelian inheritance pattern, high penetrance, and large genetic effect [14]. Polygenic obesity is more common and prevalent and has inheritance derived from many variants in several genes with low penetrance. The interaction between phenotype and environmental factors influence obesity types and manifestations. The influence of genetics on obesity can be considered a continuous spectrum and a distinct classification can not be very accurate [14].

GWAS for obesity specific obesity traits like percentage of body fat, lean body mass, imaging-derived adipose tissue, serum leptin, leptin receptor levels, persistent healthy thinness have been conducted, revealing more detailed phenotypes, more accurate aspects of appetite and body weight regulation, and more relevant biological pathways underlying obesity [14]. Common variants of candidate genes in GWAS were tested for association with obesity risk, BMI, other body composition traits, demographic factors (age, sex) and environmental factors (physical activity, diet, smoking) and only 12 loci have been identified, with effects on obesity that are attenuated or exacerbated by non-genetic factors. Environmental factors can increase or decrease the impacts of genetic variations in obesity [8,14]. Besides the FTO locus, research was conducted for few other obesity-associated GWAS loci: TMEM18, CADM1, CADM2, NEGR1 [8]. In the last 15 years, variants in only six genes showed association with obesity (ADRB3, BDNF, CNR1, MC4R, PCSK1, and PPARG). A recent study identified 16 genes rare variants that were associated with BMI, from which five were brain-expressed G protein-coupled receptors (CALCR, MC4R, GIPR, GPR151 and GPR75) [8]. With ongoing research, GWAS have discovered more obesity-associated loci in already identified genes: MC4R, BDNF, SH2B1, POMC, LEP, LEPR, NPY, SIM1, NTRK2, PCSK1 and KSR2. Most of these genes encode components of the leptin–melanocortin and BDNF–TrkB signalling pathways. Genetic mutations of these components determine severe obesity, while genetic variants in or near these same genes have diminished effects on their expression on the distribution of BMI. A locus harbouring ADCY3 was first identified in GWAS for common obesity, then for extreme obesity. There is some evidence that ADCY3 colocalizes with MC4R at the primary cilia of paraventricular nucleus neurons67 and have roles in the control of energy homeostasis [8]. For the majority of the >1,000 GWAS-identified loci, it is not known which genes are causal and how they specifically affect cells, tissues, organs and total body weight, and the underlying mechanisms are not understood [8].

Other methods used for genetic testing include candidate gene studies, genome-wide linkage studies and alternative genome-wide screens [8].

Genetic Factors Influencing Fat Distribution. Genetic factors play a crucial role in determining fat distribution, with notable differences observed between sexes. More specific obesity phenotypes, such as waist-to-hip ratio (WHR) and body fat percentage, have been studied, revealing direct biological relevance. Three major studies confirmed the significant genetic component of WHR. Genetic components account for 30-55% of fat distribution, with significant loci showing sex dimorphism. Recent studies identified 56 protein-coding variants affecting fat distribution, with 19 showing sex-specific effects. Variants near THNSL2, BBS9, and CYCSP30 were associated with abdominal visceral adipose tissue (VAT) in women. The UBE2E2 locus was linked to the VAT: subcutaneous fat ratio, impacting adipocyte differentiation in mouse models [2].

Gene Expression in Visceral Adipose Tissue. The study of gene expression patterns in the visceral adipose tissue (VAT) of pediatric individuals with obesity identified 184 overlapping VAT specific differentially-expressed genes (DEGs) from two datasets: GSE9624 and GSE88837. There were 1182 upregulated and 1226 downregulated DEGs in GSE9624, and 378 upregulated and 514 downregulated DEGs in GSE88837. Functional enrichment analysis revealed significant pathways

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related to obesity, including TGF-β signaling and immune response. Upregulated genes were enriched in pathways related to hormone response, adipocyte differentiation, and Akt signaling. Downregulated genes were associated with the complement cascade, inflammatory response, and diseases like meningioma and acute myocardial infarction. Disease-gene interactions indicated links to conditions such as vascular inflammation, kidney failure, and unipolar depression [19].

Protein-Protein Interaction Network in Obesity. In a recent study, a protein-protein interaction (PPI) network was constructed to identify significant gene clusters and interactions. The PPI network included 44 upregulated and 71 downregulated overlapping genes with 552 interactions. Six significant clusters were identified, with Cluster 1 having the highest score and including genes like KIF20A and AURKA. The analysis highlighted the interconnectedness of genes involved in obesity-related pathways. The study identified 19 key hub genes and their regulatory transcription factors (TFs), with TOP2A being the most prominent. The TF-gene interaction network revealed 90 hub gene–TF pairs, and 24 key TFs which are implicated in obesity-related pathways were identified including JUN, APOE, and LEP [19].

Another study identified key genes and pathways involved in obesity-related mechanisms. Twelve hub-bottleneck genes were identified: INS, LEP, STAT3, POMC, ALB, TNF, BDNF, CAT, GCG, PPARG, VEGFA, and ADIPOQ. Four functional clusters were formed, with cluster 1 showing the highest interaction score. Cluster 1 enriched genes related to inflammation, carbohydrate metabolism, and lipid metabolism. 256 genes were differentially expressed between fit and unfit children with overweight/obesity after adjusting for sex and maturation. Pathways associated with inflammation, cardiovascular disease, metabolic syndrome, hypertension, and asthma were identified [9].

Impact of Sex on Genetic Associations. Sex differences significantly influence genetic associations with obesity-related traits, with varying effects across populations. Several waist-related traits show stronger associations in women, while some BMI loci are more significant in males. Specific loci like MC4R and LYPLAL1 were linked to female visceral fat area, while ALDH2 was associated with males. Sexual dimorphism in genetic associations varies by ethnicity and population [2].

Ethnic Variability in Obesity Genetics. Because the majority of GWAS have been perfomed on in populations of European descent, the results can not usually be applied on Asian, African, Hispanic, or other ancestries populations [14]. Most GWAS have focused on European populations, but additional loci have been discovered in diverse ethnic groups. Smaller sample sizes in non-European populations have revealed unique loci with different allele frequencies and effect sizes. Increasing statistical power through larger GWAS in specific ancestries is essential for uncovering additional loci. Notable examples include CREBRF in Samoans and ADCY3 in Greenlanders [2].

Rare and Low-Frequency Genetic Variants. Advancements in technology have enabled the detection of rare and low-frequency variants that may contribute to obesity risk. Initial GWAS focused on common variants (MAF > 5%), but recent efforts have identified variants with MAF < 5%. A study involving 700,000 subjects uncovered coding mutations across 13 genes linked to BMI variation. Rare and low-frequency variants are more likely to reside in coding and regulatory elements [2].

Functional Annotation of Target Genes. Understanding the mechanisms of GWAS-identified loci remains challenging, with many variants residing in non-coding regions. Functional follow-up studies are limited, but they can reveal insights into obesity etiology. Various methods, including SNP enrichment analysis and transcriptome-wide association studies (TWAS), are employed to connect variants to effector genes. Machine learning and AI are increasingly used to predict effector genes, requiring further validation [2].

3. Mitochondrial Dysfunction and Energy Metabolism

Mitochondria regulate cellular energy metabolism through oxidative phosphorylation and fatty acid oxidation. In childhood obesity, mitochondrial dysfunction has been documented in skeletal muscle, liver, and adipose tissue. Reduced mitochondrial density, impaired oxidative capacity, and increased reactive oxygen species (ROS) production have been observed in children with obesity,

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contributing to insulin resistance and lipid accumulation [20]. Nutrient overload can cause mitochondrial dysfunction, contributing to obesity [5]. Obesity leads to reduced mitochondrial biogenesis and altered mitochondrial dynamics. Mitochondrial fission and fusion processes are disrupted in obesity, contributing to insulin resistance [13].

Molecular Drivers of Mitochondrial Dysfunction. Key molecular regulators of mitochondrial biogenesis include peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and AMP-activated protein kinase (AMPK). PGC-1α is a key regulator of mitochondrial biogenesis, and its dysfunction is associated with obesity and type 2 diabetes mellitus. Suppressed activity of these regulators in obesity reduces mitochondrial efficiency and energy expenditure. Epigenetic suppression of mitochondrial genes has also been reported in pediatric obesity, linking early-life environmental exposures to long-term metabolic impairment [13,21].

4. Epigenetic Regulation and Developmental Programming

Epigenetic processes, influenced by environmental factors, play a crucial role in the development of childhood obesity and can alter gene expression without changing the genetic code, further affecting obesity risk and complicating obesity's etiology. Genetic predispositions alone cannot account for the rapid rise in childhood obesity. Epigenetic mechanisms are heritable, reversible modifications that regulate gene expression without altering DNA sequence [3,5,13].

4.1. Gene-Environment Interactions and Epigenetics

Epigenetic modifications contribute to obesity pathogenesis. Gene-environment interactions, particularly through epigenetic mechanisms, play a significant role in obesity susceptibility. Environmental factors can induce epigenetic changes that affect gene expression and contribute to obesity phenotypes [2–4,21–23].

Understanding epigenetic mechanisms is vital for comprehending gene regulation and its implications for health. Epigenetic mechanisms regulate gene activity from embryonic stages through aging. Disturbances in the epigenome can lead to various pathologies, including obesity [3].

Environmental factors such as diet, physical activity, and endocrine disruptors significantly impact epigenetic processes and can lead to epigenetic changes, influencing obesity risk and metabolic health. The agouti mouse model illustrates how epigenetic changes can influence obesity, with dietary factors affecting gene expression. Prenatal exposures, including maternal nutrition, can result in inherited epigenetic patterns affecting offspring obesity risk [2,4].

DNA methylation, histone modifications, and non-coding RNAs are key epigenetic changes associated with obesity. DNA methylation at specific genes, such as LEP and adiponectin, shows associations with obesity and metabolic disease. Histone modifications regulate genes related to adipogenesis and appetite control, with changes linked to high-fat diets [2–4,21–23].

DNA Methylation Patterns

DNA methylation, the addition of methyl groups to cytosines in CpG dinucleotides, is the most intensively studied epigenetic mechanism in childhood obesity. Numerous studies have shown that obesity and related metabolic parameters correlate with altered methylation at key loci. For example, differential methylation of FTO, HIF3A, and IRS1 genes is associated with higher BMI and adiposity [17]. Systematic reviews reveal that methylation patterns established in early life, particularly during prenatal and early postnatal periods, can persist and influence metabolic outcomes. These modifications may affect genes involved in fatty acid metabolism, adipogenesis, and mitochondrial function [1].

DNA methylation can alter gene expression patterns. DNA methylation can silence genes like LEP and ADIPOQ, affecting energy homeostasis and insulin sensitivity. In most cases, hypermethylation leads to repression of the gene transcription hence causing gene silencing, while hypomethylation or loss of methylation, in general, leads to gene activation. Hypermethylation of

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the LEP promoter correlates with increased BMI in persons with obesity. DNA methylation alters the expression of the leptin gene (LEP) and adiponectin gene (ADIPOQ), which regulate energy homeostasis in obesity. It was noted a negative correlation between DNA methylation of the LEP promoter and BMI in persons with obesity. Hypomethylation of the LEP promoter causes upregulation of LEP and increased levels of circulating leptin that cannot utilize its anorexigenic effect in leptin-resistant persons with obesity. In contrast, a positive correlation has been found between DNA methylation of ADIPOQ promoter in the adipose tissue and BMI in subjects with obesity. DNMT-induced hypermethylation of ADIPOQ promoter causes downregulation of ADIPOQ and decreased adiponectin levels in the adipose tissue with decrease insulin sensitivity and glucose uptake. Obesity-induced promoter hypermethylation also downregulates the expression of insulin-signaling genes, such as insulin (INS) and insulin receptor substrate 1 (IRS1) with impairment of glucose metabolism regulation and increase the risk of developing type 2 diabetes mellitus (T2DM). Anorexigenic pro-opiomelanocortin (POMC) and the orexigenic neuropeptide Y (NPY) genes involved in the appetite-regulating pathway have altered methylation in obesity. Altered methylation in the inflammation and hypoxia-related genes, like hypoxia-inducible factor (HIF), tumor necrosis factor (TNF), and interleukin 6 (IL6), was associated with BMI and obesity [13]. Methylation occurs at CpG dinucleotides, often in gene promoters, affecting transcriptional activity. Methyltransferases like DNMT1, DNMT3A, and DNMT3B are involved in adding methyl groups to DNA [3]. Higher methylation percentages at the TAPBP gene are observed in individuals with high BMI. Differential methylation patterns are noted between high and low BMI individuals, particularly in the TAPBP and TAOK3 genes. Epigenetic changes appear to be sex-specific, with most differences in methylation being female-specific in offspring of individuals with obesity [24].

The augmentation of gene expression is linked to histone acetylation, whereas histone methylation may either stimulate or hinder gene expression, contingent on the location and extent of methylation [25].

DNA methylation is crucial for gene regulation and is influenced by various DNA methyltransferases. Environmental factors during critical developmental periods can disrupt DNA methylation patterns, potentially leading to long-term health issues [4].

Three main approaches to study methylation's impact on obesity include *epigenome-wide association studies (EWAS), integrated GWAS and EWAS analyses*, and *candidate-gene approaches* [5].

Genome-Wide DNA Methylation Studies of Obesity. Genome-wide studies identify obesity-associated alterations in DNA methylation patterns across numerous genes. Unlike genetic variants, DNA methylation patterns can be stable or modified due to environmental changes.

Interactions Between Genetics and Epigenetics. Genetic variations significantly influence DNA methylation patterns and obesity risk, complicating the understanding of their causal relationships with obesity. Methylation quantitative trait loci (meQTL) studies reveal genetic influences on methylation levels in adipose tissue. Studies reported strong interactions between genetic and epigenetic variations affecting metabolic phenotypes [5].

Epigenome-Wide Association Studies (EWAS) have identified DNA methylation patterns associated with childhood obesity, revealing potential biomarkers. Studies have linked specific CpG sites to obesity traits in children and adolescents. Variability in results is attributed to technical limitations and differences in obesity measurement methods [3].

Candidate Gene Approaches for DNA Methylation in Obesity. Candidate gene studies focus on specific genes known to influence obesity, revealing significant associations with methylation status. FTO gene methylation has been linked to obesity and type 2 diabetes, with specific SNPs showing associations. POMC gene methylation is sensitive to nutritional programming and correlates with weight-related outcomes. IGF2/H19 hypermethylation is associated with greater subcutaneous adiposity, indicating a heritable component. Paternal obesity is linked to hypomethylation at IGF2 DMR in newborns, suggesting environmental influences on epigenetic marks [5].

Genetic variation is a crucial factor in the regulation of DNA methylation. As methylated DNA predominantly arises on cytosine nucleotides after a guanine, it is evident additions or deletions of

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variants of cytosine-guanine dinucleotides (CG dinucleotides) affect the likelihood of methylated DNA at the loci. Remarkably, roughly one-fourth of single nucleotide polymorphisms (SNPs) add or delete CpG site. More than 100000 DNA methylation quantitative trait loci (mQTLs) were identified by GWAS, which were linked to adipose-tissue gene expression, BMI, and insulin levels [25].

Telomere Length and Obesity. Obesity is linked to telomere length (TL) and subtelomeric methylation, which may indicate accelerated aging. No significant correlation between TL and BMI was detected, but higher BMI was associated with subtelomeric demethylation. Obesity may promote aging before TL shortening is evident, necessitating dietary and exercise interventions. Caloric restriction influences telomere length and telomerase activity, potentially improving cardiac function by increasing telomerase activity and reducing oxidative stress. CR affects cell signaling pathways related to survival factors, impacting cardiac health [5].

MicroRNAs and Noncoding RNAs

In addition to DNA methylation, *noncoding RNAs*, such as *microRNAs (miRNAs)* and *long noncoding RNAs (lncRNAs)*, play crucial roles in regulating gene expression related to obesity [3,26]. miRNAs are *small ncRNAs* (19-25 nucleotides) and lncRNAs are *longer ncRNAs* that play important roles in post-transcriptional gene regulation, they are dysregulated in both DM and obesity and may serve as potential early diagnostic markers for these conditions [4,25].

Role of miRNAs. Although research in pediatric populations is still emerging, studies indicate that specific miRNAs (e.g., miR-15b-5p, miR-486-5p, miR-122-5p) are differentially expressed in children with obesity compared to lean peers, implicating them in lipid metabolism, inflammation, and adipocyte differentiation. The pathogenesis of metabolic diseases has been linked to the expression of various miRNAs [25,26]. At least 65 miRNAs are linked to obesity, with potential as biomarkers for type 2 diabetes [13]. One research found that 221 of the 1736 Loci associated with obesity coincided with miRNAs [25].

miRNAs have role in regulating hub genes associated with obesity. 115 miRNAs were identified, with the top five being miR-34a-5p, miR-16-5p, miR-124-3p, miR-103a-3p, and miR-107. These miRNAs were linked to pathways involving glucose and lipid metabolism, immune response, and vascular inflammation [19]. miRNA-126 has been shown to be downregulated in individuals with obesity and may serve as a potential early diagnostic marker in obesity [25]. miRNA-221 is upregulated in obesity and affects fat metabolism, while miRNAs such as miR-143 and miR-134 are involved in adipocyte differentiation and metabolism [13]. miR-34a and miR-122 have been studied as biomarkers for obesity and its comorbidities [3]. miRNA-29a regulates insulin signaling by targeting IRS1 in adipocytes. Additionally, miRNA-103 and miRNA-107 have been shown to promote IR by targeting the insulin receptor and GLUT4, respectively [25]. In prepubertal obesity, some miRNAs may become deregulated, as evidenced by a study which showed that the expression of miRNA-130b in plasma was upregulated and directly correlated with BMI and other indicators of obesity in children [25]. The expression of miR-130a and miR-130b is reduced in individuals with obesity, indicating their potential role in adipogenesis and inflammation. miR-34a is upregulated in obese adipose tissue, promoting inflammation and insulin resistance. Increased levels of miR-144-3p in individuals with obesity are linked to insulin resistance and oxidative stress and correlate with high urinary zinc concentration [24].

Exosomal miRNAs from adipose tissue play a role in systemic metabolic regulation and inflammation. miR-148b and miR-23b are enriched in rat adipose tissue secretome, indicating their role in metabolic signaling. These exosomal miRNAs target metabolic pathways like TGF-β and Wnt/β-catenin [24].

Dietary interventions can rapidly normalize miRNA levels associated with metabolic health in individuals with obesity. Significant decreases in fasting glucose levels are observed post-intervention. Circulating miR-122 and miR-21 levels decrease with weight loss in women with obesity [24].

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miRNAs are crucial regulators of cellular processes that control metabolism and homeostasis. miRNAs typically silence target messenger RNA (mRNAs) by base-pairing with complementary sequences, affecting approximately 30% of human genes and they are involved in various biological processes, including cell proliferation and differentiation, and have been linked to obesity and adipogenesis. They regulate metabolic processes such as adipocyte differentiation, insulin production, glucose metabolism, and insulin resistance. Deregulation of miRNA pathways is linked to obesity and diabetes, affecting cellular mechanisms. Altered miRNA expression in obesity suggests their potential role in regulating energy balance and fat metabolism. Profiling studies show altered miRNA expression in metabolic tissues of individuals with obesity [4].

miRNAs play a significant role in the regulation of adipogenesis, the process of fat cell formation, and their expression is altered in obesity. Adipogenesis involves the differentiation of mesenchymal stem cells into adipocytes, regulated by transcription factors. Numerous miRNAs, such as miR-143 and miR-103, are differentially expressed during adipocyte maturation. Obesity leads to deregulation of miRNA pathways, affecting adipocyte biology and correlating with metabolic parameters. Specific miRNAs, like miR-21 and miR-30c, promote adipogenesis, while others, such as the miR-27 family, inhibit it [4].

Role of lncRNAs. lncRNAs exhibit differential expression patterns in adipose tissue of children with obesity versus children without obesity, potentially affecting pathways such as fatty acid biosynthesis, immune response, and energy metabolism [5,13,26]. lncRNAs are associated with obesity, adipogenesis and adipocyte differentiation. Various lncRNAs are potent modulators of diverse genetic pathways linked to white adipose tissue (WAT) compartmentalization and activity. The first adipogenesis-related lncRNA was a steroid receptor RNA activator (SRA), which acts as a coactivator of peroxisome proliferator-activated receptor (PPAR)γ. Among the lncRNAs involved in adipogenesis, ASMER-1 and ASMER-2 are upregulated in subcutaneous adipose tissue (ScAT) and are linked to adipocyte-specific metabolism and insulin resistance (IR). Several lncRNAs have roles in adipogenesis (the formation of fat cells), lipolysis (the breakdown of fat), and adiponectin secretion in human adipocytes (fat cells). ADNCR is an endogenous competitive RNA for miR-204, and overexpression of SIRT-1 inhibits adipocyte differentiation and impairs the PPARγ pathway in vitro, while HOTAIR is implicated in preadipocyte differentiation [25].

lnc RNAs common in obesity and diabetes mellitus:

- SRA Steroid receptor RNA activator
- ASMER-1 Adipocyte-associated metabolic related lncRNA 1
- ASMER-2 Adipocyte-associated metabolic related lncRNA 2
- ADNCR Adipocyte differentiation-associated lncRNA
- HOTAIR HOX antisense intergenic RNA
- Blnc1 Brown fat lncRNA 1
- H19 LncRNA H19
- MALAT1 Metastasis-associated lung adenocarcinoma transcript 1 [25].

Another lncRNA, NEAT1, has been shown to regulate the expression of genes involved in the inhibition of high glucose-induced diabetic retinopathy [25].

Brown adipose tissue (BAT) is a specialized form of adipose tissue that is mainly responsible for thermogenesis and energy expenditure. It is characterized by the presence of uncoupling protein 1 (UCP1), leading to increased energy expenditure and weight loss. Recent studies have identified several lncRNAs that are involved in BAT regulation, including brown fat lncRNA1 (Blnc1) and H19. Research has indicated that Blnc1 plays a role in regulating thermogenic genes, resulting in an increase in the expression of UCP1 and mitochondrial genes. Conversely, H19 has been found to have an inverse correlation with body mass index (BMI) and a positive correlation with browning markers. H19 is involved in modulating adipogenesis, oxidative metabolism, and mitochondrial respiration in BAT. One study found reduced expression of three lncRNAs in subjects with obesity, but not in lean subjects. The expression of these lncRNAs was inversely correlated with waist-to-hip ratio, BMI and fasting plasma insulin levels. lncRNA-p19461 was upregulated following weight loss due to a 12-wk

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diet, suggesting that bariatric interventions could manage expressed lncRNA profiles. Alterations in the expression levels of lncRNAs were found following bariatric surgery in animals, particularly those engaged in digestive, absorptive and inflammatory pathways [13,25].

Role of circular RNAs (circRNAs). circRNAs are a class of ncRNAs that form covalently closed circular RNA molecules, which have recently been observed in the dysregulation in both DM and obesity and may be early diagnostic markers [25].

Histone Modifications in Obesity

Histone modifications influence gene expression related to adipogenesis and inflammation. Increased histone acetylation at inflammation-related genes is observed in obesity [13]. Histone modifications are important in regulating gene expression related to obesity and can influence chromatin accessibility and gene transcription, though studies in children are limited [3]. Histone modifications play a significant role in chromatin structure and gene expression regulation. Histones are proteins that package DNA into chromatin, with modifications occurring mainly on histone tails. Key post-translational modifications include acetylation, methylation, phosphorylation, and ubiquitination, which influence gene expression. Acetylation generally promotes gene activation by loosening chromatin structure, while specific methylation patterns can indicate either active or repressed states. The interplay between histone modifications and DNA methylation is crucial for gene silencing and expression regulation [4]. The role of histone modifications in childhood obesity remains underexplored compared with DNA methylation and noncoding RNAs, representing a significant gap for future research [5,13,26].

Other Epigenetic Factors

Epigenetic Studies Related to Obesity. Epigenetic marks are tissue-specific and play a crucial role in obesity-related gene expression changes. Studies have shown that peripheral blood leukocytes can be used to explore epigenetic differences related to obesity. Hypermethylation in the FTO gene's first intron is associated with obesity and type 2 diabetes mellitus. Recent research indicates that differentially variable CpG sites in individuals with obesity are enriched in genes linked to obesity traits. The Dutch Hunger Winter study highlighted the long-term effects of prenatal famine exposure on DNA methylation and obesity risk.

Nutritional Influences on Epigenetics. Nutrition significantly impacts epigenetic mechanisms, particularly during early life stages. Early life nutrition, including breastfeeding, is associated with DNA methylation changes in genes related to appetite regulation. Poor or excessive nutrition during critical developmental periods can increase the risk of metabolic syndromes, including obesity. Specific nutrients, such as folate and methionine, are essential for DNA methylation processes, influencing gene expression. Dietary components like polyphenols and short-chain fatty acids can modify histone marks and affect gene regulation [4].

4.2. Systems Biology and Multi-Omics Approaches - Integrative Omics in Childhood Obesity

Advances in *genomics, epigenomics, transcriptomics, proteomics, metabolomics and miRNAs* have enabled systems-level analysis of childhood obesity. *Multi-omics* studies reveal coordinated disruptions across metabolic pathways, inflammatory signaling, lipid metabolism, and mitochondrial function. They also highlight the interplay between gene-nutrient interactions and microbiota dynamics in obesity treatment [24]. Metabolomic profiling of children with obesity shows elevated branched-chain amino acids (BCAAs), acylcarnitines, and lipid intermediates-metabolites linked to insulin resistance and mitochondrial overload [27].

A recent study explored the molecular mechanisms and environmental determinants of childhood obesity through extensive multi-omics profiling (methylome, miRNome, transcriptome, proteins, metabolites), on six longitudinal cohorts across two European regions (Northern/Western and Southern/Mediterranean). Blood samples were analyzed across five omics layers, including DNA

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methylation, miRNA expression, transcriptomics, proteomics, and metabolomics. The study identified key molecular features contributing to the definition of a high-risk obesity cluster in children and provided insights into obesity mechanisms. The research found significant associations between multi-omics clusters and metabolic health outcomes and identified three distinct clusters of children based on multi-omics profiles, with one cluster (Cluster C, high-risk cluster) showing higher adiposity and metabolic complications, inflammation-related biological pathways. Children in Cluster C exhibited the highest metabolic dysfunction, characterized by increased adiposity and adverse metabolic outcomes, higher BMI, fat mass, waist circumference, and insulin levels and had higher odds of being metabolically unhealthy: 39.1% in N/W cohort and 52.5% in S/M cohor compared to Cluster A. Higher levels of 14 specific miRNAs and altered transcription levels of 52 genes were linked to Cluster C. Proteomic profile of Cluster C included elevated levels of inflammatory markers like IL-6 and TNF-alpha. Pathway analysis revealed associations with immune response and insulin action pathways. Children in Cluster B showed a healthier metabolic profile and associations primarily with anthropometric outcomes, but still faced risks for future complications. Environmental factors, including pre-pregnancy BMI and pollutants like perfluorooctanoate and mercury, identified as significant prenatal determinants. The study highlighted the role of prenatal exposures in determining obesity risk in children and the prenatal factors influencing multi-omics cluster membership in children. In the N/W cohort, higher pre-pregnancy BMI and PFOA exposure were significant for Cluster C membership. In the S/M cohort, maternal mercury exposure was linked to increased likelihood of belonging to Cluster C. The study emphasizes the importance of modifiable prenatal environments in relation to childhood obesity risk [28].

Another comprehensive trans-omics research which explored the molecular mechanisms underlying obesity to verify interactions and causal relationships among omic molecules identified 8 differentially expressed hub genes (DEHGs), 14 differentially methylated regions (DMRs), and 12 differentially accumulated metabolites (DAMs) related to obesity and discovered 18 causal pathways with mediation effects among the identified biomarkers, including pathways where metabolites influence gene expression and DNA methylation. Bi-directional Mendelian Randomization (MR) to assess causal relationships among different omics data (gene expression, methylation, and metabolite profiles) found 7 significant causal pairs between DEHGs and DMRs, and 40 causal pairs between DMRs and DAMs and highlighted specific causal relationships, such as ANO6 influencing methylation at region 6.110721178. Five causal pairs showed gene-driven methylation, while two indicated the reverse relationship. The study identified several key genes and regions that may play significant roles in obesity and related diseases. Six previously reported genes (UGGT1, ANO6, MPEG1, PTGS1, CLU, IQGAP1) and two novel genes (LUZP6, PLCB2) were linked to obesity. Identified DMRs were associated with genes previously implicated in obesity, such as DDO and SEPT9. The study identified metabolites associated with obesity, highlighting both known and novel compounds that may influence obesity risk. Ten metabolites previously linked to obesity were found, along with two novel metabolites: Indole-3-acetate and N-methyl-D-aspartic acid (NMDA). Out of 20 biomarkers, 17 were previously associated with obesity or related diseases, while three (NMDA, indole-3-acetate, and PACRG-AS1) were linked to other complex diseases. The findings emphasize the complexity of interactions among gene expression, methylation, and metabolites and suggest focusing on causal pathways rather than global relationships to better understand disease processes [29].

4.3. Prenatal and Early Life Epigenetic Programming

Developmental Origins of Obesity. Early life factors, including maternal health, prenatal and neonatal environment significantly influence the risk of obesity later in life. Environmental exposures during development can lead to lasting changes in metabolism. Maternal obesity, gestational weight gain and gestational diabetes are linked to increased risk of obesity and permanent metabolic

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alterations in children. Prenatal exposure to stress and undernutrition during pregnancy can lead to metabolic programming and obesity in offspring [3,7].

Birth weight is a critical indicator of future obesity risk, with both low birth weight (<2500g) and high birth weight (>4000g) being associated with metabolic disease and increased obesity risk. A J-shaped relationship exists between birth weight and obesity, indicating risks at both extremes. Maternal obesity significantly increases the likelihood of high birth weight and subsequent obesity in children. Also early growth patterns and rapid weight gain during infancy (an increase in >0.67 in weight-for-age z-scores within the first 2 years of life) are critical indicators of future obesity risk, later adiposity and metabolic issues. Studies show that rapid weight gain is associated with a 38% increased risk of overweight status by age 7 [3,7].

Maternal health and behaviors during pregnancy significantly affect the risk of childhood obesity. Maternal nutritional status can modify gene expression in newborns, impacting growth and development. Maternal smoking during pregnancy is linked to prenatal undernutrition, increasing the risk of postnatal obesity [3]. Maternal dietary patterns during pregnancy can impact infant birth outcomes and later obesity risk. Nutrition during early life stages plays a vital role in preventing childhood obesity [3]. Also, regular maternal physical activity during pregnancy can reduce excessive gestational weight gain by approximately 20%. It is essential for reducing the risk of childhood obesity and is associated with lower risks of gestational diabetes and macrosomia. Only 15% of pregnant women meet the recommended 150 minutes of moderate-intensity physical activity weekly. Recommendations include promoting healthy nutrition and normal weight status before and during pregnancy. Maternal BMI should be in the normal range to reduce the risk of childhood obesity. Gestational weight gain recommendations vary based on maternal pre-pregnancy BMI, ranging from 5-18 kg [3].

Exclusive breastfeeding is crucial for infant nutrition and is linked to lower obesity risk later in life, with a 13%-26% reduction in the risk of excess body weight and adiposity. It is recommended for infants up to 6 months, with benefits extending to 2 years when combined with complementary foods. Key bioactive substances in breast milk may influence metabolic health and obesity risk, including the lipidome and gut microbiome. Evidence on the protective effect of breastfeeding against future obesity is inconclusive, necessitating more robust studies [3].

Complementary feeding is a critical period that can establish long-term nutritional habits that influence growth trajectories and can influence childhood obesity through dietary practices. Differences in growth trajectories are observed between breastfed and formula-fed infants, with rare exceptions. Complementary feeding typically starts when breast milk is insufficient, continuing until 2 years of age. The timing, content, and method of complementary feeding can significantly impact growth trajectories and body composition. Early introduction of complementary foods (before 3-4 months) is linked to higher obesity risk, while delaying beyond 6 months shows no protective effect. Feeding practices and dietary patterns during infancy play a significant role and are more influential than timing in determining obesity risk. Responsive feeding practices that align with infant hunger and satiety cues can reduce obesity risk. High protein intake during infancy, particularly from animal sources and especially from dairy, is associated with rapid weight gain and increased obesity risk later in childhood. Sugar intake should be minimized during complementary feeding, as it is linked to obesity risk [3].

Maternal feeding practices can contribute to disparities in early childhood obesity when they are less likely to exclusively breastfeed and more likely to introduce unhealthy foods early or have restrictive feeding styles. Parental styles and home environments play a critical role in shaping children's eating and activity behaviors. Parents act as gatekeepers, influencing access to food and opportunities for physical activity. Authoritarian parenting is linked to higher obesity rates in children [3].

Maternal nutritional status and metabolic health exert profound influences on the *offspring's epigenome*. Maternal obesity creates an obesogenic environment with high nutrient levels, hormonal imbalances and programs fetal adipogenesis, potentially leading to long-term obesity and metabolic

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disorders in offspring. Studies demonstrate *epigenetic reprogramming* linked to maternal obesity and gestational diabetes that persists beyond birth, influencing the child's metabolic pathways. These alterations involve genes linked to fatty acid metabolism and mitochondrial bioenergetics, suggesting mechanisms by which early environmental exposures prime obesity risk [1,30]. This evidence aligns with the *Developmental Origins of Health and Disease (DOHaD) hypothesis*, positing that in utero and early postnatal conditions contribute to lifelong tendencies toward obesity and metabolic dysfunction through persistent epigenetic changes [31].

Obesity and gestational diabetes mellitus can program metabolic pathways in both mothers and offspring with lasting effects on the metabolic programming of offspring and on their health. The pathways affected include those related to insulin sensitivity and fat metabolism. They alter gene expression related to mitochondrial and lipid metabolism in infants [32]. Maternal obesity is a risk factor for premature obesity (up to 41.7% of childhood overweight/obesity), metabolic syndrome, cardiovascular disease, and type 2 diabetes in children. Fetuses of mothers with obesity have increased access to nutrients, leading to metabolic adaptations and increased adiposity. Hyperglycemia and hyperinsulinemia from mothers with obesity contribute to increased neonatal adiposity. Neonates from mothers with obesity are often insulin resistant and prone to metabolic compromise [6]. Higher maternal BMI correlates with increased offspring body fat and BMI. Animal studies suggest that maternal obesity affects fetal development as early as implantation [13]. Mothers significantly impact offspring obesity risk through gestational and lactational factors. Maternal BMI is a strong predictor of offspring obesity, often more influential than paternal BMI. Maternal obesity during pregnancy is linked to increased offspring weight and metabolic complications. Nutritional conditions during gestation, including both undernutrition and overnutrition, shape offspring metabolic phenotypes. The thrifty phenotype hypothesis explains the association between poor fetal nutrition and later metabolic disorders [6].

Fetal nutritional availability significantly impacts long-term health outcomes, particularly in the context of maternal obesity. High-fat diet (HFD) consumption during pregnancy enhances nutrient transport and fetal overgrowth. Increased expression of mTOR complex 1 is associated with enhanced nutrient uptake. Maternal obesity alters steroid hormone levels, affecting pregnancy outcomes and fetal development. Placental analysis shows reduced fatty acid oxidation and increased lipid accumulation in pregnancies with obesity. Evidence suggests that maternal obesity-induced changes in nutrient uptake are critical for obesity inheritance [6].

Role of Mesenchymal Stem Cells in Adipogenesis. Adipose tissue develops by the 14th week of gestation, with *mesenchymal stem cells (MSCs)* differentiating into preadipocytes. Adipogenesis involves transcription factors like PPARγ and C/EBP, crucial for lipid storage and metabolism. Dysfunctional adipocytes in obesity lead to altered metabolic pathways and increased oxidative stress [30]. MSCs are multipotent progenitor cells that differentiate into adipocytes during fetal development. They are critical in the early development of adipose tissue and are influenced by maternal obesity. The obesogenic intrauterine environment influences MSC differentiation towards adipocytes, increasing fat mass in offspring. Infants born to mothers with obesity show altered mesenchymal stem cell metabolism, leading to increased adiposity, due to increased lipid accumulation in MSCs. *MSCs from neonates of mothers with obesity (OB-MSCs)* may be programmed differently and show increased adipogenic potential (expressing higher levels of adipogenic genes like PPARγ and FABP4/aP2.), contributing to early programming of adipose tissue. OB-MSCs exhibit a dysfunctional phenotype with slower growth and lower stemness potential compared to MSCs from normal-weight mothers (NW-MSCs). Higher adipogenic commitment in OB-MSCs could lead to increased adipocyte numbers, contributing to higher body fat percentages in neonates. Increased expression of adipogenic markers like PPARγ is observed in these MSCs compared to those from normal-weight mothers. The presence of reactive oxygen species (ROS) in OB-MSCs triggers earlier activation of adipogenesis through the PPARγ pathway. High levels of aminopeptidase N/CD13 in amniotic mesenchymal stem cells enhance their adipogenic potential.

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Insulin is crucial for activating adipogenesis in MSCs by stimulating pathways like PI3K/Akt and MAPK. OB-MSCs show downregulation of insulin signaling pathways, leading to insulin resistance which is associated with lower GLUT4 translocation and disrupted glucose and lipid metabolism. These differences may contribute to early commitment towards adipocyte lineage.

The *MSC secretome* plays a vital role in cellular communication and homeostasis during development and contains bioactive molecules that promote tissue repair and regeneration. The secretome indicates lipid metabolic imbalance and an inflammatory environment in the adipose tissue of neonates from mothers with obesity. The findings suggest a potential hypertrophic phenotype in adipocytes, limiting the pool of MSCs available for healthy adipocyte proliferation.

MSCs can lead to either *adipocyte or osteoblast differentiation* under the influence of various factors. Maternal obesity may affect differentiation in other mesodermal tissues like bone and muscle with possibly decreased *differentiation towards muscle, bone, and cartilage cells*. Obesity is linked to disturbed muscle and bone physiology, higher intramuscular fat, and osteoporosis. Downregulation of the Wnt signaling pathway in MSCs from pregnancies with obesity promotes adipogenic differentiation over myogenic differentiation. The potential for dysfunctional adipocytes in neonates remains an open question [32].

Mitochondrial Dysfunction in MSCs. Mitochondria play a key role in energy production and metabolic regulation in MSCs and adipocytes. Mitochondrial dysfunction in OB-MSCs is linked to oxidative stress and metabolic disruption, impaired mitochondrial respiration and lower ATP production efficiency. Increased oxidative stress and reduced antioxidant defenses in OB-MSCs contribute to cellular damage and inflammation. Altered mitochondrial function may lead to premature aging and senescence in MSCs from pregnancies with obesity (OB-MSCs) [32].

Forkhead Box O1 (FoxO1) is a FoxO transcription factor which regulates adipocyte differentiation and is involved in the transcriptional regulation of genes associated with fat cell development, influencing metabolic processes. The interaction between FoxO1 and other factors, such as SIRT2 and PPARγ, modulates adipogenesis. FoxO transcription factors are influenced by redox states, which can affect their function in metabolic regulation. Redox regulation of FoxO factors is critical for maintaining cellular homeostasis and responding to oxidative stress. The balance of oxidative and reductive signals can modulate FoxO1 activity, impacting adipocyte differentiation (from preadipocytes into mature adipocytes) and metabolism. The convergence of signaling pathways involving FoxO1 and PPARγ is crucial for effective adipocyte formation. The presence of reactive oxygen species (ROS) in OB-MSCs triggers earlier activation of adipogenesis through the PPARγ pathway [32].

4.4. Intergenerational and Transgenerational Inheritance of Molecular Effects

Beyond individual development, childhood obesity risk may be shaped by *intergenerational and transgenerational molecular mechanisms* [33].

Besides *genetic transmission, epigenetic modifications* play a crucial role in the *intergenerational transmission* of obesity, influenced by environmental factors. Intergenerational phenotypes arise from epigenetic changes rather than direct DNA sequence alterations. DNA methylation, histone modifications, and non-coding RNAs are key epigenetic mechanisms involved [6]. Epigenetic marks influenced by parental nutrition, obesity, and metabolic health can be transmitted to offspring via gametes or through the intrauterine environment. Animal studies and human observational data suggest that parental obesity is associated with altered DNA methylation and noncoding RNA profiles in offspring, even when postnatal environments differ [34]. For instance, altered methylation in genes regulating insulin signaling, lipid metabolism, and appetite regulation (IGF2, LEP, RXRA) has been detected in children born from parents with obesity. These modifications may persist into adolescence, increasing susceptibility to obesity and metabolic disease later in life [33].

Maternal and paternal environments can significantly impact the epigenetic landscape of offspring, affecting metabolic outcomes [6].

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Obesity can be inherited across generations, as transgenerational transmission, through both *genetic and epigenetic mechanisms*, affecting offspring health. Parental obesity significantly increases the risk of childhood obesity, with children of parents with obesity nearly twice as likely to have obesity. The risk escalates with both parents having obesity (odds ratio: 12.0) and severe obesity (odds ratio: 22.3). Maternal and paternal obesity both contribute to offspring obesity, but their relative impacts vary across studies. Transgenerational effects are defined as changes that manifest in subsequent generations independent of direct genetic changes [6].

Transgenerational epigenetic inheritance may increase susceptibility to childhood obesity through parental exposures. Ancestral exposures can reprogram the epigenome of germline cells, affecting descendants [3]. Understanding sexual dimorphism in obesity inheritance is crucial for developing targeted interventions [6].

Maternal Transgenerational Obesity Inheritance. Research indicates that maternal obesity can lead to transgenerational inheritance of obesity through epigenetic modifications and environmental factors. Maternal obesity may transmit epigenetic changes to offspring, influencing their metabolic health. Studies show correlations between RXRA promoter methylation and childhood adiposity. Targeted Bisulfite Sequencing revealed reduced methylated cytosines in umbilical cord blood of offspring from mothers with obesity. Epigenetic alterations are linked to increased risks of metabolic disorders, cancer, and cardiomyopathy. Maternal surgical interventions can reverse some epigenetic changes, improving offspring metabolic profiles. Animal studies demonstrate progressive obesity exacerbation across generations, with the F2 generation showing severe metabolic dysfunction [6].

Paternal Influence on Obesity Inheritance. While maternal effects have been more extensively studied, paternal obesity also contributes to offspring metabolic risk. Sperm epigenetic alteration, including changes in DNA methylation, histone retention, and small noncoding RNAs, have been shown to influence embryonic gene expression related to metabolism and adipogenesis [34]. Fathers contribute to obesity inheritance through genetic and epigenetic factors, impacting offspring health. Paternal age and environmental exposures can induce DNA damage and de novo mutations in the male germline. Paternal obesity has been linked to adverse offspring health outcomes, including metabolic dysfunction. Studies show that paternal high-fat diet (HFD) adversely affects offspring health independent of genotype. Epigenetic modifications in sperm due to dietary habits can influence offspring metabolic health [6].

These findings emphasize that childhood obesity risk is not solely shaped by the child's own environment but is partly embedded in *parental molecular histories*, reinforcing the need for family-based prevention strategies.

4.5. Sex-Specific Molecular Mechanisms

Hormonal Differences and Adipose Distribution. Sex differences in childhood obesity emerge early and are influenced by molecular and hormonal factors. Estrogens, androgens, and growth hormone interact with adipose tissue, insulin signaling, and inflammation, leading to sex-specific fat distribution and metabolic risk. Girls tend to accumulate more subcutaneous adipose tissue, whereas boys exhibit higher visceral fat deposition, which is more metabolically harmful. These differences are mediated by sex hormone receptors expressed in adipocytes and hypothalamic neurons [35].

Sex-Specific Epigenetic Patterns. Epigenomic analyses have revealed *sex-dependent DNA methylation patterns* in obesity-related genes during childhood. These differences may influence how boys and girls respond to environmental exposures such as diet, physical activity, and endocrine-disrupting chemicals (EDCs). Understanding sex-specific molecular pathways is critical for tailoring prevention and intervention strategies in pediatric populations [36–43].

5. Adipose Tissue Biology and Adipogenesis

Adipose Tissue as a Dynamic Metabolic Organ. Various organs and mechanisms are responsible for the regulation of adiposity and metabolic function. Hormonal control is crucial for adipose tissue differentiation, development, and maintenance. Metabolic dysfunction can arise from changes in fat

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depots due to environmental influences [7]. Adipose tissue appears between the 14th and 24th week of gestation in humans and develops through increased cell number and size, influenced by various factors. Healthy adipose tissue is characterized by smaller, more numerous adipocytes, while unhealthy obesity features larger adipocytes and increased inflammation. Three types of fat depots have different impacts on metabolic health. Subcutaneous adipose tissue (SAT) is less harmful and can be protective against metabolic diseases. Visceral adipose tissue (VAT) is more metabolically active and linked to increased insulin resistance and type 2diabetes risk. Ectopic fat in the liver and muscle is associated with metabolic dysfunction and is harmful to health [7].

Obesity is influenced by various molecular and hormonal factors, including adipose tissue dynamics and metabolic pathways. Adipose tissue consists of adipocytes and extracellular matrix (ECM) components. Obesity results from adipocyte hypertrophy and hyperplasia. Unique metabolic profiles identified in children with obesity through metabolomics studies. Low-grade inflammation affects metabolites related to lipid, carbohydrate, and amino acid pathways.

Hormones like leptin play a crucial role in appetite regulation and obesity [9].

Adipose tissue is no longer regarded as a passive fat storage site but rather as a *dynamic, metabolically active endocrine organ* that plays a central role in energy homeostasis. In childhood obesity, adipose tissue undergoes structural, cellular, and molecular remodeling that promotes lipid accumulation, inflammation, and insulin resistance. There are two main types of adipose tissue relevant to obesity: white adipose tissue (WAT), which stores excess energy, and brown adipose tissue (BAT), which dissipates energy through thermogenesis. A third subtype, beige adipocytes, displays intermediate characteristics. Dysregulation of the balance between these tissues contributes to obesity development. Reduced BAT activity and impaired browning of WAT have been reported in children with obesity, limiting energy expenditure and favoring fat accumulation. At the molecular level, adipose tissue expansion occurs via hypertrophy (increase in adipocyte size) and hyperplasia (increase in adipocyte number). Childhood is a critical window for adipocyte hyperplasia; excess adipocyte formation during early life increases lifelong obesity risk because adipocyte number remains relatively stable in adulthood [5,13,44].

Molecular Regulation of Adipogenesis. The differentiation of preadipocytes into mature adipocytes (adipogenesis) is tightly regulated by transcription factors and signaling pathways. The master regulators include: peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding proteins (C/EBPα, C/EBPβ). Activation of these transcription factors promotes lipid uptake, triglyceride synthesis, and insulin sensitivity. In childhood obesity, *PPARγ signaling* is often dysregulated, leading to excessive adipocyte differentiation and lipid accumulation [45]. Inflammatory cytokines released from hypertrophic adipocytes suppress healthy adipogenesis while promoting dysfunctional fat expansion, contributing to ectopic lipid storage in liver and muscle [46].

Epigenetic modifications also influence adipogenesis. DNA methylation changes in adipogenic genes (e.g., PPARG, C/EBPA) have been observed in children with obesity, suggesting that early-life exposures can permanently alter adipocyte development pathways [47].

Various receptors and hormones regulate energy metabolism and adipose tissue function. Key transcription factors include *PPARγ, retinoid X receptor (RXR), and liver X receptor (LXR),* which influence adipogenesis and metabolic health. Hormonal receptors such as insulin, estrogen, and glucocorticoid receptors play significant roles in energy storage and expenditure [7].

LXR agonism influences lipid metabolism, adipocyte differentiation, and metabolic health. LXR agonism increases triglyceride accumulation and adipocyte differentiation. LXRα is primarily involved in lipolysis, while LXRβ regulates cholesterol. LXR-null mice show inhibited lipid metabolism and resistance to diet-induced obesity. LXR agonists in humans lead to increased cholesterol and triglycerides, despite some benefits in adipose distribution [7].

Pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are liver-enriched receptors that regulate lipid metabolism and energy homeostasis. PXR knockouts show resistance to diet-induced obesity and insulin resistance. PXR agonists promote hepatic triglyceride accumulation

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and fatty liver disease. CAR agonists enhance insulin sensitivity and improve glucose metabolism. In humans, CAR activation can decrease glucose levels and improve insulin sensitivity [7].

Farnesoid X receptor (FXR) regulates bile acid synthesis and lipid metabolism, impacting adipocyte differentiation. FXR agonists enhance insulin signaling and adipocyte differentiation. FXR knockout mice exhibit decreased adiposity and increased energy expenditure. FXR agonist treatment in obese mice can exacerbate weight gain and glucose intolerance. In humans, FXR agonists reduce hepatic lipid accumulation but may increase LDL cholesterol [7].

Aryl hydrocarbon receptor (AhR) signaling is linked to obesity and metabolic regulation through environmental interactions. AhR activation inhibits adipogenic differentiation in MSCs. Conditional AhR knockout in hepatocytes leads to obesity resistance in mice. AhR levels are significant in liver metabolism and cholesterol biosynthesis [7].

The extracellular matrix (ECM) is crucial in regulating adipose tissue function and its expansion in obesity. Integrins mediate cell adhesion and signaling in adipose tissue. Collagen is a major ECM component, providing structural support to adipocytes. Matrix metalloproteinases (MMPs) are involved in ECM remodeling and are elevated in children with obesity. Research on ECM in obesity is limited, particularly in pediatric populations [9]. The remodeling of the extracellular matrix (ECM) in adipose tissue plays a significant role in obesity and metabolic diseases. Osteopontin plasma levels correlate with reduced body weight, BMI, and improved insulin sensitivity in humans. Thrombospondin shows increased expression in white adipose tissue (WAT) of obese mice and humans, suggesting its role in obesity development and insulin signaling suppression. Hyaluronan levels are elevated in WAT of obese mice and humans, linked to monocyte adhesion and decreased adipogenesis; its inhibition improves adipose inflammation and insulin resistance. Angiogenesis is crucial for adipose tissue expansion, with factors like VEGF-A being implicated; however, obesity often leads to inadequate angiogenesis, contributing to tissue dysfunction. ECM components like CD248 and F13A1 are associated with hypoxia and inflammation in adipose tissue, indicating their potential as therapeutic targets [5].

6. Hormonal and Metabolic Control Mechanisms

Adipose tissue is an active endocrine organ that secretes adipokines - signaling molecules that regulate energy balance, appetite, insulin sensitivity, and inflammation. Dysregulated adipokine secretion characterizes obesity and impacts metabolic homeostasis. Hormones released from adipose tissue significantly influence obesity and metabolic health. Hormones and neurotransmitters are key regulators of appetite and energy expenditure, influencing obesity development. Leptin, ghrelin, and other hormones affect satiety and energy balance. Mutations in these hormones or their receptors can trigger weight gain. Estrogens influence adipocyte function and fat distribution [9]. White adipocytes release free fatty acids (FFAs), contributing to insulin resistance and hepatosteatosis.

6.1. Adipocitokines

Leptin, produced by adipocytes, is a key adipokine that regulates hunger/appetite and energy balance. It is crucial for regulating appetite and energy metabolism, especially in children. Its levels are inversely related to energy expenditure and play a role in glycemic control and insulin sensitivity. Leptin acts as a satiety signal in the central nervous system. The leptin receptor is crucial for mediating leptin's effects on metabolism [13]. Leptin communicates body fat energy stores to the brain, primarily acting on hypothalamic receptors to suppress appetite and increase energy expenditure [9,17]. Leptin signaling maintains body weight stability through a metabolic setpoint. Body weight autoregulation is similar to blood pressure and temperature control [7].

Low leptin levels due to fasting can induce overfeeding and suppress energy expenditure. Individuals with leptin signaling impairment experience intense hunger and reduced sympathetic tone. Most individuals with obesity have high leptin levels but exhibit resistance to its effects. Increased leptin expression is linked to obesity and insulin resistance [9].

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In childhood obesity, leptin levels are typically elevated due to increased fat mass, but *leptin resistance* - a diminished central response - reduces satiety signaling, increases appetite and promotes continued caloric intake with consequent weight gain [5,7,13,17]. Genetic mutations affecting leptin or its receptor lead to metabolic changes resembling negative energy balance [9,17]. Leptin receptor mutations cause leptin resistance, resulting in obesity despite high leptin levels. Less than 100 known cases of leptin receptor deficiency exist, with a prevalence of about 1.3 in one million [13]. Hyperinsulinemia is a likely contributor to leptin resistance [7].

Physical activity is essential for managing obesity and influencing leptin levels in children and adolescents. Regular physical activity increases energy expenditure and helps balance energy levels. Children with obesity have higher circulating leptin levels that decrease with lowering BMI. Low leptin levels are associated with higher physical activity in lean children. Studies indicate that longer exercise duration correlates with lower leptin concentrations. Aerobic exercise can positively affect serum leptin levels in children with obesity. In adolescents, leptin concentrations correlate with physical activity and fitness levels. Physical activity is the most effective non-pharmacological remedy for treating obesity [9].

Adiponectin is an important adipokine with anti-inflammatory, insulin-sensitizing properties and protective effects against metabolic and cardiovascular diseases. Adiponectin levels are inversely related to obesity and insulin resistance, while low adiponectin levels are associated with metabolic syndrome [13]. Adiponectin is secreted by white adipose tissue and is more abundant in subcutaneous fat [9,13]. Adiponectin enhances insulin sensitivity and fatty acid oxidation but is often decreased in obesity, contributing to metabolic dysregulation [5]. It decreases before obesity and insulin resistance develop, playing a role in inflammation and insulin sensitivity. Adiponectin signaling leads to metabolic improvements, including reduced hepatic glycogenolysis and increased fatty acid oxidation. Higher adiponectin levels are associated with a lower risk of developing diabetes [9].

Other adipokines, such as *resistin* and *pro-inflammatory cytokines* like *tumor necrosis factor-alpha (TNF-α)* and *interleukin-6 (IL-6),* further link adipose tissue dysfunction to systemic inflammation and insulin resistance [5].

Resistin is linked to the development of insulin resistance and type 2 diabetes. The RETN gene encodes resistin, which impairs glucose homeostasis and is associated with visceral obesity. Resistin levels are low in human adipose tissue, but high in circulating mononuclear leukocytes and macrophages. Recent studies suggest resistin may induce mitochondrial dysfunction, representing a potential therapeutic target [9]. Resistin is linked to inflammation and insulin resistance in obesity. Resistin levels are elevated in individuals with obesity and correlate with inflammation. This adipokine promotes pro-inflammatory cytokine production [13].

Vistafin, a multifunctional adipokine also known as Pre-B colony enhancing factor (PBEF), is involved in energy metabolism and immune response. Vistafin is a 52 kDa protein secreted by visceral adipose tissue, functioning as a phosphoribosyltransferase and cytokine. It enhances TNF-α and IL-6 production, promoting inflammation. Vistafin is involved in NAD+ synthesis, impacting energy metabolism. It activates various signaling pathways, including PI3K and MAPK, influencing protein synthesis and angiogenesis [5].

Tumor necrosis factor-α (TNF-α), a key inflammatory cytokine, has an important role in regulating immune function and energy metabolism, particularly in obesity. TNF-α is a 23 kDa protein that can exist as a soluble molecule after cleavage. It is primarily produced by macrophages infiltrating adipose tissue in obesity. Increased TNF-α levels correlate with insulin resistance and activate multiple signaling pathways, including NFκB and MAPK [5].

Interleukin-6 (IL-6) is an adipokine that influences metabolism and is linked to obesity-related cardiovascular issues. Adipose tissue secretes about 30% of the body's IL-6. Elevated IL-6 levels are associated with coronary artery disease and insulin resistance. IL-6 signaling can inhibit insulin receptor phosphorylation, affecting glucose metabolism [5].

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Angiotensin is a key component of the renin-angiotensin system, influencing blood pressure and adipose tissue function. Adipose tissue is a significant source of angiotensin, second only to the liver. Angiotensin II regulates adipocyte growth, lipid metabolism, and adipokine secretion [5].

6.2. Insulin Signaling and Resistance

Insulin, a central regulator of glucose and lipid metabolism, is deeply involved in obesity pathophysiology. In children with obesity, chronic exposure to elevated glucose and free fatty acids contributes to impaired insulin signaling — particularly in adipose tissue, muscle, and liver — leading to *insulin resistance (IR),* a precursor to type 2 diabetes [48]. IR is characterized by decreased sensitivity of peripheral tissues to insulin (decreased tissue response to insulin, particularly in the liver, muscle and brain), leading to impaired glucose uptake. Hepatic IR leads to increased glucose output and fat accumulation. Adipose tissue IR promotes inflammation and further metabolic issues [7]. It is increasingly prevalent in children with obesity, contributing to the development of type 2 diabetes mellitus and other metabolic diseases. Key risk factors for IR include lipid metabolism disorders, oxidative stress, mitochondrial dysfunction, inflammation, and genetic factors. Excessive reactive oxygen species (ROS) production leads to cellular damage and insulin signaling disruption. Nutritional oxidative stress arises from overnutrition, causing glucotoxicity and lipotoxicity [13,49].

More than 90% of primary insulin resistance is linked to genetic mutations, while obesity is a significant environmental factor. The likelihood of developing insulin resistance in children with obesity is estimated at 38.7% [49].

Insulin-resistance in obesity is generated by and associated with several pathological mechanisms: dysfunctional adipose tissue and abnormal lipid metabolism; increased free fatty acids (FFA) and diacylglycerol (DAG) levels due to obesity which inhibit insulin signaling pathways and contribute to hepatic insulin resistance; imbalance or dysregulation of adipokines (such as leptin, adiponectin, galectin-12, leptin resistance); adipose tissue chronic inflammation by inflammatory mediators like TNF-α and IL-6 from macrophages in adipose tissue; natural killer (NK) cells that regulate macrophage recruitment; increased glucose levels; mitochondrial dysfunction due to fat overload and oxidative damage which exacerbates oxidative stress and inflammation; endoplasmic reticulum stress (ERS) due to accumulation of misfolded proteins that inhibits insulin receptor signaling, generating specific markers of ERS in adipose tissue; genetic predisposition with over 300 identified obesity-related genes (including FTO / rs9939609, LEPR, and MC4R); epigenetic modifications (DNA methylation); dysbiosis in gut microbiota [49].

Insulin resistance in children with obesity is linked to various metabolic and inflammatory factors. Adiponectin levels are lower in children with obesity compared to children without obesity, correlating negatively with triglycerides and HOMA-IR. Increased free fatty acids (FFA) and adipokines like leptin promote inflammation in adipose tissue, leading to insulin resistance. Inflammatory cytokines such as TNF-α and IL-6 interfere with insulin signaling pathways, contributing to insulin resistance. Resistin, secreted by adipocytes, antagonizes insulin action and is positively correlated with insulin resistance. Chronic low-grade inflammation from macrophage accumulation in adipose tissue exacerbates insulin resistance and can lead to type 2 diabetes mellitus. Elevated serum uric acid levels in children with obesity are associated with insulin resistance and can damage pancreatic β cells [49].

Adolescence is a critical period for the development of insulin resistance, influenced by hormonal changes and obesity. Insulin resistance typically increases during puberty, peaking at its onset and returning to baseline afterward. Growth hormone and insulin-like growth factor-1 (GH/IGF-1) are key drivers of insulin resistance during this period. Early insulin resistance is linked to a higher risk of hypertension and hypertriglyceridemia in later years. Leptin plays a significant role in regulating puberty and insulin sensitivity, with elevated levels potentially leading to early onset of puberty [49].

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Systematic reviews of animal models demonstrate that maternal obesogenic diets can reduce expression and activity of critical insulin signaling proteins (including IRS-1, PI3K, and AKT) in offspring tissues, disrupting glucose uptake and metabolic flexibility [48].

Insulin resistance also exacerbates adipose tissue expansion and ectopic lipid deposition, further entrenching obesity and metabolic disorder. These molecular disruptions illustrate the interplay between hormonal control mechanisms and energy metabolism [48].

The *insulin receptor* is crucial for fat cell differentiation and energy balance. Lack of insulin during fetal development leads to reduced adipose tissue. Insulin signaling is essential for adipogenesis, mediated through Forkhead box O (FOXO) transcription factors. Knockout of the insulin receptor results in a significant loss of white adipose tissue. Estrogen receptors play a significant role in adipose tissue development and metabolism. Estrogen deficiency during pregnancy leads to reduced subcutaneous adipose tissue. Estrogen replacement can reverse fat distribution changes. Estrogen receptor knock-out (ERKO) mice show increased adiposity and insulin resistance, indicating the importance of estrogen in fat regulation. Androgens are generally anti-obesogenic, influencing adipose tissue development and metabolism. Decreased androgen levels are associated with increased adiposity. Androgen receptor knockout mice exhibit increased body weight and insulin resistance. Androgen treatment can inhibit adipogenesis and improve lipid profiles. The glucocorticoid receptor (GR) drives visceral fat differentiation and metabolic dysfunction. High glucocorticoid levels, as seen in Cushing's syndrome, lead to excessive visceral fat. GR agonists promote triglyceride accumulation and pre-adipocyte proliferation. GR antagonists inhibit adipocyte differentiation and improve metabolic profiles. Thyroid hormone receptors (TR) are essential for regulating metabolism and adipose tissue. TRα regulates thermogenesis, while TRβ regulates cholesterol metabolism and lipogenesis and also governs several genes and enzymes essential for pre-adipocyte proliferation and adipocyte differentiation, either directly or via PPARγ. TRα agonists determine increased adiposity, increased cholesterol, triglycerides, while TRβ stimulation results in reduction of cholesterol, triglycerides, and adiposity. TR agonists are pro-adipogenic, while TRα-null mice are leaner and more resistant to obesity. Low thyroxine (T4) and triiodothyronine (T3) levels in humans are associated with weight gain and metabolic dysfunction [7].

Leptin plays a significant role in regulating energy balance and insulin sensitivity. Leptin levels are associated with body fat and metabolic health. Increased leptin expression is linked to obesity and insulin resistance. The leptin receptor is crucial for mediating leptin's effects on metabolism [13]. *Retinol binding protein 4 (RBP4)* is an adipokine that influences insulin resistance and is associated with cardiovascular risks. RBP4 is secreted by adipose tissue and transports retinol from the liver to surrounding tissues. Increased RBP4 levels correlate with atherosclerosis severity and type 2 diabetes risk. RBP4 inhibits insulin signaling in skeletal muscles, contributing to insulin resistance. *Thiazolidinediones* can reduce RBP4 secretion, enhancing insulin sensitivity [5]. *Increased levels of leptin* and *decreased adiponectin* are associated with obesity and insulin resistance [5].

7. Immune and Inflammatory Molecular Pathways

Adipose tissue is recognized as a active, dynamic organ that plays a crucial role in metabolic health beyond mere fat storage. The European Association for the Study of Obesity suggests redefining obesity as "adiposity-based chronic disease" (ABCD). In obesity, dysfunctional adipose tissue is involved in chronic low-grade inflammation and oxidative stress due to increased pro-inflammatory cytokines and immune dysfunction which contribute to insulin resistance and metabolic syndrome [5,7]. The immune system's balance is critical for maintaining metabolic homeostasis. Immune cells play a critical role in the inflammatory response linked to metabolic dysfunction. Adipokines, such as resistin, are involved in the inflammatory processes affecting metabolism [5,7].

As adipocytes enlarge and fat mass increases, immune cells infiltrate adipose depots - especially macrophages - and produce *inflammatory cytokines* such as *TNF-α, IL-6,* and *Monocyte Chemoattractant Protein-1 (MCP-1).* These factors activate intracellular signaling pathways (e.g., Janus kinase/Signal

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Transducer and Activator of Transcription (*JAK/STAT*), nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*)), which impair insulin signaling, promote adipocyte dysfunction, and perpetuate metabolic imbalance [26]. Emerging multi-omics studies have identified upregulation of inflammatory pathways and immune cell activation in high-risk pediatric obesity profiles, suggesting that inflammation is not merely a consequence of adiposity but an active contributor to metabolic dysfunction [26].

Oxidative stress promotes pre-adipocyte differentiation and fat accumulation. Excess adipose tissue releases pro-inflammatory adipocytokines, contributing to chronic inflammation and impaired fat cell development in hypertrophic obesity [5,32].

Chronic inflammation from obesity contributes to metabolic dysfunction and cardiovascular disease progression. Adipose tissue releases inflammatory cytokines, leading to insulin resistance and hypercoagulability. Obesity is linked to increased levels of high-sensitivity C reactive protein (hsCRP) and TNFα, which worsen glucose intolerance. Adiponectin, an anti-inflammatory adipocytokine, is decreased in obesity and has potential therapeutic role. Lifestyle modifications, including diet and exercise, can reduce inflammation and improve metabolic health [13].

The *immune system* plays a crucial role in the inflammatory response, involving both innate and adaptive components. The innate immune system is the first line of defense, responding rapidly to pathogens. Key cells include macrophages, dendritic cells, and natural killer (NK) cells, which detect and respond to infections. The adaptive immune system develops specific responses to pathogens and retains memory for future encounters. T cells and B cells are the main effector cells, with CD8 T cells directly killing infected cells and B cells producing antibodies. The immune system significantly influences obesity-related inflammation and metabolic health. Macrophage infiltration in adipose tissue is associated with obesity. Dendritic cells contribute to inflammation and insulin resistance in obesity. B cells and T cells play roles in modulating inflammation and metabolic responses. Both innate and adaptive immune cells contribute to the inflammatory response in adipose tissue during obesity. Macrophages infiltrate WAT, changing from anti-inflammatory to pro-inflammatory phenotypes and producing cytokines. Neutrophils increase in number and contribute to inflammation shortly after high-fat diet initiation. Dendritic cells and mast cells also play roles in modulating inflammation and immune responses in adipose tissue. B and T cells contribute to chronic inflammation through antibody production and cytokine secretion [13].

Reactive oxygen species (ROS) are critical in the pathophysiology of obesity and its related complications. Obesity leads to an imbalance between antioxidants and pro-oxidants, causing oxidative stress. Major sources of ROS in adipose tissue include Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidases and mitochondrial monoamine oxidase (MAO). Hydrogen peroxide (H2O2) is a key molecule involved in both physiological and pathological oxidative stress.

Monoamine Oxidase (MAO) is an enzyme that contributes to oxidative stress and is implicated in obesity and cardiovascular diseases. It is located at the outer mitochondrial membrane and metabolizes neurotransmitters, generating H2O2 as a byproduct. Two isoforms, MAO-A and MAO-B, have distinct roles in various tissues, including the brain and peripheral organs. MAO plays a significant role in endothelial dysfunction, which is prevalent in obesity and diabetes. Increased MAO expression is observed in aortas from hypertensive and diabetic models, contributing to vascular impairment. Inhibition of MAO has shown potential benefits in improving vascular function (relaxation) and reducing oxidative stress. MAO is involved in lipid metabolism and adipose tissue function, influencing obesity outcomes. Increased MAO activity is reported in the adipose tissue of obese animals and humans. MAO inhibitors have been shown to reduce body weight and enhance lipolysis in experimental models. MAO-A expression is upregulated in visceral adipose tissue from patients with obesity, linking it to oxidative stress. MAO is associated with chronic inflammation, a significant factor in obesity-related cardiovascular diseases. MAO-A is involved in ROS generation in activated macrophages, contributing to inflammation. Upregulation of MAO has been observed in response to inflammatory stimuli, indicating its role in mediating inflammation. MAO-related oxidative stress is implicated in the vascular complications of diabetes. MAO-B is overexpressed in

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diabetic aortas, contributing to endothelial dysfunction. MAO inhibitors have shown promise in improving vascular reactivity and reducing oxidative stress in diabetic models [5].

8. Neurobiological Mechanisms

Genetic influences. The hypothalamus is crucial for regulating appetite and energy balance, processing signals from peripheral organs and coordinating hormonal responses. Disruptions in the leptin-melanocortin pathway lead to severe obesity and eating disorders. Cognitive impairments, including decision-making and memory issues, are linked to obesity, suggesting that both monogenic and polygenic forms affect brain health [12].

Mutations in the leptin-melanocortin pathway involving genes like LEP, LEPR, and MC4R and regulatory factors, such as MRAP2 and ADCY3, can cause hyperphagia and eating disorders leading to early-onset severe obesity and other metabolic diseases, highlighting the interconnectedness of genetic influences on obesity and brain function. Gain-of-function variants in MC4R are associated with binge eating disorder, indicating a complex relationship between genetic factors and eating behaviors. Hypoleptinemia, common in anorexia nervosa, triggers psychological adaptations that can lead to severe mental health issues [12].

Research shows a significant overlap between obesity and *cognitive deficits*, with shared genetic vulnerabilities. Inflammatory cytokines released by adipose tissue may impair cognitive function, while sleep disorders and vascular changes associated with obesity can further contribute to cognitive decline. Neuroimaging studies reveal structural and functional brain changes in individuals with obesity, particularly in areas related to decision-making and impulse control [12].

The leptin-melanocortin pathway is crucial for *appetite regulation and energy balance*, linking fat mass to eating behavior. Leptin levels correlate with fat mass and influence energy balance. The balance between Pro-opiomelanocortin (POMC) and Agouti-related protein (AGRP) neurons in the hypothalamus regulates food intake and energy expenditure as they sense circulating leptin levels. These neurons signal to MC4R-expressing neurons in the paraventricular nucleus (PVN) from hypothalamus, which control appetite. Class 3 semaphorins influence POMC neuron projections to the PVN. Brain-derived neurotrophic factor (BDNF) signaling is involved in leptin-mediated synaptic plasticity, affecting arcuate nucleus (ARC) and PVN neurons. Genetic disruptions in BDNF and TrkB lead to hyperphagia and severe obesity.

Additional neuronal circuits and molecules are implicated in severe obesity, highlighting the complexity of energy balance regulation. Leptin modifies synaptic connections rapidly, contributing to structural plasticity crucial for its functions. BDNF is downregulated by nutritional deprivation and upregulated by leptin in the ventromedial nucleus (VMN) of the hypothalamus. A study found 40 rare loss-of-function variants in class 3 semaphorins (SEMA3A–G) enriched in individuals with severe obesity. More data are needed to confirm the role of class 3 semaphorins in energy homeostasis. The central nervous system (CNS), particularly the hypothalamus and pituitary gland, is highlighted as key in body-weight regulation [8].

Neurobiological Mechanisms of Appetite Regulation - Hypothalamic Control of Energy Balance. The central nervous system (CNS) plays a critical role in regulating appetite and energy balance [22]. Energy balance regulation involves the integration of peripheral signals by the CNS. Homeostatic feeding meets physiological needs, while hedonic feeding is pleasure-driven. Key hormones like leptin, ghrelin, and insulin play roles in appetite regulation. CNS serotonin levels influence feeding behavior and energy intake. Hedonic feeding is driven by reward pathways and can lead to binge eating. Dopaminergic reward centers interact with impulsivity-control networks in the brain. Chronic exposure to palatable foods alters reward pathways, promoting obesity. Individuals with obesity show increased activation in limbic areas when exposed to food cues [7].

Satiation and satiety are key concepts in understanding eating behavior. The hypothalamus and brain stem are central to appetite control, influenced by various hormones. Dysregulation of the reward system contributes to hedonistic eating behaviors [22]. Energy homeostasis is primarily regulated by neuropeptides in the hypothalamus. The hypothalamus integrates hormonal and

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nutrient signals to regulate hunger and satiety. Two key neuronal populations are involved: orexigenic neurons and anorexigenic neurons.

Orexigenic neuropeptides (Neuropeptide Y/ Agouti-related protein - NPY/AgRP) stimulate appetite, increase food intake and decrease energy expenditure. NPY/AgRP neurons, located in the hypothalamic arcuate nucleus, are key orexigenic cells that stimulate hunger, increase food intake, and reduce energy expenditure. Activated by ghrelin and inhibited by leptin and insulin, these neurons co-release neuropeptide Y (NPY), agouti-related peptide (AgRP), and GABA to promote feeding behavior and drive food-seeking.

Anorexigenic neuropeptides (pro-opiomelanocortin/cocaine-and amphetamine-regulated transcript - POMC/CART and Alpha-melanocyte-stimulating hormone α - α-MSH) suppress appetite, decrease food intake and increase energy expenditure - POMC/CART neurons in the arcuate nucleus of the hypothalamus are critical regulators of energy homeostasis, functioning as an anorexigenic (appetite-suppressing) system that reduces food intake and increases energy expenditure. Activated by leptin and insulin, these neurons produce pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) to promote satiety. α-MSH is an endogenous peptide hormone and neuropeptide. It is primarily known for its role in skin pigmentation, but it also functions as a potent anti-inflammatory and antimicrobial agent [4,50].

In children with obesity, chronic exposure to *high-fat diets and inflammatory cytokines* disrupts hypothalamic signaling, promoting hyperphagia and reduced energy expenditure [4,50].

In hypothalamic lesion-induced obesity animal models, surgical or chemical lesions in the hypothalamus can induce obesity. VMH lesions lead to hyperphagia and obesity due to disrupted energy regulation. ARC lesions, induced by monosodium glutamate (MSG) treatment, result in metabolic syndrome features, including insulin resistance and adiposity [4].

The *hypothalamus* plays a crucial role in regulating appetite and energy balance, influencing the development of obesity through hormonal signaling and stress responses. Leptin is an anorexigenic hormone produced by adipose tissue that regulates hunger and satiety by acting on the hypothalamus. Dysregulation of leptin signaling, particularly through leptin resistance, contributes to overeating and weight gain [5]. Blood-borne signals like leptin, insulin, and ghrelin interact with hypothalamic receptors to regulate energy balance. Recent studies suggest that brain areas related to emotion and cognition also influence energy regulation [4].

Chronic stress is a significant factor in the development of obesity, influencing eating behaviors and metabolic processes. The hypothalamic-pituitary-adrenal (HPA) axis mediates stress responses, with chronic activation linked to obesity and metabolic dysfunction. Stress activates the HPA axis, leading to increased cortisol levels, which can promote overeating and weight gain. Chronic exposure to high glucocorticoid levels due to stress can lead to hypothalamic dysfunction, reducing anorectic hormone production and increasing obesity risk. Chronic stress and overeating can result in obesity through dysregulation of leptin signaling and the Janus kinases/ Signal Transducers and Activators of Transcription (JAK/STAT) pathway [5].

Disruption of hypothalamic function can lead to significant metabolic changes and weight gain, highlighting potential therapeutic targets for obesity treatment. Damage to the hypothalamus can disrupt metabolic functions and lead to weight gain [5].

Eating behavior. A complex interplay of genetic and environmental factors significantly influences appetite control and obesity risk in children. Genetic susceptibility to obesity is expressed through suboptimal eating behaviors, particularly in environments with high access to palatable foods. Various factors, including food groups, eating behaviors, physical activity, sleep, and knowledge-based work, impact appetite control. Understanding these influences is crucial for developing effective obesity prevention strategies.

Different *food groups and components* can significantly affect appetite regulation and satiety. High-protein foods are the most satiating and influence the release of anorexigenic hormones while reducing ghrelin levels. Low-energy-density foods, such as fruits and vegetables, are important for managing energy intake and body weight.

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Ultra-processed foods are linked to increased obesity risk due to their high energy density, refined carbohydrates, and added sugars, which enhance palatability, leading to overeating. The consumption of ultra-processed foods is a significant environmental factor contributing to obesity in children. Studies show that individuals consume about 500 more calories when on an ultra-processed diet compared to unprocessed diets. The negative health effects of ultra-processed foods are attributed to their low protein and fiber content, along with high sugar and fat levels.

Dairy products, particularly yogurt, may positively influence appetite control and body composition in children. Increased consumption of dairy is associated with lower body fat and reduced obesity risk. Yogurt consumption is linked to improved metabolic outcomes and insulin sensitivity, especially in genetically predisposed youth. Mechanisms include high protein content, effects on gut microbiota, and stimulation of anorexigenic hormones.

Certain *non-nutrient food components* can significantly impact appetite control and energy balance. Caffeine may reduce energy intake, but its effects on appetite regulation in children are not well established. Capsaicin has potential appetite-suppressing effects, though studies in children are limited. Prebiotics and probiotics can alter gut microbiota, influencing appetite and metabolic profiles, with some evidence supporting their role in obesity management.

Strategies for Enhancing Satiety. Combining multiple satiating food elements may enhance satiety and help manage childhood obesity. Highly satiating meals can promote self-regulation of eating in children, particularly those at higher risk of obesity. Previous studies indicate that meals rich in protein, fiber, and low in energy density can increase satiety and reduce hunger. Offering low-energy-dense snacks after meals may help mitigate overeating tendencies in susceptible children.

Eating behavior traits are critical determinants of obesity risk and are influenced by genetic and environmental factors: food responsiveness and low satiety responsiveness (assessed by CEBQ) were linked to higher BMI; cognitive restraint, uncontrolled eating, and emotional eating (assessed by TFEQ), were associated with body weight. Genetic correlations exist between eating behaviors and BMI, indicating a shared genetic architecture influencing appetite control.

Physical Activity's Role in Appetite Control. Physical activity significantly influences appetite regulation and energy intake in children. Short durations of physical activity can decrease appetite, while longer durations may increase it. High-intensity activities are more effective in reducing energy intake compared to lower intensities. Structured physical activity, especially combining aerobic and resistance training, is recommended for better appetite control.

Sleep duration and quality are linked to obesity risk, with short sleep associated with increased appetite and energy intake. Short sleepers exhibit higher levels of ghrelin and lower levels of leptin, leading to increased hunger. Behavioral strategies can improve sleep quality, but their impact on weight control remains unclear. Understanding the neuroendocrine mechanisms underlying sleep and appetite is essential for obesity prevention.

Knowledge-Based Work and Energy Intake. Cognitive demands can influence energy intake, with increased mental effort linked to higher food consumption. Stressful cognitive tasks have been associated with increased body fat in children. Incorporating physical activity between mental tasks and meals can help mitigate the impact of cognitive work on energy intake. Balancing mental and physical activities is crucial for maintaining healthy energy balance in children.

Stress and Emotional Factors in Obesity. Children from vulnerable groups face higher psychosocial stress, which can lead to unhealthy eating behaviors. Stressful environments contribute to emotional eating, which is linked to obesity and poor dietary habits. Emotional eating is associated with increased depression symptoms and psychological distress [3].

Leptin and Insulin Resistance in the Brain. Leptin and insulin act centrally to inhibit appetite. However, obesity is associated with central leptin and insulin resistance, partly due to inflammatory signaling and impaired transport across the blood–brain barrier. Molecular activation of Suppressor of Cytokine Signaling 3 (SOCS3) and c-Jun N-terminal kinase (JNK) pathways inhibits leptin receptor signaling, perpetuating overeating behavior [51].

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Leptin is a key hormone in regulating energy balance which is produced by adipocytes and helps regulate caloric homeostasis by inhibiting hunger, but its effectiveness can be compromised in obesity, leading to increased food intake. The leptin receptor (Ob-R) activates the Janus kinases/ Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway, which is crucial for mediating leptin's effects on appetite and energy expenditure. *Leptin resistance* can develop in individuals with obesity, leading to ineffective appetite suppression and increased food consumption. Chronic overexpression of leptin can lead to increased SOCS3 levels, further contributing to leptin resistance. SOCS3 levels function as a critical regulator of immune responses and inflammation, often acting as a negative feedback loop for cytokine signaling (e.g., IL-6) [5].

9. Gut Microbiota

The gastrointestinal (GI) tract plays a crucial role in obesity through nutrient absorption, motility, and microbiome composition [22].

The intestinal microbiota plays a significant role in health and is influenced by various factors, including diet. The microbiome consists of diverse microorganisms that can impact metabolic health. Diet, particularly a Western diet, is associated with reduced microbial diversity and increased obesity risk [3].

The *gut microbiome* plays a significant role in obesity and metabolic health and it can influence energy metabolism and immune responses. Dysbiosis in gut microbiota is associated with obesity, low-grade inflammation and metabolic disorders and is characterized by a less diverse microbiome and altered Firmicutes/Bacteroidetes ratios. Specific bacterial phyla are linked to metabolic dysfunction and obesity risk. Short-chain fatty acids produced by gut bacteria have both pro- and anti-inflammatory effects [7,22].

Gastrointestinal signaling hormones significantly influence appetite and motility, impacting obesity management. Ghrelin levels are decreased in patients with obesity, leading to delayed gastric emptying. Elevated levels of cholecystokinin (CCK) and somatostatin in obesity inhibit gastric motility. Glucagon-Like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) are incretin hormones that enhance insulin secretion and suppress appetite [22].

Gut Microbiome in Childhood Obesity. Comparative studies show that children with obesity exhibit altered gut microbial composition, often characterized by: reduced microbial diversity; increased Firmicutes-to-Bacteroides ratio; enrichment of pro-inflammatory bacterial taxa. Specific bacterial genera, such as Lactobacillus and Bacteroides, show varying abundances in children with obesity compared with normal weight children. Specific profiles of fecal microbiome have been linked to the onset of childhood obesity. These changes affect host metabolism through microbial metabolites, immune signaling, and nutrient extraction efficiency [3,52].

Microbial Metabolites and Host Signaling. Gut bacteria produce metabolites such as short-chain fatty acids (SCFAs) - acetate, propionate, and butyrate, which influence host energy balance by interacting with G-protein-coupled receptors (GPR41, GPR43). SCFAs regulate energy, appetite, glucose metabolism, adipogenesis, and inflammation. Acetate's effects on appetite regulation and energy metabolism are being studied [22,53]. In children with obesity, altered SCFA profiles may promote increased energy harvest and lipogenesis, exacerbating adiposity [53]. Additionally, microbial lipopolysaccharides (LPS) can enter circulation, triggering metabolic endotoxemia, which activates inflammatory signaling pathways (e.g., TLR4–NF-κB) and worsens insulin resistance [54].

Epigenetic and Immune Interactions. The gut microbiota can also modulate host epigenetic programming. Microbial metabolites influence histone acetylation and DNA methylation in intestinal and hepatic cells, linking diet, microbiota, and gene expression. Early-life microbial colonization is therefore critical for metabolic programming and obesity susceptibility [55–60]. Food-derived microRNAs may influence gut microbiota and intestinal barrier functions, impacting overall health [24].

10. Environmental Influences on Obesity

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Various environmental factors, such as inadequate nutrition, physical inactivity, and exposure to obesogens contribute to the obesity epidemic. The built environment and social disparities also impact obesity rates. Environmental chemicals, termed obesogens, can disrupt metabolic processes, pathways, hormonal control of adipose tissue and promote weight gain. These disruptions can lead to obesity, especially in genetically susceptible populations. The fetus is identified as the most susceptible to these environmental alterations. The review suggests that poor nutrition and exposure to endocrine-disrupting chemicals are significant contributors to the obesity epidemic [7,8].

10.1. Nutrition

The *complex role of nutrition* is multifaceted, with calorie quality being more important than quantity. Hyperinsulinemia is proposed as a primary driver of weight gain. Different macronutrients have varying effects on metabolism and energy storage. The nature of calories consumed significantly impacts obesity risk [7,8]. Nutrients are external factors which influence energy balance, fat stores and metabolic processes.

Molecular Mechanisms Regulating Food Intake. Complex neuroendocrine mechanisms regulate food intake and energy balance. Nutritional homeostasis involves digestion, absorption, and energy expenditure, controlled by the central nervous system, particularly the hypothalamus. Short-term food intake is regulated by sensory signals and hormonal responses, with key peptides like cholecystokinin (CCK) inducing satiety. Medium-term appetite regulation is primarily managed by peptide YY, which decreases food intake significantly. Long-term regulation involves peripheral adiposity signals like leptin and insulin, which inhibit appetite and stimulate energy expenditure [4].

Dietary Patterns and Childhood Obesity. Dietary patterns are defined by the combinations and frequencies of foods consumed, reflecting cultural and social influences. Dietary habits and nutrition are critical factors influencing childhood obesity, with specific patterns linked to increased risk. The evolution of dietary patterns significantly impacts childhood obesity and related health outcomes. Dietary patterns (DPs) evolve from toddlerhood to childhood, establishing more consistent patterns later. Unhealthy dietary patterns, characterized by highly processed and energy-dense foods with low fiber are linked to increased fat mass and childhood obesity. Studies indicate that children following unhealthy dietary patterns are more likely to experience obesity and related health issues. Poor dietary patterns contribute to over half of cardiovascular disease deaths. Low adherence to Mediterranean diets correlates with higher obesity prevalence in children. Adherence to Mediterranean dietary patterns show promise in reducing body mass index (BMI) and obesity prevalence in children. Dietary patterns may better explain the risk of noncommunicable diseases (NCDs) than specific nutrients. Evidence linking diet quality to NCDs in children is limited but suggests that healthy patterns lead to better health outcomes. Healthy dietary patterns are associated with reduced risks of chronic diseases, while unhealthy patterns increase risks. Actual recommendations consider dietary patterns and food combinations rather than just individual nutrients. Dietary quality encompasses food components, patterns of consumption, and dietary habits. High-quality diets include nutrient-dense foods with minimal added sugars, sodium, and saturated fats. Various dietary patterns can reduce cholesterol and insulin resistance [3].

Establishing Dietary Patterns in Early Life. Dietary patterns are shaped by family environments and persist into later childhood and adulthood. Family meals and parental modeling significantly influence children's eating behaviors. Longitudinal studies show that dietary patterns established in early childhood often persist. Maternal education is a predictor of healthier dietary patterns in children. Establishing healthy dietary patterns early in life is crucial for preventing childhood obesity and promoting long-term health [3].

10.2. Environment

Obesogenic Environments and Vulnerable Groups. The environments where children grow up significantly influence their health, particularly in vulnerable communities. Access to parks and walking pathways correlates with higher physical activity levels in children. Children in high

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socioeconomic status (SES) areas have better access to healthy food options and safe recreational spaces. Vulnerable communities often lack infrastructure that supports healthy living, contributing to obesity risk.

Built Environment and Health Outcomes. The built environment can influence health behaviors and outcomes, including obesity and includes man-made surroundings like buildings and parks, which can affect physical activity and dietary choices. Factors such as street connectivity, residential density, and access to green spaces are linked to obesity risk. An obesogenic environment promotes sedentary lifestyles and poor eating habits.

Food Prices and Diet Affordability. High costs of healthy foods are a significant barrier to healthy eating, especially for low SES groups. Healthy foods cost over twice as much as unhealthy options, with a price ratio of 1.99. Price promotions for unhealthy foods are more common, influencing consumer choices. Policies to reduce unhealthy food promotions may help decrease consumption of unhealthy options.

Food Availability and Accessibility. Access to healthy foods is crucial for improving dietary habits, particularly in disadvantaged neighborhoods. Food environments in low-income areas often lack healthy food retailers and have a high density of fast-food outlets. Food deserts hinder access to fresh produce, impacting dietary quality. Proximity to grocery stores does not always guarantee access to healthy foods; public transport and neighborhood safety are also important.

Cultural Influences on Food Choices. Cultural practices and beliefs significantly shape dietary patterns and lifestyle choices, impacting obesity rates. Traditional foods may be energy-dense and contribute to obesity, despite their cultural significance. Cultural norms influence portion sizes and food consumption during social events, potentially leading to overeating. Limited nutritional education in some cultures exacerbates misconceptions about healthy eating.

Principles of Sustainable Healthy Dietary Patterns. Sustainable diets are essential for health and environmental sustainability, focusing on low-impact food choices. Sustainable diets should be nutritionally adequate, culturally acceptable, and environmentally friendly. Sustainable dietary practices contribute to food security and environmental health. Education and supportive environments are key to fostering healthy eating habits in children [3].

10.3. Physical Activity / Sedentary Behavior

Exercise and Its Impact on Obesity. Physical activity is crucial for managing obesity and improving metabolic health. Exercise enhances insulin sensitivity and reduces inflammation. It positively affects mitochondrial function and energy metabolism. Regular physical activity can lead to significant health benefits and weight loss. Exercise training can mitigate immunometabolic disturbances associated with obesity [7].

Sedentary behaviors significantly contribute to childhood overweight and obesity, influenced by various factors including physical inactivity and sleep disturbances. Sedentary behaviors are defined as waking activities performed in a sitting, lying, or reclining position with energy expenditure ≤ 1.5 METs. Children spend about 8 hours of their waking time in sedentary behaviors, exceeding the recommended 2 hours of screen time daily. The prevalence of sedentary behaviors increases with age. Increased sedentary time correlates with higher body mass index (BMI) and fat mass index, with studies showing a 0.04 kg/m^2 increase in BMI for each additional hour of sedentary time. Screen time is particularly associated with adiposity, with 29% of European children aged 2-10 exceeding recommended limits.

Physical inactivity is a major health risk factor for children, contributing to obesity and related health issues. Over 80% of adolescents globally are physically inactive, failing to meet WHO recommendations for physical activity. Many children are physically inactive, with girls being less active than boys and activity levels decreasing with age. Engaging in at least 60 minutes of moderate to vigorous physical activity daily can reduce the risk of childhood obesity by 30%.

Importance of Physical Activity for Children. Physical activity is crucial for child health, impacting obesity rates and chronic disease development. The Global Action Plan on Physical Activity

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emphasizes a system-based approach to promote physical activity through social, cultural, economic, and environmental factors. Children and adolescents should engage in an average of 60 minutes of moderate to vigorous physical activity daily, with specific guidelines for children under 5 years. Recommendations include 180 minutes of physical activity for children aged 1-2 years and at least 60 minutes of moderate to vigorous activity for children aged 3-4 years.

Barriers to Healthy Eating and Physical Activity. Various factors impede children's ability to adopt healthy eating and physical activity habits. Parental approaches to nutrition, financial limitations, and restricted access to health-enhancing initiatives are significant barriers. The belief that healthy eating is more expensive and the reliance on electronics for entertainment further exacerbate unhealthy behaviors. The COVID-19 pandemic has worsened these challenges, increasing the prevalence of unhealthy dietary habits and sedentary lifestyles among children.

Stigma and Body Positivity Movement in Children. Obesity-related stigma negatively impacts children's mental and physical health, complicating healthcare access. Stigma is prevalent among healthcare professionals, leading to misconceptions about obesity and its causes. The body positivity movement can obscure the health risks associated with obesity, creating a delicate balance in addressing obesity without promoting harmful narratives. Effective communication and education are essential to combat stigma and provide comprehensive care for children with obesity.

Role of Physical Activity in Child Health. Physical activity is a vital component of maintaining a healthy weight and preventing obesity in children. The WHO recommends regular physical activity for children to combat obesity and improve overall health. Studies show that physical inactivity is a significant risk factor for childhood obesity, necessitating increased opportunities for active play and exercise. Policies promoting physical activity in schools and communities are essential for fostering healthier environments for children [3].

10.4. Endocrine-Disrupting Chemicals (Obesogens)

Endocrine-disrupting chemicals (EDCs), known as *obesogens* are chemicals that disrupt metabolic processes and may contribute to weight gain and obesity at both individual and societal levels. Obesogens include bisphenol A (BPA), phthalates, perfluoroalkyl substances, and pesticides. Evidence supporting the obesogen hypothesis includes in vitro studies, animal research, and epidemiological data linking chemical exposure to increased adiposity [8,61,62].

Obesogens act through multiple molecular mechanisms: they can mimic or antagonize hormone receptors, alter adipocyte differentiation via pathways such as peroxisome proliferator-activated receptor γ (PPARγ), disrupt gut microbiota, promote inflammation, and induce transgenerational epigenetic changes. Through these mechanisms, they interfere with hormonal signaling, adipocyte development, fat storage, appetite regulation, energy metabolism, adipose tissue function and metabolic processes, generating obesity and metabolic disorders [8,61]. They may disrupt normal metabolic functions through various mechanisms, such as increasing inflammation, altering gut microbiota, and affecting brain centers that regulate hunger and satiety. The potential for transgenerational effects was evaluated, indicating that obesogen exposure could impact not only the exposed individuals but also their descendants [8,62].

Experimental studies reveal that prenatal exposures to synthetic estrogens (e.g., diethylstilbestrol) and phthalates can increase adiposity and alter metabolic regulators — potentially via epigenetic programming that persists into later life [63].

Environmental factors, including exposure to toxicants, play a significant role in the transgenerational inheritance of obesity. Endocrine disruptors like BPA and phthalates are linked to obesity and metabolic disorders. Prenatal BPA exposure correlates with early childhood obesity and DNA methylation changes. Transgenerational studies show that grandparental exposure to chemicals like tributyltin increases fat deposition in offspring. Paternal cold exposure has been shown to enhance brown adipose tissue activity in offspring. Maternal gut microbiome influences fetal development and obesity risk, with cesarean delivery linked to higher obesity rates [6].

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Bisphenol A (BPA) is an organic compound structurally similar to estrogens, which allows it to disrupt endocrine signaling. BPA is widely used in plastics and consumer products, and its exposure has been associated with increased adipocyte differentiation, adipocytes number, adipocyte size, fat accumulation, increased total body fat, and altering of metabolic processes. Common sources of BPA exposure include food and beverage containers, thermal papers, and environmental contamination from industrial processes. BPA levels in urine can significantly increase after consuming canned foods compared to fresh foods, highlighting its pervasive presence in the environment. BPA influences adipogenesis by activating glucocorticoid receptors and altering gene expression related to fat storage and metabolism. It suppresses adiponectin release, a hormone that regulates glucose levels and fatty acid breakdown, potentially leading to obesity. BPA exposure has been shown to increase pro-inflammatory cytokines in adipose tissue, which can hinder lipolysis and promote fat accumulation.

Epidemiological studies show mixed results regarding the association between BPA exposure and obesity, with some indicating a positive correlation, particularly in children and women. Numerous animal studies have demonstrated that BPA exposure during critical developmental periods leads to increased body weight and fat accumulation in offspring. In vitro studies reveal that BPA enhances the proliferation of pre-adipocytes and increases the expression of adipogenic markers, further supporting its role in obesity development [8,64].

11. Molecular Links Between Childhood Obesity, Comorbidities and Other Conditions

11.1. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Childhood obesity is a major risk factor for pediatric Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Molecular mechanisms linking the two include increased hepatic lipid influx, impaired β-oxidation, mitochondrial dysfunction, and inflammatory signaling. *Dysregulation of transcription factors* such as SREBP-1c, ChREBP, and PPARα promotes hepatic lipogenesis and steatosis [65]. Epigenetic alterations in hepatic metabolic genes have been observed in children with obesity and MASLD, suggesting that molecular programming contributes to disease progression.

Recent research highlights the complex relationship between the gut microbiome and host genetics in the development of metabolic dysfunction-associated steatotic liver disease (MASLD) and its progression to hepatocellular carcinoma (HCC). Host genetic variants and gene expression influence the composition of the gut microbiome, affecting the risk of MASLD. Key genetic variants include PNPLA3, TM6SF2, MBOAT7, GCKR, and HSD17B13, which are associated with lipid metabolism and liver fat content. A study found that specific gut bacteria abundance correlates with the PNPLA3 rs738409 variant, predicting hepatic fat fraction. Genetic variants like TM6SF2 rs58542926 and MBOAT7 rs641738 influence gut microbiome composition and liver health. Gut microbiota and their metabolites can induce epigenetic modifications that impact MASLD development. Epigenetic modifications, such as DNA methylation and histone modifications, influence gene expression related to MASLD. The m6A RNA modification has been implicated in MASLD-HCC progression, with proteins like METTL3 and YTHDF1 playing critical roles [66].

Sexual dimorphism in MASLD. Development show that males are more prone to MASLD, MASH, fibrosis, and HCC compared to females. Female hormones, particularly estrogen, may provide protective effects against MASLD. A study showed that male patients had lower microbial α-diversity and higher abundance of certain bacteria compared to females. Genetic variants like PNPLA3 rs738409 increase MASLD risk more in females, while TM6SF2 rs58542926 impacts males more significantly [66].

11.2. Cardiometabolic Risk and Atherosclerosis

Obesity-associated inflammation and dyslipidemia contribute to early vascular changes in children. Elevated cytokines, oxidative stress, and altered lipid metabolism impair endothelial

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function and promote early atherogenesis. Molecular markers of oxidative stress and inflammation correlate with arterial stiffness and intima-media thickness in youth with obesity [67].

Role of Oxidative Stress in Cardiovascular Dysfunction. Oxidative stress plays a critical role in the cardiovascular complications associated with obesity. Excess reactive oxygen species (ROS) disrupts the balance between ROS generation and antioxidant capacity. Increased ROS production is linked to obesity, diabetes, and metabolic syndrome. Oxidative stress contributes to cardiac dysfunction through pathological remodeling in myocardial Ca2+-handling. Biomarkers like malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) indicate oxidative stress in obesity. Dysregulated metabolic parameters amplify oxidative stress, leading to cardiovascular diseases [5].

Inflammation and Vascular Pathologies. Chronic inflammation significantly contributes to the development and progression of cardiovascular diseases, including atherosclerosis and myocardial infarction. Vascular pathologies like ischemic heart disease and stroke are leading causes of death globally. Chronic inflammation is a key factor in cardiovascular disease (CVD) progression, leading to plaque development. Obesity promotes atherosclerotic cardiovascular disease (ASCVD) through low-grade inflammation. Despite advances in treatment, obesity rates continue to rise, exacerbating ASCVD mortality [13].

Pathogenesis of Inflammation in Atherosclerosis. The inflammatory response is crucial in the chronic progression of atherosclerosis, from initial fatty streak formation to complex plaque development. Endothelial injury activates inflammatory responses, leading to monocyte recruitment and macrophage differentiation. Macrophages transform into foam cells by taking up modified lipoproteins, contributing to plaque formation. Cytokines like IL-1, TNFα, and IFN-γ play roles in monocyte adhesion and foam cell formation. The NLRP3 inflammasome in macrophages produces IL-1β and IL-18, amplifying inflammation and promoting CVD. Advanced atherosclerosis involves plaque destabilization through apoptosis and matrix degradation [13].

Inflammation and Lipid Profile. Elevated triglycerides and low-density lipoprotein (LDL) cholesterol are linked to atherosclerosis, with triglyceride-rich lipoproteins (TRLs) playing a significant role. TRLs include chylomicrons and very low-density lipoproteins (VLDLs), which are hydrolyzed to release free fatty acids. TRL remnants are more cholesterol-rich than LDL and contribute to endothelial damage and inflammation. Oxidized free fatty acids activate inflammatory pathways, increasing cytokine expression and promoting foam cell formation. TRLs can enhance endothelial dysfunction by increasing reactive oxygen species (ROS) and reducing nitric oxide [13].

Inflammation in Acute Myocardial Infarction. Acute myocardial infarction occurs when atherosclerotic plaques rupture, leading to coronary artery occlusion and inflammatory responses. Plaque rupture exposes prothrombotic materials, triggering a cascade of inflammatory cytokines and cell migration. IL-1β is crucial for producing matrix metalloproteinases (MMPs) that degrade collagen in the fibrous cap, increasing rupture risk. Inflammatory markers like high-sensitivity CRP and IL-6 correlate with worse outcomes post-infarction. The immune response involves macrophages and neutrophils, which clear debris and promote tissue repair [13]. Obesity enhances coronary atherosclerosis through mechanisms like dyslipidemia and inflammation [4].

11.3. Sleep Role in Obesity

Sleep duration and quality are critical factors influencing childhood obesity, with insufficient sleep linked to weight gain. A narrative review found that 37% of children experience sleep difficulties, which can lead to obesity. Studies show a strong negative association between sleep duration and adiposity, with children sleeping less than recommended at higher risk for obesity. Increasing sleep duration has been associated with weight loss, highlighting the importance of adequate sleep for maintaining a healthy weight. The National Sleep Foundation recommends 9-11 hours of sleep for children aged 6-13 years [3].

Circadian Rhythms and Metabolic Health. Circadian rhythms regulate metabolic processes and energy balance and can impact obesity risk. Disruptions in circadian rhythms are linked to obesity, metabolic disorders, insulin resistance and affect lipid metabolism and overall energy homeostasis.

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Timing of food intake and physical activity can influence metabolic health. Gut microbiota may influence circadian rhythms through metabolic products. Maintaining regular circadian patterns is important for metabolic health and weight management [7].

Synchronization of Circadian Clock and Meal Timing. Meal timing aligned with the circadian clock can improve metabolic health and prevent obesity and diabetes. Irregular eating patterns disrupt circadian rhythms, increasing obesity and type 2 diabetes risk. Circadian misalignment, such as skipping breakfast, is linked to weight gain and insulin resistance. The circadian clock regulates metabolic processes, optimizing them for specific times of the day. Eating in synchrony with the circadian clock enhances weight loss and glycemic control. High energy and carbohydrate breakfasts improve postprandial glucose and insulin responses. Synchronization of food intake with the light/dark cycle enhances the expression of clock genes involved in glucose metabolism and is crucial for metabolic homeostasis. Evidence supports that meal timing can lead to more effective weight loss, reduced glycemic excursions, and improved appetite control [5].

Conflicting Circadian Rhythms of Hunger and Craving. There is a paradox between recommended meal timing and the natural rhythms of hunger and cravings. Hunger and craving scores peak in the evening, conflicting with the recommendation to consume more calories earlier in the day. Breakfast is often the smallest meal for individuals with obesity, while cravings for sweets peak in the late afternoon and evening. Skipping breakfast exacerbates evening cravings, highlighting the need for strategic meal timing [5].

Benefits of High Energy Breakfast – Morning Eating. A high-energy breakfast is critical for achieving metabolic homeostasis and improving appetite regulation. A high-energy breakfast can effectively reduce hunger and cravings throughout the day. Consuming a high-energy and carbohydrate-rich breakfast leads to significant ghrelin suppression and increased satiety. This dietary approach has been shown to improve weight loss and glycemic control, particularly in the afternoon and evening when cravings are highest. The addition of sweet snacks to breakfast can lower the reward value of those snacks later in the day [5].

Circadian rhythms significantly influence the expression and secretion of adiponectin, which plays a crucial role in metabolic processes, with its expression peaking in the morning (10:00 AM). The suprachiasmatic nucleus controls the expression of adiponectin-related genes in adipose tissue over a 24-hour cycle. A phase delay of 7 hours exists between adiponectin mRNA expression in adipose tissue and its secretion into the plasma. Disruption of circadian rhythms is linked to obesity and metabolic syndrome (MetS), affecting adiponectin levels and insulin sensitivity. Studies show that genetic circadian rhythms correlate with metabolic syndrome components, particularly in women with obesity [5].

Chronodisruption, such as sleep deprivation and shift work, is associated with an increased risk of developing metabolic syndrome and type 2 diabetes. Circadian clock genes are present in various tissues, including the liver and pancreas, influencing metabolism and insulin sensitivity [5].

12. Vitamins and Other Molecules/Factors

Vitamin A (VA) could regulate the adipogenic process, inflammation, oxidative stress and metabolism-related gene expression in mature adipocytes. *Vitamin A deficiency (VAD)* increases the risk of childhood obesity, a finding consistently reported in pregnant women. VAD disrupts the balance of obesity-related metabolism, thus affecting lipid metabolism and insulin regulation. VAD is linked to increased insulin resistance, lipid deposition and may exacerbate inflammatory responses, increasing the risk of obesity-related complications. Maternal VA levels can influence offspring adipose progenitor cell populations, potentially offering a preventive strategy against obesity [68].

Retinol-binding protein 4 (RBP4) is a transporter protein for retinol (vitamin A alcohol) and an adipokine produced in adipose tissue associated with obesity and insulin resistance. *Retinoic acid (RA)*, a lipid-soluble derivative of vitamin A, promotes the browning of white adipose tissue, potentially increasing energy expenditure and inhibiting obesity progression. RA regulates adipocyte

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differentiation and apoptosis, primarily through interactions with retinoic acid receptors (RAR) and peroxisome proliferator-activated receptor gamma (PPARγ), inhibiting adipogenesis. Studies indicate that RA can alter gene expression related to adipogenesis, lipid metabolism, and insulin sensitivity, suggesting a complex interplay between VA and metabolic health [68].

Vitamin D deficiency is commonly associated with obesity, impacting various health parameters, including leptin levels, which are crucial for energy regulation and inflammation. Obesity in children is linked to elevated leptin levels, particularly in those with vitamin D deficiency [69].

Role of Ion Channels in Obesity. Ion channels play a critical role in insulin secretion and the pathophysiology of diabetes and obesity. Voltage-gated K+ (Kv) channels, particularly KV2.1 and KV2.2, are essential for electrical excitability in human β-cells. KATP channels act as glucose sensors in β-cells, with mutations linked to congenital hyperinsulinism and neonatal diabetes. Calcium-activated potassium channels (CAPC) are crucial for repolarization during action potentials in β-cells, influencing insulin secretion. G protein-gated inwardly rectifying K+ channels (GIRK) are activated by adrenoreceptors and somatostatin receptors, affecting insulin release. TRP channels, including TRPV1 and TRPA1, are involved in metabolic regulation and can be targeted for therapeutic interventions in diabetes and obesity. TRPV1, TRPM2, and TRPM3, are implicated in insulin secretion and metabolic regulation. TRPV1 activation by capsaicin can enhance energy expenditure and prevent obesity. TRPM2 knockout mice show increased insulin sensitivity and reduced inflammation, indicating its role in diabetes pathogenesis. TRPM4 and TRPM5 channels are involved in glucose-induced insulin secretion, with mutations linked to metabolic syndrome [5].

Obesity alters the expression and function of ion channels in the heart, which can lead to arrhythmias. Obese Wistar rats show significant changes in gene expression of ion channels, including upregulation of Cav1.2 and HCN4. Fructose-fat fed Sprague-Dawley rats exhibit QRS prolongation and decreased conduction velocity, indicating impaired cardiac conduction. High-energy diets do not lead to cardiac hypertrophy but show similar ionic current densities in obese and control rats. Decreased protein expression of voltage-gated potassium channels in obese hearts contributes to prolonged QT intervals. Obesity affects calcium transport and signaling, with alterations in L-type calcium current and related proteins [5].

Metabotrophic Factors and Their Role. Metabotrophic factors (MTF) are crucial in understanding obesity and related diseases. MTF includes neurotrophins like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), as well as adipomyokines like adiponectin and irisin. MTF are involved in glucose and lipid metabolism, cardiovascular health, and cognitive functions. Obesity and related diseases may be viewed as MTF-deficient conditions. Reduced levels of NGF and BDNF are linked to obesity and related diseases. MTF deficiencies may contribute to the progression of metabolic syndrome and neurodegenerative diseases.

Neurotrophins, Key Players in Metabolism. Neurotrophins play a significant role in both neuronal health and metabolic processes. NGF and BDNF are essential for neuronal differentiation, function, and survival. They also influence glucose, lipid, and energy homeostasis, linking them to obesity and cardiometabolic diseases. Decreased levels of NGF and BDNF are observed in conditions like coronary atherosclerosis and type 2 diabetes.

Adipokines, Myokines, and Their Functions. Adipokines and myokines are signaling proteins that mediate communication between adipose tissue, skeletal muscle, and other organs. Adipokines include leptin, adiponectin, and resistin, while myokines include irisin and fibroblast growth factor-21. These proteins regulate metabolism, inflammation, and energy balance. Over 500 adipokines have been identified, highlighting the complexity of adipose tissue's endocrine functions [5].

Adipose tissue hypoxia is prevalent in obesity affects adipokine secretion and contributes to metabolic dysfunction in obesity. Hypoxia-inducible factors regulate gene expression related to metabolism and inflammation. Impaired mitochondrial function in adipocytes is linked to obesity [13].

Viral Infections and Obesity. Certain viral infections have been linked to obesity development in humans and animals. Ad-36 infection is associated with increased body weight and altered

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metabolism. Infected individuals show lower serum lipid levels despite higher body fat. Viral infections may induce changes in adipose tissue and metabolic regulation [7].

Zinc alleviates obesity primarily by modulating adipose tissue function, reducing chronic inflammation, and improving insulin sensitivity through mechanisms like enhancing Zinc-α2-glycoprotein (ZAG) and regulating PPARγ signaling. It also reduces oxidative stress and lowers leptin resistance, acting as a metabolic regulator that promotes fatty acid oxidation and suppresses lipogenesis. It is Essential for enzymatic functions and immune responses. Zinc is a vital micronutrient essential for numerous biological functions, with significant implications for health and disease. Zinc is the second most abundant transition metal in organisms, with high intracellular concentrations. It is crucial for cell proliferation, differentiation, and various enzymatic functions. The average daily zinc intake is 11 mg for men and 8 mg for women, with a tolerable upper limit of 40 mg/day. Zinc deficiency is a global health issue, affecting immune function and increasing oxidative stress.Zinc deficiency is prevalent in individuals with obesity and is linked to metabolic dysfunction [70–75].

Key molecular mechanisms for *zinc (Zn) functions* are described as follows.

Adipocyte Metabolism and Lipolysis. Zinc increases the production of ZAG, a lipid-mobilizing hormone that stimulates adipose tissue lipolysis and inhibits lipogenesis. It enhances adipose tissue expression of PPARγ and adiponectin, which improves insulin sensitivity. Adequate zinc levels are necessary for normal adipocyte function and leptin synthesis. Zinc deficiency exacerbates hepatic lipid metabolism and insulin resistance. Zinc influences the activity of adipokines like adiponectin and ZAG, which regulate lipid metabolism.

Anti-inflammatory and Antioxidant Effects. Zinc deficiency is associated with increased inflammatory markers such as CRP and IL-1β and it is linked to increased susceptibility to infections and inflammatory diseases. Zinc supplementation has been shown to reduce levels of inflammatory cytokines and improve metabolic parameters. The anti-inflammatory effects of zinc may involve inhibition of the NF-κB pathway (which prevents the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6) and upregulation of adiponectin. Zinc supplementation lowers pro-inflammatory cytokines (IL-6, TNF-α, MCP-1, CRP) and activates antioxidant enzymes, combating the oxidative stress and chronic low-grade inflammation typical of obesity. Physiological zinc concentrations inhibit reactive oxygen species production. It is involved in the integrity of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). Zinc serves as a cofactor for Cu,Zn-Superoxide Dismutase (SOD1) and induces Metallothionein (MT) synthesis, both of which neutralize reactive oxygen species (ROS) that exacerbate obesity. Zn activates antioxidant enzymes like Cu/Zn superoxide dismutase (SOD1), reducing oxidative stress. Zinc homeostasis and redox metabolism are intricately linked and significantly impacted in obesity, contributing to oxidative stress and metabolic dysfunction. Impairment of cellular zinc and redox homeostasis is common in chronic diseases, including obesity. Zinc modulates nitric oxide formation, contributing to its anti-inflammatory effects. *Metallothionein* plays a critical role in zinc storage and release in cells. It regulates zinc transfer and protects against zinc toxicity. Metallothionein is involved in oxidative stress responses and cellular signaling. Its interaction with nitric oxide influences zinc homeostasis and cellular functions.

Insulin Regulation. Zinc is essential for the structure, crystallization, and storage of insulin in the pancreas, helping to maintain normal insulin levels and mitigating hyperglycemia. Zinc acts as an insulin-mimetic. Zinc ions inhibit Protein Tyrosine Phosphatase 1B (PTP1B), a negative regulator of the insulin receptor. This inhibition enhances the PI3K/Akt signaling pathway, facilitating glucose uptake into cells via GLUT4. Zinc supplementation can improve insulin sensitivity and reduce insulin resistance.

Appetite Regulation. Zinc modulates appetite by potentially increasing leptin sensitivity in the hypothalamus, which helps in reducing food intake. It regulates leptin levels and neuropeptide Y (NPY), influencing appetite and energy balance. Zinc deficiency leads to decreased leptin gene expression, impacting appetite regulation. Zinc reduces the expression of Hypothalamic

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Neuropeptides: Neuropeptide Y (NPY) and Agouti-related protein (AgRP), the brain's primary hunger signals, while promoting the activity of anorexigenic (appetite-suppressing) POMC/CART neurons. Zinc may increase gastrointestinal motility and satiety by stimulating the release of serotonin and other appetite-regulating peptides.

miRNA Regulation. Zinc status influences the expression of specific miRNAs (e.g., miR-21, miR-34a, miR-122) that regulate lipid metabolism, inflammation, and adipogenesis. Key miRNAs affected by zinc include miR-21, miR-34a, miR-122, and miR-144-3p, which influence inflammation, lipid metabolism, and insulin signaling. Zinc repletion can restore miRNA levels and improve insulin sensitivity, suggesting potential reversibility of metabolic dysregulation. Excessive zinc may upregulate miR-144-3p, exacerbating oxidative stress. Zinc deficiency increases pro-inflammatory miRNAs like miR-21 and miR-31, promoting inflammation. The effects of zinc on miRNA expression are cell-type specific, complicating its regulatory role. Maintaining optimal zinc levels is crucial for metabolic health through its regulation of miRNAs involved in inflammation and insulin signaling. Both zinc deficiency and excess disrupt miRNA expression, leading to metabolic dysfunction.

Thermogenesis. Through the activation of metallothionein (MT), zinc can reduce obesity-induced cardiac stress and improve metabolic function [70–75].

Zinc transporters are crucial for regulating adipocyte metabolism and insulin sensitivity. Individuals with obesity show altered expression of zinc transporters like ZnT1 and Zip14. Altered zinc transporter expression in obesity leads to impaired immunity and increased inflammation. Disruption of zinc transporter function is associated with impaired lipid metabolism and glucose uptake and metabolic disorders, including obesity and type 2 diabetes. Zinc transporters are linked to inflammatory signaling and metabolic regulation. Zinc transporters like ZIP13 enhance beige adipocyte biogenesis and energy expenditure. ZnT8 is vital for insulin secretion in pancreatic beta-cells, influencing glucose homeostasis. ZnT8 transports zinc into insulin secretory granules, essential for insulin function. Zinc deficiency can lead to ZnT8 depletion, increasing the risk of type 2 diabetes mellitus. Mutations in ZnT8 are associated with a higher risk of diabetes. ZnT7 is implicated in glucose-insulin homeostasis, affecting insulin degradation in the liver. Increased levels of cytosolic zinc are linked to enhanced glucose uptake and glycogen storage in muscles. Zinc transporter ZIP13 regulates beige adipocyte biogenesis, impacting energy expenditure and obesity resistance. Zinc transporters play a significant role in insulin signaling, particularly in skeletal muscle. Skeletal muscle contains about 60% of total body zinc, with ZIP7 facilitating insulin receptor signaling. Weight loss can increase the expression of zinc transporters in adipose tissue [24,72,76].

Zinc acts as a *signaling factor* influencing various metabolic processes. ZIP10 signaling regulates B cell function and promotes pro-B cell survival [72]. Zinc acts as a cofactor for over 300 enzymes and is vital for DNA replication, gene expression, and cell signaling. It regulates the expression and activation of over 300 metalloenzymes and has antioxidant properties [24,77].

Physiological functions of zinc are often impaired in individuals with *obesity*, who commonly suffer from *low serum zinc levels*, which is corrected through supplementation, allowing for the restoration of these metabolic pathways. Zinc deficiency is prevalent in 14-30% of individuals with obesity. Zinc supplementation can reduce body weight by approximately 0.5 kg in overweight individuals, may enhance appetite control, inhibit eating behaviors and reduce obesity-related hyperphagia, improve blood pressure, decrease glucose levels, total cholesterol, LDL cholesterol, and triglycerides [76]. Short-term weight loss in low-income women with overweight/obesity can significantly improve plasma zinc levels and reduce metabolic syndrome risk factors [79]. Zinc homeostasis is linked to sarcopenia, with potential therapeutic targets identified in zinc transporters and metallothioneins [76].

Zinc-α2-Glycoprotein (ZAG) is a novel adipokine that plays a significant role in lipid and glucose metabolism. ZAG promotes lipolysis (fat breakdown) and inhibits lipogenesis (fat synthesis). ZAG stimulates the cAMP pathway, increasing the activity of hormone-sensitive lipase (HSL) to mobilize lipids. ZAG is linked to weight reduction and improved insulin sensitivity. It has a zinc binding site, indicating its role in mediating zinc's effects on lipid metabolism. ZAG stimulates lipolysis in

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adipocytes and regulates the metabolism of free fatty acids. Elevated ZAG levels are associated with improved insulin sensitivity and reduced obesity. ZAG increases lipolysis in white adipose tissue through the cyclic AMP pathway. It stimulates the expression of key molecules involved in energy expenditure and fat metabolism. Physiological ZAG levels vary, with higher concentrations in healthy adults compared to fetuses and young individuals. ZAG production is influenced by factors such as PPARγ, glucocorticoids, and thyroid hormones. It stimulates lipolysis and inhibits lipid accumulation in adipose tissue. ZAG levels are lower in patients with obesity and correlate negatively with body weight, body mass index (BMI) and fat mass. ZAG expression in adipocytes is inversely related to fat mass. ZAG levels are linked to metabolic syndrome (MetS) severity and risk. Serum ZAG levels decrease progressively with the number of MetS components. Individuals in the lowest tertile of ZAG have a 1.946-fold higher risk of developing MetS. In women with polycystic ovary syndrome (PCOS), circulating ZAG levels are significantly lower than in healthy controls. Treatment with exenatide or metformin increases ZAG levels in PCOS patients. ZAG expression positively correlates with adiponectin, an insulin-sensitizing adipokine [77].

Increased levels of free fatty acids (FFAs) reduce the availability of zinc binding sites on albumin, impacting zinc speciation in plasma. Zinc alpha-2-glycoprotein (ZAG) is another plasma protein that binds both zinc and FFAs, influencing fat metabolism. High concentrations of zinc can lead to ZAG oligomerization, affecting its function in fat mobilization. The affinity of ZAG for FFAs decreases in the presence of high zinc concentrations (500–2000 μM) [78].

Zinc is involved in the *metabolism of lipids, proteins, and carbohydrates*. Low zinc levels are associated with increased total cholesterol, triglycerides, and LDL cholesterol. Zinc supplementation has been shown to reduce total cholesterol, LDL cholesterol, and triglycerides in overweight individuals. Zinc levels are negatively correlated with body fat percentage and inflammatory markers in individuals with obesity. Zinc administration has been shown to reduce inflammation in metabolic syndrome patients [77].

Deficiency in zinc is linked to reduced lean body mass, increased fat deposition, and obesity, particularly in children and adolescents. Zinc plays a significant role in maintaining lean body mass and is necessary for synthesizing nucleic acids and proteins. Zinc positively affects proteogenesis, with implications for lean body mass and fat mass. Lean body mass is rich in zinc, and supplementation can enhance its synthesis, particularly in malnourished children. In sports and physical activities, adequate zinc levels are essential for improving strength and performance. Studies indicate that marginal zinc deficiency can lead to reduced appetite and increased adiposity [80].

Zinc ions play crucial roles in various physiological processes, including *enzyme catalysis and protein regulation*. Zn2+ ions are essential for enzyme catalysis, protein stabilization, and regulation. Zinc is essential for maintenance of immune function and modulation of inflammatory responses. It influences cytokine production and immune cell activity. Zinc deficiency can lead to impaired immune responses and increased susceptibility to infections. Adequate zinc levels are crucial for the proper functioning of immune cells. *Nutritional immunity* refers to the host's strategy to limit pathogen access to essential nutrients like zinc. S100 proteins and lactoferrin play roles in sequestering zinc to restrict its availability to pathogens [81].

Excessive zinc intake/levels can disrupt metabolic processes and contribute to chronic health conditions. Chronic overexposure can lead to oxidative stress, dyslipidemia, and hormonal imbalances. Recommended Dietary Allowance (RDA) is 8 mg/day for women and 11 mg/day for men, with a Tolerable Upper Intake Level (UL) of 40 mg/day. Long-term intake exceeding the UL is linked to copper depletion and adverse lipid alterations [75].

High levels of zinc intake disrupts the activity of *key antioxidant enzymes (Cu/Zn superoxide dismutase (SOD) activity), enhancing oxidative stress*; reduces GPX and CAT activities, leading to hydrogen peroxide accumulation. Zinc overload disrupts the activity of antioxidant Cu/Zn SOD, leading to increased oxidative stress, increased reactive oxygen species (ROS) and endothelial dysfunction. Excess zinc (Zn) amplifies oxidative stress, leading to increased pro-inflammatory cytokine (TNF-α and IL-6) release which worsen leptin resistance by disrupting receptor signaling

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pathways. Zn-induced oxidative stress impairs redox signaling in the hypothalamus and decrease leptin sensitivity. Prolonged zinc exposure upregulates leptin receptor expression, but causes leptin resistance and systemic inflammation, exacerbating obesity-related complications. Zinc overload alters the balance of essential trace elements, exacerbating oxidative stress and metabolic dysfunction [75].

Excessive zinc intake *increases body fat and visceral adiposity* and leads to significant alterations in lipid profiles (increased triglycerides, total cholesterol, and very-low-density lipoprotein (VLDL) levels, decreased high-density lipoprotein (HDL) levels), and hormonal balance. Elevated serum insulin and C-reactive protein (CRP) levels indicate disrupted glucose metabolism and systemic inflammation [75].

Excessive zinc supplementation is linked to *obesity, diabetes, hypertension, and cardiovascular diseases* through overlapping pathophysiological pathways which impair insulin signaling and glucose metabolism, leading to hyperglycemia and insulin resistance. Elevated Zn levels *impair insulin receptor phosphorylation and GLUT4 translocation*, contributing to insulin resistance. Both deficiency and excess zinc are linked to an increased risk of diabetes, particularly type 2 diabetes mellitus. Zinc's role in blood pressure regulation is mediated through oxidative stress and mineral balance. Excessive zinc intake is associated with increased mean arterial pressure and reduced renal function. High dietary zinc-to-copper ratios are associated with increased atherosclerosis risk. Excessive zinc intake promotes oxidative stress and inflammation, contributing to cardiovascular risks [75].

While excessive Zn supplementation is harmful, optimal levels may offer protective benefits, highlighting the need for further research due to contrasting results. Optimal Zn intake supports antioxidant defense, immune regulation, glucose metabolism, and lipid homeostasis [75].

13. Future Aspects of Research and Treatment in Obesity

13.1. Future Research

Childhood obesity should be understood as a systems-level disorder, emerging from the integration of molecular events across multiple organs and developmental stages. Genetic susceptibility establishes baseline risk, epigenetic programming modulates gene expression in response to early exposures, hormonal and neural circuits regulate appetite and energy expenditure, immune pathways drive chronic inflammation, and environmental factors amplify vulnerability. Future research priorities include: longitudinal multi-omics studies beginning prenatally; identification of early molecular biomarkers; personalized interventions based on molecular profiles; policy-level reduction of obesogenic exposures.

Genetic prospects. Molecular diagnostics for syndromic obesity have advanced significantly, improving the identification of genetic causes. Traditional methods often miss actionable mutations found in 25-30% of early-onset severe obesity cases. Genetic testing is essential for guiding treatment and understanding the genetic architecture of obesity. Whole exome and genome sequencing are becoming essential tools for investigating the genetic basis of obesity. The use of next-generation sequencing has facilitated the identification of mutations in obesity-related genes. Next-generation sequencing (NGS) and whole-exome sequencing (WES) have increased diagnostic yields to ~60% in suspected cases [11]. Continued research, including GWAS and advanced genetic techniques, is essential for understanding obesity's genetic basis and developing novel therapeutic strategies. The integration of genetic findings into clinical practice can enhance and personalize treatment options and improve outcomes for individuals with obesity [8,14]. The convergence of research on monogenic and polygenic obesity highlights the brain's central role in weight regulation. GWAS continues to reveal new genes and pathways, but many causal mechanisms remain unclear. Increasing sample sizes and refined phenotypes will enhance gene discovery. Translating GWAS findings into therapeutic targets could lead to precision medicine for obesity and related diseases [8]. The genetic studies also suggest the need for further investigation into large structural variants and intronic

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regions that may contribute to obesity [15]. Recent genetic research is enhancing the understanding of obesity mechanisms. Whole-exome sequencing (WES) and other techniques are revealing new genetic insights. Genetic elucidation aids in refining diagnosis and treatment options [2].

Understanding the genetic architecture of obesity can lead to personalized treatment strategies. Continued research is needed to explore the complex interactions between genetics, environment, and lifestyle in obesity. The development of comprehensive genetic panels for obesity could enhance diagnostic accuracy and treatment efficacy. Future research in syndromic obesity is needed to enhance understanding and treatment through innovative approaches. Ongoing challenges include the need for novel gene discovery and addressing phenotypic variability. Investigating gene-environment interactions can clarify phenotypic variability. Access to genetic testing remains limited in resource-poor settings, necessitating collaborative efforts for equitable diagnostics. Standardization of clinical protocols and expanding access to genetic testing are essential for early intervention. International collaboration is necessary for data sharing and validating novel genetic variants [11].

The post-genomic era presents opportunities for genotype-informed treatments and obesity prevention strategies. Ongoing large-scale studies and biobanks will enhance the understanding of obesity genetics and its biological implications. Gene-by-environment interaction studies are challenging but essential for understanding obesity risk factors. Polygenic scores (PGS) are being developed to predict obesity risk based on genetic susceptibility. Effective prediction models will need to incorporate both genetic and non-genetic factors [8].

Epigenetic prospects. Continued exploration of gene-environment interactions is essential for understanding obesity etiology. Complex inheritance patterns are being observed, necessitating updated classifications based on genetic profiles. The future of obesity research focuses on precision medicine and genetic profiling. Identifying individual risk profiles can improve treatment responses. Epigenetic modifications present opportunities for therapeutic interventions. Continued exploration of gene-environment interactions is essential for understanding obesity etiology [2]. ncRNAs (miRNAs, lncRNAs) have emerged as potential early diagnostic biomarkers for diagnosing and managing obesity [25]. Circulating miRNAs in blood can serve as non-invasive biomarkers for obesity and metabolic diseases. Altered levels of circulating miRNAs reflect their expression in metabolic tissues. The potential for using circulating miRNAs in diagnostics and predicting disease risk is significant. The role of miRNAs in metabolism highlights their potential as therapeutic targets and biomarkers for obesity and related diseases. Understanding miRNA biology can lead to innovative therapies for metabolic disorders. Future research should focus on the specific modulation of miRNAs in various tissues affected by obesity. The development of effective delivery methods for miRNA modulation is crucial for therapeutic applications [4,24]. Future research should focus on larger cohorts to explore molecular pathways and develop miRNA-based therapeutics for obesity and metabolic diseases [19]. Zinc-sensitive miRNAs can serve as biomarkers for monitoring metabolic health and guiding interventions. Circulating miRNAs like miR-10b and miR-155 are repressed during zinc deficiency and activated upon repletion. These miRNAs can indicate early zinc depletion and monitor the efficacy of dietary interventions. Future studies should validate the use of miRNAs as biomarkers for metabolic disorders. Integrating multi-omics approaches will enhance understanding of zinc's role in metabolic health through miRNA regulation. The gut microbiome's influence on zinc absorption and miRNA expression needs further exploration. Future research should focus on tissue-specific zinc-miRNA interactions and their implications for obesity for personalized interventions and the clinical application of zinc-responsive miRNAs. Personalized nutrition strategies should consider individual variations in zinc metabolism and miRNA responses [24]. Zinc-α2-Glycoprotein (ZAG) may serve as a potential biomarker for diagnosing MetS [77].

Omics data have identified potential biomarkers for early obesity risk, including specific DNA methylation signatures, circulating miRNAs, and metabolic fingerprints detectable before overt weight gain. These biomarkers hold promise for early diagnosis and personalized prevention strategies [24,82]. The research of Stratakis et al. (2025) underscores the need for longitudinal studies

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to track the trajectory of multi-omics profiles and their implications for metabolic health. The study acknowledges limitations and suggests areas for future research. Omics measurements were taken concurrently with phenotype assessments, limiting causal inference. The metabolomic platform used had limitations in metabolite coverage, suggesting the need for more comprehensive methods in future studies. Future research should include diverse populations and consider the effects of maternal conditions like diabetes and preeclampsia on offspring health [28].

13.2. Therapeutic and Preventive Implications

Understanding molecular mechanisms opens new avenues for intervention: precision nutrition based on genetic and epigenetic profiles; microbiota-targeted therapies (probiotics, prebiotics); pharmacological modulation of appetite pathways (e.g., MC4R agonists); epigenetic reversibility through lifestyle modification. Importantly, early intervention during childhood may reverse or attenuate adverse molecular programming, emphasizing prevention over treatment [83].

Genetic testing can reveal rare variants contributing to obesity susceptibility, aiding in personalized treatment strategies [4]. The integration of microRNA profiling with dietary interventions shows potential for precision nutrition strategies [24].

MicroRNAs as Therapeutic Targets. Modulating miRNA levels presents a potential therapeutic strategy for obesity and related metabolic disorders. Targeting pro-adipogenic miRNAs could reduce fat deposits and prevent pre-adipocyte differentiation. Caution is needed as this approach may lead to lipid accumulation in other organs. Synthetic nucleic acids can be used to mimic or inhibit specific miRNAs, showing promise in animal models. Anti-miR treatments have demonstrated potential in improving insulin sensitivity and glucose tolerance [4]. Manipulation of lncRNA expression shows promise as a therapeutic approach for metabolic diseases. This could involve enhancing BAT activity or inducing browning in WAT [25].

Understanding *epigenetic mechanisms* may develop new opportunities and methods for obesity treatment and prevention. Epigenetic changes can be influenced by lifestyle factors, including diet, which may help in managing obesity. Identifying individuals with specific methylation profiles could lead to personalized dietary interventions for weight management. The potential for "epigenetic foods" to modulate gene expression through dietary components is an emerging area of research. Diets rich in methyl donors (e.g., folate, choline), physical activity, and reduced exposure to obesogens may favorably modify epigenetic profiles. Microbiome-targeted strategies — including prebiotics, probiotics, and dietary fiber — aim to restore microbial diversity and metabolic signaling, though long-term pediatric data remain limited. Continued exploration of epigenetic mechanisms is essential for developing targeted therapies for obesity and related disorders [4,84].

Preventing childhood obesity requires innovative strategies that address the multifactorial nature of the disease. *Effective interventions* must consider cultural, social, and environmental factors influencing childhood obesity. Family involvement is crucial; strategies should empower families to take control of their health. Screening for mental health issues and eating disorders is essential in obesity treatment. The variability in appetite control among children necessitates targeted interventions to address obesity risk. Health professionals should adopt a comprehensive approach to assess eating behaviors from an early age. Identifying susceptible phenotypes can guide the design of interventions focused on appetite regulation. Children with increased food responsiveness or reduced satiety responsiveness may require intensive interventions. Behavioral strategies are essential for safely addressing appetite control issues, as pharmacological treatments and bariatric surgery carry health risks. Recommendations should include specific food groups, physical activity, sleep, and knowledge-based strategies as part of a comprehensive intervention. Lifestyle precision medicine aims to mitigate childhood obesity by enhancing appetite control in vulnerable children [3].

13.3. Molecular Therapeutic Targets and Pharmacological Approaches

Recent advances in molecular understanding have led to targeted pharmacotherapies for pediatric obesity, particularly in severe or monogenic cases. These therapies act on central and

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peripheral molecular pathways, demonstrating how mechanistic insights translate into clinical interventions.

GLP-1 receptor agonists influence appetite regulation, insulin secretion, and inflammation have been approved for treatment of pediatric obesity [85].

Current therapeutic approaches for syndromic obesity face challenges, but advancements in precision medicine offer new hope. New anti-obesity therapies are being developed based on genetic insights, emphasizing precision medicine. *Genetic-based pharmacological treatments* are emerging as promising options for *syndromic and monogenic obesity.* These therapeutic approaches could be also effective in common *polygenic obesity*. Future therapies may include gene editing, targeted pharmacotherapy, and modulation of gut microbiota [11,14,85].

Setmelanotide is a selective a melanocortin-4 receptor (MC4R) agonist that mimicks the POMC derivative α-MSH. The Food and Drug Administration (FDA) approved the use of setmelanotide for treatment of severe monogenic obesity due to hypothalamic dysfunction (POMC, PCSK1) or leptin receptor deficiency in adults and children aged 6 years and older. Phase II or phase III clinical trials evaluate the efficacy of setmelanotide for other genetic disorders of the MC4R pathway and also for syndromic obesity (Bardet-Biedle syndrome, Alstrom syndrome) and chromosomal rearrangement of the 16p11.2. The adverse events of setmelanotide, such as hyperpigmentation, nausea, vomiting, and injection site reactions were mild [8,11,14,85].

Metreleptin is a recombinant leptin treatment effective for leptin deficiency, with rapid improvement in food-seeking behavior, a decrease of food intake, reduction of fat mass and body weight. It also ameliorates metabolic and endocrine abnormalities, such as hyperinsulinemia, hyperlipidemia, fatty liver, and hypogonadotrophic hypogonadism. The side effects of metreleptin include production of neutralizing antibodies and an increased risk of lymphomas [8,14]. Leptin replacement therapy is effective for LEP deficiency, leading to weight loss and improved metabolic parameters. LEPR deficiency does not respond to leptin treatment due to nonfunctional receptors; alternative treatments are under investigation [4].

Lifestyle modifications, including diet and exercise, can reduce inflammation in obesity and improve metabolic health [13].

Adiponectin, an anti-inflammatory adipocytokine, may have a potential therapeutic role [13].

Targeting the *JAK/STAT pathway* may offer new therapeutic approaches for treating obesity, especially in cases of leptin resistance [5].

MAO inhibitors present therapeutic potential in obesity and its comorbidities, but they need further research. The evidence suggests that targeting MAO can mitigate oxidative stress and improve metabolic health [5].

Other emerging therapeutic agents show promise in managing obesity-related cardiovascular disorders. *Selective beta-3 adrenergic receptor (β3-AR) agonists* have anti-obesity and anti-diabetic effects. *Thiazolidinediones* reduce epicardial adipose tissue and inflammation but may increase heart failure risk. *Dipeptidyl peptidase-4 inhibitors* provide cardioprotection and reduce epicardial fat accumulation. *Sodium-glucose cotransporter-2 (SGLT2) inhibitors* show beneficial effects on cardiovascular morbidity and mortality [5].

Pharmacological modulation of *ion channels* presents potential therapeutic targets for managing diabetes and obesity [5].

Further research on *metabotrophic factors (MTF): neurotrophins* like *nerve growth factor (NGF)* and *brain-derived neurotrophic factor (BDNF), adipomyokines* like *adiponectin* and *irisin* could lead to new therapeutic strategies against obesity and its complications. Therapeutic strategies targeting MTF could improve metabolic health and cognitive functions [5].

Vitamin A levels can influence offspring adipose progenitor cell populations, potentially offering a preventive strategy against obesity [68].

Zinc supplementation. Zinc deficiency is prevalent in 14-30% of individuals with obesity, indicating a potential therapeutic role for zinc supplementation which presents a promising avenue for obesity management and improvement in lipid metabolism, appetite regulation, insulin

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sensitivity and metabolic health. The interaction between zinc and leptin may help mitigate leptin resistance commonly seen in obesity. Zinc supplementation can restore dysregulated miRNAs and improve metabolic health, but requires careful management. Zinc repletion increases levels of miR-10b, miR-155, and miR-145, which are suppressed during deficiency. The effectiveness of zinc supplementation may vary based on dose, duration, and individual genetic factors. Further research is needed to clarify the effects of zinc supplementation in healthy individuals with obesity without deficiency [24,70]. It is important to avoid zinc overload, that can result in adverse reactions and aggravation of metabolic disturbances. Excessive zinc intake is linked to obesity, diabetes, hypertension, and cardiovascular risks through multiple mechanisms. Discrepancies in zinc effects are influenced by baseline nutritional status, genetic factors, and dietary sources. Individualized approaches to zinc supplementation are necessary to avoid excessive intake and its associated risks. Continued exploration of zinc's mechanisms may lead to novel strategies for obesity treatment and prevention [75]. *Zn^{64} Aspartate* is a bioavailable isotopically enriched zinc complex that shows promise in correcting metabolic disturbances associated with obesity [86].

14. Limitations and Gaps in Research

Despite substantial progress, several limitations persist in the study of molecular mechanisms of childhood obesity:

1. *Causality vs association*: Many studies are observational, limiting causal inference.
2. *Tissue accessibility*: Most human pediatric studies rely on blood samples, which may not fully reflect adipose or brain molecular changes.
3. *Population diversity*: Many cohorts lack ethnic and socioeconomic diversity.
4. *Longitudinal data*: Long-term follow-up from infancy to adulthood remains scarce.

Addressing these gaps will be essential for translating molecular insights into effective prevention and treatment strategies.

15. Conclusions

Childhood obesity is not merely the result of excessive caloric intake or insufficient physical activity. It is a biologically embedded condition driven by intricate molecular mechanisms. Childhood obesity is a complex molecular disorder driven by the interaction of genetic susceptibility, epigenetic programming, adipose tissue dysfunction, endocrine disruption, neuroendocrine dysregulation, immune activation, mitochondrial impairment, gut microbiota interactions, and environmental exposures collectively. All these factors shape obesity risk from the earliest stages of life. Understanding these molecular pathways reframes childhood obesity as a preventable, programmable disease, highlighting the urgency of early, mechanistically informed interventions. Advances in molecular biology, systems medicine, and precision health offer unprecedented opportunities to curb the childhood obesity epidemic and its lifelong consequences.

Future research must prioritize longitudinal multi-omics studies, mechanistic validation in pediatric populations, and translation into personalized interventions. Addressing childhood obesity at the molecular level offers the greatest potential for reducing its lifelong health burden.

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