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Recent Advances in Obesity Biology: From Genetics to Transgenerational Effects

Obezite Biyolojisindeki Son Gelişmeler: Genetikten Nesiller Arası Etkilere

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ABSTRACT

Obesity, which is a global problem regarded as a complex disorder, is influenced by environmental, genetic, and epigenetic factors. Genetic discoveries, epigenetic alterations, nutritional roles, hormonal effects, inflammation, and the precise problem of middle-aged abdominal fat development are prominent factors. This article provides a summary of current theories related to the biology of obesity. The distinct role of neuroestrogens in the development of obesity has also been described. This review also explores how maternal obesity affects the development of the fetal liver and subsequent childhood obesity, emphasizing the long-term metabolic effects of maternal overnutrition. The article also underlines the latest data concerning adolescent obesity and its influence on the subsequent development of obesity in offspring and the impact of paternal obesity, not only maternal obesity, on offspring. New prospects for clinical study and medication development are illustrated by the newly identified role of neuroestrogens in appetite regulation and energy balance. In addition, creating efficient management and prevention measures for obesity requires an understanding of the mechanisms that cause increases in abdominal fat in middle-aged individuals, such as hormonal changes, metabolic alterations, and lifestyle factors. A conceptual shift from late-stage obesity care to early, preventive, and personalized interventions is supported by the clinical application of mechanistic insights from developmental biology, genetics, and epigenetics.

Keywords: Adipose progenitors, neuroestrogen, epigenetics, FGF19, CP-As

ÖZ

Karmaşık bir bozukluk olarak kabul edilen küresel bir sorun olan obezite, çevresel, genetik ve epigenetik faktörlerden etkilenir. Genetik keşifler, epigenetik değişiklikler, beslenme rolleri, hormonal etkiler, inflamasyon ve orta yaşta karın bölgesinde yağlanmanın kesin sorunu öne çıkan faktörlerdir. Bu makale, obezitenin biyolojisiyle ilgili güncel teorilerin bir özetini sunmaktadır. Nöroöstrojenlerin obezite gelişimindeki belirgin rolü de açıklanmıştır. Bu derleme ayrıca, anne obezitesinin fetal karaciğer gelişimini ve daha sonraki çocukluk çağı obezitesini nasıl etkilediğini, anne aşırı beslenmesinin uzun vadeli metabolik etkilerini vurgulayarak incelemektedir. Makale ayrıca, ergenlik obezitesi ve bunun yavruda obezite gelişimine etkisi ile ilgili en son verilerin ve sadece anne obezitesinin değil, baba obezitesinin de yavru üzerindeki etkisinin altını çizmektedir. Nöroöstrojenlerin iştah düzenlemesi ve enerji dengesindeki yeni tanımlanmış rolü, klinik çalışma ve ilaç geliştirme için yeni perspektifler göstermektedir. Ayrıca, obezite için etkili yönetim ve önleme tedbirleri oluşturmak, orta yaşlı bireylerde karın bölgesindeki yağ artışına neden olan mekanizmaları (hormonal değişiklikler, metabolik değişimler ve yaşam tarzı faktörleri gibi) anlamayı gerektirir. Gelişim biyolojisi, genetik ve epigenetikten elde edilen mekanistik bilgilerin klinik uygulaması, obezite bakımında geç aşamadan erken, önleyici ve kişiselleştirilmiş müdahalelere doğru kavramsal bir geçişi desteklemektedir.

Anahtar Sözcükler: Yağ dokusu öncü hücreleri, nöroöstrojen, epigenetik, FGF19, CP-As

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INTRODUCTION

Obesity is a global health concern that increases the risk of type 2 diabetes, heart disease, and several types of cancer, and is associated with other metabolic health concerns (1). The genetic and epigenetic basis of obesity, as well as the role of nutrition and lifestyle in its development and treatment, has been clarified by recent advances in obesity biology (2). This article discusses recent research on the various pathways involved in obesity and highlights important subjects linked to adolescent and maternal obesity.

Genetic Insights into Obesity

Recent genetic studies have identified many loci linked to obesity, offering insights into its genetic architecture. More than 97 loci associated with body mass index (BMI) were identified in a study by Locke et al. (3), who demonstrated the polygenic nature of obesity. These genetic correlations suggest the molecular processes underlying adipogenesis and energy homeostasis. For example, variations in the *FTO* gene affect caloric intake and expenditure, and this gene has been repeatedly associated with obesity (4). However, according to a recent study by Künzel et al. (5), morbid obesity is not linked to genes, whereas only milder forms of obesity are. Lonky's (6) explanation of the heredity of obesity, which is nearly entirely epigenetic, represents an insightful contribution. Therefore, how genes are turned on or off in response to environmental factors such as pollutants, diet, sleep, and prenatal exposure than the DNA sequence does (6).

Epigenetic Modifications and Obesity

Environmental influences can affect epigenetic alterations, including DNA methylation and histone modifications, which are important in controlling gene expression (7). Macartney-Coxson et al. (8)'s genome-wide DNA methylation analysis revealed that people with obesity have distinct methylation patterns across adipose tissue types. These epigenetic modifications may affect metabolic processes and adipogenesis, potentially leading to obesity. Moreover, famine exposure during pregnancy leads to long-lasting epigenetic alterations associated with metabolic diseases (8).

The Role of Diet in Obesity and Metabolic Health

Obesity and metabolic health are influenced by the type of diet. A balanced diet is essential for preserving metabolic health, a conclusion consistent with a recent analysis by Wali et al. (9) that explored the effects of macronutrients on obesity and IR. In animal models, high-carb diets have been shown to cause obesity and alter genes linked to inflammation and eating habits. A holistic approach to dietary studies that considers the interconnections between macronutrients may provide more thorough insights into obesity, according to the geometric context for nutrition.

Hormonal Effects and Obesity

The development of obesity is considerably affected by hormonal regulation, with new research highlighting the significance of brain estrogen (neuroestrogen) in energy balance and appetite control.

Brain Oestrogen (Neuroestrogen) and Obesity

A new role of neuroestrogen, a form of estrogen produced in the brain, in regulating hunger and body weight. According to a study by Hayashi et al. (10), neurogenesis increases the expression of the hypothalamic melanocortin-4 receptor *(MC4R)*, a crucial receptor implicated in appetite regulation. Compared with healthy control mice, mice lacking ovaries or the aromatase enzyme, which is required for the generation of neuroestrogen, presented greater food intake and body weight. However, *MC4R* expression increased, and food intake decreased when the aromatase gene was specifically reactivated in the brains of these mice (Figure 1). This finding makes neuroestrogen a viable target for the development of novel therapies for obesity (10).

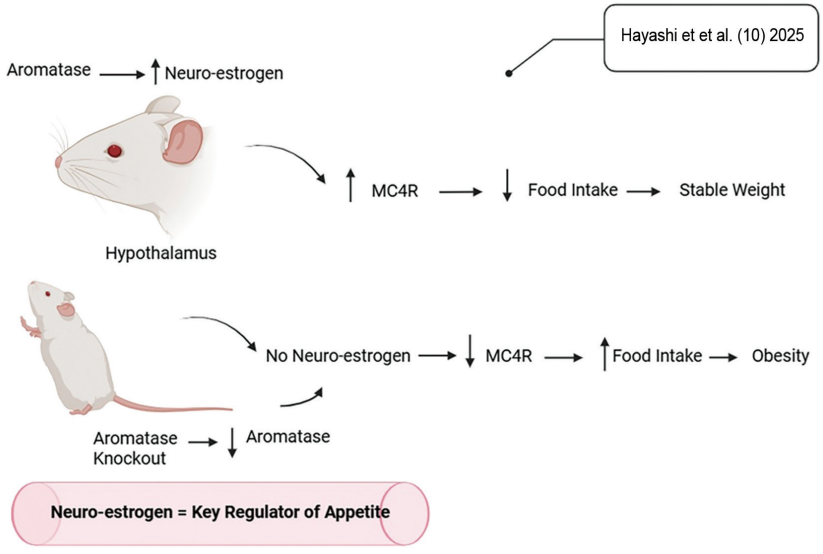

Figure 1. Role of neuroestrogen in regulating appetite and body weight.

MC4R: Melanocortin-4 receptor.

Hormones have been shown to speed up fat burning and aid in weight loss in obese rats. In an experiment, the intestinal production of fibroblast growth factor 19, or FGF19, affects brain regions, causing increased energy expenditure for heat production. This finding opens the door to novel medications. In obese animals, FGF19 activates pathways that increase energy expenditure, promote fatty acid oxidation, and support regulation of blood glucose and body weight. These outcomes are linked to the activity of FGF19 in the hypothalamus, a specific brain region that integrates ambient and peripheral cues to regulate energy metabolism. The authors reported that increased thermogenic adipocyte activity, i.e., the activity of fat cells that burn energy to produce heat, results from FGF19 signalling in the hypothalamus (Figure 2) (11).

Hypoxia and Inflammation in Obesity

A key factor in the pathophysiology of obesity-related insulin resistance (IR) is the interaction among hypoxia, inflammation, and metabolic dysregulation. Adipose tissue, especially visceral adipose tissue, secretes a variety of bioactive compounds that affect systemic metabolic processes, making it an active endocrine organ (12). Hypoxia is a common feature of expanding adipose tissue in obesity, initiating a series of molecular processes that exacerbate IR and inflammation. One important factor in these processes is hypoxia-induced dysregulation of miRNAs and adipokines. Proinflammatory cytokines and adipokines, including vascular endothelial growth factor, adiponectin, and leptin, are responsible for the metabolic dysregulation and inflammatory environment observed in obese individuals. Furthermore, miRNAs alter gene expression, impacting inflammatory and insulin receptor signalling pathways. Although our understanding of these systems has advanced considerably, many unresolved questions remain. Determining the sequence of the molecular events that trigger IR, the primary contributing variables, and the interactions among various signalling pathways remains necessary (13). Thus, hypoxia, or low oxygen levels in adipose tissue, may inhibit weight loss and cause inflammation (6).

Why Does Belly Fat Expand in Middle Age?

Fat accumulation in middle-aged individuals is common and is influenced by several factors, including lifestyle choices, hormonal changes, and metabolic adaptations (14).

Hormonal Changes

Decreasing Estrogen Levels: One of the main reasons for increased abdominal fat in women is the decline in estrogen levels after menopause. The distribution and storage of fat are considerably affected by estrogen; when estrogen levels decline, fat is redistributed from the hips and thighs to the belly (15).

Stress and Cortisol: Cortisol, the stress hormone, promotes the accumulation of abdominal fat. Increased visceral fat storage can result from elevated cortisol levels, which are commonly produced in response to chronic stress. A lack of sleep contributes to this worsening by altering the balance of appetite-regulating hormones, such as ghrelin and leptin (16).

Metabolic Shifts

Slowing Metabolism: People's metabolism slows with age, making it more difficult to burn calories effectively. This metabolic slowdown, associated with a natural decrease in muscle mass, contributes to increased fat storage, particularly in the abdominal area (17).

Cellular Alterations: Recent studies indicate that age-related cellular alterations can increase adipogenesis. As people age, adipocyte progenitor cells in adipose tissue become more active, promoting adipogenesis and increasing abdominal adiposity. Age-enriched

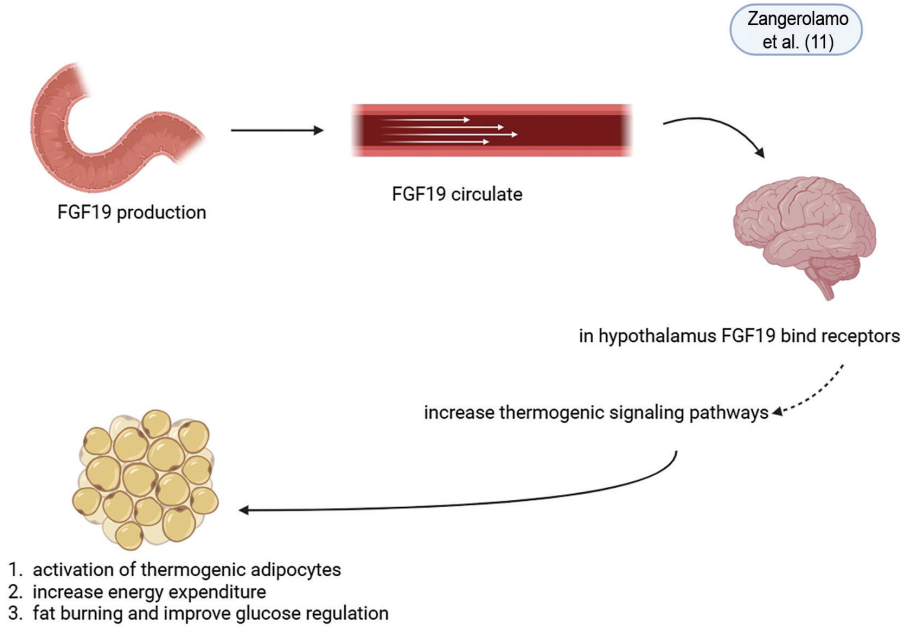

Figure 2. FGF19 promotes fat burning and weight loss via the hypothalamic action.

FGF19: Fibroblast growth factor 19.

committed preadipocytes (CP-As) constitute a novel population of fat-cell precursors that arise particularly during middle age and contribute to the rapid accumulation of visceral fat, according to a study published in science (18).

Emergence of CP-As: These special progenitor cells are almost non-existent in children, but become prevalent in middle-aged adults, particularly in individuals with excess abdominal fat. The activation of CP-As to generate new fat cells depends on the leukemia inhibitory factor receptor (LIFR) pathway. Visceral fat growth in mice was inhibited by blocking this route (19). Similarly, human tissue samples demonstrated the presence and activity of CP-As, indicating a comparable process. This study advances our understanding of age-related fat accumulation, moving beyond lifestyle influences to encompass specific cellular changes. There may be novel ways to treat or prevent visceral obesity and related health concerns by targeting CP-As or the LIFR pathway (Figure 3) (18).

Lifestyle Factors

Diet and Exercise: High-calorie diets and sedentary lifestyles are major contributors to weight gain in middle-aged individuals. A balanced diet rich in fruits, vegetables, and lean meats, combined with regular exercise, can help counteract this effect (20).

Stress and Sleep Management: Hormonal balance can be disrupted by excessive stress and inadequate sleep, resulting in increased appetite and cravings for high-calorie foods. Abdominal fat can be reduced through relaxation techniques to manage stress and by ensuring adequate sleep (21).

Maternal Obesity and Its Effects on the Fetal Liver and Future Child Obesity

In addition to increasing the risk of obesity and metabolic diseases in progeny, maternal obesity and overnutrition during pregnancy can have major long-term effects on fetal liver development.

Fetal Metabolic Disorders Associated with Maternal Obesity

Maternal diet may have a persistent impact on fetal gene expression through epigenetic mechanisms that lead to metabolic disorders. Because of transgenerational inheritance, epigenetic changes that occur during crucial stages of fetal development may have long-term effects. Determining the relationship between epigenetic changes and clinical and molecular outcomes in children associated with maternal obesity is crucial (22).

Maternal Obesity, High-Fat Diet, and Inflammation

Hyperlipidemia, systemic IR, and inflammation of adipose tissue are linked to maternal obesity. Proinflammatory cytokines can be activated during pregnancy by high-fat diets (HFDs) (FFTs) (23). Maternal IR and inflammation cause increased adipose tissue lipolysis and uptake of free fatty acids (FFAs). Maternal during pregnancy HFD significantly increased fetal FFA levels. Early-life obesity is exacerbated by both maternal IR and HFD (24).

Systemic inflammation, which includes elevated levels of tumor necrosis factor-alpha and monocyte chemoattractant protein-1, is positively associated with maternal BMI. An HFD has been shown to increase placental production of proinflammatory cytokines. Toll-like receptor 4 activation via FFAs may trigger the c-Jun N-terminal kinase and nuclear factor kappa B inflammatory signalling pathways in obese animals. Maternal HFDs result in IR through inflammatory alterations in fetal adipose tissue (25).

Epigenetic Mechanisms: Fetal metabolic disorders associated with maternal obesity.

An HFD during pregnancy caused the fetal liver to exhibit hyperacetylation of histones H3K14, H3K9, and H3K18, increased *DNMT1* expression, decreased *HDAC1* expression, and elevated hepatic triglyceride levels. Recent research indicates that maternal HFD induces metabolic programming of the fetal liver and heart

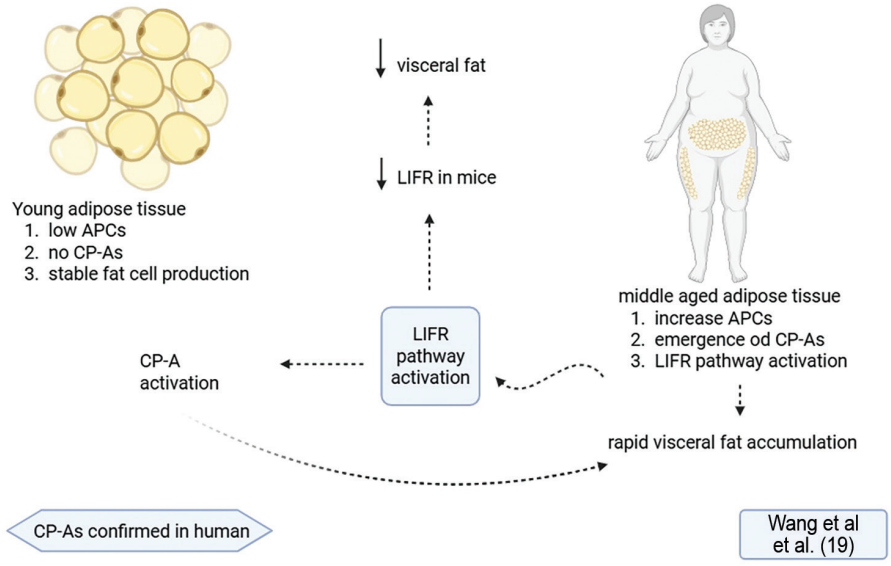

Figure 3. Age-related cellular changes promote visceral fat accumulation via CP-As.

CP-As: Committed preadipocytes, LIFR: Leukemia inhibitory factor receptor, APCs: Adipocytes precursor cells.

by decreasing *SIRT1* expression and increasing histone H3K14 acetylation (26).

Kupffer Cell Programming by Maternal Obesity

According to a recent study, maternal obesity causes HIF1α-dependent metabolic reprogramming of yolk sac-derived Kupffer cells (KCs) that persists into adulthood and leads to fatty liver disease (FLD). Using multiomic profiling together with fate mapping, depletion, and conditional knockout models, researchers discovered that KCs act as intergenerational messengers converting maternal dietary signals into chronic liver dysfunction (27).

The inflammatory response of KCs induced by maternal obesity alters their metabolic state at the transcriptional level. Through paracrine signalling, this reprogramming causes FLD and reduces the metabolic potential of progeny KCs (28).

A novel pathway linking maternal obesity to metabolic disease in offspring, independent of postnatal lifestyle, has recently been described in Nature. During pregnancy, fetal KCs undergo epigenetic reprogramming (27).

Cellular metabolism changes from oxidative phosphorylation to glycolysis as a result of oxidative phosphorylation to glycolysis (27).

Even in the absence of a "bad" diet, metabolic changes cause KCs to encourage fat buildup and inflammation in the livern. The immune system of the liver retains memories of early encounters. In addition to affecting delivery outcomes, maternal obesity leaves biological imprints that may lead to chronic illness. Because more than 25% of American adults suffer from NAFLD, this study highlights that immediate maternal health measures are essential. Diagnosis is not the first step in prevention. It begins prior to birth (28).

Impact on Fetal Liver Development

Significant alterations in the fetal liver, such as elevated lipid accumulation and oxidative stress, can result from maternal obesity and an HFD. Maternal HFD/obesity was associated with increased expression of lipid metabolism-related genes in the fetal liver, including ACC isoform 1 and LPL. Furthermore, the development of fatty liver is linked to elevated indicators of oxidative stress and decreased levels of antioxidant enzymes in the fetal liver (29,30).

Long-Term Consequences for Offspring

Offspring exposed to FFTs and maternal obesity during pregnancy experience long-term metabolic effects, such as a greater chance of becoming obese, developing IR, and suffering from FLD than adults do. The significance of maternal nutrition during pregnancy for long-term health consequences is highlighted by the fact that these effects are mediated by metabolic reprogramming of hepatic cells and epigenetic alterations (24). The following actions must be taken:

• Healthcare executives should incorporate weight management and prenatal nutrition into standard care as lifestyle and disease-prevention measures.

• Employers and insurers can fund maternal wellness initiatives that lower the risk of chronic diseases in the next generation and yield long-term returns on investment.

• Public health groups should expand campaigns that demonstrate how prenatal exposures affect our children's health well into adulthood.

• Researchers and clinicians need to look for biomarkers to identify KC dysregulation before symptoms appear.

• The prevention of liver disease may begin in the womb.

Effect of Teenage Obesity on Child's DNA

In a recent epigenome-wide association study published in Nature Communications Biology, 739 participants were tracked across two generations. This study examined the relationships between adolescent body-shape changes, especially during voice breaks, and DNA methylation patterns in offspring, focusing on 339 father-child pairs (31).

Fathers who gained additional weight throughout puberty exhibited the most pronounced effects. More than 2,000 methylation differences—chemical indicators that control gene activity—were detected in their offspring. Many of these variations (31) are located in genes involved in inflammation, lung function, and fat metabolism.

Methylation alterations were detected in imprinted genes, such as *VTRNA21* and *BLCAP*, which are sensitive to environmental influences, and in genes important for metabolic regulation, such as *KCNJ10*, *NCK2*, and *ATP5B*. These alterations are particularly evident in daughters, who exhibit sex-specific patterns of inheritance (32).

The timing of puberty is crucial. The biological effects that occur during this brief embryonic stage could last into subsequent generations.

This, together with maternal programming highlights that the health of both parents during critical periods—puberty and pregnancy—contributes to the transgenerational inheritance of obesity risk.

Epigenetic mechanisms alter gene expression without changing the DNA sequence. Not only are we transferring genes, but we are also transferring their behavior.

Adolescent obesity is a chronic issue. This may leave the following generation with epigenetic fingerprints.

Human Research Equivalent to Animal Research

Many studies in humans have taken into account findings from experimental animal research regarding various topics related to the biology of obesity. One of these findings was explained by Heijmans et al. (33), who reported that adults exposed to famine in utero exhibited persistent DNA methylation in *IGF2* and other metabolism-related genes for more than 60 years. Jaddoe et al. (34) emphasized that maternal BMI prior to pregnancy was associated with offspring's fat mass and the development of cardiometabolic problems at 6–10 years of age. Another study by Sharp et al. (35) found DNA methylation in children of obese mothers. Conversely, Soubry et al. (36) reported altered DNA methylation at the *IGF2* and *MEG3* genes in the offspring of obese fathers. Other researchers, such as Berenson et al. (38), have previously linked childhood obesity to adolescent and adult obesity, and to the development of metabolic syndrome and cardiovascular disease through their lifelong cohort studies (37).

Clinical Implications

The increasing number of studies linking developmental programming, genetics, and epigenetics to obesity is of substantial clinical significance. First, polygenic risk scores and newly discovered

epigenetic biomarkers enable early risk stratification and may permit prenatal diagnosis of high-risk offspring. Integrating these tools into clinical practice could guide personalized counselling and prompt treatments.

Improving maternal health before and during pregnancy is the second important objective. Preconception weight control, dietary support, and reduction of inflammation may reduce the risk of intergenerational transmission of obesity. Furthermore, human data from cohorts of women who underwent bariatric surgery indicate that enhanced maternal metabolism before conception could substantially influence offspring health. Importantly, current research suggests that paternal obesity and pubertal weight status might affect sperm epigenetics and consequent adverse child health outcomes, indicating that fathers' health should not be neglected.

Third, this is more likely to occur during puberty and adolescence. By intervening early, we can reduce the effects of obesity in future generations and prevent its progression into adulthood. This highlights the need to clinically assess pubertal development in obese children and to implement adolescent-centered public health programs.

Finally, new findings in hormones and neuroendocrine systems, such as leptin, ghrelin, neuroestrogen, and FGF19, are ushering in a new era of pharmacological treatments. Future therapies might combine these substances with dietary and lifestyle strategies based on each patient's unique hormonal and epigenetic characteristics. Concurrently, public health frameworks ought to adopt family-centered, multigenerational approaches more consistently, recognizing obesity as a disorder that affects people of all ages and has long-term consequences.

In decision-making, a paradigm shift from late-stage obesity care to early, preventive, and personalized interventions is strengthened by the clinical application of mechanistic information from developmental biology, genetics, and epigenetics.

CONCLUSION

Our knowledge of the genetic, epigenetic, nutritional, and hormonal organization underlying obesity has increased owing to recent developments in the biology of this condition. Numerous loci linked to obesity have been identified through genetic studies, whereas epigenetic studies have focused on the impact of environmental factors on gene expression. A balanced and broad approach to nutrition affects obesity and metabolic health. The newly identified role of neuroestrogens in appetite regulation and energy balance offers new opportunities for clinical studies and drug development. In addition, developing effective prevention and management strategies for obesity requires an understanding of the mechanisms that promote fat accumulation in middle-aged individuals, such as hormonal changes, metabolic alterations, and lifestyle factors. Additionally, the long-term metabolic effects of maternal overnutrition are underscored by the influence of maternal obesity on fetal liver development and on subsequent childhood obesity. Obesity in teenagers may increase the risk of obesity in their offspring and influence their DNA. These complex relationships should be investigated in future studies to develop more effective obesity management and prevention strategies. Future research should emphasize integrating multi-omics data with longitudinal cohort studies to inform the development of targeted preventive guidelines across the lifespan.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.I.N., Concept: K.I.N., S.S.A., N.H.K., Design: K.I.N., Data Collection or Processing: K.I.N., Analysis or Interpretation: K.I.N., S.S.A., Literature Search: K.I.N., N.H.K., Writing: K.I.N.

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