REVIEW ARTICLES

Exploring the Intricate Interplay of Epigenetic Mechanisms in the Pathophysiology of Obesity: an Overview

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ABSTRACT

Epigenetics, a multifaceted and intricate scientific domain, plays a substantial role in the aetiology of non-communicable diseases, particularly obesity. Its unique capacity to regulate gene expression and cellular processes endows it with remarkable power and potential to mitigate and investigate this global scourge. In this review, the three most widely recognised and complex epigenetic mechanisms implicated in the pathophysiology of obesity - DNA methylation, histone modifications, and non-coding RNAs, and their multifarious and complex interplay with obesity are explored. The review highlights the potential of epigenetic interventions, particularly lifestyle modifications, in managing and ameliorating obesity and related disorders and their reversibility. These interventions present a promising target for designing and developing effective and sustainable strategies to alleviate the enormous burden of obesity worldwide. The crucial insights provided by this review are indispensable for informing and shaping public health policies and interventions that aim to combat and mitigate the insidious and pernicious impact of obesity on individuals and societies.
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INTRODUCTION

Obesity is distinguished by a singular and atypical deposition of adipose tissue, which incites maleficent and intimidating health consequences such as metabolic syndrome, Type 2 Diabetes Mellitus, and cardiovascular diseases. The budding pervasiveness of this condition on a global magnitude makes it an intimidating and exigent public health quandary that necessitates expeditious attention and intervention (1,2). Although the incontrovertible implication of genetic elements in the inception of obesity is acknowledged, the pivotal role of epigenetic modifications in regulating gene expression and influencing the pathophysiology of this malaise is gaining increasing recognition from the scientific community (3).

The intricate pathophysiology of obesity involves the interplay of environmental components, lifestyle, and gene expressions. Moreover, the gene expression modifications are thought to be accompanied by epigenetic changes that associate epigenetics with obesity (Fig. 1). The current widespread adoption

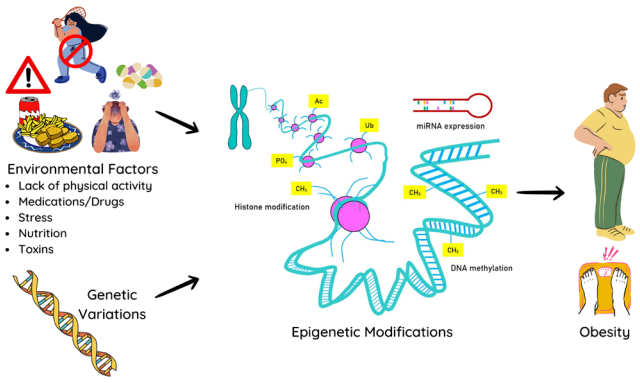

Fig. 1 : The interplay between genetic variants, environmental factors and epigenetic modifications in the development of obesity.

of a sedentary lifestyle alongside the consumption of calorie-dense foods is typically viewed as the primary driver of the obesity epidemic. Nevertheless, genetic predisposition also significantly influences the disrupted energy metabolism that characterises obesity. Therefore, the complex interaction between epigenetics and obesity has aroused great curiosity and controversy among researchers, and the ongoing investigations are divulging the mechanisms that undergird this health problem.

The endlessly captivating and impressive realm of epigenetics focuses on the complex and tangled

modifications that hold the potential to influence gene expression without impacting the deoxyribonucleic acid (DNA) sequence. The field of epigenetics and its association with obesity has been the subject of extensive research. Numerous studies have explored various aspects of this topic, shedding light on the epigenetic mechanisms in the pathophysiology of obesity, including DNA methylation, histone modifications, and non-coding ribonucleic acids (RNAs). These delicate mechanisms can intricately change gene expression, meticulously regulating the structure of chromatin and its accessibility to transcription factors, thereby inciting a web of perplexing and bewildering pathways (2,3).

Epigenetic changes, with their magnificent complexity and inexplicable pathways, have been found to be instrumental in altering gene expression, thereby acting as a stepping stone to the development of obesity through complex mechanisms, such as alterations in lipid metabolism, glucose homeostasis, and a predisposition to inflammation, to mention a few (4,5). The multidimensional nature of this expanding field of research has given us a deep and unmatched understanding of the intricacies involved in obesity, unveiling numerous new possibilities for preventive or therapeutic strategies that are not restricted or limited by conventional approaches. Diet and physical activity have been observed to have a notable impact on epigenetic modifications in obese individuals, highlighting their potential significance as environmental factors. Investigating epigenetics in the pathogenesis of obesity holds significant promise for providing a deeper comprehension of the underlying mechanisms and innovative targets for therapeutic interventions.

Obesity is a public health problem that is increasing in prevalence worldwide. However, despite the growing body of research on the association between epigenetics and obesity, there is a lack of a comprehensive review that synthesises and critically evaluates the available evidence. This gap hinders the holistic understanding of the field and the identification of research gaps, thereby impeding the development of effective preventive and therapeutic strategies for obesity. Therefore, the primary problem addressed by this review is further exploration of this topic, which can help us understand how these epigenetic modifications contribute to the disordered energy metabolism in obesity and to what degree lifestyle and weight reduction strategies can restore energy balance by restoring normal epigenetic profiles. This review will contribute to the existing body of knowledge by offering an unbiased assessment of the current state of research, thereby guiding future research directions and facilitating evidence-based decision-making in the field of epigenetics and obesity. Moreover, this field is less explored in Malaysia.

Overall, the review aims to provide an overview of the current state of research on epigenetics and obesity from around the world, with a focus on identifying gaps in knowledge and opportunities for future research and practice. This review could contribute to informing public health policies and interventions targeting the reduction of the obesity burden, especially among the Malaysian population, by shedding light on the potential of epigenetic interventions in preventing or treating obesity.

EPIGENETIC MECHANISMS INVOLVED IN OBESITY

The development and progression of obesity are strongly influenced by epigenetic modifications, which have been the focus of several investigations. These investigations have explored various epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, to understand their role in obesity (6).

DNA methylation

Epigenetic mechanisms, specifically DNA methylation, have been extensively investigated regarding obesity. DNA methylation includes adding a methyl group to cytosine residues in the DNA molecule, leading to the suppression of gene expression (7). Hypermethylation is an epigenetic modification that occurs when DNA is methylated at a higher-than-normal level (8). DNA methylation is a natural process that helps regulate gene expression, but abnormally high methylation levels can silence genes. This condition can lead to a variety of health problems, including obesity. Multiple studies have established the association between DNA methylation and traits related to obesity.

Recent surveys have recognised various epigenetically regulated genes, such as Peroxisome Proliferator-Activated Receptor Gamma (*PPARγ*), an essential factor in lipid metabolism and adipogenesis (8,9). Adipogenesis is the process by which cells called preadipocytes differentiate into adipocytes or fat cells. Adipocytes are responsible for storing energy as fat and releasing it as needed. DNA methylation in genes that promote adipogenesis has been identified in preadipocytes from obese individuals. In the context of obesity, *PPARγ*, a nuclear receptor, experiences deregulation, as shown by low levels in obese patients (9). Therefore, hypermethylation is associated with decreased *PPARγ* expression and altered lipid metabolism. The research on the role of epigenetic changes in adipogenesis is still in its early stages. However, it is clear that epigenetic changes play a role in this process. Further research is needed to understand the specific epigenetic changes that are involved in adipogenesis and how these changes can be targeted for therapeutic purposes.

Adiponectin (*ADIPOQ*), another gene that regulates

glucose and lipid metabolism, is implicated in the epigenetic regulation of obesity. In the placenta of mothers with obesity, a downregulation of the *ADIPOQ* gene was observed, along with linked epigenetic changes (10). Lower levels of adiponectin production can contribute to obesity by increasing appetite and decreasing energy expenditure. DNA methylation of the *ADIPOQ* gene is thought to be a contributing factor to obesity, and it may be a potential target for future therapies for this disease. These findings highlight the molecular mechanisms involved in the placental adaptation to a harmful maternal environment. Consequently, maternal obesity may negatively impact placental function, potentially increasing the risk of metabolic syndrome in adulthood. The study provides insight into the molecular mechanisms underlying the placental adaptive response to maternal obesity, facilitating the development of interventions to prevent or mitigate the harmful effects of maternal obesity on foetal development.

Furthermore, current research has demonstrated a noteworthy link between aberrant DNA methylation patterns and the emergence of obesity and related metabolic illnesses. CpG sites are stretches of DNA that are rich in cytosine and guanine, two of the four bases that make up DNA (7). CpG sites and genes have been designated as likely targets for epigenetic alterations that result in obesity, with gender-specific effects on CpG sites associated with pre-pregnancy obesity observed in both male and female descendants (11). Specifically in the study, the TAP Binding Protein (*TAPBP*) gene has been recognised as a potential target for such alterations. Additionally, decreased methylation at the cg21178254 site that is upstream of Cyclin L1 (*CCNL1*) contributes to obesity by heightening the expression of this gene (12). DNA methylation could potentially influence the expression of the *TAPBP* gene in the context of obesity-associated inflammation or immune dysregulation. However, further research is needed to establish specific connections between *TAPBP* gene methylation, immune responses, and obesity and to develop potential therapeutic strategies targeting this epigenetic modification.

Pre-pregnancy Body Mass Index (BMI) has also been extensively related to DNA methylation at three CpG sites of BMI-associated genes in the placenta, which are involved in metabolism and appetite regulation (13). The genes are Fatty Acid Synthase (*FASN*), Hypoxia Inducible Factor 3 Subunit Alpha (*HIF3A*) and Phosphoglycerate Dehydrogenase (*PHGDH*). *FASN* is a gene that encodes an enzyme that is involved in the synthesis of fatty acids, which are a major component of body fat (13). When *FASN* is methylated, this can lead to increased fat synthesis and accumulation in the body, contributing to obesity. Meanwhile, *HIF3A* is a gene that encodes a transcription factor involved in regulating metabolism and the response to hypoxia, also known as low oxygen levels (13). When *HIF3A* is methylated, this can lead to changes in metabolism that favour the storage of fat and the development of obesity. As for *PHGDH*, this is a gene that encodes an enzyme that is involved in the glycolysis pathway, which is a series of reactions that break down glucose into energy (13). A methylated *PHGDH* can lead to decreased glucose metabolism and increased fat accumulation, contributing to obesity.

Furthermore, the DNA methylation level at the promoter region of the leptin gene was negatively related to weight in obese subjects, proposing that the leptin epigenetic profile could have a notable association with obesity and its related metabolic risk factors (14). In short, these findings provide critical insights into the underlying mechanisms by which DNA methylation at CpG sites may be a contributing factor to obesity in both children and adults. Maternal obesity before or during pregnancy may impact foetal growth and heighten the risk of obesity throughout life.

Conversely, a study discovered that the measurement of BMI was more liable to cause changes in DNA methylation instead of being the effect, and it contributes to identifying DNA methylation locations linked with obesity among Asian demographics (15). The research employed epigenome-wide association study (EWAS) data on BMI in multi-racial individuals of Asian origin. Then, a causal relationship analysis was used to assess the temporal relationship between BMI and DNA methylation. The study also suggests that BMI-associated methylation might play a role in inflammatory and lipoprotein-related biological pathways. However, it is important to note that this is an observational study, and further research is needed to confirm these findings. The consequences of this research might also support the formulation of individualised remedies for illnesses correlated with obesity within Asian populations, encompassing Malaysians.

Histone modifications

Histones are proteins that wrap around DNA and help to organise it into chromosomes (16). Histone modifications play a crucial function in the epigenetic regulation of gene expression through the chemical addition or removal of groups to the histone proteins that structure the chromatin of DNA. The modification of histone can influence DNA accessibility to transcription factors, resulting in genetic expression modifications. There are four main types of histone modifications: acetylation, methylation, phosphorylation, and ubiquitination (16). Histone acetylation is a process by which acetyl groups are added to histone proteins. Acetylation loosens the structure of chromatin, making it easier for genes to

be expressed. Meanwhile, histone methylation is a process by which methyl groups are added to histone proteins. Methylation can either activate or silence genes, depending on the location of the methyl group. Next, histone phosphorylation is a process by which phosphate groups are added to histone proteins. Phosphorylation can also activate or silence genes, depending on the location of the phosphate group. Histone ubiquitination is a process by which ubiquitin molecules are added to histone proteins. Ubiquitination can lead to the degradation of histone proteins and the silencing of genes.

A growing corpus of literature explores histone modifications concerning obesity. Histone changes, like acetylation and methylation, have also been implicated in regulating adipocyte metabolism and differentiation (17). Adipocytes are derived from preadipocytes, which are immature cells that can differentiate into adipocytes. The process of adipocyte differentiation is complex and involves several genes and proteins. Histone acetylation promotes adipocyte differentiation, while histone methylation inhibits adipocyte differentiation. The changes in histone modifications can then lead to changes in gene expression, which can affect the function of adipocytes and contribute to obesity. People with obesity have lower levels of histone acetylation in genes involved in metabolism and appetite regulation differentiation (17). Therefore, this could lead to decreased expression of these genes and contribute to obesity. On the contrary, people with obesity have higher histone methylation levels in genes involved in metabolism and appetite regulation differentiation (17), leading to increased expression of these genes and contributing to obesity.

A study has detected differentially expressed genes in adipose tissue of non-obese, obese with low insulin resistance, and obese with high insulin resistance, which could be controlled by the differentially enhanced H3K4me3 (18). H3K4me3 is a histone modification that is associated with gene activation. It promotes adipocyte differentiation and increase gene expression in fat storage. In contrast, histone H3K4me3 reduces gene expression in fat burning. People with obesity have higher levels of histone H3K4me3 in adipocytes (18); hence, suggesting that histone H3K4me3 may play a role in the development of obesity.

Moreover, H3K4me3 is also involved in insulin resistance, a condition in which cells do not respond normally to insulin. Insulin is a hormone that helps cells to absorb glucose from the blood. People with obesity have higher levels of histone H3K4me3 in adipocytes (18). This condition suggests that histone H3K4me3 may play a role in the development of insulin resistance. The changes in histone H3K4me3 levels can then lead to changes in gene expression, which can affect the function of adipocytes and contribute to obesity and insulin resistance. These findings illuminate the functioning of adipose tissue in obesity and insulin resistance.

Likewise, another group of researchers has discovered that an H3K4me3 increase in the promoter region of specific genes linked to lipid metabolism, adipogenesis, and inflammation is directly correlated with an increase in BMI and metabolic decline (19). Regarding adipogenesis, H3K4me3 promotes adipocyte differentiation by increasing the expression of genes involved in adipogenesis, thus leading to increased fat storage and an increase in BMI. Besides, H3K4me3 inhibits lipid metabolism by decreasing gene expression in lipid breakdown. This condition can lead to increased lipid accumulation and metabolic decline. Furthermore, H3K4me3 promotes inflammation by increasing the expression of genes involved in inflammation. This condition can also lead to metabolic reduction.

In addition, the same group of researchers have also shown that people with obesity have higher levels of H3K4me in the promoter region of the E2F Transcription Factor 1 (*E2F1*) and Lipoprotein Lipase (*LPL*) genes (19). The *E2F1* gene is involved in regulating a number of genes, including genes involved in fat metabolism and adipocyte differentiation. H3K4me can promote adipocyte differentiation by increasing the expression of genes involved in this process. When there are more adipocytes, there is more space for fat to be stored. This condition can lead to increased fat storage and an increase in BMI. Meanwhile, the *LPL* gene is involved in breaking triglycerides into fatty acids and glycerol. The fatty acids can then be used for energy or stored in fat cells. When the *LPL* gene is expressed, more *LPL* enzyme is produced. This condition can lead to an increased breakdown of triglycerides and decreased body fat, followed by weight loss and BMI decrease.

The research on the role of histone modifications in obesity is still in its early stages. However, the evidence presented here suggests that histone modifications may be a contributing factor to obesity, and it may be a potential target for effective therapeutic strategies for this disease.

Non-coding RNAs (ncRNAs)

Non-coding RNA (ncRNA) molecules are a variety RNA molecules that perform an essential role in regulating gene expression but do not encode proteins. This collection of RNA molecules contains two primary types, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). In the context of obesity, miRNAs function as critical gene expression regulators. ncRNA can regulate the expression of genes involved in fat metabolism by binding to DNA and RNA, which can affect the transcription and translation of genes

(20). For example, ncRNAs can inhibit the expression of genes involved in fat breakdown, leading to increased fat storage. Besides, ncRNA can promote adipocyte differentiation by increasing the expression of genes involved in this process. Moreover, ncRNA can regulate inflammation by binding to DNA and RNA, affecting the expression of genes involved in this process.

Epigenetic changes linked to CpG methylation and miRNA expression patterns have been detected in patients with obesity at every stage of adipocyte differentiation, which affects their lipid metabolism and adipose tissue insulin sensitivity, resulting in β-cell dysfunction (21). In people with obesity, the methylation of genes involved in fat metabolism increases. This condition can lead to decreased expression of these genes and impaired fat breakdown. Similarly, there is increased expression of miRNAs that are involved in the inhibition of fat breakdown and the promotion of fat storage in people with obesity. These epigenetic alterations persist even without high-fat diets or sedentary lifestyles, resulting in sustained inflammation that leads to metabolic memory. Consequently, vascular damage and cardiovascular disease development occur, and the immune system is compromised, making patients with obesity more susceptible to infections, morbidity, and mortality (22).

Recent studies have explored the link between miRNA expression patterns and obesity-related complications. For example, a study noted a significant correlation between the expression pattern of three types of miRNAs as well as clinical and biochemical markers of obesity (23). These miRNAs are involved in the regulation of adipocyte differentiation, regulation of inflammation and regulation of adipogenesis. Similarly, a team of researchers found a considerable increase in miRNA-192 expression in metabolically unhealthy obesity, implying that miRNA patterns could differentiate between metabolically healthy and unhealthy paediatric patients with obesity (24). These findings indicate that miRNA markers may aid in the identification of obesity-related complications in childhood. Besides, these outcomes could help identify children at risk for developing metabolic complications of obesity and target them for preventive interventions. Further research is needed to understand the full role of miRNAs in the development of obesity and its complications. However, the evidence presented here suggests that miRNAs may be a major contributing factor to obesity.

EPIGENETIC INTERVENTIONS FOR OBESITY

Epigenetic modifications have been identified as potential therapeutic targets for obesity and related metabolic disorders. The reversibility of epigenetic modifications makes them suitable targets for intervention strategies. Various epigenetic interventions, including dietary interventions, lifestyle modifications, and pharmacological agents, have been investigated for their potential to prevent or treat obesity. A key question is the degree to which epigenetic changes are a cause or a consequence of obesity (Fig. 2). Epigenetic programming might play a role in the progression of obesity, in addition to contributing to the resulting risk of cardiovascular and metabolic disorders. Demonstrating causality can be challenging in human studies, but inferences can be drawn from several lines of evidence, as discussed in this review.

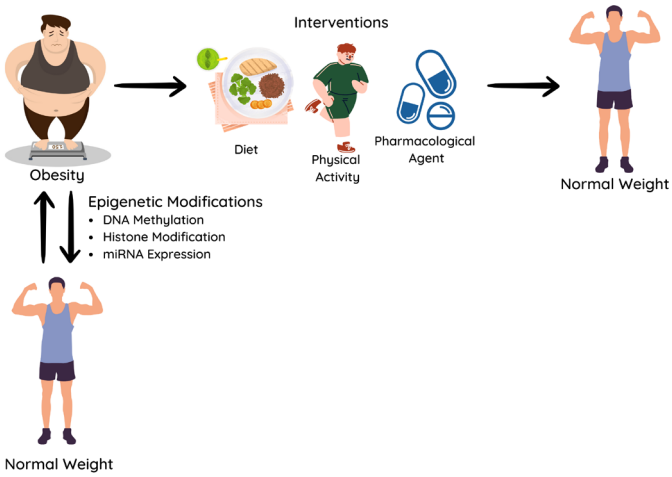

Fig. 2 : Epigenetic modifications as a cause or consequence of obesity.

Dietary Interventions

Over the past decade, researchers investigating the role of dietary risk factors for obesity have also focused on understanding how diet affects DNA methylation. Diet-induced obesity cannot be attributed solely to an energy imbalance or excessive food consumption. In fact, a variety of epigenetic mechanisms have been implicated in the development of obesity. Research on associations between human DNA methylation profiles and specific dietary patterns has provided evidence for this claim (25). Studying DNA methylation in experimental research can help reveal the molecular mechanisms underlying differential responses to weight loss programs and interventions. Moreover, a reduced calorie intake leads to a metabolic shift towards the breakdown of adipose tissues and glycogenolysis, which reduces body weight (26).

A team of researchers analysed the methylation profile of the genome in blood samples from men who were overweight or obese and participated in an eight-week program to limit energy consumption (27). Before the intervention, responders and non-responders had different ATPase Phospholipid Transporting 10A (*ATP10A*) and *CD44* Molecule (*CD44*) methylation levels, whereas, after the intervention, the response was linked to the Wilms' tumour 1 (*WT1*) gene methylation status. *ATP10A* enciphers an amino-phospholipid

transporter responsible for modulating bodily adipose tissue, whereas *CD44* is a surface-cell glycoprotein with indirect involvement in fibrosis and inflammation. The *WT1* gene encodes for a protein involved in cell growth and differentiation. These findings suggest that epigenetic changes may play a role in response to dietary interventions for obesity, specifically the *WT1* gene, which may be a potential target for dietary interventions for obesity. Nevertheless, three limitations were observed in the study. First, since the study was conducted in men who were overweight or obese, it is not clear if the findings would be the same in women or people with different levels of obesity. Second, the study only lasted for eight weeks; thus, it is not clear if the observed epigenetic changes would persist over a longer period. Third, the study did not assess the impact of dietary intervention on weight loss. Therefore, it is possible that the epigenetic changes that were observed were due to other factors, such as changes in energy expenditure or appetite. Despite these constraints, the study provides valuable insights into the role of epigenetic changes in the response to dietary interventions for obesity.

Another group of investigators partially confirmed these findings, demonstrating that subjects who exhibited weaker responses to a weight-loss program over six months had lower *CD44* Molecule (*CD44*) methylation levels compared to high responders (28). This result suggests that *CD44* methylation may play a role in the response to dietary interventions for obesity. Nonetheless, two limitations were remarked in the study. First, this randomised controlled and longitudinal trial study only lasted for six months; hence, it is not certain if the findings would be the same over a longer period. Second, the study did not assess the impact of the dietary intervention on other health outcomes, such as blood pressure or blood sugar levels. Not with standing these weaknesses, the study supplies beneficial insights into the role of *CD44* methylation in the response to dietary interventions for obesity.

In a separate investigation, researchers examined the impact of consuming extra calories (+750 kcal/day) of either saturated fatty acids (SFA) or polyunsaturated fatty acids (PUFA) for seven weeks on genome-wide DNA in healthy young people's subcutaneous adipose tissue (29). The weight gain levels were similar in both interventions; however, there were variations in the extent of the adipose tissue's DNA methylation. A comparison of the two diets showed that PUFA intake led to differential methylation of 1797 genes, such as Proopiomelanocortin (*POMC*), Interleukin 6 (*IL6*), INSR, Neuronal Growth Regulator 1 (*NEGR1*), while SFA overfeeding resulted in differential methylation of 125 genes, such as *ADIPOQ*. These findings suggest that the type of fat consumed can significantly impact the epigenetic profile of adipose tissue. PUFA can have beneficial effects on metabolism and weight loss, whereas SFA may have adverse effects on metabolism and weight gain.

Epigenetic changes can affect how genes are expressed, which can affect metabolism and weight gain. Consequently, based on the study findings, dietary interventions that focus on increasing PUFA intake and reducing SFA intake may be beneficial for weight loss and obesity prevention. However, the study was bounded to three limitations. First, the study was conducted on healthy young people; thus, it is unclear if the findings would be the same in people of different ages or with different health conditions. Second, the study only lasted for seven weeks; hence, it is not evident if the findings would be the same over a longer period. Third, the study did not assess the impact of dietary interventions on weight loss. It is possible that the epigenetic changes that were observed were due to other factors, such as changes in energy expenditure or appetite. Regardless of these drawbacks, the study grants worthy understanding of the role of dietary fat in epigenetic regulation and weight gain.

In the same way, a randomised controlled trial designated CENTRAL, lasting 18 months, investigated the differences in DNA methylation between responders and non-responders to the low-fat or low-carbohydrate/Mediterranean diet (30). Both dietary interventions were equal in calories and maintained over the entire study period. However, the study did not compare the effectiveness of the two diets in inducing epigenetic changes. Therefore, the study did not provide any evidence to suggest which diet may be more effective for inducing epigenetic changes. Responders who reduced their body weight by more than 16% demonstrated substantial differences in DNA methylation. Several genes exhibited significant changes in DNA methylation, including Nudix Hydrolas 3 (*NUDT3*), Nuclear Receptor Corepressor 2 (*NCOR2*), Leucine Rich Repeat Containing 27 (*LRRC27*), Cysteine Rich Secretory Protein 2 (*CRISP2*), and Schlafen Family Member 12 (*SLFN12*), which are involved in regulating calcium signalling and metabolism, among others. The study discovered that methylation differences in the identified genes could serve as prognostic biomarkers to predict a successful weight-loss therapy, thus contributing to advances in patient-tailored obesity treatment. Consequently, the study proposes that specific dietary interventions can lead to successful weight loss and that DNA methylation changes can serve as predictors for successful weight loss.

Energy-producing carbohydrates are an essential macronutrient that may lead to overeating and weight gain. Nevertheless, compared to fat, carbohydrates are less dense in energy. Studies on low-carbohydrate diets have yielded conflicting results regarding their influence on weight reduction and other health

outcomes, in contrast to low-fat diet treatments. The inconsistency in the results can be caused by the different types of carbohydrates in our diets, which have varying glycaemic indices; therefore, distinct effects on our health. Limited research has investigated the impact of carbohydrate consumption on causing epigenetic modifications that could potentially modify the risk of obesity. For instance, according to a study, eating carbs, the proportion of carbohydrates to fat, and having a higher level of methylation in the Carnitine Palmitoyltransferase 1 (*CPT1*) gene are all related (31). Because of its role in appetite control and insulin-mediated glucose and fatty acid metabolism, *CPT1* has been associated with a lower risk of obesity due to higher DNA methylation levels.

In the same manner, previous research has shown that hypermethylation and downregulation of dopamine are linked to signs of obesity and eating problems (3). Several genes have been linked to dopamine production and function, including Dopamine D4 Receptor (*DRD4*) and Dopamine Transporter (*DAT1*) (32). Mutations in these genes can lead to changes in dopamine levels and function, which may contribute to obesity. Moreover, dopamine, a neurotransmitter that governs the central reward system and regulates food intake, was found to be methylated and has a relationship with carbohydrate consumption (20). Their findings suggest that DNA methylation on genes involved in dopamine signalling might be a key epigenetic mechanism that contributes to the intake of carbohydrates and calories as well as the storage of fat in the body.

Eating carbohydrates can increase dopamine levels because carbohydrates are broken down into glucose, a major energy source for the brain (20). When glucose levels rise, dopamine levels also rise. Then, this condition can lead to feelings of pleasure and satisfaction, making people more likely to overeat. Similarly, fats can also affect dopamine levels in the brain. On the contrary, the effects are not as strong as those of carbohydrates because fats are not as easily broken down into glucose as carbohydrates. In short, dopamine plays an important role in regulating food intake, weight, and BMI. One intervention that can be used to treat obesity is by focusing on increasing dopamine levels, which may be effective for weight loss.

Comparable discoveries were noted in the Metabolic Syndrome Reduction in Navarra (RESMENA) initiative, where individuals with greater weight reduction, regardless of the intervention, demonstrated elevated LINE-1 methylation levels at baseline (33). This result implies that people who are more likely to lose weight have different epigenetic profiles than people who are less likely to lose weight. The randomised nutritionally controlled trial study suggests that a diet rich in antioxidants may be beneficial for weight loss and may influence epigenetic markers, particularly DNA methylation. The study also highlights the role of the epigenome in the development of obesity and the individual response to dietary factors. Therefore, this study contributes to personalised weight-loss treatments by identifying LINE-1 methylation levels as a potential biomarker of weight loss response and suggesting that these levels are influenced by diet composition. However, further studies with a larger sample size and a longer intervention period are required to confirm the influence of the dietary approach on methylation status.

Conversely, other studies have reported conflicting results regarding LINE-1 methylation and its link to dietary interventions. For example, a study in Spain demonstrated a decrease in methylation levels of LINE-1 following a year-long program aimed at encouraging compliance with the Mediterranean diet and physical activity (34). The Mediterranean diet is a diet that is rich in fruits, vegetables, whole grains, legumes, nuts, and olive oil. It is also low in saturated fat, red meat, and processed foods, which is deemed effective for weight loss and improving overall health. The contradictory finding indicates that the study findings could be affected by confounding factors, such as the age, sex, and health status of the participants.

Besides, another study in the United States of America failed to observe a substantial variance in LINE-1 methylation levels between overweight women who were randomly allocated to three distinct intervention groups (35). The three groups were a reduced-calorie weight-loss diet, an exercise program, and a combination of reduced-calorie weight-loss diet and an exercise program. Therefore, the finding of no significant difference in LINE-1 methylation levels in any intervention group versus controls implies that lifestyle changes sufficient to reduce weight over 12 months significantly may not change LINE-1 DNA methylation levels. In general, it seems that overfeeding more rapidly induces methylation alterations than caloric intake reduction does to reverse them.

In short, dietary intake can be an effective intervention for obesity concerning epigenetic mechanisms and weight loss. Diet has been shown to cause changes in DNA methylation in several other genes involved in metabolism and weight regulation. DNA methylation influenced by diet is reversible, so if we change our diet, the changes in DNA methylation will eventually go away. Moreover, DNA methylation induced by diet is specific to the type of diet we eat, which means that the type of diet we eat will affect the genes that are involved. Another point to note is that DNA methylation that is induced by diet is cumulative; hence, the more we eat a specific type of diet, the greater the changes in DNA methylation will be.

Physical Activity Interventions

Researchers have become interested in examining metabolic pathways due to changes in global profile methylation caused by exercise. The assessment of DNA methylation began with the analysis of genes that showed significant expression modifications and were relevant to the workouts performed. When examining the effects of physical activity, it is crucial to consider the nature of the activity, whether it is a one-time, intense exercise or part of a longer-term training plan.

Several studies have shown changes in the global DNA methylation profile in response to exercise, highlighting the involvement of epigenetic modifications in gene expression regulation and adaptation to environmental stimuli (3,36,37). While white blood cells are readily available for methylation pattern analysis due to the ease of sample collection, large-scale changes in DNA methylation are also anticipated in skeletal muscle and adipose tissue in response to exercise (38). However, these tissues require more invasive sampling methods. The study findings suggest that exercise can induce changes in DNA methylation in skeletal muscle and adipose tissue, leading to changes in gene expression that promote weight loss. Moreover, it implies that exercise may be able to target epigenetic changes involved in regulating metabolism and weight gain. Consequently, this study proposes that physical activity intervention could lead to the development of new and more effective treatments for obesity.

Despite the growing interest in investigating the relationship between physical activity and global DNA methylation in blood, conflicting results across studies persist (39). The contradictory results suggest that the relationship between physical activity and DNA methylation is complex and may be affected by a number of factors, hence the need for more research to be conducted. The study design, sample size, and confounding factors can significantly impact the results.

Researchers observed a trend towards increased demethylation in a cohort of elderly males who reported habitual physical activity over their lifespans, and this trend was verified by measurements of endurance and body composition (36). Physically active individuals showed lower gene promoter methylation levels than sedentary individuals. Specifically, 714 gene promoters demonstrated significant hypomethylation or reduction in the level of DNA methylation, while 31 gene promoters showed remarkable hypermethylation or an increase in DNA methylation. The finding suggests that physical activity may help turn on genes involved in metabolism and weight loss. Therefore, it helps to explain why physical activity is an effective intervention for obesity.

Moreover, it is intriguing that no substantial disparities were observed between the two groups regarding methylation in CpG islands, exons, and introns regions. This outcome implies that the demethylation observed in gene promoters was not due to changes in methylation in other genome regions. Instead, the demethylation observed in gene promoters may be a specific response to physical activity. Further research is needed to confirm these findings and to understand the mechanisms by which physical activity leads to changes in DNA methylation. Nonetheless, the study provides promising evidence that physical activity may have a long-lasting impact on gene expression and health.

In another study, the researchers revealed that although short-term resistance exercise did not inhibit an inflammatory response by a high-fat diet, it prompted an epigenomic response that may shield skeletal muscle from atrophy (37). They found that a high-fat diet alone induced a notable degree of hypermethylation, while concomitant resistance exercise caused a preference towards hypomethylation of DNA. Their findings indicate that resistance exercise may help protect skeletal muscle from atrophy caused by a high-fat diet. This information could be practical for developing exercise interventions to prevent or treat obesity associated with high-fat diets. Additionally, the identification of specific genes and epigenetic modifications associated with exercise and high-fat feeding could lead to the development of targeted therapies for obesity.

In addition, physical activity has been shown to modify adipocyte metabolism through DNA methylation mechanisms, as evidenced by a study of inactive middle-aged males who participated in two sessions of aerobics and one session of spinning for an hour per week and endurance exercise for six months (40). This exercise-induced alteration led to hypermethylation in adipocytes, resulting in decreased expression of genes such as Gamma-Aminobutyric Acid Type B Receptor Subunit 1 (*GABBR1*), Euchromatic Histone Lysine Methyltransferase 1 (*EHMT1*), Euchromatic Histone Lysine Methyltransferase 2 (*EHMT2*), Histone Deacetylase 4 (*HDAC4*), and Nuclear Receptor Corepressor 2 (*NCOR2*). Additionally, hypermethylation of potential genes for obesity was monitored in the study, with reduced expression in Transcription Factor 7 Like 2 (*TCF7L2*), JAZF Zinc Finger 1 (*JAZF1*), Cytoplasmic Polyadenylation Element Binding Protein 4 (*CPEB4*), Insulin-Like Growth Factor 2 mRNA Binding Protein 2 (*IGF2BP2*), and Haematopoietically Expressed Homeobox (*HHEX*). This outcome indicates that physical activity may help reduce body fat by changing how adipocytes function.

On the other hand, a study on obese adolescents who underwent high-intensity interval training (HIIT) for six months did not show epigenetic modification

or expression changes in the RalA Binding Protein 1 (*RALBP1*) gene, possibly due to changes in the test group and training style (41). The finding that HIIT did not lead to epigenetic modification or expression changes in the *RALBP1* gene is surprising because HIIT is a type of exercise known to be effective for weight loss. Moreover, this finding implies that HIIT may not have the same effects on gene expression as endurance exercise.

The differences between the two studies make it difficult to compare the findings. The disparities may arise due to variations in the experimental cohort and the form of exercise. Physical activity may affect gene expression differently depending on the individual's age, the type of exercise, and the specific genes being studied. Thus, more research is required to explore the full effects of physical activity on gene expression. However, the two studies suggest that physical activity may have a role in regulating gene expression and metabolism.

In summary, physical activity can be an effective intervention for obesity in relation to epigenetic mechanisms. Physical activity can induce changes in DNA methylation, leading to changes in gene expression and weight loss. DNA methylation that is induced by physical activity is reversible, which means that if we stop exercising, the changes in DNA methylation will eventually go away. Besides, DNA methylation that is induced by physical activity is specific to the type of exercise that we do, which means that the type of exercise that we do will affect the genes that are affected. Another point to note is that DNA methylation induced by physical activity is cumulative, so the more we exercise, the greater the changes in DNA methylation will be.

Pharmacological Agents Interventions

In addition to their use as indicators of obesity development and responsiveness to interventions, the epigenetic changes mentioned in this review can also be targeted for therapeutic purposes using epigenetic modifying agents. These agents are drugs that can alter how genes are expressed without changing the DNA sequence and can work in several ways. Some epigenetic modifying agents can bind to DNA and cause changes in DNA methylation. Other epigenetic modifying agents can bind to proteins involved in gene expression and cause changes in gene transcription. Although these medications have long been accepted for cancer treatment, it has only recently come to light that they may also have the ability to improve metabolic function and restore energy homeostasis (3).

Additionally, these pharmacological agents are aimed at DNA methyltransferases (*DNMTs*), histone demethylases (*HDMs*), protein arginine methyltransferases (*PRMTs*) and histone deacetylases (*HDACs*). *HDAC* inhibitors are a class of drugs that inhibit the activity of *HDAC* enzymes, which are responsible for removing acetyl groups from histone proteins, leading to changes in gene expression. Due to their impact on adipogenesis and insulin sensitivity, *HDAC* inhibitors have received the subject of most investigations (3). They can increase the expression of genes involved in fat metabolism and weight loss.

Nevertheless, there are limited studies conducted among human subjects to explore the potential drug mechanisms and their associations with epigenetic modifications. Clinical trials have been conducted using valproic acid and sodium phenylbutyrate among *HDAC* inhibitors for treating obesity. In one study, subjects were pretreated with sodium phenylbutyrate, which protected against β-cell dysfunction and insulin resistance caused by lipid infusion (42). This result suggests that sodium phenylbutyrate may be a promising new treatment for obesity. However, the trials were conducted in adults for a short term, so it is unclear whether sodium phenylbutyrate is safe and effective for children. Therefore, more research is required to determine its safety and efficacy for the treatment of obesity.

In summary, pharmacological intervention for obesity using epigenetic modifying agents is a promising new approach to treating obesity due to their potential to target the underlying causes of obesity and reverse the epigenetic changes rather than simply treating the symptoms. The initial premise is that *HDAC* could aid in the treatment of obesity, but there have been difficulties in determining which specific *HDAC* is responsible for this action. Nonetheless, the development of epigenetic drugs for the treatment of obesity is an exciting area of research that could lead to new and effective treatments for this disease.

CONCLUSION

Overall, this review offers significant insights into the intricate relationship between epigenetics and obesity. Recent studies have revealed that epigenetic mechanisms have been implicated in regulating gene expression in obesity. These changes are reversible; hence, the review emphasises the potential of epigenetic interventions for preventing or treating obesity. The discovery that epigenetic mechanisms are involved in the development of obesity has led to the development of new potential strategies for the prevention and treatment of this disease. Lifestyle interventions, such as diet and exercise, can help to improve epigenetic profiles and reduce the risk of obesity. These interventions have been proven to alter gene expression, which then affects weight regulation. Moreover, pharmacological interventions that target epigenetic mechanisms, such as *HDAC* inhibitors, are also being investigated to treat obesity.

Notably, the evidence presented in this review suggests that epigenetic interventions may mitigate the epigenetic changes implicated in obesity and related disorders. Epigenetic interventions are still in the early stages of development, but they can potentially revolutionise how we treat obesity. In consideration of the increasing prevalence of obesity in Malaysia, future research and practice should aim to address this concern. Based on the current review, several recommendations for future research and practice can be drawn, including the need for further investigations into high-risk groups for obesity in Malaysia. Addressing the increasing prevalence of obesity requires extensive population-based studies examining epigenetic changes and their associations with key risk factors such as diet, physical activity, and socioeconomic status. Early intervention is imperative in managing and preventing these conditions. Therefore, future research must prioritise evaluating the safety and effectiveness of intervention strategies.

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