INOSR APPLIED SCIENCES 13(2):88-95, 2025
ISSN: 2705-165X

INOSR13.2.000
International Network Organization for Scientific Research
https://doi.org/10.59298/INOSRAS/2025/13.2.8895

# Epigenetic Regulation in Obesity-Induced Insulin Resistance and Type 2 Diabetes

**Ssenkayi Julius**

**Department of Pharmacy Kampala International University Uganda**
**Email:Julius.ssenkayi@studwc.kiu.ac.ug**

## ABSTRACT

Obesity-induced insulin resistance is a primary contributor to the development of type 2 diabetes mellitus (T2DM), a global health crisis with increasing prevalence. Beyond genetic predisposition and environmental factors, epigenetic modifications—heritable changes in gene expression without altering the DNA sequence—are now recognized as pivotal in linking obesity to insulin resistance and T2DM. Mechanisms such as DNA methylation, histone modifications, and non-coding RNAs play significant roles in modulating key metabolic pathways involved in glucose and lipid homeostasis, inflammation, and adipocyte function. These modifications are dynamic and influenced by diet, physical activity, and exposure to metabolic stress, making them promising therapeutic targets. This review delves into the complex network of epigenetic regulation in the context of obesity-related insulin resistance and T2DM. It highlights emerging evidence from human and animal studies, explores epigenetic biomarkers, and discusses the potential for epigenetic therapy in metabolic disease management. Understanding how the epigenome mediates the metabolic dysfunctions of obesity offers new insights for early diagnosis, personalized medicine, and innovative treatment strategies.
**Keywords:** Epigenetics, Obesity, Insulin Resistance, Type 2 Diabetes, DNA Methylation

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity are among the most pressing global health challenges, both of which have seen a marked increase in prevalence over recent decades[1–4]. These two metabolic disorders often coexist, sharing not only epidemiological features but also overlapping pathophysiological mechanisms[5–7]. Central to this link is insulin resistance, a defining characteristic of T2DM that is closely associated with obesity—especially visceral adiposity, which contributes significantly to metabolic dysregulation. Although genetic predisposition and lifestyle-related factors such as poor diet, physical inactivity, and sedentary behavior are well-established contributors to both conditions, they do not fully account for the heterogeneity observed in disease onset, severity, and response to treatment among individuals. Increasingly, scientific attention has turned to epigenetic regulation as a crucial interface that mediates the complex interaction between genes and the environment[8, 9].

Epigenetics refers to a set of heritable and reversible modifications in gene expression that occur independently of changes to the underlying DNA sequence. The primary epigenetic mechanisms include DNA methylation, histone modification, and the action of various non-coding RNAs (such as microRNAs and long non-coding RNAs)[10]. These molecular changes influence chromatin structure and gene accessibility, thereby modulating transcriptional activity in a tissue- and context-specific manner. Importantly, these epigenetic changes are not static[11]. They can be triggered or reshaped by external cues such as dietary components, physical activity, stress, toxins, and inflammation, and may persist through multiple cell generations resulting in what is referred to as metabolic memory.

In the context of obesity, excess nutrients particularly glucose and fatty acids induce chronic low-grade inflammation, oxidative stress, and altered adipokine secretion[12]. These pathological stimuli promote aberrant epigenetic modifications in insulin-sensitive tissues, including the liver, skeletal muscle, and adipose tissue. For instance, increased DNA methylation of key genes involved in insulin signaling, such as *IRS1* (insulin receptor substrate 1), *GLUT4* (glucose transporter type 4), and *PI3K*, has been observed in obese and diabetic individuals, leading to reduced gene expression and impaired glucose uptake[13]. Similarly, alterations in histone acetylation and methylation patterns have been implicated in the dysregulation of metabolic pathways, including gluconeogenesis, lipid metabolism, and mitochondrial function[13].

Moreover, non-coding RNAs play an important role in post-transcriptional regulation of genes linked to insulin sensitivity and glucose metabolism. Certain microRNAs (miRNAs), such as miR-29, miR-103, and miR-223, have been found to be upregulated in obesity and T2DM, where they inhibit insulin signaling components and exacerbate insulin resistance[14]. Conversely, other miRNAs may act protectively, and their downregulation in obesity can lead to metabolic dysfunction. Emerging studies also suggest that long non-coding RNAs (lncRNAs), although less well characterized, are involved in chromatin remodeling and transcriptional control in metabolic tissues, further underscoring the complexity of epigenetic networks in metabolic disease[15].

Given the dynamic and reversible nature of epigenetic modifications, they represent promising biomarkers for early detection of metabolic disorders and potential therapeutic targets for intervention[16]. Dietary compounds such as polyphenols, omega-3 fatty acids, and certain phytochemicals have shown the ability to modulate epigenetic marks, offering a compelling avenue for nutritional epigenomics in preventing or mitigating insulin resistance and T2DM. Additionally, pharmacological agents that target histone deacetylases (HDACs) or DNA methyltransferases (DNMTs) are under investigation for their potential to restore normal metabolic gene expression profiles[17].

In sum, epigenetic regulation serves as a vital molecular bridge connecting environmental exposures and genetic susceptibility in the pathogenesis of obesity-induced insulin resistance and T2DM. A deeper understanding of these mechanisms not only enhances our insight into disease etiology but also opens up novel strategies for precision medicine, enabling individualized prevention and treatment approaches tailored to a person's unique epigenetic landscape.

## Overview of Epigenetic Mechanisms

**DNA Methylation**: DNA methylation is a fundamental epigenetic modification that primarily involves the addition of a methyl group to the 5-carbon position of cytosine residues, especially within CpG dinucleotides[1, 13]. This process is catalyzed by DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B. Methylation of gene promoter regions is typically associated with transcriptional repression, as it can hinder the binding of transcription factors or recruit methyl-binding proteins that compact chromatin. Conversely, global DNA hypomethylation, often seen in metabolic disorders, may lead to aberrant gene activation. In obesity and type 2 diabetes mellitus (T2DM), abnormal DNA methylation patterns have been observed in key metabolic tissues such as adipose tissue, liver, and skeletal muscle [18, 19]. For example, hypermethylation of genes involved in insulin signaling, such as *IRS1* or *GLUT4*, can reduce their expression and impair glucose uptake[20]. Hypomethylation of inflammatory genes like *TNF-α* or *IL-6* can lead to chronic low-grade inflammation, a hallmark of insulin resistance. Moreover, epigenetic changes can be influenced by environmental and lifestyle factors such as diet, physical activity, and exposure to toxins[20]. These findings suggest that DNA methylation serves as a dynamic and reversible interface between genetic predisposition and environmental influences in metabolic diseases.

**Histone Modifications**: Histone modifications are critical epigenetic mechanisms that influence chromatin structure and gene expression by altering the accessibility of DNA to transcriptional machinery [21, 22]. The core histones—H2A, H2B, H3, and H4—can undergo various post-translational modifications, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation[22]. These modifications typically occur at the histone tails and are catalyzed by specific enzymes. For instance, histone acetylation, mediated by histone acetyltransferases (HATs), generally relaxes chromatin structure and enhances gene transcription by allowing transcription factors to access DNA. In contrast, histone deacetylases (HDACs) remove these acetyl groups, leading to chromatin compaction and transcriptional repression[23]. Histone methylation, catalyzed by histone methyltransferases (HMTs), can either activate or repress gene expression depending on the specific amino acid residue and the number of methyl groups added. In metabolic tissues, alterations in histone modification patterns have been associated with insulin resistance and obesity[23]. For example, decreased acetylation of genes involved in mitochondrial function or fatty acid oxidation can impair energy metabolism. Conversely, increased methylation of promoters regulating insulin signaling pathways may downregulate critical genes, contributing to insulin resistance. These modifications are often reversible, making them attractive targets for therapeutic intervention in obesity-associated metabolic disorders[24].

**Non-Coding RNAs**: Non-coding RNAs (ncRNAs) are a diverse group of RNA molecules that do not code for proteins but play essential regulatory roles in gene expression[21, 25]. Among the most studied are microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), which contribute significantly to post-transcriptional and epigenetic regulation in metabolic pathways. miRNAs are short, approximately 18–25 nucleotides in length, and function mainly by binding to complementary sequences in the 3′ untranslated regions (3′ UTRs) of target messenger RNAs (mRNAs)[26]. This interaction typically results in mRNA degradation or translational inhibition, thereby fine-tuning protein expression. In the context of obesity and type 2 diabetes, miRNAs such as miR-103, miR-143, and miR-375 have been implicated in insulin resistance by targeting genes involved in insulin signaling, glucose transport, and adipogenesis[14, 27, 28]. Long non-coding RNAs, which exceed 200 nucleotides, regulate gene expression through diverse mechanisms including chromatin remodeling, transcriptional interference, and acting as molecular sponges for miRNAs. lncRNAs such as H19, MALAT1, and MEG3 have been associated with inflammatory responses and metabolic dysfunctions characteristic of obesity. Dysregulation of ncRNAs disrupts metabolic homeostasis and contributes to the pathogenesis of

obesity-related insulin resistance[29]. Due to their tissue-specific expression and regulatory potential, ncRNAs are also emerging as promising biomarkers and therapeutic targets in metabolic diseases.

## Epigenetic Alterations in Obesity-Induced Insulin Resistance

### Adipose Tissue Epigenetics

Adipose tissue functions not only as a site of energy storage but also as a dynamic endocrine organ, secreting various adipokines and cytokines that regulate metabolic homeostasis[30–33]. In the context of obesity, adipose tissue undergoes significant remodeling characterized by adipocyte hypertrophy and increased infiltration of pro-inflammatory immune cells. These alterations are associated with changes in the epigenetic landscape that modulate gene expression[34]. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, regulate the transcriptional activity of genes involved in adipogenesis, lipid metabolism, and inflammation. For example, hypermethylation of the promoter region of *PPARγ*, a master regulator of adipocyte differentiation, is observed in obese individuals, leading to its downregulation and impaired adipocyte function. Additionally, histone deacetylation at the *ADIPOQ* gene promoter contributes to reduced expression of adiponectin, an insulin-sensitizing hormone[35]. These epigenetic alterations exacerbate insulin resistance and metabolic dysfunction, highlighting adipose tissue as a critical site of obesity-induced epigenetic reprogramming.

### Liver and Skeletal Muscle

The liver and skeletal muscle are key metabolic organs involved in glucose and lipid homeostasis. In obesity and type 2 diabetes, epigenetic changes in these tissues play a major role in disrupting metabolic pathways[36]. In the liver, DNA methylation of key gluconeogenic genes such as *PEPCK* (phosphoenolpyruvate carboxykinase) and *G6PC* (glucose-6-phosphatase) can be altered by nutritional cues, chronic inflammation, and obesity, leading to increased hepatic glucose production and contributing to hyperglycemia[37]. Similarly, histone modifications in these genes can further influence their transcriptional activity. In skeletal muscle, which accounts for the majority of insulin-stimulated glucose uptake, obesity is associated with hypermethylation of genes like *IRS1* (insulin receptor substrate 1) and *GLUT4* (glucose transporter type 4)[38]. These epigenetic changes reduce the expression of insulin signaling and glucose transport genes, impairing glucose uptake and promoting insulin resistance. Thus, tissue-specific epigenetic modifications in the liver and skeletal muscle are key contributors to metabolic dysregulation in obesity and diabetes.

### Pancreatic β-Cells

Pancreatic β-cells are responsible for producing and secreting insulin in response to rising blood glucose levels. In the pathogenesis of type 2 diabetes mellitus (T2DM), progressive β-cell dysfunction is a hallmark feature that contributes to chronic hyperglycemia[39]. Epigenetic modifications in β-cells influence the expression of genes essential for maintaining β-cell identity and function. For instance, *PDX1* (pancreatic and duodenal homeobox 1) and *INS* (insulin) are key genes involved in β-cell development and insulin synthesis. In diabetic states, persistent hyperglycemia can induce aberrant histone methylation (e.g., H3K9me2 and H3K27me3) at the promoters of these genes, leading to chromatin condensation and transcriptional repression[40]. Additionally, DNA methylation changes at these loci have been observed, further suppressing insulin gene expression. These epigenetic alterations not only reduce insulin production but also impair β-cell responsiveness to glucose, contributing to glucose intolerance. As such, targeting β-cell epigenetic dysregulation represents a promising avenue for therapeutic intervention in T2DM.

## Non-Coding RNAs in Metabolic Regulation

### MicroRNAs and Insulin Signaling

MicroRNAs (miRNAs) are small non-coding RNAs that post-transcriptionally regulate gene expression and play critical roles in insulin signaling and glucose metabolism[41]. Several miRNAs, such as miR-375, miR-29, and miR-103/107, have been found to impact key components of insulin pathways. miR-375 inhibits insulin secretion by targeting Myotrophin (Mtpn), which is involved in exocytosis. miR-29 family members impair insulin signaling by suppressing insulin receptor substrate 1 (IRS1) and phosphatidylinositol 3-kinase (PI3K), thus disrupting downstream signaling such as AKT activation[42]. Altered miRNA expression profiles have been observed in the plasma and tissues of obese and diabetic individuals, highlighting their potential as both mechanistic contributors and biomarkers of insulin resistance. The ability of miRNAs to circulate in stable forms within exosomes or protein complexes enhances their appeal as non-invasive diagnostic tools[42]. Therapeutically, modulation of specific miRNAs could represent a novel strategy to restore proper insulin signaling in metabolic disorders like type 2 diabetes.

### Long Non-Coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs) are a diverse class of RNA transcripts exceeding 200 nucleotides in length that regulate gene expression through multiple mechanisms, including chromatin remodeling, transcriptional interference, and control of mRNA stability and translation[43]. In metabolic disease contexts, lncRNAs are increasingly recognized as key modulators. For example, H19, an imprinted lncRNA, plays a role in hepatic glucose production and lipid metabolism, affecting gluconeogenesis by interacting with transcriptional coactivators. MEG3, another well-studied lncRNA, has been linked to increased β-cell apoptosis in diabetic models, potentially through p53-mediated pathways[44]. Dysregulation of these lncRNAs contributes to

impaired insulin secretion, hepatic insulin resistance, and systemic glucose imbalance. Although the precise molecular functions of most lncRNAs in metabolic tissues remain under investigation, emerging evidence suggests they are integral to epigenetic control in obesity and diabetes[45]. Their tissue specificity and stability also make them promising targets for therapeutic intervention and potential biomarkers for early diagnosis and disease progression.

**Diet and Epigenetics**

Diet profoundly affects epigenetic regulation through the provision of key nutrients that serve as cofactors or substrates for epigenetic enzymes[46]. Nutrients such as folate, choline, vitamin B12, and methionine supply methyl groups for DNA and histone methylation via the one-carbon metabolism pathway. Similarly, polyphenols, fatty acids, and vitamins influence histone modifications and DNA methylation states[46]. High-fat diets have been shown to induce hypermethylation or hypomethylation of genes involved in glucose and lipid metabolism, contributing to insulin resistance and adiposity. In contrast, diets enriched in methyl donors or specific bioactive compounds like resveratrol, curcumin, and sulforaphane may reverse harmful epigenetic modifications and promote metabolic health[47]. Caloric restriction has also demonstrated beneficial epigenetic effects, including activation of sirtuins and PGC-1α, which support mitochondrial function and insulin sensitivity. These findings underscore the dynamic nature of the epigenome and how dietary patterns can modulate gene expression in a manner that influences metabolic disease risk and progression.

**Physical Activity**

Physical activity is a powerful modulator of the epigenome and can induce beneficial molecular changes that enhance metabolic health. Regular exercise has been shown to alter DNA methylation, histone acetylation, and microRNA expression in key metabolic tissues such as skeletal muscle, adipose tissue, and the liver[48]. For example, endurance training promotes the demethylation of the promoter region of *PPARγ coactivator-1α* (PGC-1α), a master regulator of mitochondrial biogenesis and oxidative metabolism[49]. This leads to improved glucose uptake, insulin sensitivity, and fatty acid oxidation. Additionally, exercise stimulates histone acetylation at genes involved in glucose transport and energy expenditure, enhancing their transcriptional activity[49]. These epigenetic effects are not transient; some changes persist long after cessation of physical activity, suggesting a form of metabolic memory[50]. Thus, the adaptive responses to exercise at the epigenetic level contribute significantly to its protective role against obesity, type 2 diabetes, and related metabolic disorders.

**Early Life Exposures and Transgenerational Epigenetics**

Epigenetic modifications established during early development can have lifelong consequences for metabolic health. The concept of fetal programming posits that environmental conditions in utero, including maternal diet, stress, obesity, and gestational diabetes, shape the epigenetic landscape of the developing fetus[51]. These influences may result in altered DNA methylation or histone modifications of genes governing energy homeostasis, insulin sensitivity, and lipid metabolism. For example, maternal undernutrition has been associated with hypomethylation of the IGF2 gene, predisposing offspring to insulin resistance and obesity[51]. Similarly, prenatal exposure to high-fat diets or endocrine disruptors can trigger lncRNA and miRNA alterations linked to metabolic dysfunction[52]. These epigenetic marks can persist into adulthood and potentially be transmitted across generations, raising concerns about the heritability of disease risk. Studies in animal models and human cohorts support these findings, emphasizing the critical need for maternal nutritional and metabolic health as a determinant of long-term metabolic outcomes in offspring.

## Epigenetic Biomarkers and Therapeutic Targets

**Biomarker Development**

The unique features of epigenetic modifications, particularly their reversibility, dynamic nature, and tissue specificity, offer significant potential for developing novel biomarkers in metabolic diseases such as obesity-induced insulin resistance and type 2 diabetes mellitus (T2DM)[53]. Epigenetic biomarkers can capture both genetic susceptibility and environmental exposures, providing a more comprehensive picture of disease risk and progression[53]. One promising area is the analysis of circulating cell-free DNA (cfDNA), which can reflect methylation changes in affected tissues. Aberrant DNA methylation patterns in genes associated with insulin signaling, inflammation, and lipid metabolism have been detected in cfDNA from individuals with metabolic disorders, making it a non-invasive tool for early diagnosis and monitoring. Histone modification signatures, although more technically challenging to detect in circulation, can provide information about chromatin accessibility and gene regulation in response to metabolic stress. MicroRNA (miRNA) profiling has also gained traction as several miRNAs are dysregulated in obesity and diabetes, influencing processes like insulin secretion, glucose uptake, and lipid metabolism[53]. These circulating miRNAs are stable in blood and can be readily quantified using high-throughput technologies, supporting their use as minimally invasive diagnostic and prognostic markers. Despite these advances, challenges remain in translating these findings into clinical practice. Variability in detection methods, lack of standardization in pre-analytical procedures, and the need for large, well-characterized cohorts for validation are major hurdles[54]. Furthermore, while some biomarkers show disease-specific patterns, others may reflect general metabolic stress, reducing specificity. Addressing these issues will be critical for realizing the full potential of epigenetic biomarkers in personalized medicine. Integrating epigenetic data with other omics layers such as genomics, transcriptomics, and metabolomics could

further improve biomarker accuracy and facilitate the development of multi-marker panels for disease stratification, risk prediction, and therapy monitoring in metabolic disorders.

**Epigenetic Therapy**

Epigenetic therapy is emerging as a novel and promising avenue for the treatment of metabolic diseases, including obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). This therapeutic strategy targets the enzymes and molecular machinery responsible for writing, reading, and erasing epigenetic marks, thereby modulating gene expression profiles associated with metabolic dysfunction[55]. Among the most studied pharmacological agents are DNA methyltransferase (DNMT) inhibitors, such as 5-azacytidine and decitabine, which reverse aberrant DNA methylation patterns and restore normal gene expression. Histone deacetylase (HDAC) inhibitors, including valproic acid and trichostatin A, act by increasing histone acetylation and enhancing the transcription of genes involved in insulin sensitivity and glucose metabolism[56]. Bromodomain and extraterminal domain (BET) inhibitors, which interfere with the reading of acetylated histones, are also under exploration for their anti-inflammatory and metabolic regulatory effects. In addition to synthetic drugs, nutraceuticals and dietary components such as curcumin, resveratrol, and sulforaphane have shown potential to modify epigenetic marks and improve metabolic outcomes in preclinical studies[57]. These agents offer a potentially safer alternative to traditional pharmaceuticals and can be integrated into lifestyle interventions. However, the clinical translation of epigenetic therapies is still in its infancy. Key challenges include ensuring tissue specificity to avoid off-target effects, understanding long-term safety profiles, and identifying appropriate therapeutic windows for intervention[58]. Moreover, the pleiotropic nature of epigenetic regulators necessitates careful modulation to prevent unintended gene expression changes. Precision medicine approaches, including epigenetic profiling of patients, may enhance the efficacy of these therapies by enabling patient stratification and personalized treatment plans. Future research should focus on optimizing drug delivery systems, improving the specificity of epigenetic modulators, and conducting robust clinical trials to evaluate their safety and efficacy in human populations. Ultimately, integrating epigenetic therapy into metabolic disease management holds the promise of addressing disease mechanisms at their regulatory core.

## Challenges and Future Directions

Despite growing evidence supporting the involvement of epigenetic mechanisms in obesity-induced insulin resistance and type 2 diabetes mellitus (T2DM), several critical challenges continue to hinder the full translation of epigenetic insights into clinical applications. One of the foremost challenges is tissue accessibility. Most human studies investigating epigenetic changes rely on peripheral blood samples, which may not accurately reflect the epigenetic landscape of key metabolic tissues such as the liver, adipose tissue, and skeletal muscle. These tissues are central to the pathophysiology of insulin resistance and metabolic dysfunction, yet they remain difficult to access in a routine or ethical manner. Additionally, a major limitation in current epigenetic research is the difficulty in distinguishing causality from correlation. Many observed epigenetic changes in metabolic diseases may be secondary consequences rather than primary drivers of the disease process. Addressing this issue requires longitudinal studies that track epigenetic alterations over time and interventional studies that manipulate epigenetic marks to assess causal relationships. Another significant barrier is the lack of standardization across studies. Variability in sample collection methods, data analysis techniques, and study designs complicates the comparison of findings and the development of universally accepted biomarkers or therapeutic targets. Moving forward, future research must prioritize integrative, multi-omics approaches that combine epigenetic data with genomic, transcriptomic, proteomic, and metabolomic information to yield a more holistic understanding of disease mechanisms. Developing personalized epigenetic profiles could enable more accurate risk prediction and facilitate tailored interventions that are both preventive and therapeutic. Translational research efforts should also focus on converting promising preclinical findings into safe, effective, and targeted epigenetic therapies for metabolic diseases. Collaboration between basic scientists, clinicians, bioinformaticians, and pharmaceutical developers will be essential to overcome current obstacles and unlock the full potential of epigenetics in the prevention, diagnosis, and treatment of obesity-related metabolic disorders.

## CONCLUSION

Epigenetic regulation plays a central role in mediating the effects of obesity on insulin resistance and the development of type 2 diabetes. The dynamic nature of epigenetic modifications offers a mechanistic explanation for how environmental factors such as diet, physical activity, and early-life exposures influence disease susceptibility and progression. Advances in epigenomics have opened new avenues for biomarker discovery and therapeutic intervention. However, translating these insights into clinical practice requires overcoming significant challenges related to specificity, safety, and implementation. A deeper understanding of the epigenetic landscape in metabolic disease holds promise for ushering in a new era of precision medicine.

## REFERENCES

1. Ahmed, S.A.H., Ansari, S.A., Mensah-Brown, E.P.K., Emerald, B.S.: The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clin Epigenetics. 12, 104 (2020). https://doi.org/10.1186/s13148-020-00896-4
2. Chandrasekaran, P., Weiskirchen, R.: The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. International Journal of Molecular Sciences. 25, 1882 (2024). https://doi.org/10.3390/ijms25031882

3. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.Ak.: Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine. 100622 (2025). https://doi.org/10.1016/j.obmed.2025.100622
4. Lu, X., Xie, Q., Pan, X., Zhang, R., Zhang, X., Peng, G., Zhang, Y., Shen, S., Tong, N.: Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. Sig Transduct Target Ther. 9, 262 (2024). https://doi.org/10.1038/s41392-024-01951-9
5. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR-γ expressions with reciprocal suppression of TNF-α gene in obesity. J Cell Mol Med. 28, e70086 (2024). https://doi.org/10.1111/jcmm.70086
6. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. Natural Product Communications. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035
7. Uti, D.E., Atangwho, I.J., Eyong, E.U., Umoru, G.U., Egbung, G.E., Rotimi, S.O., Nna, V.U.: African walnuts (Tetracarpidium conophorum) modulate hepatic lipid accumulation in obesity via reciprocal actions on HMG-CoA reductase and paraoxonase. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 20, 365–379 (2020)
8. Singh, S., Kriti, M., K.s., A., Sarma, D.K., Verma, V., Nagpal, R., Mohania, D., Tiwari, R., Kumar, M.: Deciphering the complex interplay of risk factors in type 2 diabetes mellitus: A comprehensive review. Metabolism Open. 22, 100287 (2024). https://doi.org/10.1016/j.metop.2024.100287
9. Ruze, R., Liu, T., Zou, X., Song, J., Chen, Y., Xu, R., Yin, X., Xu, Q.: Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front. Endocrinol. 14, (2023). https://doi.org/10.3389/fendo.2023.1161521
10. Ikpozu, E.N., Offor, C.E., Igwenyi, I.O., Obaroh, I.O., Ibiam, U.A., Ukaidi, C.U.A.: RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 22, 14791641251334726 (2025). https://doi.org/10.1177/14791641251334726
11. Handy, D.E., Castro, R., Loscalzo, J.: Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease. Circulation. 123, 2145–2156 (2011). https://doi.org/10.1161/CIRCULATIONAHA.110.956839
12. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obesity Medicine. 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
13. Kaimala, S., Ansari, S.A., Emerald, B.S.: Chapter Six - DNA methylation in the pathogenesis of type 2 diabetes. In: Litwack, G. (ed.) Vitamins and Hormones. pp. 147–169. Academic Press (2023)
14. Macvanin, M.T., Gluvic, Z., Bajic, V., Isenovic, E.R.: Novel insights regarding the role of noncoding RNAs in diabetes. World J Diabetes. 14, 958–976 (2023). https://doi.org/10.4239/wjd.v14.i7.958
15. Aja, P.M., Agu, P.C., Ogbu, C., Fasogbon, I.V., Musyoka, A.M., Ngwueche, W., Egwu, C.O., Tusubira, D., Ross, K.: RNA research for drug discovery: Recent advances and critical insight. Gene. 947, 149342 (2025). https://doi.org/10.1016/j.gene.2025.149342
16. NL, S., Shakhatreh, Z., Tahir, A., Singh, J., Sulaiman, S., H, A., Sadhankar, A., Patel, P., Patel, R., Nashwan, A.J.: Epigenetic Mechanisms in the Transfer of Metabolic Disorders: A Comprehensive Review. Cureus. 17, e80418. https://doi.org/10.7759/cureus.80418
17. Borsoi, F.T., Neri-Numa, I.A., de Oliveira, W.Q., de Araújo, F.F., Pastore, G.M.: Dietary polyphenols and their relationship to the modulation of non-communicable chronic diseases and epigenetic mechanisms: A mini-review. Food Chem (Oxf). 6, 100155 (2022). https://doi.org/10.1016/j.fochms.2022.100155
18. Lee, H.-T., Oh, S., Ro, D.H., Yoo, H., Kwon, Y.-W.: The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis. J Lipid Atheroscler. 9, 419–434 (2020). https://doi.org/10.12997/jla.2020.9.3.419
19. Kim, M.: DNA methylation: a cause and consequence of type 2 diabetes. Genomics Inform. 17, e38 (2019). https://doi.org/10.5808/GI.2019.17.4.e38
20. Ahmed, S.A.H., Ansari, S.A., Mensah-Brown, E.P.K., Emerald, B.S.: The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clin Epigenetics. 12, 104 (2020). https://doi.org/10.1186/s13148-020-00896-4
21. Bure, I.V., Nemtsova, M.V., Kuznetsova, E.B.: Histone Modifications and Non-Coding RNAs: Mutual Epigenetic Regulation and Role in Pathogenesis. Int J Mol Sci. 23, 5801 (2022). https://doi.org/10.3390/ijms23105801
22. Liu, R., Wu, J., Guo, H., Yao, W., Li, S., Lu, Y., Jia, Y., Liang, X., Tang, J., Zhang, H.: Post-translational modifications of histones: Mechanisms, biological functions, and therapeutic targets. MedComm (2020). 4, e292 (2023). https://doi.org/10.1002/mco2.292

23. Wang, Z., Qin, G., Zhao, T.C.: Histone Deacetylase 4 (HDAC4): Mechanism of Regulations and Biological Functions. Epigenomics. 6, 139–150 (2014). https://doi.org/10.2217/epi.13.73
24. Yang, Q., Vijayakumar, A., Kahn, B.B.: Metabolites as regulators of insulin sensitivity and metabolism. Nat Rev Mol Cell Biol. 19, 654–672 (2018). https://doi.org/10.1038/s41580-018-0044-8
25. Alum, E.U.: Career Advancement towards Nascent Technologies: RNA in Focus. IDOSR-JSR. 9, 49–53 (2024). https://doi.org/10.59298/IDOSRJSR/2024/9.2.4953.100
26. Gill, S.K., Gomer, R.H.: Translational Regulators in Pulmonary Fibrosis: MicroRNAs, Long Non-Coding RNAs, and Transcript Modifications. Cells. 14, 536 (2025). https://doi.org/10.3390/cells14070536
27. Saville, L., Wu, L., Habtewold, J., Cheng, Y., Gollen, B., Mitchell, L., Stuart-Edwards, M., Haight, T., Mohajerani, M., Zovoilis, A.: NERD-seq: a novel approach of Nanopore direct RNA sequencing that expands representation of non-coding RNAs. Genome Biol. 25, 233 (2024). https://doi.org/10.1186/s13059-024-03375-8
28. Wilkes, M.C., Repellin, C.E., Sakamoto, K.M.: Beyond mRNA: The Role of Non-coding RNAs in Normal and Aberrant hematopoiesis. Mol Genet Metab. 122, 28–38 (2017). https://doi.org/10.1016/j.ymgme.2017.07.008
29. Dandare, A., Khan, M.J., Naeem, A., Liaquat, A.: Clinical relevance of circulating non-coding RNAs in metabolic diseases: Emphasis on obesity, diabetes, cardiovascular diseases and metabolic syndrome. Genes & Diseases. 10, 2393 (2022). https://doi.org/10.1016/j.gendis.2022.05.022
30. Anguita-Ruiz, A., Bustos-Aibar, M., Plaza-Díaz, J., Mendez-Gutierrez, A., Alcalá-Fdez, J., Aguilera, C.M., Ruiz-Ojeda, F.J.: Omics Approaches in Adipose Tissue and Skeletal Muscle Addressing the Role of Extracellular Matrix in Obesity and Metabolic Dysfunction. International Journal of Molecular Sciences. 22, 2756 (2021). https://doi.org/10.3390/ijms22052756
31. Bartelt, A., Widenmaier, S.B., Schlein, C., Johann, K., Goncalves, R.L.S., Eguchi, K., Fischer, A.W., Parlakgül, G., Snyder, N.A., Nguyen, T.B., Bruns, O.T., Franke, D., Bawendi, M.G., Lynes, M.D., Leiria, L.O., Tseng, Y.-H., Inouye, K.E., Arruda, A.P., Hotamisligil, G.S.: Brown adipose tissue thermogenic adaptation requires Nrf1-mediated proteasomal activity. Nat Med. 24, 292–303 (2018). https://doi.org/10.1038/nm.4481
32. Bienboire-Frosini, C., Wang, D., Marcet-Rius, M., Villanueva-García, D., Gazzano, A., Domínguez-Oliva, A., Olmos-Hernández, A., Hernández-Ávalos, I., Lezama-García, K., Verduzco-Mendoza, A., Gómez-Prado, J., Mota-Rojas, D.: The Role of Brown Adipose Tissue and Energy Metabolism in Mammalian Thermoregulation during the Perinatal Period. Animals (Basel). 13, 2173 (2023). https://doi.org/10.3390/ani13132173
33. Atangwho, I.J., Omang, W.A., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
34. Arias, C., Álvarez-Indo, J., Cifuentes, M., Morselli, E., Kerr, B., Burgos, P.V.: Enhancing adipose tissue functionality in obesity: senotherapeutics, autophagy and cellular senescence as a target. Biological Research. 57, 51 (2024). https://doi.org/10.1186/s40659-024-00531-z
35. Pant, R., Firmal, P., Shah, V.K., Alam, A., Chattopadhyay, S.: Epigenetic Regulation of Adipogenesis in Development of Metabolic Syndrome. Front Cell Dev Biol. 8, 619888 (2021). https://doi.org/10.3389/fcell.2020.619888
36. Ling, C., Rönn, T.: Epigenetics in Human Obesity and Type 2 Diabetes. Cell Metab. 29, 1028–1044 (2019). https://doi.org/10.1016/j.cmet.2019.03.009
37. Kirchner, H., Sinha, I., Gao, H., Ruby, M.A., Schönke, M., Lindvall, J.M., Barrès, R., Krook, A., Näslund, E., Dahlman-Wright, K., Zierath, J.R.: Altered DNA methylation of glycolytic and lipogenic genes in liver from obese and type 2 diabetic patients. Mol Metab. 5, 171–183 (2016). https://doi.org/10.1016/j.molmet.2015.12.004
38. Rosen, E.D.: Epigenomic and transcriptional control of insulin resistance. J Intern Med. 280, 443–456 (2016). https://doi.org/10.1111/joim.12547
39. Alum, E.U.: Optimizing patient education for sustainable self-management in type 2 diabetes. Discov Public Health. 22, 44 (2025). https://doi.org/10.1186/s12982-025-00445-5
40. Dludla, P.V., Mabhida, S.E., Ziqubu, K., Nkambule, B.B., Mazibuko-Mbeje, S.E., Hanser, S., Basson, A.K., Pheiffer, C., Kengne, A.P.: Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. World J Diabetes. 14, 130–146 (2023). https://doi.org/10.4239/wjd.v14.i3.130
41. Beilerli, A., Kudriashov, V., Sufianov, A., Kostin, A., Begliarzade, S., Ilyasova, T., Liang, Y., Mukhamedzyanov, A., Beylerli, O.: Regulation and mechanism of action of miRNAs on insulin resistance in skeletal muscles. Noncoding RNA Res. 8, 218–223 (2023). https://doi.org/10.1016/j.ncrna.2023.02.005
42. Rottiers, V., Näär, A.M.: MicroRNAs in Metabolism and Metabolic Disorders. Nat Rev Mol Cell Biol. 13, 239–250 (2012). https://doi.org/10.1038/nrm3313

43. Zhang, X., Wang, W., Zhu, W., Dong, J., Cheng, Y., Yin, Z., Shen, F.: Mechanisms and Functions of Long Non-Coding RNAs at Multiple Regulatory Levels. Int J Mol Sci. 20, 5573 (2019). https://doi.org/10.3390/ijms20225573
44. Zhang, T.-N., Wang, W., Yang, N., Huang, X.-M., Liu, C.-F.: Regulation of Glucose and Lipid Metabolism by Long Non-coding RNAs: Facts and Research Progress. Front Endocrinol (Lausanne). 11, 457 (2020). https://doi.org/10.3389/fendo.2020.00457
45. Wang, Z., Ma, J., Wu, R., Kong, Y., Sun, C.: Recent advances of long non-coding RNAs in control of hepatic gluconeogenesis. Front Endocrinol (Lausanne). 14, 1167592 (2023). https://doi.org/10.3389/fendo.2023.1167592
46. Choi, S.-W., Friso, S.: Epigenetics: A New Bridge between Nutrition and Health. Advances in Nutrition. 1, 8–16 (2010). https://doi.org/10.3945/an.110.1004
47. Mahmoud, A.M.: An Overview of Epigenetics in Obesity: The Role of Lifestyle and Therapeutic Interventions. Int J Mol Sci. 23, 1341 (2022). https://doi.org/10.3390/ijms23031341
48. Plaza-Diaz, J., Izquierdo, D., Torres-Martos, Á., Baig, A.T., Aguilera, C.M., Ruiz-Ojeda, F.J.: Impact of Physical Activity and Exercise on the Epigenome in Skeletal Muscle and Effects on Systemic Metabolism. Biomedicines. 10, 126 (2022). https://doi.org/10.3390/biomedicines10010126
49. Rius-Pérez, S., Torres-Cuevas, I., Millán, I., Ortega, Á.L., Pérez, S.: PGC-1α, Inflammation, and Oxidative Stress: An Integrative View in Metabolism. Oxidative Medicine and Cellular Longevity. 2020, 1452696 (2020). https://doi.org/10.1155/2020/1452696
50. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? Obesity Medicine. 55, 100610 (2025). https://doi.org/10.1016/j.obmed.2025.100610
51. Peral-Sanchez, I., Hojeij, B., Ojeda, D.A., Steegers-Theunissen, R.P.M., Willaime-Morawek, S.: Epigenetics in the Uterine Environment: How Maternal Diet and ART May Influence the Epigenome in the Offspring with Long-Term Health Consequences. Genes (Basel). 13, 31 (2021). https://doi.org/10.3390/genes13010031
52. Abdulkadir, A., Kandel, S., Lewis, N., D'Auvergne, O., Rosby, R., Hossain, E.: Epigenetic Consequences of In Utero PFAS Exposure: Implications for Development and Long-Term Health. International Journal of Environmental Research and Public Health. 22, 917 (2025). https://doi.org/10.3390/ijerph22060917
53. Jazieh, C., Arabi, T.Z., Asim, Z., Sabbah, B.N., Alsaud, A.W., Alkattan, K., Yaqinuddin, A.: Unraveling the epigenetic fabric of type 2 diabetes mellitus: pathogenic mechanisms and therapeutic implications. Front. Endocrinol. 15, (2024). https://doi.org/10.3389/fendo.2024.1295967
54. Condrat, C.E., Thompson, D.C., Barbu, M.G., Bugnar, O.L., Boboc, A., Cretoiu, D., Suciu, N., Cretoiu, S.M., Voinea, S.C.: miRNAs as Biomarkers in Disease: Latest Findings Regarding Their Role in Diagnosis and Prognosis. Cells. 9, 276 (2020). https://doi.org/10.3390/cells9020276
55. Odimegwu, C.L., Uwaezuoke, S.N., Chikani, U.N., Mbanefo, N.R., Adiele, K.D., Nwolisa, C.E., Eneh, C.I., Ndiokwelu, C.O., Okpala, S.C., Ogbuka, F.N., Odo, K.E., Ohuche, I.O., Obiora-Izuka, C.E.: Targeting the Epigenetic Marks in Type 2 Diabetes Mellitus: Will Epigenetic Therapy Be a Valuable Adjunct to Pharmacotherapy? DMSO. 17, 3557–3576 (2024). https://doi.org/10.2147/DMSO.S479077
56. Connolly, R., Stearns, V.: Epigenetics as a Therapeutic Target in Breast Cancer. J Mammary Gland Biol Neoplasia. 17, 191–204 (2012). https://doi.org/10.1007/s10911-012-9263-3
57. Matuszewska, M., Wilkaniec, A., Cieślik, M., Strawski, M., Czapski, G.A.: The Inhibition of Bromodomain and Extraterminal Domain (BET) Proteins Protects Against Microglia-Mediated Neuronal Loss In Vitro. Biomolecules. 15, 528 (2025). https://doi.org/10.3390/biom15040528
58. Roy, S., Deka, D., Kondaveeti, S.B., Ayyadurai, P., Siripragada, S., Philip, N., Pathak, S., Duttaroy, A.K., Banerjee, A.: An overview of potential of natural compounds to regulate epigenetic modifications in colorectal cancer: a recent update. Epigenetics. 20, 2491316. https://doi.org/10.1080/15592294.2025.2491316

**CITE AS: Ssenkayi Julius (2025). Epigenetic Regulation in Obesity-Induced Insulin Resistance and Type 2 Diabetes. INOSR APPLIED SCIENCES 13(2):88-95. https://doi.org/10.59298/INOSRAS/2025/13.2.8895**