RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 5(1):42-49, 2026
©RIJRMS Publications
ONLINE ISSN: 1115- 6198
Print ISSN: 1597-3107
https://doi.org/10.59298/RIJRMS/2026/514249

Metabolic Memory in Obesity-Driven Diabetes: Epigenetic Imprints and their Reversibility

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ABSTRACT

Obesity-driven type 2 diabetes (T2D) is increasingly recognized as a chronic disorder of "metabolic memory" (MM), in which prior exposure to obesogenic and hyperglycemic milieus leaves long-lasting molecular scars that sustain insulin resistance, β-cell dysfunction, and complications even after risk factors are controlled. Epigenetic mechanisms such as DNA methylation, histone modifications, chromatin remodeling, noncoding RNAs, and epitranscriptomic marks provide a plausible substrate for this persistence. Human and experimental data show that obesity and hyperglycemia reshape epigenetic landscapes in adipose tissue, liver, skeletal muscle, vascular endothelium, kidney, immune cells, and pancreatic islets, altering networks that regulate nutrient sensing, inflammation, oxidative stress, mitochondrial function, and cell survival. This review focuses on MM in obesity-driven diabetes rather than classical microvascular complication models. We summarize how obesogenic diets, lipotoxicity, and chronic low-grade inflammation generate epigenetic imprints that lock in pathogenic transcriptional programs across metabolic tissues. Particular attention is given to DNA methylation changes at adipokine, lipid handling, and insulin signaling genes; histone acetylation and methylation patterns that sustain inflammatory and oxidative pathways; and noncoding RNA networks that stabilize these phenotypes. We then review evidence for the reversibility of these imprints. Weight loss, dietary quality, physical activity, bariatric surgery, and antidiabetic drugs can partially remodel epigenetic marks, with tissue- and locus-specific differences in plasticity. Emerging data suggest that early-life and puberty represent critical windows during which epigenetic programming by obesogenic environments is particularly durable. Finally, we discuss pharmacological epigenetic modifiers, including histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors, and small molecules targeting chromatin readers and writers, as potential tools to erase MM, balanced against safety and specificity concerns. Understanding MM in obesity-driven diabetes reframes prevention and treatment as a race between early, aggressive metabolic control and the establishment of hard-to-reverse epigenetic scars. Mapping which marks are stable, which are plastic, and which predict clinical outcomes will be central to developing biomarker-guided, epigenetically-informed therapies.

Keywords: metabolic memory; obesity; type 2 diabetes; epigenetics; DNA methylation

INTRODUCTION

Obesity (OB) and T2D are tightly intertwined pandemics. Excess adiposity perturbs whole-body energy homeostasis through elevated free fatty acids (FFAs), ectopic lipid deposition, chronic low-grade inflammation, and altered adipokine secretion, collectively driving insulin resistance and β-cell stress[1–4]. Yet even when weight is reduced or glycemic control improves, many individuals retain a high risk of vascular, renal, hepatic, and cardiovascular complications. Clinical trials such as DCCT/EDIC and UKPDS established the concept that early periods of poor glycemic control exert long-lasting effects on complication risk—a phenomenon termed metabolic memory (MM)[5].

Classically, MM was described in the context of microvascular and macrovascular complications, where transient hyperglycemia left persistent marks on endothelial, mesangial, and immune cells, sustaining oxidative stress and inflammation[6]. However, obesity itself is a chronic metabolic exposure. High-fat, high-sugar diets, sedentariness, and associated dyslipidemia precede overt hyperglycemia by years and induce durable changes in many of the same tissues that drive insulin resistance and β-cell failure. This has led to the broader concept of "obesity-driven metabolic memory," where early or prolonged OB imprints a lasting molecular program that promotes T2D even after partial weight loss or lifestyle modification.

From a mechanistic standpoint, MM requires a molecular substrate that can: (i) sense metabolic and inflammatory cues; (ii) persist over many cell divisions; and (iii) influence gene expression and cellular phenotypes over time. Epigenetic mechanisms are heritable but reversible changes in gene regulation that do not involve DNA sequence alterations and fulfill these criteria. These include DNA methylation at CpG sites; histone post-translational modifications (PTMs) such as acetylation, methylation, acylation, and phosphorylation; ATP-dependent chromatin remodeling; noncoding RNAs (miRNAs, lncRNAs, circRNAs); and RNA modifications like N6-methyladenosine (m6A)[7].

Metabolic tissues are particularly susceptible to epigenetic modulation because the enzymes that write and erase epigenetic marks use metabolic intermediates as substrates or cofactors. Examples include S-adenosylmethionine (SAM) for DNMTs, α-ketoglutarate for TET dioxygenases and some histone demethylases, and acetyl-CoA and NAD^+ for histone acetyltransferases and sirtuins, respectively[8]. In an obesogenic environment, altered nutrient flux, mitochondrial dysfunction, and redox imbalance can therefore be directly translated into epigenetic changes[9].

In OB/T2D, patient and animal studies reveal characteristic epigenetic disturbances across tissues. Adipose tissue from individuals with OB and insulin resistance shows differential DNA methylation at genes involved in adipogenesis (e.g., PPARG), lipolysis, adipokine production (LEP, ADIPOQ), and inflammatory mediators (TNF, IL6), often correlating with gene expression and metabolic traits[10, 11]. Liver and skeletal muscle exhibit methylation and histone changes at genes governing gluconeogenesis, lipid handling, and mitochondrial biogenesis. Pancreatic islets from donors with T2D show altered DNA methylation and histone marks at genes critical for insulin secretion and β-cell identity[12, 13].

Crucially, some of these changes persist after short- to medium-term improvements in diet or glycemia, supporting their role as MM substrates. For example, endothelial cells exposed transiently to high glucose maintain heightened inflammatory gene expression mediated by persistent histone methylation/acetylation patterns at key promoters[14]. Similarly, adipose tissue and liver retain altered DNA methylation signatures months to years after bariatric surgery or significant weight loss, even when metabolic parameters normalize, hinting at only partial epigenetic "resetting." [14]

Obesity-driven MM has important clinical implications. First, it provides a mechanistic explanation for why early, intensive interventions before epigenetic scars consolidate—yield disproportionately large long-term benefits. Second, it cautions that later lifestyle changes might be insufficient to fully reverse risk, especially in individuals exposed to OB and hyperglycemia from childhood or adolescence[15]. Third, it suggests that epigenetic marks themselves could serve as biomarkers to stratify risk or monitor response to intervention. Finally, it opens the possibility of targeted "epigenetic therapies" designed to overwrite pathogenic memory while preserving essential gene regulation.

This review situates MM explicitly within obesity-driven T2D. Section 2 outlines cellular and molecular frameworks of MM in metabolic tissues. Sections 3 and 4 examine DNA methylation and histone/chromatin changes in adipose tissue, liver, muscle, and β-cells. Section 5 integrates noncoding RNAs, epitranscriptomics, and 3D chromatin organization. Sections 6 and 7 focus on reversibility, how lifestyle, surgical, and pharmacologic interventions can remodel epigenetic landscapes, and discuss biomarker and therapeutic perspectives. By connecting OB-induced epigenetic programming with the persistence of T2D and its complications, we highlight key targets and open questions in efforts to "erase" metabolic memory.

2. Cellular and Molecular Basis of Metabolic Memory in Obesity-Driven Diabetes

At the cellular level, MM reflects a durable shift from an acute stress response to a chronically reprogrammed state. In obesity-driven diabetes, multiple cell types, adipocytes, hepatocytes, myocytes, β-cells, endothelial, and immune cells experience sustained exposure to FFAs, glucose, advanced glycation end-products, and inflammatory cytokines. These cues activate signaling pathways (NF-κB, JNK, PKC, STATs) that acutely modify transcription factor activity and chromatin accessibility[2, 16, 17].

For memory to persist, such transient responses must be stabilized. Mechanistically, this occurs when transcription factors and stress-responsive pathways recruit epigenetic writers and erasers to key loci. For instance, hyperglycemia-induced ROS and inflammatory signaling can drive recruitment of histone acetyltransferases (HATs) and histone methyltransferases (HMTs) to promoters of genes like TXNIP, p66Shc, and pro-inflammatory cytokines, leading to sustained H3K4me3 and H3K9/K14 acetylation that maintain high transcription even after normalization of glucose[18].

Similarly, obesity-related metabolic signals can alter DNA methylation patterns through modulation of DNMTs and TET enzymes. For example, changes in SAM availability, one-carbon metabolism, and oxidative stress influence global and locus-specific methylation. Diet-induced obesity models show that methylation at metabolic genes in adipose tissue and liver can remain altered long after diet switching, correlating with persistent insulin resistance[10, 19, 20].

Another layer involves chromatin structure and nuclear architecture. ATP-dependent remodelers reposition nucleosomes, exposing or occluding regulatory elements. Obesity and hyperglycemia can reconfigure enhancer landscapes, creating "super-enhancers" associated with pro-inflammatory or lipogenic genes. Once formed, these enhancer hubs are stabilized by cooperative binding of transcription factors and coactivators, reinforcing the memory state[21]. Noncoding RNAs function both upstream and downstream of these changes. miRNAs

induced by obesogenic signals can repress anti-inflammatory or insulin-sensitizing transcripts, while lncRNAs scaffold chromatin modifiers at specific loci, stabilizing epigenetic states. Many of these ncRNAs are themselves epigenetically regulated, creating feedback loops that reinforce MM[22, 23].

Importantly, not all epigenetic marks are equally stable. Some histone acetylation events are relatively labile and respond quickly to metabolic improvement, while certain histone methylation marks (e.g., H3K9me2/3, H3K27me3) and DNA methylation at specific CpGs can be highly persistent[22]. The balance of stable versus plastic marks, together with cell turnover rates, likely determines how "hard-wired" obesity-driven MM becomes in each tissue.

Finally, developmental timing is critical. Epigenetic programming during in utero life, childhood, and puberty appears particularly sensitive to nutritional and obesogenic exposures, leading to long-lasting changes in metabolic set-points. Trans-generational effects where parental OB or diabetes influences offspring epigenetic profiles and disease risk further extend the MM concept beyond a single life course[24].

3. DNA Methylation Signatures in Metabolic Tissues

DNA methylation (DNAm) is the most extensively studied epigenetic mechanism in OB/T2D. Numerous epigenome-wide association studies (EWAS) in blood, adipose tissue, liver, muscle, and pancreatic islets reveal differential methylation patterns linked to obesity, insulin resistance, and glycemic traits[25].

In adipose tissue, obesity is associated with altered methylation at genes controlling adipogenesis (PPARG, CEBPA), lipolysis (LIPE, ATGL), adipokines (LEP, ADIPOQ), and inflammatory mediators (TNF, IL6, CCL2). Many of these changes correlate with gene expression and metabolic phenotypes such as BMI, HOMA-IR, and circulating adipokines. Recent work shows that DNA methylation reshapes adipokine expression and inflammatory profiles in expanding adipose tissue, contributing to systemic insulin resistance[11, 26, 27].

Liver methylomes in non-alcoholic fatty liver disease (NAFLD) and T2D reveal DNAm changes at genes involved in de novo lipogenesis (SREBF1, FASN), gluconeogenesis (PCK1, G6PC), and lipid export (APOB, MTTP). Many of these marks are shared with obesity-related insulin resistance, supporting a continuum from OB to NAFLD to T2D mediated in part by DNAm[28]. Skeletal muscle, a major site of glucose disposal, also exhibits obesity- and T2D-associated methylation changes at genes regulating oxidative phosphorylation, mitochondrial biogenesis (PGC1A), and insulin signaling. Some methylation differences track with cardiorespiratory fitness and physical activity, highlighting environmental modulation[4, 18].

Pancreatic islets provide a direct link to β-cell MM. Islets from donors with T2D show altered DNAm at key β-cell genes, including those governing insulin secretion, ion channel function, and identity-maintaining transcription factors. Experimental models suggest that glucotoxicity and lipotoxicity can induce DNAm changes at β-cell genes that persist beyond the exposure period and blunt the response to later metabolic improvement[29].

Evidence for persistence of these DNAm marks after weight loss or glycemic improvement comes from bariatric surgery and intensive lifestyle intervention studies. In some cohorts, global and locus-specific methylation changes partially revert after substantial weight loss, particularly at genes related to inflammation and lipid metabolism; however, many obesity-associated CpGs remain differentially methylated compared with never-obese controls years after surgery[30]. This "epigenetic scar" may explain why residual cardiometabolic risk persists even in metabolically improved individuals. MM is also evident in blood-based DNAm markers. CpG sites at genes such as TXNIP consistently associate with fasting glucose, HbA1c, and progression to T2D across cohorts[30]. These sites may integrate cumulative glycemic exposure and thus act as molecular readouts of MM. Whether they are causal participants or biomarkers remains under investigation.

Collectively, DNAm signatures in metabolic tissues capture both current and past exposures to obesogenic and hyperglycemic environments. Their relative stability, accessibility in blood, and functional links to gene expression make them attractive candidates for MM biomarkers and potential therapeutic targets.

4. Histone Modifications, Chromatin Remodeling, and Metabolic Memory

Histone PTMs profoundly influence chromatin structure and transcriptional output. In obesity-driven diabetes, both classical marks (acetylation, methylation) and emerging acylation marks contribute to MM, particularly in inflammatory and oxidative stress pathways[31, 32]. Hyperglycemia and lipotoxicity can induce persistent increases in activating marks such as H3K9ac, H3K14ac, and H3K4me3 at promoters and enhancers of pro-inflammatory genes (e.g., IL6, TNF, CCL2) in endothelial cells, macrophages, and renal cells. Even brief high-glucose exposure leads to long-lasting "open" chromatin states and sustained inflammatory gene expression, a core example of MM at the chromatin level[33–35].

Conversely, repressive marks such as H3K9me2/3 and H3K27me3 may be reduced at pathological genes or increased at protective genes, tipping the balance toward disease. For instance, alterations in H3K9 methylation have been reported at antioxidant and metabolic genes in diabetic tissues, contributing to oxidative damage and mitochondrial dysfunction[36, 37].

HDACs and histone acetyltransferases (HATs) sit at the nexus of metabolic and epigenetic regulation. Several HDAC isoforms modulate β-cell survival, insulin secretion, hepatic gluconeogenesis, and insulin sensitivity in muscle and adipose tissue. Inhibition or genetic deletion of specific HDACs can improve metabolic phenotypes in preclinical models, partly by normalizing histone acetylation at metabolic gene loci[38]. Sirtuins (class III HDACs), which depend on NAD^+, act as metabolic sensors linking nutrient status to chromatin states, with

roles in mitochondrial function, inflammation, and aging. Chromatin remodelers further refine MM by repositioning nucleosomes and altering higher-order structure. Obesity and T2D have been associated with changes in occupancy of SWI/SNF complexes and other remodelers at key metabolic genes, although this area remains less mapped than DNAm and histone marks[38].

Emerging histone acylation marks such as crotonylation, β-hydroxybutyrylation, and succinylation are dictated by levels of their corresponding acyl-CoA metabolites[39]. In obesity, altered lipid and ketone body metabolism shifts these marks, potentially encoding a fine-grained metabolic history into chromatin. The reversibility and functional impact of these modifications in human OB/T2D are active research areas but likely contribute to MM by stabilizing or dampening gene programs responsive to specific nutrient states. Collectively, histone PTMs and chromatin remodeling provide a dynamic yet potentially persistent layer of MM. Their dependence on metabolic cofactors suggests that therapies targeting upstream metabolism (e.g., GLP-1 receptor agonists, SGLT2 inhibitors, or ketogenic strategies) might indirectly reprogram chromatin landscapes, while direct epigenetic drugs (HDAC/HAT/HMT inhibitors) could more specifically erase pathogenic memory—if targeted safely.

5. Noncoding RNAs, Epitranscriptomics, and 3D Genome Organization

Noncoding RNAs (ncRNAs) and RNA modifications add post-transcriptional and architectural layers to MM in obesity-driven diabetes. Numerous miRNAs are dysregulated in OB/T2D, affecting insulin signaling, lipid metabolism, inflammation, and β-cell function[40]. For instance, miR-375 and miR-7 regulate β-cell development and insulin secretion, while miR-29 and miR-143 modulate insulin sensitivity and adipogenesis. Obesity-associated induction of specific miRNAs can repress insulin receptor substrates, glucose transporters, or anti-inflammatory factors, reinforcing insulin resistance. Many miRNAs are themselves regulated by DNAm and histone marks at their promoters, embedding them within MM circuitry[40].

Long noncoding RNAs (lncRNAs) act as scaffolds, decoys, or guides for chromatin modifiers and transcription factors. In metabolic tissues, lncRNAs have been identified that control hepatic gluconeogenesis, adipocyte differentiation, and β-cell identity. Some lncRNAs recruit HMTs or HDACs to specific loci, establishing lasting chromatin states that persist after removal of the initial metabolic cue[22].

Epitranscriptomic marks, especially m6A, further shape MM by adjusting mRNA stability, splicing, and translation in response to metabolic cues. m6A writers (METTL3/14), erasers (FTO, ALKBH5), and readers (YTH family) are expressed in metabolic tissues and respond to nutrient statu[41]s. In pancreatic islets, m6A modifications on mRNAs related to insulin secretion, β-cell development, and cell stress are altered in obesity and T2D; FTO risk variants linked to obesity and T2D converge on m6A regulatory pathways[42]. Because RNA turnover is faster than DNA or histone marks, epitranscriptomic contributions to MM may be more plastic but still capable of integrating long-term metabolic exposures via feedback with DNA/histone modifications.

3D genome organization provides a physical framework for MM. Enhancer–promoter looping, topologically associating domains (TADs), and nuclear compartmentalization all influence which genes respond to metabolic signals[43]. Obesity-related inflammation and oxidative stress can remodel enhancer landscapes and loop architecture, clustering pro-inflammatory genes into highly interactive hubs. Some of these higher-order changes persist after normalization of metabolic parameters, suggesting a structural memory[43]. NcRNAs often interface with 3D genome architecture by tethering loci to particular nuclear compartments or by recruiting chromatin modifiers to loop anchors. Thus, ncRNAs, epitranscriptomics, and chromatin organization form a tightly interwoven system capable of encoding both immediate and long-term responses to obesity and hyperglycemia.

Understanding which ncRNAs and RNA marks function as drivers versus passengers of MM is crucial for therapeutic translation. Their relative accessibility (e.g., circulating miRNAs) also makes them attractive as minimally invasive biomarkers of obesity-driven epigenetic reprogramming.

6. Reversibility of Epigenetic Imprints: Lifestyle, Nutritional, and Surgical Interventions

A key translational question is the extent to which obesity-driven MM is reversible. Lifestyle and surgical interventions provide human "experiments" probing the plasticity of epigenetic marks in vivo.

Weight loss through hypocaloric diets, improved diet quality (e.g., Mediterranean or plant-based patterns), and increased physical activity influence DNAm, histone marks, and ncRNA profiles in metabolic tissues and blood. Intervention studies report partial normalization of obesity-associated methylation at genes involved in lipid metabolism, inflammation, and insulin signaling, often paralleling improvements in insulin sensitivity and liver fat[44]. Exercise can modulate muscle methylation and histone acetylation at genes governing mitochondrial biogenesis and glucose uptake; some of these changes persist for weeks to months, suggesting a form of "beneficial metabolic memory" that contrasts with pathogenic MM[44].

Diet composition matters beyond calories. Nutrients that feed one-carbon metabolism (folate, B-vitamins, choline) influence SAM levels and thus DNAm capacity, while polyphenols and short-chain fatty acids (SCFAs) from fiber fermentation can inhibit HDACs, promoting open chromatin at anti-inflammatory genes[45]. These observations suggest that "epigenetically smart" diets might more effectively remodel obesogenic imprints than calorie restriction alone.

Bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy) induces rapid and profound metabolic improvements, including remission of T2D in many patients. Epigenetic analyses show that surgery partially

reverses obesity-related DNAm changes in blood and adipose tissue, with some loci approaching lean-control methylation patterns within 1–3 years. However, many marks remain intermediate, neither fully obese nor fully lean, and the degree of epigenetic normalization varies between tissues and genomic regions[46]. This supports a model in which some epigenetic scars especially those established early in life or at key regulatory hubs are harder to erase.

Timing and duration of intervention are critical. Early aggressive control of weight and glycemia appears more effective at limiting MM than late intervention, analogously to findings in classic diabetes complication trials[47]. In children and adolescents with obesity, lifestyle programs can modulate DNAm at metabolic genes, but the long-term durability of these changes is not fully known.

Overall, lifestyle and surgical approaches can meaningfully remodel but not completely erase obesity-driven epigenetic imprints. This partial reversibility highlights the need for early prevention, sustained intervention, and possibly adjunctive therapies that directly target epigenetic machinery to fully reset pathogenic memory[17].

7. Pharmacologic Epigenetic Modulation, Biomarkers and Future Directions

Given the central role of epigenetics in MM, pharmacologic manipulation of epigenetic enzymes is an attractive but challenging strategy. Broad-spectrum DNMT and HDAC inhibitors are already used in oncology, demonstrating that epigenetic reprogramming is clinically feasible. However, their systemic, non-selective actions raise safety concerns for chronic metabolic indications[48].

Preclinical studies indicate that selective targeting of specific HDACs or HATs can improve insulin sensitivity, β-cell survival, and diabetic complications. For example, inhibition of particular HDAC isoforms can enhance insulin secretion and reduce hepatic gluconeogenesis, while modulating sirtuin activity influences mitochondrial function and inflammation[49]. Similarly, small molecules targeting histone methyltransferases or demethylases implicated in MM (e.g., those controlling H3K9 or H3K27 marks) might erase persistent inflammatory or fibrotic programs in metabolic tissues and organs such as kidney and heart[50]. Drugs already used in T2D may exert epigenetic effects. Metformin can influence DNAm and histone acetylation, partially via AMPK activation and effects on one-carbon metabolism. GLP-1 receptor agonists and SGLT2 inhibitors modulate inflammatory and oxidative stress pathways and may secondarily reprogram chromatin[50]. Understanding these pleiotropic actions could enable rational combination therapies where metabolic and epigenetic mechanisms synergize to counteract MM.

On the biomarker side, blood-based DNAm signatures, ncRNAs, and perhaps circulating nucleosomes or histone PTMs offer minimally invasive windows into tissue MM. CpGs at genes like TXNIP and other glycemia-associated loci, as well as obesity-related methylation patterns, have shown promise for predicting T2D onset and complications[50]. Circulating miRNAs linked to adiposity, insulin resistance, and β-cell stress could complement traditional clinical markers, enabling earlier detection of individuals with substantial epigenetic scars despite apparently controlled metabolic parameters.

Future research should address several key gaps:

1. **Tissue-resolved MM maps:** Systematic multi-omic profiling (DNAm, histone marks, chromatin accessibility, 3D structure, ncRNAs, epitranscriptomics) across adipose depots, liver, muscle, β-cells, vascular and immune compartments in longitudinal cohorts of obese individuals undergoing various interventions.
2. **Causality and prioritization:** Integrative approaches combining human genetics, CRISPR epigenome editing, and animal models to distinguish causal MM marks from bystanders and to identify high-value therapeutic targets.
3. **Windows of vulnerability and opportunity:** Characterizing critical periods (prenatal, early childhood, puberty, early adulthood) when obesity-driven epigenetic programming is most powerful and most amenable to reversal.
4. **Precision epigenetic medicine:** Developing isoform-selective, tissue-targeted epigenetic modulators (e.g., HDAC, HMT, or DNMT inhibitors; PROTACs; locus-specific epigenetic editors) with safety profiles suitable for chronic use in metabolic disease.
5. **Equity and trans-generational perspectives:** Recognizing that obesogenic environments and MM intersect with socioeconomic, dietary, and intergenerational factors, requiring public health strategies alongside molecular interventions.

CONCLUSION

In summary, metabolic memory in obesity-driven diabetes emerges from a complex but increasingly decipherable network of epigenetic imprints. While many marks are only partially reversible, growing evidence suggests that timely lifestyle interventions, metabolic drugs, and future epigenetic therapies can together soften or even erase the most harmful scars, shifting the trajectory of OB/T2D from inevitable progression to modifiable fate.

REFERENCES

1. Abbasi, M., Boka, D.A., DeLoit, H.: Nanomaterial-Enhanced Microneedles: Emerging Therapies for Diabetes and Obesity. Pharmaceutics. 16, 1344 (2024). https://doi.org/10.3390/pharmaceutics16101344

2. Acevedo-Román, A., Pagán-Zayas, N., Velázquez-Rivera, L.I., Torres-Ventura, A.C., Godoy-Vitorino, F.: Insights into Gut Dysbiosis: Inflammatory Diseases, Obesity, and Restoration Approaches. Int. J. Mol. Sci. 25, 9715 (2024). https://doi.org/10.3390/ijms25179715
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. Obes. Med. 100622 (2025). https://doi.org/10.1016/j.obmed.2025.100622
4. Uti, D.E., Ibiam, U.A., Omang, W.A., Udeozor, P.A., Umoru, G.U., Nwadum, S.K., Bawa, I., Alum, E.U., Mordi, J.C., Okoro, E.O., Obeten, U.N., Onwe, E.N., Zakari, S., Opotu, O.R., Aja, P.M.: Buchholzia coriacea Leaves Attenuated Dyslipidemia and Oxidative Stress in Hyperlipidemic Rats and Its Potential Targets In Silico. Pharm. Fronts. 05, e141–e152 (2023). https://doi.org/10.1055/s-0043-1772607
5. Choi, W., Woo, G.H., Kwon, T.-H., Jeon, J.-H.: Obesity-Driven Metabolic Disorders: The Interplay of Inflammation and Mitochondrial Dysfunction. Int. J. Mol. Sci. 26, 9715 (2025). https://doi.org/10.3390/ijms26199715
6. Roy, B.: Pathophysiological Mechanisms of Diabetes-Induced Macrovascular and Microvascular Complications: The Role of Oxidative Stress. Med. Sci. 13, 87 (2025). https://doi.org/10.3390/medsci13030087
7. Al Aboud, N.M., Tupper, C., Jialal, I.: Genetics, Epigenetic Mechanism. In: StatPearls. StatPearls Publishing, Treasure Island (FL) (2025)
8. Paro, P.D.R., Grossniklaus, P.D.U., Santoro, D.R., Wutz, P.D.A.: Epigenetics and Metabolism. In: Introduction to Epigenetics [Internet]. Springer (2021)
9. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? Obes. Med. 55, 100610 (2025). https://doi.org/10.1016/j.obmed.2025.100610
10. Barquissau, V., Léger, B., Beuzelin, D., Martins, F., Amri, E.-Z., Pisani, D.F., Saris, W.H.M., Astrup, A., Maoret, J.-J., Iacovoni, J., Déjean, S., Moro, C., Viguerie, N., Langin, D.: Caloric Restriction and Diet-Induced Weight Loss Do Not Induce Browning of Human Subcutaneous White Adipose Tissue in Women and Men with Obesity. Cell Rep. 22, 1079–1089 (2018). https://doi.org/10.1016/j.celrep.2017.12.102
11. Bensussen, A., Torres-Magallanes, J.A., Roces De Álvarez-Buylla, E.: Molecular tracking of insulin resistance and inflammation development on visceral adipose tissue. Front. Immunol. 14, 1014778 (2023). https://doi.org/10.3389/fimmu.2023.1014778
12. Andersen, P.A.K., Petrenko, V., Rose, P.H., Koomen, M., Fischer, N., Ghiasi, S.M., Dahlby, T., Dibner, C., Mandrup-Poulsen, T.: Proinflammatory Cytokines Perturb Mouse and Human Pancreatic Islet Circadian Rhythmicity and Induce Uncoordinated β-Cell Clock Gene Expression via Nitric Oxide, Lysine Deacetylases, and Immunoproteasomal Activity. Int. J. Mol. Sci. 22, 83 (2021). https://doi.org/10.3390/ijms22010083
13. McAndrews, K.M., Xiao, F., Chronopoulos, A., LeBleu, V.S., Kugeratski, F.G., Kalluri, R.: Exosome-mediated delivery of CRISPR/Cas9 for targeting of oncogenic KrasG12D in pancreatic cancer. Life Sci. Alliance. 4, e202000875 (2021). https://doi.org/10.26508/lsa.202000875
14. Russell-Hallinan, A., Karuna, N., Lezoualc'h, F., Matullo, G., Baker, H., Bernard, M., Devaux, Y., Badimon, L., Vilahur, G., Rieusset, J., Derumeaux, G.A., Watson, C.J.: Established and Emerging Roles of Epigenetic Regulation in Diabetic Cardiomyopathy. Diabetes Metab. Res. Rev. 41, e70081 (2025). https://doi.org/10.1002/dmrr.70081
15. Nohesara, S., Mostafavi Abdolmaleky, H., Pirani, A., Pettinato, G., Thiagalingam, S.: The Obesity–Epigenetics–Microbiome Axis: Strategies for Therapeutic Intervention. Nutrients. 17, 1564 (2025). https://doi.org/10.3390/nu17091564
16. Almeida, A.F., Miranda, M.S., Reis, R.L., Gomes, M.E., Rodrigues, M.T.: Using Hybrid Nanoplatforms to Combine Traditional Anti-Inflammatory Drug Delivery with RNA-Based Therapeutics for Macrophage Reprograming. Int. J. Mol. Sci. 25, 10693 (2024). https://doi.org/10.3390/ijms251910693
17. Izah, S.C., Betiang, P.A., Paul-Chima Ugwu, O., Ainebyoona, C., Uti, D.E., Echegu, D.A.: The Ketogenic Diet in Obesity Management: Friend or Foe? Cell Biochem. Biophys. (2025). https://doi.org/10.1007/s12013-025-01878-0
18. Sánchez-Ceinos, J., Hussain, S., Khan, A.W., Zhang, L., Almahmeed, W., Pernow, J., Cosentino, F.: Repressive H3K27me3 drives hyperglycemia-induced oxidative and inflammatory transcriptional programs in human endothelium. Cardiovasc. Diabetol. 23, 122 (2024). https://doi.org/10.1186/s12933-024-02196-0
19. Ahmed, F., Alhodieb, F.S., Alsanie, S.A., Rasheed, M., Ndagire, C.T.: Relationship between stress, diet, and gut microbiota: a cross-sectional study. Nutr. Metab. 22, 122 (2025). https://doi.org/10.1186/s12986-025-01014-y
20. Aremu, S.O., Akute, B., Aremu, D.O., Zando, C., Aremu, E.D., Nwachukwu, O.J., Omosebi, M.O., Akute, V.O., Oluwole, S.T., Barkhadle, A.A., Aremu, M.O.: Dietary strategies for preventing and managing obesity through evidence-based nutritional interventions. Discov. Public Health. 22, 424 (2025). https://doi.org/10.1186/s12982-025-00818-w

21. Posters. FEBS Open Bio. 15, 67–527 (2025). https://doi.org/10.1002/2211-5463.70071
22. Schmitz, S.U., Grote, P., Herrmann, B.G.: Mechanisms of long noncoding RNA function in development and disease. Cell. Mol. Life Sci. CMLS. 73, 2491–2509 (2016). https://doi.org/10.1007/s00018-016-2174-5
23. 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. Diab. Vasc. Dis. Res. 22, 14791641251334726 (2025). https://doi.org/10.1177/14791641251334726
24. Sivakumar, S., Lama, D., Rabhi, N.: Childhood obesity from the genes to the epigenome. Front. Endocrinol. 15, (2024). https://doi.org/10.3389/fendo.2024.1393250
25. Juvinao-Quintero, D.L., Marioni, R.E., Ochoa-Rosales, C., Russ, T.C., Deary, I.J., van Meurs, J.B.J., Voortman, T., Hivert, M.-F., Sharp, G.C., Relton, C.L., Elliott, H.R.: DNA methylation of blood cells is associated with prevalent type 2 diabetes in a meta-analysis of four European cohorts. Clin. Epigenetics. 13, 40 (2021). https://doi.org/10.1186/s13148-021-01027-3
26. Barber, T.M., Kyrou, I., Randeva, H.S., Weickert, M.O.: Mechanisms of Insulin Resistance at the Crossroad of Obesity with Associated Metabolic Abnormalities and Cognitive Dysfunction. Int. J. Mol. Sci. 22, 546 (2021). https://doi.org/10.3390/ijms22020546
27. Bigornia, S.J., Farb, M.G., Mott, M.M., Hess, D.T., Carmine, B., Fiscale, A., Joseph, L., Apovian, C.M., Gokce, N.: Relation of depot-specific adipose inflammation to insulin resistance in human obesity. Nutr. Diabetes. 2, e30 (2012). https://doi.org/10.1038/nutd.2012.3
28. Berlanga, A., Guiu-Jurado, E., Porras, J.A., Auguet, T.: Molecular pathways in non-alcoholic fatty liver disease. Clin. Exp. Gastroenterol. 7, 221–239 (2014). https://doi.org/10.2147/CEG.S62831
29. Yau, B., Ghislain, J., Kebede, M.A., Hughes, J., Poitout, V.: The role of the beta cell in type 2 diabetes: new findings from the last 5 years. Diabetologia. 68, 2092–2103 (2025). https://doi.org/10.1007/s00125-025-06499-z
30. 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
31. Kaisar, M.M.M., Pelgrom, L.R., van der Ham, A.J., Yazdanbakhsh, M., Everts, B.: Butyrate Conditions Human Dendritic Cells to Prime Type 1 Regulatory T Cells via both Histone Deacetylase Inhibition and G Protein-Coupled Receptor 109A Signaling. Front. Immunol. 8, (2017). https://doi.org/10.3389/fimmu.2017.01429
32. Li, D., Peng, X., Hu, Z., Li, S., Chen, J., Pan, W.: Small molecules targeting selected histone methyltransferases (HMTs) for cancer treatment: Current progress and novel strategies. Eur. J. Med. Chem. 264, 115982 (2024). https://doi.org/10.1016/j.ejmech.2023.115982
33. Aouadi, M., Vangala, P., Yawe, J.C., Tencerova, M., Nicoloro, S.M., Cohen, J.L., Shen, Y., Czech, M.P.: Lipid storage by adipose tissue macrophages regulates systemic glucose tolerance. Am. J. Physiol. - Endocrinol. Metab. 307, E374–E383 (2014). https://doi.org/10.1152/ajpendo.00187.2014
34. Li, M., Yang, Y., Xiong, L., Jiang, P., Wang, J., Li, C.: Metabolism, metabolites, and macrophages in cancer. J. Hematol. Oncol.J Hematol Oncol. 16, 80 (2023). https://doi.org/10.1186/s13045-023-01478-6
35. Prabhu, S., Deng, H., Cross, T.-W.L., Shahoei, S.H., Konopka, C.J., Medina, N.G., Applegate, C.C., Wallig, M.A., Dobrucki, L.W., Nelson, E.R., Smith, A.M., Swanson, K.S.: Nanocarriers Targeting Adipose Macrophages Increase Glucocorticoid Anti-Inflammatory Potency to Ameliorate Metabolic Dysfunction. Biomater. Sci. 9, 506–518 (2021). https://doi.org/10.1039/d0bm01142h
36. Bhatti, J.S., Bhatti, G.K., Reddy, P.H.: Mitochondrial dysfunction and oxidative stress in metabolic disorders - A Step towards mitochondria based therapeutic strategies. Biochim. Biophys. Acta. 1863, 1066–1077 (2017). https://doi.org/10.1016/j.bbadis.2016.11.010
37. Li, X., Chen, W., Jia, Z., Xiao, Y., Shi, A., Ma, X.: Mitochondrial Dysfunction as a Pathogenesis and Therapeutic Strategy for Metabolic-Dysfunction-Associated Steatotic Liver Disease. Int. J. Mol. Sci. 26, 4256 (2025). https://doi.org/10.3390/ijms26094256
38. Sandonà, M., Cavioli, G., Renzini, A., Cedola, A., Gigli, G., Coletti, D., McKinsey, T.A., Moresi, V., Saccone, V.: Histone Deacetylases: Molecular Mechanisms and Therapeutic Implications for Muscular Dystrophies. Int. J. Mol. Sci. 24, 4306 (2023). https://doi.org/10.3390/ijms24054306
39. Khan, A., Bridgers, J.B., Strahl, B.D.: Expanding the reader landscape of histone acylation. Struct. Lond. Engl. 1993. 25, 571–573 (2017). https://doi.org/10.1016/j.str.2017.03.010
40. Amine, I.M., Salsabil, H., Fadil, B., Adnane, B., Khaoula, E.: The impact of ncRNAs on type 2 diabetes: A comprehensive review covering molecular mechanisms to clinical applications. Mol. Ther. Nucleic Acids. 36, 102629 (2025). https://doi.org/10.1016/j.omtn.2025.102629
41. Ejemot-Nwadiaro, R.I., Basajja, M., Uti, D.E., Ugwu, O.P.-C., Aja, P.M.: Epitranscriptomic alterations induced by environmental toxins: implications for RNA modifications and disease. Genes Environ. 47, 14 (2025). https://doi.org/10.1186/s41021-025-00337-9
42. Petri, B.J., Klinge, C.M.: m6A readers, writers, erasers, and the m6A epitranscriptome in breast cancer. J. Mol. Endocrinol. 70, e220110 (2023). https://doi.org/10.1530/JME-22-0110

43. Kumar, S., Kaur, S., Seem, K., Kumar, S., Mohapatra, T.: Understanding 3D Genome Organization and Its Effect on Transcriptional Gene Regulation Under Environmental Stress in Plant: A Chromatin Perspective. Front. Cell Dev. Biol. 9, 774719 (2021). https://doi.org/10.3389/fcell.2021.774719
44. Feidantsis, K., Methenitis, S., Ketselidi, K., Vagianou, K., Skepastianos, P., Hatzitolios, A., Mourouglakis, A., Kaprara, A., Hassapidou, M., Nomikos, T., Papadopoulou, S.K.: Comparison of short-term hypocaloric high-protein diets with a hypocaloric Mediterranean diet: Effect on body composition and health-related blood markers in overweight and sedentary young participants. Nutr. Burbank Los Angel. Cty. Calif. 91–92, 111365 (2021). https://doi.org/10.1016/j.nut.2021.111365
45. den Besten, G., van Eunen, K., Groen, A.K., Venema, K., Reijngoud, D.-J., Bakker, B.M.: The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J. Lipid Res. 54, 2325–2340 (2013). https://doi.org/10.1194/jlr.R036012
46. Clark, M., Thomaseth, K., Dirikolu, L., Ferguson, D.C., Hoenig, M.: Effects of Pioglitazone on Insulin Sensitivity and Serum Lipids in Obese Cats. J. Vet. Intern. Med. 28, 166–174 (2014). https://doi.org/10.1111/jvim.12255
47. An, X., Zhang, Y., Sun, W., Kang, X., Ji, H., Sun, Y., Jiang, L., Zhao, X., Gao, Q., Lian, F., Tong, X.: Early effective intervention can significantly reduce all-cause mortality in prediabetic patients: a systematic review and meta-analysis based on high-quality clinical studies. Front. Endocrinol. 15, 1294819 (2024). https://doi.org/10.3389/fendo.2024.1294819
48. Mabe, N.W., Perry, J.A., Malone, C.F., Stegmaier, K.: Pharmacologic Targeting of the Cancer Epigenome. Nat. Cancer. 5, 844–865 (2024). https://doi.org/10.1038/s43018-024-00777-2
49. Alharbi, H.O.A., Alshebremi, M., Babiker, A.Y., Rahmani, A.H.: The Role of Quercetin, a Flavonoid in the Management of Pathogenesis Through Regulation of Oxidative Stress, Inflammation, and Biological Activities. Biomolecules. 15, 151 (2025). https://doi.org/10.3390/biom15010151
50. Ma, Y., Lv, W., Guo, Y., Yin, T., Bai, Y., Liu, Z., Chen, C., WenjuanYang, Feng, J., Qian, W., Tang, R., Su, Y., Shan, S., Dong, H., Bao, Y., Qu, L.: Histone demethylases in autophagy and inflammation. Cell Commun. Signal. 23, 24 (2025). https://doi.org/10.1186/s12964-024-02006-w

CITE AS: Odile Patrick Thalia (2026). Metabolic Memory in Obesity-Driven Diabetes: Epigenetic Imprints and their Reversibility. RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 5(1):42-49. https://doi.org/10.59298/RIJRMS/2026/514249