IAA Journal of Scientific Research 13(1):111-118, 2026. www.iaajournals.org

©IAAJOURNALS ISSN: 2636-7319

https://doi.org/10.59298/IAAJSR/2026/131111118 IAAJSR:1311

Epigenetic Alterations in Obesity-Driven Type 2 Diabetes: Implications for Personalized Medicine

Abaho Areeba Fortunate

Department of Pharmacy Kampala International University Uganda
Email address: fortunate.abaho@studwc.kiu.ac.ug

ABSTRACT

Obesity-driven type 2 diabetes (T2D) reflects chronic environmental stress overnutrition, inactivity, and circadian disruption imprinted onto chromatin in metabolic tissues. Epigenetic changes integrate nutrient, hormonal, and inflammatory cues into durable programs of gene expression without altering DNA sequence. Across adipose tissue, liver, skeletal muscle, pancreatic islets, and hypothalamus, obesity associates with characteristic shifts in DNA methylation; histone acetylation/methylation; nucleosome positioning and 3-D genome architecture; and non-coding RNA networks. These programs rewire pathways for insulin signaling, substrate partitioning, mitochondrial biogenesis, and secretory function, helping explain heterogeneity in diabetes risk and treatment response. Importantly, many marks remain plastic: weight loss, exercise, bariatric/metabolic surgery, and diet quality partially reset epigenomes; conversely, "metabolic memory" preserves adverse marks after glycemic normalization, contributing to residual risk. Microbiome-derived metabolites (e.g., short-chain fatty acids) and endocrine disruptors add upstream layers of modulation. Translational opportunities include (i) blood-based and tissue-informed epigenetic biomarkers to stage disease and predict drug response; (ii) repurposed or next-generation "epidrugs" that modulate writers, erasers, and readers; (iii) nutriepigenomic strategies aligned to an individual's epigenetic phenotype; and (iv) targeted epigenome editing that alters regulatory elements without changing DNA sequence. Safety, durability, and equity are central challenges. This review synthesizes organ-specific epigenetic mechanisms linking obesity to T2D, examines interactions with inflammation and mitochondrial stress, and outlines a precision-medicine roadmap that leverages multi-omics and modifiable exposures to restore metabolic flexibility and reduce long-term complications.

Keywords: DNA methylation; histone modification; non-coding RNAs; metabolic memory; precision medicine

INTRODUCTION

Type 2 diabetes (T2D) emerges when chronic nutrient surplus overwhelms the body's capacity to maintain flexible control of glucose and lipid fluxes across the liver, skeletal muscle, adipose tissue (AT), and pancreatic islets[1–3]. Genetics sets baseline risk, but environment and behavior, diet composition, physical activity, sleep/circadian patterns, psychosocial stress, and early-life exposures dominate population-level variance[4, 5]. Epigenetics provides the mechanistic bridge between these exposures and durable shifts in cellular function. Epigenetic information comprises DNA methylation at cytosines, post-translational histone marks (acetylation, methylation, phosphorylation, ubiquitination), chromatin remodeling that repositions nucleosomes, higher-order chromatin looping, and regulatory non-coding RNAs (miRNAs, lncRNAs, circRNAs)[6–9]. Together, these layers govern access of transcription factors and the transcriptional machinery to enhancers and promoters, thereby shaping gene expression programs that regulate insulin sensitivity, mitochondrial capacity, adipogenesis, inflammation, and β-cell insulin secretion.

Obesity perturbs epigenomes through sustained hormonal and metabolic signals. Hyperinsulinemia and hyperglycemia alter acetyl-CoA and S-adenosylmethionine pools, influencing histone acetylation and DNA methylation capacity[10–12]. Lipotoxic species (diacylglycerols, ceramides) activate stress kinases and redox programs that recruit chromatin modifiers. Inflammation, such as TNF-α, IL-1β, IL-6—drives NF-κB/AP-1 binding at accessible chromatin, installing activating marks such as H3K27ac at inflammatory enhancers and

repressive marks at insulin-sensitizing loci. Mitochondrial dysfunction shifts NAD+/NADH and α-ketoglutarate/succinate ratios that regulate sirtuins (class III HDACs) and α-ketoglutarate-dependent dioxygenases (TET DNA demethylases and JmjC histone demethylases)[13]. The gut microbiome contributes metabolites with epigenetic effects: short-chain fatty acids inhibit class I/II HDACs; bile acid species signal through FXR/TGR5 to refashion metabolic gene networks; tryptophan-derived indoles engage the aryl hydrocarbon receptor to maintain barrier and immune tone[14, 15].

Epigenetic responses are tissue- and depot-specific. In subcutaneous WAT, healthy expansion relies on adipogenesis programs regulated by PPARγ, C/EBPs, and chromatin remodelers; in visceral WAT, fibrosis and inflammation dominate, with enhancer landscapes biased toward chemokine and ECM genes[7, 16, 17]. In skeletal muscle, chromatin at oxidative metabolism genes and insulin-responsive enhancers becomes less accessible with inactivity and high fat intake, reducing GLUT4 translocation and mitochondrial biogenesis. In the liver, obesity remodels enhancers controlling gluconeogenesis and lipogenesis, favoring steatosis. In pancreatic β-cells, glucolipotoxic stress reshapes enhancer–promoter loops, suppressing genes needed for stimulus-secretion coupling and promoting dedifferentiation.

Crucially, many epigenetic marks are plastic on the time scale of weeks to months. Exercise training increases enhancer acetylation at oxidative and glucose-handling genes in muscle; weight loss reduces inflammatory enhancer activity in AT and the liver; bariatric/metabolic surgery resets methylation at energy-homeostasis loci in multiple tissues[18]. Yet some marks exhibit metabolic memory persisting after glycemia improves, helping explain why early glycemic control reduces long-term complications. Early-life programming adds another layer: maternal obesity or gestational diabetes associates with altered methylation at metabolic genes in the placenta, cord blood, and offspring tissues, with potential transgenerational echoes through the germline[19].

For precision medicine, the promise is two-fold. First, epigenetic profiles can enrich risk prediction beyond genetics and clinical metrics, stratifying who will benefit from lifestyle, surgery, or specific drugs[20]. Second, epigenetic mechanisms are actionable: enzymes that write, erase, or read marks are druggable; nutrient patterns can tune cofactor availability; and CRISPR-based tools can retune regulatory DNA without editing sequence. Implementation requires robust assays, causal inference, and attention to safety and equity. The following sections review (1) DNA methylation landscapes in metabolic tissues; (2) histone marks and chromatin remodeling; (3) non-coding RNA circuits and extracellular vesicles; (4) developmental and environmental programming; (5) epigenetic crosstalk with immunometabolism and mitochondrial stress, including metabolic memory; and (6) a translational roadmap to individualized therapy.

2. DNA Methylation Landscapes Across Metabolic Tissues

DNA methylation at CpG dinucleotides modulates transcription by recruiting methyl-CpG–binding proteins, excluding transcription factors from binding sites, and shaping chromatin compaction. In obesity and T2D, methylation shifts occur at promoters, enhancers, and CpG shores, often in tissue-specific patterns[7, 9, 17, 21]. Adipose tissue from individuals with obesity shows differential methylation at genes governing adipogenesis (PPARG, CEBPA), lipolysis (LIPE), insulin signaling (IRS1), and extracellular-matrix remodeling. Visceral adipose depots often display hypermethylation of insulin-sensitizing genes and hypomethylation of pro-inflammatory loci, aligning with higher cytokine output and lipolysis[2, 22–24].

In skeletal muscle, methylation changes affect oxidative phosphorylation, lipid handling (CPT1B, PDK4), and glucose transport (SLC2A4/GLUT4). Physical inactivity increases methylation at exercise-responsive enhancers; endurance training partly reverses these marks in weeks, paralleling improved insulin sensitivity[23, 25–27]. Liver methylomes in NAFLD/NASH and T2D display changes at gluconeogenic genes (G6PC, PCK1), lipid synthesis regulators (SREBF1, FASN), and inflammatory pathways, reflecting combined nutrient and cytokine stress[28–30]. Pancreatic islets in T2D exhibit altered methylation at insulin secretory genes and β-cell identity factors; chronic hyperglycemia imprints promoter/enhancer methylation patterns that blunt stimulus-secretion coupling[31].

Methylation dynamics are maintained by DNA methyltransferases (DNMT1 for maintenance; DNMT3A/B for de novo) and reversed by TET dioxygenases (TET1/2/3), which oxidize 5-methylcytosine to 5-hydroxymethylcytosine and successive derivatives[7, 17, 32]. These enzymes respond to metabolic cofactors: DNMTs use S-adenosylmethionine (SAM) as a methyl donor, linking one-carbon metabolism (folate, B12, choline, methionine) to methylation capacity; TETs require Fe2+ and α-ketoglutarate, connecting to the TCA cycle. NAD+ availability modulates sirtuin activity, indirectly influencing methylation through transcriptional crosstalk[9, 32].

Importantly, not all methylation changes are causal. Integrative analyses combining methylation with chromatin accessibility (ATAC-seq), histone marks (ChIP/CUT&Tag), and gene expression (RNA-seq) are needed to identify regulatory sites that genuinely control transcription. Mendelian randomization and perturbation studies (e.g., CRISPR interference/activation at enhancers) help infer directionality[33]. For translation, circulating cell-free DNA (cfDNA) methylation profiles and leukocyte methylomes serve as accessible proxies for tissue states. Panels targeting metabolic pathways, adipokine signaling, or inflammatory enhancers could stage disease, detect NAFLD activity, or stratify responders to thiazolidinediones, GLP-1 RAs,

or SGLT2 inhibitors. Finally, methylation captures exposure history, dietary patterns, smoking, sleep/circadian disruption—providing a "biosocial" layer to risk assessment[33].

3. Histone Modifications and Chromatin Remodeling in Metabolic Control

Histone tails integrate environmental signals into chromatin states that either promote or restrict transcription[34–36]. Acetylation (e.g., H3K27ac, H3K9ac) correlates with active enhancers and promoters; methylation can activate (H3K4me1/3) or repress (H3K27me3, H3K9me3) depending on residue and context. Writers (HATs/KATs such as p300/CBP; HMTs such as MLL/KMT2, EZH2/KMT6), erasers (HDACs, sirtuins; KDMs such as KDM5/6), and readers (BET bromodomains like BRD4; chromodomains; PHD fingers) regulate these marks and are modulated by metabolites (acetyl-CoA, NAD+, α-KG, SAM) that fluctuate with diet and energy status[37, 38].

In adipose tissue, thermogenic and adipogenic programs are epigenetically controlled. Beige/brown fate requires enhancer priming by PPARγ/PRDM16 coactivator complexes with p300/CBP, deposition of H3K27ac at UCP1 and oxidative genes, and removal of repressive H3K27me3 by KDM6A/B. Obesity suppresses these programs while enhancing inflammatory enhancer activity via NF-κB/AP-1 and BRD4 recruitment[39]. Fibrotic remodeling involves SWI/SNF (BAF) and ISWI complexes reconfiguring chromatin at ECM and TGF-β genes, limiting healthy hyperplasia.

In skeletal muscle, inactivity and high-fat feeding reduce H3K27ac at enhancers near PGC-1α targets and insulin-responsive genes, compromising mitochondrial biogenesis and glucose uptake; exercise reverses these changes within days, highlighting rapid chromatin plasticity[25, 25, 27]. Hepatic chromatin integrates carbohydrate/fat fluxes via ChREBP/SREBP1c at lipogenic enhancers and FOXO/PGC-1α at gluconeogenic loci; obesity increases enhancer acetylation at de novo lipogenesis genes while installing repressive marks at fatty-acid oxidation loci. β-cells under glucolipotoxic stress lose H3K27ac at identity genes and gain repressive marks, accompanying dedifferentiation[40–42].

Chromatin architecture adds a 3D layer. Cohesin/CTCF organizes associating domains (TADs) and enhancer–promoter loops; metabolic stress can alter loop strength, rewiring gene control. Nuclear lamina interactions (LADs) sequester regions into repressive compartments; shifts toward lamina association can lock metabolic genes in low-expression states[43]. ATP-dependent remodelers (SWI/SNF, INO80, CHD) reposition nucleosomes to control accessibility; their subunit composition changes with differentiation and inflammation.

Therapeutic implications are concrete. HDAC inhibitors increase acetylation and can promote beiging and insulin sensitivity in preclinical models, though off-target effects and tolerance limit clinical use[44]. Sirtuin activators (raising NAD+ or direct modulation) enhance mitochondrial programs and stress resistance. BET bromodomain inhibitors dampen inflammatory super-enhancers but require careful dosing to avoid hematologic toxicity. Selective PPAR modulators cooperate with chromatin remodelers to restore adipogenesis. Diet and exercise act upstream by shifting metabolite pools that co-regulate writers/erasers, providing safe, scalable levers to re-tune chromatin states[45].

4. Non-coding RNAs and Extracellular Vesicle Circuits

Non-coding RNAs (ncRNAs) are integral epigenetic regulators that fine-tune transcriptional and post-transcriptional networks. MicroRNAs (miRNAs) such as miR-103/107 (insulin signaling), miR-29 (ECM and insulin resistance), miR-33 (cholesterol/fatty-acid metabolism), and miR-375 (β-cell function) modulate key nodes across tissues. In obesity/T2D, altered miRNA expression in AT, liver, muscle, and islets contributes to impaired insulin signaling, mitochondrial dysfunction, and inflammatory tone[46]. Long non-coding RNAs (lncRNAs) guide chromatin modifiers to specific loci, scaffold enhancer–promoter contacts, or act as decoys for miRNAs. Examples include lncRNAs that coordinate adipogenesis and thermogenesis, and β-cell lncRNAs that control insulin gene transcription and exocytosis. Circular RNAs (circRNAs) can sponge miRNAs, regulate transcription, or in teract with RNA-binding proteins, adding stability to regulatory circuits [47].

Interorgan communication leverages extracellular vesicles (EVs) like exosomes and microvesicles that carry ncRNAs, proteins, and lipids. Adipocyte-derived EVs in obesity deliver miRNAs to liver and muscle, suppressing insulin signaling and promoting steatosis; EVs from inflamed AT also reprogram macrophages toward pro-inflammatory states. Conversely, exercise remodels EV cargo toward insulin-sensitizing profiles. Hepatic or muscle-derived EVs feed back on AT and islets, influencing lipolysis and insulin secretion. Circulating EV ncRNAs thus serve as minimally invasive biomarkers reflecting depot-specific pathology and therapy response[48].

NcRNA biogenesis and turnover interface with classical epigenetics. Promoter methylation and histone marks regulate miRNA/lncRNA transcription; in turn, ncRNAs recruit DNMTs, TETs, or histone modifiers to target genes, creating feedback loops. Metabolic cues (NAD+, acetyl-CoA) and stress pathways (NF-κB, HIF-1α) alter ncRNA transcription and processing, integrating environmental information[48].

Therapeutically, miRNA mimics or antagomirs can shift networks but face delivery and specificity challenges. Lipid nanoparticles and tissue-tropic EVs are promising carriers; liver-directed delivery is currently most feasible. ASOs targeting lncRNAs or circRNAs offer alternatives, while small molecules that disrupt RNA–protein interfaces are emerging. Safety considerations include immune activation and off-target effects;

combining ncRNA modulation with lifestyle or pharmacologic decompression of nutrient stress may amplify benefit while minimizing dose[49]. In near-term practice, EV-miRNA panels could stratify patients by inflammatory/steatotic burden, predict response to TZDs or GLP-1 RAs, and monitor remission after bariatric surgery.

5. Developmental and Environmental Programming of Metabolic Epigenomes

Early-life environments leave durable epigenetic imprints that shape lifelong metabolic risk. Maternal obesity and gestational diabetes are associated with altered methylation of metabolic genes in the placenta and cord blood and with shifts in neonatal adiposity and insulin sensitivity[50]. Nutrient availability, inflammatory milieu, and hormonal signals in utero influence one-carbon metabolism and histone modification enzymes, programming hypothalamic appetite circuits, β-cell mass, and adipocyte number. Paternal factors contribute via sperm DNA methylation and small RNA payloads shaped by diet, obesity, and stress, with effects observed on offspring metabolic phenotypes in animal models and increasingly in human cohorts.

Beyond perinatal windows, adolescence and puberty represent periods of epigenetic plasticity as endocrine axes mature. Sleep duration, circadian alignment, and physical activity during these stages modulate chromatin at genes governing glucocorticoid signaling, mitochondrial function, and appetite regulation[50]. Environmental chemicals, e.g., certain plasticizers, persistent organic pollutants, and air pollutants, can interact with nuclear receptors and redox pathways to alter chromatin, although effect sizes and causality vary across studies; precaution and exposure reduction remain prudent[51]. The gut microbiome contributes through SCFAs (HDAC inhibition), bile acid profiles (FXR/TGR5), and indoles (AhR), linking diet quality and microbial ecology to host epigenomes[52].

Circadian disruption, common with shift work and social jetlag, misaligns feeding–fasting cycles and the hepatic clock, altering rhythmic chromatin accessibility and histone acetylation at metabolic loci. Restoring sleep regularity and time-restricted feeding realigns oscillatory epigenomes and improves insulin sensitivity. Physical activity acts as a potent epigenetic modulator across tissues, rapidly increasing enhancer acetylation and DNA hypomethylation at oxidative genes in muscle and improving inflammatory gene regulation in AT and liver[53].

Intervention studies demonstrate partial reversibility. Caloric restriction, Mediterranean-style and high-fiber diets, and bariatric surgery induce methylation and histone acetylation changes that track with improved glycemia and hepatic steatosis. However, some adverse marks persist in metabolic memory, arguing for early prevention and sustained lifestyle alignment[53]. For personalized medicine, capturing exposure histories (diet, sleep, toxins, stress) alongside epigenetic readouts enables tailored risk counseling and targeted behavioral prescriptions that exploit periods of maximal plasticity.

6. Epigenetics, Immunometabolism, Mitochondria, and Metabolic Memory

Epigenetic and metabolic networks co-evolve during obesity to stabilize insulin resistance and β-cell stress. In adipose tissue, NF-κB/AP-1 engagement at accessible enhancers installs H3K27ac and H3K4me1 at inflammatory genes while promoting H3K9me3/H3K27me3 at adipogenic and thermogenic loci[54]. Macrophages in obese AT adopt a lipid-associated, pro-inflammatory state with enhancer landscapes tuned to foam-cell–like metabolism; trained-immunity–type reprogramming of innate cells persists after the initial stimulus, sustaining cytokine output. Hepatic Kupffer cells and stellate cells undergo similar epigenetic shifts that reinforce steatohepatitis and fibrosis. In skeletal muscle, chronic lipid overload and inactivity reduce enhancer activity at mitochondrial and insulin-responsive genes, while increased DNA methylation at key loci blunts plasticity[54].

Mitochondrial dysfunction feeds back onto chromatin by altering NAD+, acetyl-CoA, and α-KG levels, cofactors for sirtuins, HATs, and dioxygenases. ROS oxidize 5-mC bases and histone residues, perturbing writers/erasers and promoting DNA damage responses that reshape chromatin[27, 55, 56]. Conversely, sirtuin-driven deacetylation (e.g., SIRT1/3) reinforces oxidative metabolism and antioxidant programs, improving insulin sensitivity.

Metabolic memory describes the persistence of epigenetic marks and vascular risk after glycemic normalization. Hyperglycemia installs durable histone acetylation/methylation at inflammatory and profibrotic genes in endothelial and immune cells; DNA methylation changes at antioxidant and repair genes persist, sustaining oxidative stress and dysfunction[8, 19]. Early, aggressive glycemic control reduces long-term complications, likely by preventing the installation of these marks [57]. Exercise and weight loss also remodel epigenomes toward resilience; combining early metabolic control with lifestyle-induced epigenetic reprogramming may yield additive protection.

Therapeutically, targeting epigenetic–immune–mitochondrial crosstalk could break feed-forward loops: (i) NAD+ repletion and mitochondrial fitness training (exercise, cold exposure) to reset cofactor-sensitive enzymes; (ii) BET inhibition or super-enhancer disruption to dampen inflammatory circuitry; (iii) NLRP3 and IL-1 pathway modulation to reduce cytokine-driven chromatin remodeling; and (iv) adipogenesis/thermogenesis restoration (PPARγ agonism, safe thermogenic activation) to shift enhancer usage toward lipid buffering and oxidation[58]. Biomarkers of trained immunity and mitochondrial redox state may help select patients who benefit from these strategies.

7. Translational Roadmap: Biomarkers, Therapies, and Personalized Implementation

Biomarkers: Practical translation begins with accessible assays that reflect tissue epigenomes. Candidate tools include (a) targeted cfDNA methylation panels for liver steatosis/fibrosis activity and adipose inflammation; (b) leukocyte methylation signatures integrating inflammatory and metabolic loci; (c) EV-miRNA/lncRNA panels indexing depot-specific stress; and (d) composite "epi-scores" that forecast response to GLP-1 RAs, SGLT2 inhibitors, TZDs, or bariatric surgery. Single-cell multi-omics (scATAC-seq, scRNA-seq, scCUT&Tag) in biopsy cohorts can define gold standards for algorithm training.

Therapeutics: Upstream, lifestyle interventions remain the safest epigenetic medicines: endurance/resistance training, high-fiber minimally processed diets, circadian alignment, and weight loss shift cofactor pools and repress inflammatory super-enhancers. Nutriepigenomics, such as tailoring fiber types (inulin, resistant starch), methyl donors (folate, betaine), and polyphenols to baseline epigenetic/metabolic states, offers low-risk personalization. Pharmacologic options include PPARγ agonists (raising adiponectin and restoring adipogenesis), metformin/AMPK activators (influencing chromatin via acetyl-CoA/NAD+), SGLT2 inhibitors (reducing glucotoxic ER/oxidative stress), and incretin-based polyagonists (weight loss with islet protection). Experimental epigenetic drugs, selective HDAC inhibitors, BET inhibitors, EZH2/KDM modulators, and sirtuin activators require careful dosing and monitoring, given pleiotropy. CRISPR-based epigenome editing (dCas9-p300, dCas9-KRAB, base editors targeting enhancer CpGs) enables locus-specific modulation without sequence changes; near-term applications are likely ex vivo or in accessible tissues.

Implementation. Decision support should integrate clinical variables (adiposity pattern, NAFLD, CVD risk), behavior (diet, sleep, activity), and multi-omic data into transparent models that recommend lifestyle sequencing and drug choice. Pragmatic trials can test epigenetically informed care vs standard algorithms, using mechanistic endpoints (hepatic fat MRI-PDFF, CGM patterns, inflammatory/EV-miRNA panels). Ethical guardrails are essential: explainability, privacy of genomic/epigenomic data, and equitable access to lifestyle resources and advanced therapies. Health systems should prioritize interventions with high benefit-to-cost ratios, structured exercise and diet programs, while building pathways to advanced options for high-risk endotypes.

CONCLUSION

Epigenetic alterations are central to how obesity becomes diabetes: they encode environmental and metabolic exposures into chromatin states that steer insulin signaling, mitochondrial capacity, inflammation, and β-cell function. These marks are neither immutable nor uniformly detrimental; they are contextual and partly reversible. Lifestyle interventions, early glycemic control, and selected pharmacotherapies can remodel epigenomes toward resilience, while next-generation tools, biomarker panels, epidrugs, and targeted epigenome editing promise individualized restoration of metabolic flexibility. The practical path forward pairs scalable foundations (exercise, diet quality, sleep regularity) with epigenetically informed sequencing of therapies, guided by minimally invasive assays that reflect tissue health. By shifting care from glucose-centric management to exposure-aware, chromatin-aware strategies, we can prevent onset, accelerate remission, and reduce complications of obesity-driven T2D—delivering precision medicine that is scientifically grounded and clinically actionable.

REFERENCES

1. AbdlWhab, H.M., Al-Saffar, A., Mahdi, O.A., Alameri, R.B.: The impact of insulin resistance and glycaemic control on insulin-like growth factor-1 in patients with type 2 diabetes: a cross-sectional study. Clin. Diabetes Endocrinol. 10, 36 (2024). https://doi.org/10.1186/s40842-024-00202-8
2. Alzaid, F., Fagherazzi, G., Riveline, J.-P., Bahman, F., Al-Rashed, F., Al-Mulla, F., Ahmad, R.: Immune cell–adipose tissue crosstalk in metabolic diseases with a focus on type 1 diabetes. Diabetologia. 68, 1616–1631 (2025). https://doi.org/10.1007/s00125-025-06437-z
3. 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
4. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obes. Med. 56, 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
5. Izah, S.C., Betiang, P.A., Paul-Chima Ugwu, O., Ainebyoona, C., Uti, D.E., Echegu, D.A., Alum, B.N.: The Ketogenic Diet in Obesity Management: Friend or Foe? Cell Biochem. Biophys. (2025). https://doi.org/10.1007/s12013-025-01878-0
6. Cuevas-Sierra, A., Ramos-Lopez, O., Riezu-Boj, J.I., Milagro, F.I., Martinez, J.A.: Diet, Gut Microbiota, and Obesity: Links with Host Genetics and Epigenetics and Potential Applications. Adv. Nutr. 10, S17–S30 (2019). https://doi.org/10.1093/advances/nmy078
7. Hervouet, E., Peixoto, P., Delage-Mourroux, R., Boyer-Guittaut, M., Cartron, P.-F.: Specific or not specific recruitment of DNMTs for DNA methylation, an epigenetic dilemma. Clin. Epigenetics. 10, 17 (2018). https://doi.org/10.1186/s13148-018-0450-y
8. Kato, M., Natarajan, R.: Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat. Rev. Nephrol. 15, 327–345 (2019). https://doi.org/10.1038/s41581-019-0135-6

9. Maleknia, M., Ahmadirad, N., Golab, F., Katebi, Y., Haj Mohamad Ebrahim Ketabforoush, A.: DNA Methylation in Cancer: Epigenetic View of Dietary and Lifestyle Factors. Epigenetics Insights. 16, 25168657231199893 (2023). https://doi.org/10.1177/25168657231199893
10. Alum, E.U., 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
11. Akter, R., Awais, M., Boopathi, V., Ahn, J.C., Yang, D.C., Kang, S.C., Yang, D.U., Jung, S.-K.: Inversion of the Warburg Effect: Unraveling the Metabolic Nexus between Obesity and Cancer. ACS Pharmacol. Transl. Sci. 7, 560 (2024). https://doi.org/10.1021/acsptsci.3c00301
12. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B., Alum, E.U.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. Nat. Prod. Commun. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035
13. Delcheva, G., Stefanova, K., Stankova, T.: Ceramides—Emerging Biomarkers of Lipotoxicity in Obesity, Diabetes, Cardiovascular Diseases, and Inflammation. Diseases. 12, 195 (2024). https://doi.org/10.3390/diseases12090195
14. Ugwu, O.P.-C., Alum, E.U., Okon, M.B., Obeagu, E.I.: Mechanisms of microbiota modulation: Implications for health, disease, and therapeutic interventions. Medicine (Baltimore). 103, e38088 (2024). https://doi.org/10.1097/MD.0000000000038088
15. Alum, E.U., Uti, D.E., Ugwu, O.P.-C., Alum, B.N., Edeh, F.O., Ainebyoona, C.: Unveiling the microbial orchestra: exploring the role of microbiota in cancer development and treatment. Discov. Oncol. 16, 646 (2025). https://doi.org/10.1007/s12672-025-02352-2
16. An, Y., Wang, Q., Gao, K., Zhang, C., Ouyang, Y., Li, R., Ma, Z., Wu, T., Zhou, L., Xie, Z., Zhang, R., Wu, G.: Epigenetic Regulation of Aging and its Rejuvenation. MedComm. 6, e70369 (2025). https://doi.org/10.1002/mco2.70369
17. Kiselev, I.S., Kulakova, O.G., Boyko, A.N., Favorova, O.O.: DNA Methylation As an Epigenetic Mechanism in the Development of Multiple Sclerosis. Acta Naturae. 13, 45–57 (2021). https://doi.org/10.32607/actanaturae.11043
18. Gualano, B., Kirwan, J.P., Roschel, H.: Exercise is Key to Sustaining Metabolic Gains After Bariatric Surgery. Exerc. Sport Sci. Rev. 49, 197–204 (2021). https://doi.org/10.1249/JES.0000000000000253
19. Dong, H., Sun, Y., Nie, L., Cui, A., Zhao, P., Leung, W.K., Wang, Q.: Metabolic memory: mechanisms and diseases. Signal Transduct. Target. Ther. 9, 38 (2024). https://doi.org/10.1038/s41392-024-01755-x
20. Feehley, T., O'Donnell, C.W., Mendlein, J., Karande, M., McCauley, T.: Drugging the epigenome in the age of precision medicine. Clin. Epigenetics. 15, 6 (2023). https://doi.org/10.1186/s13148-022-01419-z
21. 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
22. AlZaim, I., Hammoud, S.H., Al-Koussa, H., Ghazi, A., Eid, A.H., El-Yazbi, A.F.: Adipose Tissue Immunomodulation: A Novel Therapeutic Approach in Cardiovascular and Metabolic Diseases. Front. Cardiovasc. Med. 7, 602088 (2020). https://doi.org/10.3389/fcvm.2020.602088
23. 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. Int. J. Mol. Sci. 22, 2756 (2021). https://doi.org/10.3390/ijms22052756
24. Baldelli, S., Aiello, G., Mansilla Di Martino, E., Campaci, D., Muthanna, F.M.S., Lombardo, M.: The Role of Adipose Tissue and Nutrition in the Regulation of Adiponectin. Nutrients. 16, 2436 (2024). https://doi.org/10.3390/nu16152436
25. Ahmad, K., Shaikh, S., Lim, J.H., Ahmad, S.S., Chun, H.J., Lee, E.J., Choi, I.: Therapeutic application of natural compounds for skeletal muscle-associated metabolic disorders: A review on diabetes perspective. Biomed. Pharmacother. 168, 115642 (2023). https://doi.org/10.1016/j.biopha.2023.115642
26. Barclay, R.D., Burd, N.A., Tyler, C., Tillin, N.A., Mackenzie, R.W.: The Role of the IGF-1 Signaling Cascade in Muscle Protein Synthesis and Anabolic Resistance in Aging Skeletal Muscle. Front. Nutr. 6, 146 (2019). https://doi.org/10.3389/fnut.2019.00146
27. Chen, X., Ji, Y., Liu, R., Zhu, X., Wang, K., Yang, X., Liu, B., Gao, Z., Huang, Y., Shen, Y., Liu, H., Sun, H.: Mitochondrial dysfunction: roles in skeletal muscle atrophy. J. Transl. Med. 21, 503 (2023). https://doi.org/10.1186/s12967-023-04369-z
28. Abed, H.F., Abuwatfa, W.H., Husseini, G.A.: Redox-Responsive Drug Delivery Systems: A Chemical Perspective. Nanomaterials. 12, 3183 (2022). https://doi.org/10.3390/nano12183183
29. Ahmadi, S., Rabiee, N., Bagherzadeh, M., Elmi, F., Fatahi, Y., Farjadian, F., Baheiraei, N., Nasseri, B., Rabiee, M., Dastjerd, N.T., Valibeik, A., Karimi, M., Hamblin, M.R.: Stimulus-Responsive Sequential Release Systems for Drug and Gene Delivery. Nano Today. 34, 100914 (2020). https://doi.org/10.1016/j.nantod.2020.100914

30. Besse-Patin, A., Estall, J.L.: An Intimate Relationship between ROS and Insulin Signalling: Implications for Antioxidant Treatment of Fatty Liver Disease. Int. J. Cell Biol. 2014, 519153 (2014). https://doi.org/10.1155/2014/519153
31. Wang, Z., Ni, X., Zhang, L., Sun, L., Zhu, X., Zhou, Q., Yang, Z., Yuan, H.: Toll-Like Receptor 4 and Inflammatory Micro-Environment of Pancreatic Islets in Type-2 Diabetes Mellitus: A Therapeutic Perspective. Diabetes Metab. Syndr. Obes. Targets Ther. 13, 4261–4272 (2020). https://doi.org/10.2147/DMSO.S279104
32. Canouil, M., Khamis, A., Keikkala, E., Hummel, S., Lobbens, S., Bonnefond, A., Delahaye, F., Tzala, E., Mustaniemi, S., Vääräsmäki, M., Jarvelin, M.-R., Sebert, S., Kajantie, E., Froguel, P., Andrew, T.: Epigenome-Wide Association Study Reveals Methylation Loci Associated With Offspring Gestational Diabetes Mellitus Exposure and Maternal Methylome. Diabetes Care. 44, 1992–1999 (2021). https://doi.org/10.2337/dc20-2960
33. Liorni, N., Napoli, A., Adinolfi, M., Vinciguerra, M., Mazza, T.: Integrative Analysis of CUT&Tag and RNA-Seq Data Through Bioinformatics: A Unified Workflow for Enhanced Insights. Methods Mol. Biol. Clifton NJ. 2846, 191–213 (2024). https://doi.org/10.1007/978-1-0716-4071-5_13
34. Adamkova, K., Yi, Y.-J., Petr, J., Zalmanova, T., Hoskova, K., Jelinkova, P., Moravec, J., Kralickova, M., Sutovsky, M., Sutovsky, P., Nevoral, J.: SIRT1-dependent modulation of methylation and acetylation of histone H3 on lysine 9 (H3K9) in the zygotic pronuclei improves porcine embryo development. J. Anim. Sci. Biotechnol. 8, 83 (2017). https://doi.org/10.1186/s40104-017-0214-0
35. Kourtidou, C., Tziomalos, K.: The Role of Histone Modifications in the Pathogenesis of Diabetic Kidney Disease. Int. J. Mol. Sci. 24, 6007 (2023). https://doi.org/10.3390/ijms24066007
36. Wang, L., Bai, Y., Cao, Z., Guo, Z., Lian, Y., Liu, P., Zeng, Y., Lyu, W., Chen, Q.: Histone deacetylases and inhibitors in diabetes mellitus and its complications. Biomed. Pharmacother. 177, 117010 (2024). https://doi.org/10.1016/j.biopha.2024.117010
37. Bae, W., Ra, E.A., Lee, M.H.: Epigenetic regulation of reprogramming and pluripotency: insights from histone modifications and their implications for cancer stem cell therapies. Front. Cell Dev. Biol. 13, 1559183 (2025). https://doi.org/10.3389/fcell.2025.1559183
38. 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
39. Mao, L., Lu, J., Hou, Y., Nie, T.: Directly targeting PRDM16 in thermogenic adipose tissue to treat obesity and its related metabolic diseases. Front. Endocrinol. 15, 1458848 (2024). https://doi.org/10.3389/fendo.2024.1458848
40. Basil, B., Myke-Mbata, B.K., Eze, O.E., Akubue, A.U.: From adiposity to steatosis: metabolic dysfunction-associated steatotic liver disease, a hepatic expression of metabolic syndrome – current insights and future directions. Clin. Diabetes Endocrinol. 10, 39 (2024). https://doi.org/10.1186/s40842-024-00187-4
41. Boudaba, N., Marion, A., Huet, C., Pierre, R., Viollet, B., Foretz, M.: AMPK Re-Activation Suppresses Hepatic Steatosis but its Downregulation Does Not Promote Fatty Liver Development. EBioMedicine. 28, 194–209 (2018). https://doi.org/10.1016/j.ebiom.2018.01.008
42. Han, D.-G., Seo, S.-W., Choi, E., Kim, M.-S., Yoo, J.-W., Jung, Y., Yoon, I.-S.: Impact of route-dependent phase-II gut metabolism and enterohepatic circulation on the bioavailability and systemic disposition of resveratrol in rats and humans: A comprehensive whole body physiologically-based pharmacokinetic modeling. Biomed. Pharmacother. 151, 113141 (2022). https://doi.org/10.1016/j.biopha.2022.113141
43. Willis, S.A., Bawden, S.J., Malaikah, S., Sargeant, J.A., Stensel, D.J., Aithal, G.P., King, J.A.: The role of hepatic lipid composition in obesity-related metabolic disease. Liver Int. 41, 2819–2835 (2021). https://doi.org/10.1111/liv.15059
44. Dewanjee, S., Vallamkondu, J., Kalra, R.S., Chakraborty, P., Gangopadhyay, M., Sahu, R., Medala, V., John, A., Reddy, P.H., De Feo, V., Kandimalla, R.: The Emerging Role of HDACs: Pathology and Therapeutic Targets in Diabetes Mellitus. Cells. 10, 1340 (2021). https://doi.org/10.3390/cells10061340
45. Dai, H., Sinclair, D.A., Ellis, J.L., Steegborn, C.: Sirtuin activators and inhibitors: Promises, achievements, and challenges. Pharmacol. Ther. 188, 140–154 (2018). https://doi.org/10.1016/j.pharmthera.2018.03.004
46. La Sala, L., Carlini, V., Conte, C., Macas-Granizo, M.B., Afzalpour, E., Martin-Delgado, J., D'Anzeo, M., Pedretti, R.F.E., Naselli, A., Pontiroli, A.E., Cappato, R.: Metabolic disorders affecting the liver and heart: Therapeutic efficacy of miRNA-based therapies? Pharmacol. Res. 201, 107083 (2024). https://doi.org/10.1016/j.phrs.2024.107083
47. 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
48. Le Lay, S., Scherer, P.E.: Exploring adipose tissue-derived extracellular vesicles in inter-organ crosstalk: Implications for metabolic regulation and adipose tissue function. Cell Rep. 44, 115732 (2025). https://doi.org/10.1016/j.celrep.2025.115732

49. Dasgupta, I., Chatterjee, A.: Recent Advances in miRNA Delivery Systems. Methods Protoc. 4, 10 (2021). https://doi.org/10.3390/mps4010010
50. Cleal, J.K., Poore, K.R., Lewis, R.M.: The placental exposome, placental epigenetic adaptations and lifelong cardio-metabolic health. Mol. Aspects Med. 87, 101095 (2022). https://doi.org/10.1016/j.mam.2022.101095
51. Zheng, F., Gonçalves, F.M., Abiko, Y., Li, H., Kumagai, Y., Aschner, M.: Redox toxicology of environmental chemicals causing oxidative stress. Redox Biol. 34, 101475 (2020). https://doi.org/10.1016/j.redox.2020.101475
52. Ugwu, O.P.-C., Okon, M.B., Alum, E.U., Ugwu, C.N., Anyanwu, E.G., Mariam, B., Ogenyi, F.C., Eze, V.H.U., Anyanwu, C.N., Ezeonwumelu, J.O.C., Egba, S.I., Uti, D.E., Onohuean, H., Aja, P.M., Ugwu, M.N.: Unveiling the therapeutic potential of the gut microbiota–brain axis: Novel insights and clinical applications in neurological disorders. Medicine (Baltimore). 104, e43542 (2025). https://doi.org/10.1097/MD.0000000000043542
53. 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
54. Martínez, J.A., Milagro, F.I., Claycombe, K.J., Schalinske, K.L.: Epigenetics in Adipose Tissue, Obesity, Weight Loss, and Diabetes12. Adv. Nutr. 5, 71–81 (2014). https://doi.org/10.3945/an.113.004705
55. Balan, A.I., Halaţiu, V.B., Scridon, A.: Oxidative Stress, Inflammation, and Mitochondrial Dysfunction: A Link between Obesity and Atrial Fibrillation. Antioxidants. 13, 117 (2024). https://doi.org/10.3390/antiox13010117
56. Kim, M.-B., Lee, J., Lee, J.-Y.: Targeting Mitochondrial Dysfunction for the Prevention and Treatment of Metabolic Disease by Bioactive Food Components. J. Lipid Atheroscler. 13, 306–327 (2024). https://doi.org/10.12997/jla.2024.13.3.306
57. 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
58. Ashwani, Sharma, A., Choudhary, M.K., Gugulothu, D., Pandita, D., Verma, S., Vora, L.K., Khatri, D.K., Garabadu, D.: Epigenetic and Mitochondrial Metabolic Dysfunction in Multiple Sclerosis: A Review of Herbal Drug Approaches and Current Clinical Trials. Mol. Neurobiol. 62, 10045–10090 (2025). https://doi.org/10.1007/s12035-025-04868-8

CITE AS: Abaho Areeba Fortunate (2026). Epigenetic Alterations in Obesity Driven Type 2 Diabetes: Implications for Personalized Medicine. IAA Journal of Scientific Research 13(1):111-118. https://doi.org/10.59298/IAAJSR/2026/131111118