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Epigenetics in Diabetes Management: A Comprehensive Review of Diagnostic and Preventive Strategies

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Abstract

As diabetes mellitus evolves into a global health crisis, conventional diagnostic and therapeutic paradigms are no longer sufficient and necessitate innovative treatment approaches that extend beyond traditional pharmacotherapy. Recent advances in epigenetics have uncovered heritable and reversible changes in gene regulation that contribute to the pathogenesis of diabetes.

This review provides a comprehensive analysis of various epigenetic mechanisms, including DNA methylation, histone modifications, and the role of non-coding RNAs in diabetes development, and evaluates their integration into a precision medicine framework for early diagnosis, risk stratification, and biomarker-guided therapeutic interventions. Furthermore, we discuss personalized management strategies that leverage epigenetic understanding to optimize therapeutic and preventive outcomes. Finally, we consider the upcoming obstacles and prospective scope of personalized medicine in the field of diabetes management. Incorporating epigenetic profiling into diagnostic and therapeutic workflows enables higher-resolution risk assessment, precision targeting of interventions, and improved pharmacodynamic outcomes. Epigenetically informed strategies, including HDAC inhibitors, DNMT modulators, and microbiota-driven interventions, hold promise for enhancing therapeutic efficacy, optimizing drug selection, and personalizing lifestyle interventions.

While translational challenges remain, this review highlights that the integration of epigenetic data with genomics, metabolomics, and microbiomics facilitates next-generation personalized diabetes care and has the potential to reshape both clinical practice and public health strategies in the fight against diabetes.

Keywords: Diabetes mellitus, Epigenomics, Precision medicine, Multiomics

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Introduction

Diabetes mellitus (DM) involves a range of metabolic abnormalities that are primarily marked by persistent high blood sugar levels. This condition arises from impaired insulin production, reduced insulin effectiveness, or a combination of both (1). According to the International Diabetes Federation (IDF), around 537 million adults were living with diabetes in 2021, and this number is expected to elevate to 783 million by 2045 (2). The chronic nature of diabetes and its complications emphasize the urgent need for innovative preventive and therapeutic strategies that extend beyond conventional pharmacotherapy and lifestyle interventions (3).

Recent research has underscored the significant contribution of epigenetic mechanisms to the pathophysiology of diabetes. These mechanisms encompass heritable modifications in gene expression that occur independently of changes to the underlying DNA sequence. Notable epigenetic alterations include DNA methylation, histone modifications, and the adjustment of gene expression by non-coding RNAs (4,5). As illustrated in Figure, the complex interaction between genetic predisposition and environmental agents, like lifestyle and diet, underscores the potential of epigenetic alterations to act as both biological markers for disease progression and targets for therapeutic interventions.

Pathophysiology of diabetes mellitus

The pathophysiology of diabetes is multifaceted, involving intricate engagements of genetic, epigenetic, and environmental factors. The two most common forms, Type 1 diabetes (T1D) and Type 2 diabetes (T2D), demonstrate distinct mechanisms underlying their development (6,7).

T1D is primarily represented by the autoimmune demolition of pancreatic beta cells, resulting in a complete lack of insulin production. Genetic susceptibility serves as a significant agent in the onset of T1D, with certain human leukocyte antigen (HLA) genotypes being closely linked to an elevated risk of the disease (8,9). Environmental triggers like viral infections may initiate autoimmunity in genetically susceptible individuals (10). Epigenetic modifications may also influence immune response pathways and susceptibility to autoimmune processes (11). For instance, methylation changes in genes associated with immune function have been detected in T1D patients, indicating that epigenetic dysregulation may contribute to autoimmune processes (12).

T2D is primarily defined by the presence of insulin resistance alongside a relative deficiency in insulin production. The development of insulin resistance involves multiple pathways, including defective insulin signaling, incremental hepatic glucose manufacture, and disrupted lipid metabolism (13). Central to this process is obesity, which plays a significant role in its pathogenesis by way of mechanisms including chronic low-grade inflammation and ectopic fat deposition (14,15).

In individuals with obesity, adipocytes undergo hypertrophy and hyperplasia, leading to an altered secretory profile that promotes inflammation and insulin resistance (16). Furthermore, excess free fatty acids released from enlarged adipocytes can impair insulin signaling in other tissues, including muscle and liver (17). The dysfunction of adipose tissue leads to the dysregulated secretion of hormones produced by adipose tissue like adipokines that influence insulin sensitivity (18).

The interaction between genetic susceptibility and environmental, particularly dietary habits and physical activity levels, results in epigenetic alterations that further exacerbate insulin resistance. Notably, hypermethylation of genes associated with glucose metabolism has been identified in individuals with obesity and T2D (19).

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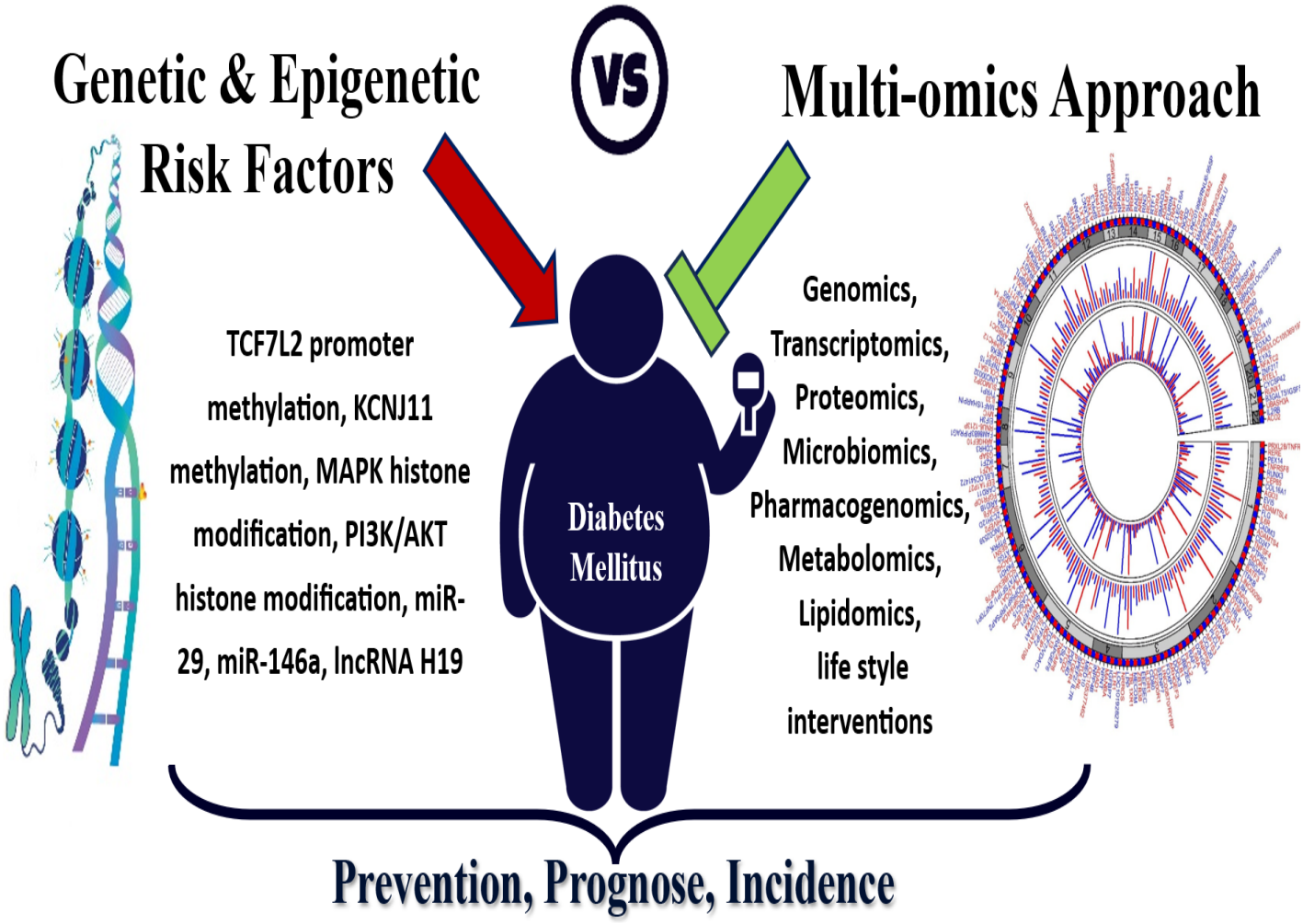

Figure: The impression of genetic and epigenetic contributing factors versus the multi-omics approach on prevention, prognosis and incidence of diabetes mellitus

For example, specific methylation changes in genes such as IL6 and TNFα correlate with insulin resistance (20).

Epigenetic mechanisms in diabetes

Epigenetics encompasses heritable modifications in gene expression that occur independently of changes in the underlying DNA sequence. These epigenetic alterations play a crucial role in modulating gene expression profiles, which are integral to key mechanisms involved in the pathogenesis of diabetes.

DNA Methylation: DNA methylation refers to the covalent addition of a methyl group to cytosine residues within CpG dinucleotides, which are specific sequences in the DNA where a cytosine nucleotide is followed by a guanine nucleotide in the 5′ to 3′ direction. This biochemical modification predominantly leads to transcriptional repression (21). Aberrant patterns of DNA methylation have been associated with a range of metabolic disorders, including T2D (22). For instance, hypermethylation of the promoter region of the PDX1 (pancreatic and duodenal homeobox 1) gene, a transcription factor critical for the development and functionality of pancreatic beta cells, has been linked to compromised insulin secretion in T2D patients (4,23). Additionally, the Transcription Factor 7-Like 2 (TCF7L2), which is integral to the Wnt signaling pathway and plays a significant role in insulin secretion and glucose homeostasis,

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demonstrates how epigenetic alterations, such as methylation at the TCF7L2 promoter, can lead to diminished expression of this factor. This reduction may impair insulin secretion and contribute to the onset of hyperglycemia. Thus, understanding an individual's TCF7L2 methylation status can help tailor interventions, such as dietary modifications or pharmacological therapies that enhance insulin sensitivity (24,25).

The KCNJ11 (Potassium Inwardly Rectifying Channel Subfamily J Member 11) gene encodes the Kir6.2 subunit, which is a critical component of ATP-sensitive potassium channels located in β-cells of the pancreas. Epigenetic modifications, particularly DNA methylation, can significantly influence the expression of KCNJ11, thereby impacting insulin secretion dynamics. Methylation changes at this locus may impair channel function, resulting in inadequate insulin secretion during hyperglycemic states (26,27).

Furthermore, studies have established a correlation between obesity and pervasive changes in DNA methylation patterns across various genes implicated in glucose metabolism and inflammatory responses (28,29).

Specific dietary components can also influence DNA methylation patterns as diets rich in folate and vitamin B12 have been associated with beneficial methylation changes that may improve metabolic health (30-32). Conversely, high-fat diets have been linked to detrimental methylation changes that promote insulin resistance (33).

Histone Modifications: Histones are fundamental proteins around which DNA is tightly coiled, playing pivotal roles in regulating chromatin architecture and gene expression. Post-translational modifications of histones, such as acetylation and methylation, have profound effects on these processes. Acetylation is generally associated with transcriptional activation, while methylation may either promote or inhibit gene expression, contingent upon the specific amino acid residue that is modified (34). Histone deacetylase (HDAC) inhibitors have emerged as promising agents for enhancing insulin sensitivity (35). For example, vorinostat (suberoylanilide hydroxamic acid) has demonstrated the capacity to improve glucose homeostasis in diabetic animal models by increasing histone acetylation at critical metabolic genes (36,37). Additionally, HDAC3 has been implicated in regulating gluconeogenesis through its interaction with transcription factors involved in glucose metabolism (38,39). A notable example is the PPARG (Peroxisome Proliferator-Activated Receptor Gamma), a nuclear receptor integral to adipocyte differentiation and lipid anabolism or catabolism. The expression of PPARG can be regulated by histone acetylation and methylation, which in turn influence chromatin structure and accessibility. Alterations in PPARG expression are linked to obesity and insulin resistance. Decreased histone acetylation at the PPARG locus may lead to reduced adipogenesis and increased free fatty acid levels, exacerbating insulin resistance (40,41).

An illustrative instance of signaling pathways influenced by epigenetic mechanisms is the Mitogen-Activated Protein Kinase (MAPK) route. This pathway serves as a critical conduit for signals originating from growth factors and stress stimuli, thereby modulating various cellular responses, including proliferation, differentiation, and apoptosis (42). The expression of key components within the MAPK pathway, such as extracellular signal-regulated kinase 1/2 (ERK1/2), is subject to regulation by histone modifications and DNA methylation. Dysregulation of these epigenetic processes can result in persistent activation of the MAPK pathway, which has been implicated in β-cell apoptosis and inflammatory responses associated with Type 2 Diabetes (T2D). Moreover, epigenetic alterations that enhance the expression of pro-inflammatory cytokines may further exacerbate this detrimental cycle (43).

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Non-Coding RNAs: Non-coding RNAs, particularly microRNAs (miRNAs), are pivotal in the modulation of gene expression associated with various biological processes relevant to diabetes (44). MiRNAs can modulate insulin signaling pathways by targeting mRNAs of key proteins involved in glucose metabolism (45, 46). For example, miR-29 has been shown to target multiple genes such as PPARγ and IRS1, thereby influencing insulin sensitivity and glucose homeostasis (47). The disturbance of some miRNAs has been linked to the onset of insulin resistance; for instance, miR-146a is upregulated in obesity and negatively regulates insulin signaling by targeting IRS2 and also, enhances inflammatory responses by targeting negative regulators of NF-kB signaling (48,49). Moreover, long non-coding RNAs (lncRNAs) appeared as important regulators in the context of diabetes; lncRNA H19 has been shown to modulate glucose metabolism by interaction with chromatin-modifying complexes, influencing gene expression related to insulin sensitivity and inflammation affect insulin signaling pathways (50,51).

Management strategies incorporating epigenetics

The integration of epigenetic insights into diabetes management represents a paradigm shift toward precision medicine. Modifying treatment approaches grounded in a personal unique epigenetic profile can optimize preventive and therapeutic outcomes (19,52).

Genetic profiling: Recent advancements in genomics have facilitated the discovery of genetic variants that contribute to susceptibility to diabetes (53,54). For instance, genome-wide association studies (GWAS) have uncovered numerous loci associated with an increased risk of T2D. So, gaining insights into a personal genetic predisposition can guide the development of targeted prevention strategies and personalized treatment regimens (55,56).

Epigenetic biomarkers: The identification of epigenetic biomarkers holds promise for predicting disease risk and treatment response (57). Notably, distinct patterns of DNA methylation have been linked to risk factors for T2D, including obesity and insulin resistance (22,58). By evaluating an individual's epigenetic profile, healthcare providers may better identify those at increased risk for diabetes onset or those who might exhibit favorable responses to particular therapeutic interventions (57). For example, under innate physiological states, insulin released postprandially activates the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway. This activation promotes glucose uptake and inhibits gluconeogenesis in hepatic and muscular tissue, enhances lipid storage, thereby reducing circulating free fatty acids in adipose tissue, stimulates pancreatic insulin secretion, and helps maintain a balance in lipid and glucose metabolism while curbing appetite through the brain. Impaired activation of this pathway due to epigenetic dysregulation like histone modifications can contribute to the development of insulin resistance. So, assessing the epigenetic landscape of key genes in this pathway may assist in identifying patients predisposed to insulin resistance and guide lifestyle or pharmacological interventions tailored to restore signaling efficacy (59).

***Lifestyle interventions*:** Precision medicine extends beyond conventional pharmacotherapy; indeed, lifestyle interventions tailored to an individual's genetic and epigenetic landscape can substantially optimize therapeutic outcomes. Accumulating evidence indicates that dietary patterns exert a profound regulatory influence on the epigenetic machinery governing metabolic homeostasis. For instance, adherence to a Mediterranean diet, rich in polyunsaturated fatty acids, has been linked to favorable epigenetic modifications that enhance insulin sensitivity (19,60). Similarly,

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exercise interventions can induce favorable epigenetic modifications that enhance metabolic health (61).

***Targeting epigenetics*:** Emerging therapies targeting epigenetic modifications offer exciting opportunities for personalized treatment approaches. Small-molecule inhibitors that modulate DNA methylation or histone acetylation may be designed to an individual's unique epigenetic landscape. For instance, patients exhibiting specific DNA methylation patterns may benefit more from DNA methyltransferase (DNMT) inhibitors or histone deacetylase (HDAC) inhibitors than others without such alterations (62,63).

***Pharmacogenomics*:** The study of genetic variations and their impact on drug metabolism and pharmacokinetics is crucial for advancing pharmacotherapy in diabetes management. Pharmacogenomics is a pivotal discipline that examines the interrelation of personal genetic profiles and their feedback to medications. Integrating pharmacogenomics data into clinical practice can optimize drug selection and dosing for individual patients (59). Variations in genes encoding drug-metabolizing enzymes can influence patient responses to medications such as metformin or sulfonylureas. This personalized approach not only enhances healing efficacy but also minimizes the pitfall of adverse drug reactions (64,65). For instance, individuals with specific PPARG polymorphisms may experience improved outcomes with targeted therapies, such as thiazolidinediones (TZDs), which act as PPARG agonists, improving insulin sensitivity based on their genetic profile (66). As discussed above, genetic testing for KCNJ11 variants, combined with epigenetic analysis, can guide individualized treatment strategies, including the use of sulfonylureas that stimulate insulin release (67,68). Genotyping for SLC22A4 gene variants could enable clinicians to predict patient responses to metformin, optimizing dosing strategies and minimizing gastrointestinal side effects commonly associated with the drug. For instance, the SLC22A4 rs1050152 variant has been associated with altered metformin transport capacity, leading to variations in drug exposure and therapeutic efficacy (69).

***Microbiomics*:** The human microbiome consists of microorganisms that reside predominantly in the gut but also in other areas such as the skin, mouth, and urogenital tract. Microbiomics is an interdisciplinary field that investigates the collective genomes of microorganisms (microbiota) residing in specific environments, with a particular emphasis on the human gut microbiome (70,71). The gut microbiota (including species like Lactobacillus rhamnosus, and Lactobacillus plantarum) plays a critical role in fermenting comestible fibers to generate short-chain fatty acids (SCFAs) like acetate, propionate and butyrate (72,73). These SCFAs enhance gut barrier integrity, regulate immune responses, and improve insulin sensitivity through the activation of G protein-coupled receptors (GPCRs), notably GPR41 and GPR43, which mediate anti-inflammatory effects and improve glucose metabolism. Conversely, diminished levels of SCFAs have been linked to insulin resistance and the pathogenesis of T2D (74,75). The gut microbiome also significantly influences the development and functionality of the immune system, particularly through the promotion of regulatory T cells that are essential for maintaining immune tolerance and mitigating excessive inflammatory responses. Dysbiosis, or microbial imbalance, can result in chronic low-grade inflammation, a characteristic feature of T2D (76). Moreover, the gut microbiome interacts with the central nervous system through the gut-brain axis, where microbial metabolites can modulate neurotransmitter synthesis, thereby impacting appetite regulation and energy metabolism. This interplay may contribute to the etiology of obesity and T2D (77). Some studies have identified distinct gut microbiome profiles in individuals with T2D compared to healthy individuals. Notably, a reduction in butyrate-

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producing bacterial populations is frequently observed among T2D patients. Additionally, alterations in the Firmicutes to Bacteroidetes ratio have been documented, with an increased ratio correlating with obesity and insulin resistance (78). Understanding an individual's unique microbiomic profile could lead to personalized dietary recommendations or targeted therapies like fecal microbiota transplantation and specific probiotics or prebiotics, aimed at restoring a healthy microbiome to prevent or manage T2D. Continued research in this field promises to uncover novel therapeutic strategies aimed at harnessing the power of the gut microbiome for diabetes prevention and management (79,80).

Challenges and future directions

Although there have been encouraging findings regarding the influence of epigenetics on diabetes management and the advancement of personalized medicine, several challenges remain:

***Heterogeneity of diabetes*:** The complexity of diabetes necessitates further research to elucidate specific pathways involved in prevention, development and prognosis. T2D encompasses a range of phenotypes influenced by genetic background, lifestyle factors, and comorbidities; understanding this heterogeneity will be crucial for developing effective personalized treatment strategies (81,82).

Ethical considerations: The incorporation of genetic and epigenetic assessments into clinical practice presents ethical dilemmas, particularly concerning issues of privacy, informed consent, and the risk of discrimination based on genetic data. Establishing guidelines for ethical practices in pharmacogenomics is crucial for maintaining patient trust. Addressing these issues will be essential as personalized medicine continues to evolve (54,83).

***Multi-Omics approaches*:** Future investigations should prioritize the implementation of multi-omics methodologies, which encompass genomics, transcriptomics, proteomics, metabolomics, microbiomics, and pharmacogenomics. This integrative approach will deepen our comprehension of the intricate interactions between genetic predisposition and epigenetic modifications in diabetes. Such a comprehensive perspective is expected to yield valuable insights into the underlying mechanisms of the disease and facilitate the formulation of targeted therapeutic interventions (84).

Research breaks: Bridging the gap between laboratory findings and clinical application remains a significant challenge. To ensure the effectiveness and safety of epigenetic interventions across diverse populations, it is essential to conduct rigorous clinical trials prior to their integration into standard clinical practice. Ongoing research efforts should focus on generating real-world evidence regarding the clinical utility of pharmacogenomic-guided therapy in diabetes management. Longitudinal studies assessing patient outcomes will be critical for validating the effectiveness of personalized approaches (85).

***Cost-effectiveness and accessibility*:** The cost of genetic testing remains a barrier for many patients. Efforts should be directed toward reducing costs and increasing insurance coverage for pharmacogenomic tests to ensure equitable access across diverse populations (86).

Conclusion

The relationship between epigenetics and diabetes is an emerging area of research that offers considerable potential for the development of novel therapeutic strategies tailored to the unique profiles of individual patients by leveraging genetic profiling, identifying epigenetic biomarkers, implementing tailored lifestyle interventions,

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targeting epigenetic modifications and utilizing pharmacogenomics, healthcare providers can optimize treatment strategies for individuals with diabetes. As our understanding deepens regarding how epigenetic alterations influence disease progression and treatment response, integrating these insights into diabetes management could lead to personalized treatment approaches that enhance patient outcomes. Personalized medicine approaches that leverage this knowledge can significantly enhance prevention and treatment strategies for individuals at risk for or living with diabetes.

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Conflict of Interest

The authors declare no conflicts of interest.

Authors' contributions

A.AB and M.AB: Conceptualization, Data gathering, Investigation, Validation, Writing and Editing.

A.AB: Visualization, Designing figure, Project administration.

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