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Epigenetic Biomarkers in Type 2 Diabetes: A Clinician's Guide to Emerging Diagnostic and Prognostic Tools

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive pancreatic β-cell dysfunction. Conventional biomarkers such as fasting plasma glucose and glycated haemoglobin (HbA1c) detect established disease but fail to capture early molecular alterations and future complication risk. Epigenetic biomarkers—including DNA methylation, histone modifications, and non-coding RNAs—are emerging as powerful, dynamic, and modifiable indicators of disease susceptibility and progression. These biomarkers not only enable early diagnosis and risk stratification but also hold promise in predicting major complications such as myocardial infarction, stroke, and diabetic kidney disease. This clinician-focused review summarizes current evidence on epigenetic biomarkers in T2DM, highlights key CpG sites, and discusses their diagnostic, prognostic, and therapeutic implications in precision medicine.

Introduction

Type 2 diabetes mellitus (T2DM) represents a major and rapidly escalating global health burden. According to the International Diabetes Federation (IDF), approximately 537 million adults worldwide were living with diabetes in 2021, a number projected to rise to 643 million by 2030 and 783 million by 2045. Notably, over 90-95% of these cases are attributed to T2DM, underscoring its dominant contribution to the global diabetes epidemic. The disease is associated with substantial morbidity and mortality, primarily due to complications such as cardiovascular disease, stroke, and chronic kidney disease, which remain the leading causes of death among diabetic patients.

In addition to its clinical burden, T2DM imposes significant economic strain, with global health expenditure on diabetes estimated to exceed USD 966 billion annually, reflecting both direct healthcare costs and indirect productivity losses. Alarmingly, a large proportion of individuals remain undiagnosed or are diagnosed late, often after the onset of irreversible vascular and metabolic complications.

Current diagnostic tools, including fasting plasma glucose and glycated haemoglobin (HbA1c), primarily detect hyperglycemia after substantial metabolic dysfunction has already occurred. These conventional markers are limited in their ability to identify early molecular changes, predict disease progression, or stratify risk for complications.

Emerging evidence suggests that epigenetic mechanisms act as a critical interface between genetic predisposition and environmental influences such as diet, obesity, physical inactivity, and intrauterine exposures. These modifications—including DNA methylation, histone alterations, and non-coding RNA regulation—can precede clinical disease onset and reflect cumulative metabolic stress.

Importantly, epigenetic changes are dynamic and potentially reversible, offering a unique opportunity for early detection, risk stratification, and targeted intervention. From a clinical perspective, epigenetic biomarkers may enable the identification of high-risk individuals before the development of overt hyperglycemia, predict the likelihood of complications, and guide personalized therapeutic strategies. As such, they represent a promising frontier in the transition toward precision medicine in T2DM.

Epigenetics: A Clinician-Oriented Overview

Epigenetics refers to heritable yet reversible modifications in gene expression that occur without alterations in the underlying DNA sequence. These regulatory mechanisms play a crucial role in modulating cellular function and phenotype in response to environmental and metabolic cues. The principal epigenetic mechanisms include DNA methylation, histone modifications, and regulation by non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs).

Among these, DNA methylation is the most extensively studied and clinically validated mechanism, involving the addition of methyl groups to cytosine residues at CpG dinucleotides, typically leading to transcriptional repression. Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, influence chromatin structure and accessibility, thereby regulating gene transcription. Non-coding RNAs further contribute to post-transcriptional and transcriptional gene regulation by modulating mRNA stability and protein translation.

In contrast to fixed genetic mutations, epigenetic modifications are dynamic and responsive to environmental influences such as diet, physical activity, obesity, and pharmacological interventions. This plasticity allows the epigenome to reflect cumulative metabolic exposures over time. Importantly, these changes can be detected in accessible biological samples, including peripheral blood and saliva, facilitating their application in clinical settings.

Collectively, these characteristics position epigenetic mechanisms

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as highly relevant to precision medicine. Their reversibility and sensitivity to therapeutic and lifestyle interventions offer promising opportunities not only for early disease detection and risk stratification but also for the development of targeted strategies aimed at disease modification and potential reversal.

DNA Methylation: Core Epigenetic Biomarkers in T2DM

DNA methylation at specific CpG (cytosine-guanine dinucleotides) sites has emerged as the most robust and clinically relevant epigenetic biomarker in T2DM.

Key CpG Sites and Their Clinical Significance

Research has identified several CpG loci detectable in blood long before clinical disease onset:

- **ABCG1 (cg06500161)**

Strongest association with T2DM incidence; hypermethylation linked to impaired insulin secretion and β-cell dysfunction. ABCG1 (ATP-binding cassette transporter G1) plays a critical role in intracellular cholesterol homeostasis by facilitating cholesterol efflux to high-density lipoproteins (HDL). Proper cholesterol balance is essential for maintaining cellular membrane integrity and normal metabolic signaling, particularly in pancreatic β-cells.

Hypermethylation at the CpG site cg06500161 within the ABCG1 gene is associated with reduced gene expression. This epigenetic silencing leads to impaired cholesterol efflux, resulting in intracellular lipid and cholesterol accumulation. In pancreatic β-cells, excess cholesterol disrupts membrane microdomains, including lipid rafts, which are crucial for insulin granule exocytosis and glucose-stimulated insulin secretion.

Furthermore, lipid accumulation induces lipotoxicity, promoting oxidative stress, mitochondrial dysfunction, and activation of inflammatory signalling pathways. These processes impair β-cell viability and function by reducing insulin synthesis and secretion. Over time, sustained metabolic stress contributes to β-cell apoptosis and progressive decline in insulin-producing capacity.

In addition to its direct effects on β-cells, altered ABCG1 methylation in peripheral tissues such as adipose tissue and macrophages exacerbates systemic insulin resistance through dysregulated lipid metabolism and chronic low-grade inflammation. This creates a dual pathogenic effect—both impaired insulin secretion and increased insulin resistance—central to the development of T2DM.

Clinically, the methylation status of ABCG1 (cg06500161) in peripheral blood has shown strong and reproducible associations with incident T2DM across multiple populations. Its role as an early biomarker reflects underlying metabolic dysregulation before overt hyperglycemia, making it a valuable tool for early risk prediction and intervention.

- **TXNIP (cg19693031)**

Hypomethylation correlates with elevated fasting glucose and HbA1c, reflecting poor glycemic control. TXNIP (Thioredoxin-Interacting Protein) is a key regulator of cellular redox balance and glucose metabolism. It binds to and inhibits thioredoxin, a major intracellular antioxidant, thereby promoting oxidative stress.

Hypomethylation at the CpG site cg19693031 within the TXNIP gene is associated with increased gene expression. This epigenetic upregulation leads to elevated TXNIP protein levels, which in turn inhibit thioredoxin activity and result in the accumulation of reactive oxygen species (ROS). Increased oxidative stress has detrimental effects on pancreatic β-cells, which are particularly vulnerable due to their relatively low antioxidant capacity.

In β-cells, elevated TXNIP expression contributes to impaired insulin secretion through multiple mechanisms. These include mitochondrial dysfunction, activation of apoptotic pathways, and suppression of insulin gene transcription. Additionally, TXNIP has been shown to activate the NLRP3 inflammasome, leading to the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), further exacerbating β-cell damage and dysfunction.

Beyond the pancreas, TXNIP plays a role in peripheral insulin resistance. Increased TXNIP expression in skeletal muscle and adipose tissue interferes with glucose uptake and insulin signalling pathways, thereby contributing to systemic hyperglycemia. Importantly, TXNIP expression is directly induced by high glucose levels, creating a feed-forward pathogenic loop: hyperglycemia increases TXNIP expression, which in turn worsens oxidative stress and β-cell dysfunction, leading to further elevations in blood glucose levels.

Clinically, hypomethylation of TXNIP (cg19693031) in peripheral blood has been consistently associated with elevated fasting glucose and HbA1c levels, making it a robust biomarker of poor glycemic control. Its dynamic nature also allows it to reflect ongoing metabolic status and response to therapeutic interventions.

- **CPT1A (cg00574958)**

CPT1A (Carnitine Palmitoyltransferase 1A) is a key mitochondrial enzyme regulating the transport of long-chain fatty acids into mitochondria for β-oxidation. Hypomethylation at cg00574958 is associated with increased gene expression, reflecting altered fatty acid metabolism. Dysregulation of CPT1A activity leads to impaired lipid oxidation and accumulation of intracellular lipids, contributing to insulin resistance in liver and skeletal muscle. This metabolic imbalance promotes hepatic steatosis and disrupts glucose homeostasis, establishing a causal link with T2DM development. Clinically, CPT1A methylation serves as an indicator of early lipid metabolic dysfunction and cardiometabolic risk.

- **SREBF1 (cg11024682)**

SREBF1 (Sterol Regulatory Element-Binding Transcription Factor 1) is a central regulator of lipogenesis, controlling the expression of genes involved in fatty acid and triglyceride synthesis. Hypermethylation at cg11024682 influences gene expression and is associated with dysregulated lipid metabolism. Altered SREBF1 activity contributes to increased hepatic lipid synthesis, insulin resistance, and features of metabolic syndrome, including dyslipidemia and central obesity. These changes exacerbate systemic metabolic stress and promote progression toward T2DM. Clinically, SREBF1 methylation is a marker of lipogenic activity and metabolic syndrome risk.

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- **PHOSPHO1(cg02650017)**

PHOSPHO1 (Phosphatase, Orphan 1) is involved in phosphate metabolism and has emerging roles in energy balance and lipid metabolism. Hypermethylation at cg02650017 has been associated with variations in high-density lipoprotein (HDL) cholesterol levels and overall metabolic health. Although its exact role in T2DM pathogenesis is still being elucidated, PHOSPHO1 methylation appears to reflect alterations in lipid handling and cardiovascular risk profiles. Clinically, it may serve as a biomarker for cardiometabolic health and HDL-related protective pathways.

Tissue-Specific Epigenetic Markers

Although blood-based markers are clinically convenient, tissue-level studies provide mechanistic insights:

- **PPARGC1A** – Regulates mitochondrial biogenesis and oxidative metabolism, playing a central role in maintaining insulin sensitivity in skeletal muscle. Hypermethylation of PPARGC1A is associated with reduced gene expression, leading to impaired mitochondrial function and contributing to insulin resistance in T2DM.
- **PDX-1** – A key transcription factor essential for pancreatic β-cell development and insulin gene expression. Epigenetic silencing through hypermethylation reduces PDX-1 activity, resulting in impaired insulin secretion and progressive β-cell dysfunction.
- **PDGFA** – Involved in cell growth and tissue remodelling, particularly in hepatic metabolism. Altered methylation of PDGFA is associated with increased liver fat accumulation and hepatic insulin resistance, contributing to metabolic dysregulation in T2DM.Thousands of differentially methylated loci have been identified across adipose tissue, skeletal muscle, and liver, reflecting systemic metabolic dysfunction.

Epigenetic Biomarkers for Prediction of Diabetic Complications

Cardiovascular Risk (Heart Attack and Stroke)

A major advancement in epigenetic research is the ability to predict long-term complications of T2DM, particularly cardiovascular disease and diabetic kidney disease. Epigenetic alterations reflect cumulative metabolic stress and may precede clinical manifestations, enabling early identification of high-risk individuals.

Epigenetic modifications in genes regulating inflammation, lipid metabolism, and endothelial function have been strongly associated with increased cardiovascular risk in T2DM. Large-scale epigenome-wide association studies (EWAS) have identified differential DNA methylation patterns linked to incident cardiovascular events. For example, a study by García-Calzón et al. (2025, Cell Reports Medicine) demonstrated that specific methylation signatures in circulating DNA could predict major adverse cardiovascular events (MACE), including myocardial infarction and ischemic stroke, in patients with T2DM. These findings suggest that epigenetic profiling can stratify patients beyond traditional risk factors such as lipid levels and blood pressure.

Similarly, methylation changes in genes such as ABCG1, SREBF1, and inflammatory pathway regulators have been associated with atherosclerosis progression and endothelial dysfunction. Altered methylation in these pathways contributes to chronic vascular inflammation, plaque instability, and thrombosis.

In addition, studies published in high-impact cardiovascular and metabolic journals have shown that epigenetic markers related to oxidative stress and immune activation correlate with subclinical atherosclerosis, measured by carotid intima-media thickness and coronary artery calcification.

Importantly, these epigenetic signatures can be detected in peripheral blood, allowing for non-invasive early identification of individuals at high risk of myocardial infarction and stroke, even before overt cardiovascular disease develops.

Diabetic Kidney Disease

Diabetic kidney disease (DKD) is one of the most serious microvascular complications of T2DM and a leading cause of end-stage renal disease worldwide. Epigenetic mechanisms, particularly DNA methylation, play a key role in its pathogenesis. A landmark study by Li et al. (2023, Nature Communications) identified specific DNA methylation markers associated with decline in renal function and progression of DKD. These methylation signatures were shown to predict changes in estimated glomerular filtration rate (eGFR) and albuminuria, independent of traditional clinical risk factors.

Epigenetic alterations in genes involved in fibrosis (e.g., TGF-β signalling), inflammation, and extracellular matrix remodelling have been consistently linked to renal injury. These changes contribute to Glomerulosclerosis, Tubulointerstitial fibrosis and Progressive loss of renal function. Furthermore, studies have demonstrated that epigenetic "metabolic memory" plays a role in DKD progression, where prior hyperglycemic exposure induces persistent epigenetic changes that continue to drive renal damage even after glycemic control improves. These findings highlight the potential of DNA methylation markers as early predictors of renal dysfunction and progression to chronic kidney disease, enabling earlier intervention.

Clinical Implication

The integration of epigenetic biomarkers into clinical practice offers significant advantages in predicting and preventing diabetic complications. An epigenetic biomarker capable of identifying complication risk at an early stage allows for:

- Preventive interventions, including early initiation of cardioprotective and renoprotective therapies.
- Aggressive risk factor modification, such as tighter glycemic, lipid, and blood pressure control.
- Targeted monitoring strategies, including more frequent cardiovascular and renal assessments.

Moreover, epigenetic profiling may help classify patients into distinct risk phenotypes, enabling a precision medicine approach where treatment strategies are tailored according to individual risk profiles. As evidence continues to grow, epigenetic biomarkers have the potential to complement existing clinical tools and transform the management of T2DM by shifting the focus from reactive treatment to proactive prevention of complications.

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Non-Coding RNAs as Circulating Biomarkers

MicroRNAs (miRNAs)

- **miR-375** – A key regulator of pancreatic β-cell function, miR-375 modulates insulin secretion and β-cell mass. Dysregulation contributes to impaired insulin release and progression of T2DM.
- **miR-29 family** – These miRNAs are associated with insulin resistance by targeting genes involved in glucose uptake and insulin signalling pathways, particularly in skeletal muscle and adipose tissue.
- **miR-126** – Primarily expressed in endothelial cells, miR-126 plays a crucial role in vascular integrity and angiogenesis. Reduced levels are linked to endothelial dysfunction and increased risk of diabetic vascular complications.

Long Non-Coding RNAs (lncRNAs)

- **H19** – Involved in glucose metabolism and insulin signalling, H19 regulates gene expression through epigenetic mechanisms and is implicated in metabolic homeostasis and insulin sensitivity.
- **MALAT1** – A regulator of inflammation and endothelial function, MALAT1 is upregulated in hyperglycemic states and contributes to vascular damage and diabetic complications.

These circulating non-coding RNAs are highly stable in body fluids such as blood and plasma, making them suitable for non-invasive "liquid biopsy" approaches for early diagnosis, prognosis, and monitoring of T2DM.

Clinical Applications of Epigenetic Biomarkers

Early Risk Assessment

Epigenetic markers significantly improve **10-year risk prediction models**, enabling:

- Identification of high-risk individuals
- Prevention of progression from prediabetes to T2DM

Complication Prediction

Distinct epigenetic profiles help classify T2DM into subgroups such as:

- Severe insulin-resistant diabetes
- High cardiovascular risk phenotypes

This allows prediction of:

- Heart attack
- Stroke
- Kidney disease

Monitoring Disease Evolution

Dynamic changes in DNA methylation track:

- Transition from normoglycemia → prediabetes → diabetes
- Progression of metabolic dysfunction

Evaluation of Therapeutic Response

Because epigenetic modifications are reversible, they can monitor:

- Lifestyle interventions (diet, exercise)
- Pharmacological treatment (e.g., metformin)

Advantages Over Traditional Biomarkers

Epigenetic biomarkers offer several advantages over conventional markers such as glycated hemoglobin (HbA1c) and fasting plasma glucose, particularly in the context of early detection, risk stratification, and personalized management of T2DM.

- **Real-Time Metabolic Insight:** Unlike HbA1c, which reflects average glycemic control over the preceding 2–3 months, epigenetic markers provide insights into ongoing metabolic alterations and tissue-specific dysfunction, enabling a more dynamic assessment of disease activity.
- **Metabolic Memory:** Epigenetic modifications capture the long-term effects of prior hyperglycemic exposure, reflecting the concept of "metabolic memory," whereby earlier glycemic insults continue to influence disease progression and complications.
- **Precision Medicine:** Epigenetic profiling allows stratification of patients into distinct molecular subtypes, facilitating individualized therapeutic approaches and improving clinical decision-making.
- **Non-Invasive Testing:** Advances in liquid biopsy techniques enable the detection of circulating cell-free DNA (cfDNA) methylation and other epigenetic markers in blood and saliva, offering a minimally invasive and clinically feasible diagnostic approach.

(Table 1) summarizes the key CpG DNA methylation biomarkers in type 2 diabetes mellitus and highlights their potential clinical applications in diagnosis, risk assessment, and disease monitoring.

Environmental and Lifestyle Influence

Epigenetic biomarkers highlight the impact of environmental exposures:

- **Diet** – alters methylation of metabolic genes
- **Obesity** – induces widespread epigenetic dysregulation
- **Physical activity** – can reverse adverse epigenetic patterns
- **Intrauterine exposure** – influences lifelong metabolic risk

This reinforces the importance of early lifestyle interventions in clinical practice.

Clinical Limitations and Challenges

Despite promising advances, several barriers remain:

Tissue Specificity

Epigenetic changes vary across tissues, making it difficult

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Table 1: Key CpG DNA Methylation Biomarkers in Type 2 Diabetes Mellitus

Gene	CpG Site ID	Direction of Methylation	Biological Role	Clinical Significance	Potential Application
ABCG1	cg06500161	Hypermethylation ↑	Cholesterol transport, lipid metabolism	Strongest association with T2DM incidence; linked to β-cell dysfunction	Early diagnosis, risk prediction
TXNIP	cg19693031	Hypomethylation ↓	Oxidative stress regulation, glucose metabolism	Correlates with fasting glucose and HbA1c; marker of poor glycemic control	Disease monitoring, prognosis
CPT1A	cg00574958	Hypomethylation ↓	Fatty acid oxidation, mitochondrial metabolism	Causally linked to T2DM; reflects lipid metabolism dysfunction	Risk stratification
SREBF1	cg11024682	Hypermethylation ↑	Lipogenesis, metabolic regulation	Associated with insulin resistance and metabolic syndrome	Early metabolic risk detection
PHOSPHO1	cg02650017	Hypermethylation ↑	Phosphate metabolism, HDL regulation	Linked to HDL levels and cardiometabolic health	Cardiovascular risk prediction
PPARGC1A	Multiple sites	Hypermethylation ↑	Mitochondrial biogenesis, insulin sensitivity	Associated with skeletal muscle insulin resistance	Mechanistic insight, tissue-specific risk
PDX-1	Multiple sites	Hypermethylation ↑	Pancreatic β-cell development/ function	Impaired insulin secretion in T2DM	β-cell dysfunction marker
PDGFA	Multiple sites	Hypermethylation ↑	Cell growth, liver metabolism	Linked to hepatic insulin resistance and fatty liver	Liver-related metabolic risk

How Clinicians Can Use This Table

- **Screening:** ABCG1, CPT1A for early identification of high-risk individuals
- **Monitoring:** TXNIP for glycemic control and disease progression
- **Complication Risk:** PHOSPHO1 and SREBF1 for cardiovascular risk profiling
- **Pathophysiology Insight:** PDX-1, PPARGC1A for β-cell and insulin resistance mechanisms

to directly correlate blood findings with pancreatic or hepatic dysfunction.

Causality vs Consequence

It remains unclear whether epigenetic changes:

- Cause T2DM
- Or result from hyperglycemia

Need for Validation

- Most studies are small or retrospective
- Large-scale, longitudinal studies are required
- Standardization of assays and thresholds is lacking

Future Directions

- Development of **standardized epigenetic panels** for clinical use
- Integration with **genomics, proteomics, and clinical data**
- Application of **artificial intelligence for risk prediction**
- Exploration of **epigenetic therapies** targeting reversible modifications

Conclusion

Epigenetic biomarkers, particularly DNA methylation, are emerging as powerful tools in the early diagnosis, risk stratification, and prognosis of T2DM and its complications. Their dynamic and modifiable nature offers a unique opportunity for preventive and personalized medicine. Importantly, the ability to predict major complications such as cardiovascular disease and kidney dysfunction at an early stage could transform clinical management. However, further validation and standardization are essential before routine clinical implementation.

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