Cardiovascular Diabetology

REVIEW

Open Access

Epigenetic crossroads in metabolic and cardiovascular health: the role of DNA methylation in type 2 diabetes and cardiovascular diseases

Suneesh Kaimala[1], Lidya K. Yassin[1], Mohammad I. K. Hamad[1], Mohammed Z. Allouh[1], Prabha Sampath[2,3], Juma AlKaabi[4], Melvin Khee-Shing Leow[5,6,7,8,9], Safa Shehab[1], Suraiya Anjum Ansari[10,11,12] and Bright Starling Emerald[1,11,12*]

Abstract

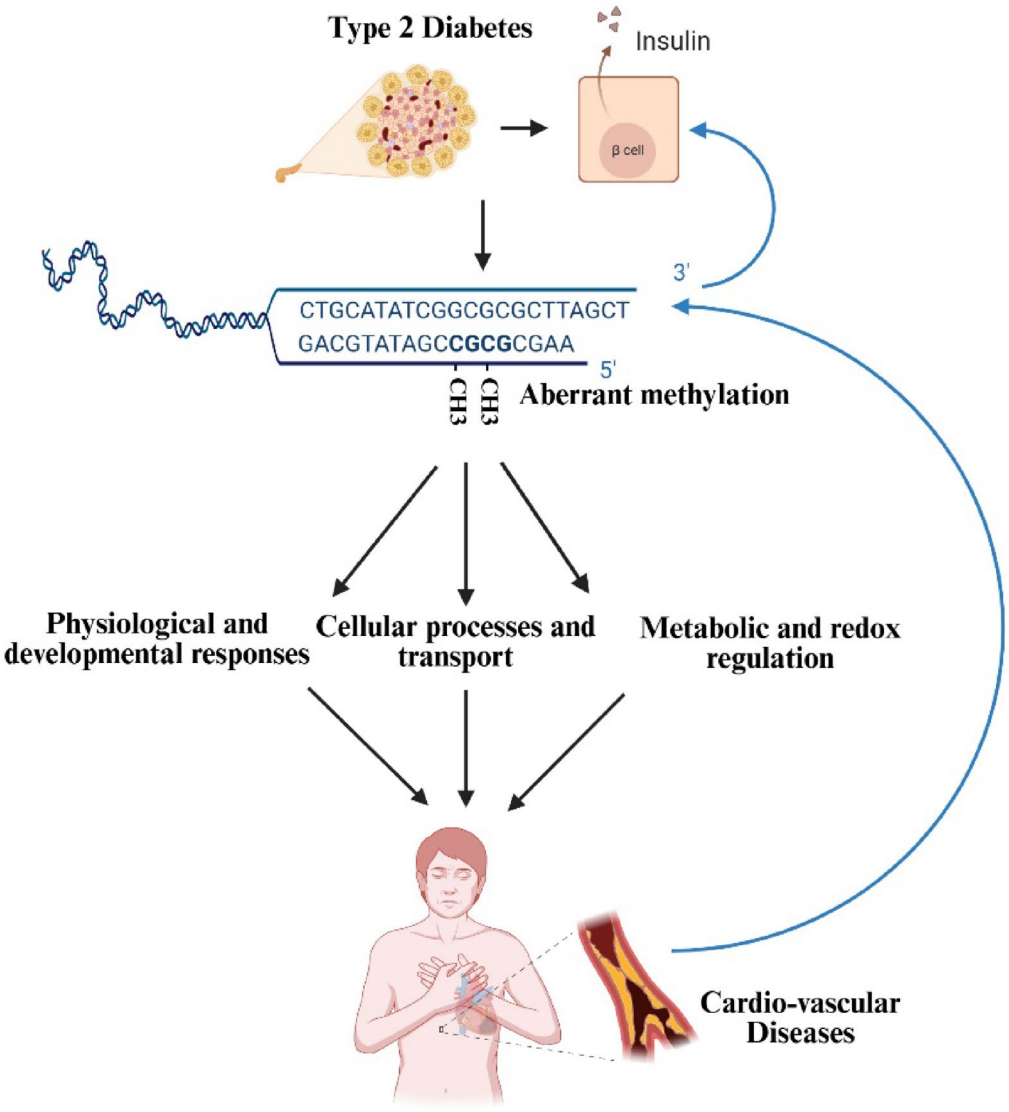
Type 2 diabetes (T2D) and cardiovascular diseases (CVD), part of the metabolic syndrome (MetS), are major contributors to the global health crisis today. A recent report from the World Health Organisation estimates that 17.9 million lives are lost each year to CVD, and one-third of these are premature. The international diabetes federation estimates that around 537 million adults aged between 20 and 79 years are living with diabetes. People with diabetes are suggested to have twice the risk of developing CVD. Epigenetic modifications are being increasingly recognised as the key mediators linking genetic and environmental conditions to metabolic dysfunction. Among these, DNA methylation plays a crucial role in modulating gene expression and influencing pathways involved in glucose homeostasis, inflammation, and vascular integrity. Despite the advances in our understanding of the role of epigenetic alterations in metabolic diseases, including that of T2D, the mechanisms driving selective methylation changes and their long-term impact on cardiovascular health are still not well understood. This review synthesises the current knowledge on DNA methylation dynamics in T2D and their role towards the progression of CVD and explores their potential as biomarkers and therapeutic targets. Understanding the interplay between metabolism and epigenetics in the pathogenesis of T2D and CVD could provide critical insights for early disease identification and the development of novel epigenome-targeted therapeutic strategies.

Keywords Metabolic diseases, Type 2 diabetes, Cardiovascular diseases, DNA methylation, Epigenetic crosstalk

*Correspondence:
Bright Starling Emerald
bsemerald@uaeu.ac.ae

Full list of author information is available at the end of the article

Graphical abstract



Introduction

Metabolic syndrome (MetS) is a major global public health concern and clinical challenge because it involves a cluster of risk factors which are associated with each other and significantly increase the incidence of developing type 2 diabetes (T2D), cardiovascular diseases (CVD), obesity and other health complications such as chronic kidney disease and hepatic steatosis [1]. Variations in genetic, epigenetic and environmental factors contribute to changes in physiological, biochemical, and clinical parameters, resulting in the development of metabolic diseases [2]. Out of the various metabolic diseases, T2D is of special importance because of its high incidence and its alarmingly high increase rate globally. According to the International diabetes federation (IDF), in 2021, globally, 537 million adults were said to be suffering from diabetes, and it is predicted to reach 783 million by the year 2045 (https://idf.org/about-diabetes/diabetes-facts-figures/). T2D is marked by insulin resistance and dysfunction of pancreatic β-cells resulting from persistent hyperglycemia [3]. Predominantly, there are three types of diabetes, viz, type 1 diabetes (T1D), T2D, and gestational diabetes mellitus (GDM). T1D is characterised by a deficiency in insulin production and is caused by autoimmune destruction of the pancreatic islets. T2D is the most common type of diabetes caused by multiple factors and is characterised by insulin resistance and subsequent reduction in insulin production. GDM is induced in females during pregnancy and is characterised by glucose intolerance during pregnancy [4].

People with diabetes are two to three times more likely to develop cardiovascular diseases (CVD) compared to non-diabetic individuals [5], including conditions such as coronary heart disease, cardiomyopathy, stroke, and peripheral arterial disease [6]. High blood sugar levels can damage blood vessels and the heart over time, contributing to the buildup of plaques in the arteries, which leads to atherosclerosis, restricting blood flow and increasing the likelihood of heart-related complications [7]. In addition to the fact that T2D and CVD share many common pathophysiological factors (such as insulin resistance, inflammation, oxidative stress, hypercoagulability, high blood pressure, dyslipidemia, and obesity) [8], it has also been suggested that the gene regulatory pathways which are associated with the development or altered in T2D also contribute to the development of CVD in T2D patients. In this review article, we discuss the role of epigenetic changes that are associated with T2D and CVD. As opposed to the different reviews that examine various epigenetic mechanisms of T2D or CVD, this article provides a more focused exploration of DNA methylation as a common link or a possible biomarker between the two diseases. It highlights the overlapping methylation patterns in important genes and the associated pathways involved in both metabolic and vascular dysfunction. By incorporating the recent findings of common DNA methylation signatures, this review offers valuable insights into the shared pathophysiology of T2D and CVD.

Methodology

We carried out a search of the PubMed database to find articles that were relevant to our research question using the keywords along with Boolean operators (DNA methylation, Type 2 Diabetes, Cardiovascular diseases, DNMTs, Insulin signaling, Insulin resistance, heart failure, myocardial infarction, cardiomyopathy, inflammation, coronary heart disease). We screened the titles and the abstracts of the results to check for relevance. A review of the full texts followed this based on how closely they related to the topic, their scientific quality, and how well they addressed the key points of our research question.

Since this is a literature review and does not involve any new data collection or interaction with human or animal subjects, ethics committee approval was not required.

Epigenetic changes associated with T2D and CVD

Epigenetic modifications are reversible and sometimes heritable changes in gene expression without changes in the underlying sequence of DNA. Epigenetic regulatory changes link environmental factors by making subtle changes in the expression of genes, contributing to development, differentiation, and maintaining homeostasis [9]. Changes in epigenetic modifications, which are induced by environmental and genetic factors, contribute to the development of various diseases, including metabolic diseases, T2D and CVD. The key mechanisms through which epigenetic regulation takes place are DNA methylation, histone modifications, and non-coding regulatory RNAs [10]. DNA methylation is a chemical modification of DNA where a methyl group is added to the DNA molecule at cytosine bases. DNA methylation leads to altered gene expression by silencing genes. A methylation quantitative trait locus (mQTL) is a genetic variant associated with differences in DNA methylation levels at specific CpG sites. These may function as genetic determinants of the epigenome, linking genotype to epigenetic regulation of gene expression. Histone modifications are chemical changes in the histone proteins which can influence chromatin structure and gene expression by making DNA more or less accessible to the transcriptional machinery. Non-coding regulatory RNAs are RNA molecules that do not code for proteins but play key roles in regulating gene expression [10]. Regulatory RNAs are considered a broader part of epigenetic regulation. They interact with the genome by different mechanisms, including binding to specific DNA regions through complementary sequences or associated proteins. Through these interactions, lncRNAs can serve as agents that recruit epigenetic modifiers such as DNA methyltransferases, histone-modifying enzymes, and chromatin-remodelling complexes to specific genomic locations, establishing and maintaining tissue-specific epigenetic landscapes [11, 12].

Epigenetic regulatory factors also interact with one another, *i.e.* changes in DNA methylation can influence histone modifications, regulatory RNAs and vice versa. These alterations, along with the subsequent recruitment of specific regulatory molecular complexes, modify gene transcription by altering chromatin structure, thereby making regulatory DNA elements either more or less open and resulting in the activation or repression of genes and associated regulatory pathways [13]. Epigenetic mechanisms, like DNA methylation, histone modifications, and non-coding RNA interactions, play a critical role in the development of cardiovascular diseases in diabetic patients. These mechanisms induce significant changes in gene expression, which eventually lead to defects in the cardiovascular system. For example, prolonged exposure to hyperglycemia can cause persistent epigenetic modifications, resulting in continuous activation of pro-inflammatory pathways that cause vascular inflammation and atherosclerosis [14].

DNA methylation changes associated with T2D and CVD

Although DNA methylation was discovered in mammals in 1948 by Rollin Hotchkiss, its role in gene regulation

was discovered only during the 1980s [15]. Compared to histone modifications, DNA methylations are more stable and are inherited in successive cell divisions and across generations [16]. In vertebrates, DNA methylation occurs predominantly at the CpG sites. It has been suggested that there are about 29 million CpG sites in the human genome, and out of these, about 60–70% are suggested to be methylated [16]. However, most of the CpG islands, where higher repeats of CpG nucleotides are seen, are non-methylated. The enzymes that catalyse DNA methylation reactions are known as DNA methyltransferases (DNMTs). The Methyltransferase domain of DNMTs catalyses the transfer of a methyl group from S-adenosylmethionine (SAM) to the 5th carbon of the cytosine ring in CpG dinucleotides (Fig. 1). DNMT3a and DNMT3b are de novo DNMTs because they add new methylations to the unmodified DNA. The methyltransferase DNMT1 copies the parental methylation patterns to the newly synthesised DNA from the parental DNA during DNA replication. DNMT1 is also involved in repairing DNA methylation, and for these reasons, DNMT1 is also known as the maintenance DNMT. DNMT3L is a non-catalytic member of the DNMT family that lacks the methyltransferase domain found in other DNMT enzymes. It is primarily expressed during early development and remains localised to germ cells and the thymus in adults. While it does not have catalytic activity, Dnmt3L interacts with Dnmt3a and Dnmt3b and enhances their methyltransferase functions. Terminally differentiated cells express low levels of DNMTs [15]. Altered methylation at the promoter region or the gene body affects gene expression. An increase in the methylation (hypermethylation) at the CpG sites would result in decreased gene expression, whereas a decrease in the methylation (hypomethylation) would result in enhancement of the gene expression. The mechanisms by which de novo DNA methyltransferases (DNMT3a and DNMT3b) target specific regions of the genome are still not fully understood. Although they are known to bind to DNA through a conserved PWWP domain, the way they precisely bind to selective DNA sequences remains mostly unclear. It is proposed that RNA interference (RNAi) mechanisms could play a role in their specificity [17]. It is also possible that transcription factors help de novo DNA methylation by recruiting DNMTs to certain regions. Additionally, DNMTs may also interact with transcription factors or repressor complexes or, in certain conditions, be guided through other epigenetic modification, histone tail modification to target specific regions for methylation [15].

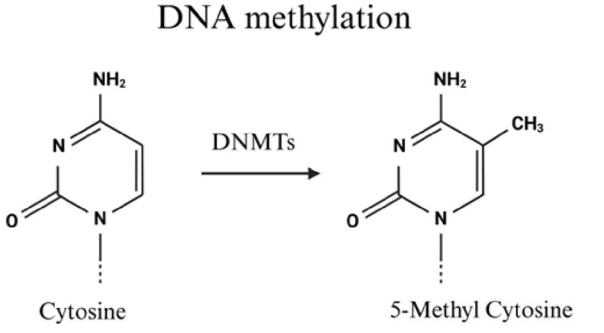


Fig. 1 The figure depicts the process of DNA methylation. During this process, a methyl group (-CH_3) is added to the cytosine base of CpG dinucleotides by DNA methyltransferases (DNMTs), leading to 5-methylcytosine (5mC) formation

DNA methylation is a dynamic process, which means that the methylation marks are added or erased through a series of stages. The main enzymes responsible for erasing CpG methylation are dioxygenases of the ten-eleven translocation (TET) family and the DNA repair enzyme thymine DNA glycosylase (TDG) [18]. DNA demethylation occurs through three different mechanisms, viz., active demethylation, passive demethylation, and 5-mC deamination [19]. During active 5-mC demethylation (also known as replication-independent demethylation), TET dioxygenases sequentially oxidise 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and finally 5-carboxylcytosine (5caC). The 5fC and 5caC bases are then recognised and removed by DNA glycosylases (primarily thymine DNA glycosylase) during base excision repair (BER) (Fig. 2).

In passive 5-mC demethylation (also known as replication-dependent demethylation), TET dioxygenases convert 5-mC to 5- hydroxymethyl cytosine (5-hmC). 5-hmCs skip the methylation step during DNA replication and result in the generation of hemimethylated DNA strands and further fully demethylated DNA strands [20] (Fig. 2). Deamination of cytosine happens spontaneously due to a deamination process catalysed by the AID/APOBEC family of deaminases. This process converts cytosine residue to uracil, resulting in the generation of G: U mismatches, which are eventually repaired by either BER or mismatch repair (MMR) enzymes [21].

DNA methylation changes in T2D and CVD progression

Whole genome DNA methylation analysis using different tissues of metabolic significance, such as the liver, muscle, pancreas and blood, has indicated alterations in methylation levels in several genes in T2D patients as well as in animal models [10, 18, 22–24]. Changes in the methylome in T2D can affect genes involved in regulating lipid metabolism, leading to dyslipidemia and ectopic fat deposition, thereby increasing the risk of cardiovascular complications. Given the interrelated but distinct nature of the processes involved, the affected processes in T2D that contribute to the progression towards CVD can be broadly classified into three categories: physiological

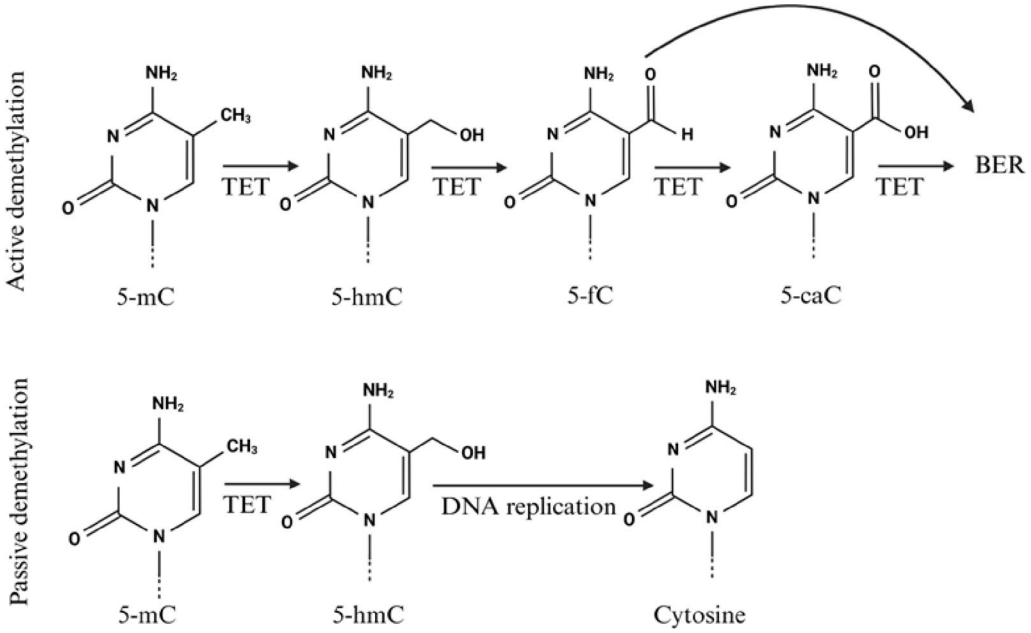


Fig. 2 The figure illustrates the active (A) and passive (B) processes of DNA demethylation, highlighting the removal of methyl groups ($-CH_3$) from cytosine residues within the genome. The ten-eleven translocation (TET) family of dioxygenases facilitate the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and further intermediates, 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), resulting in active base excision repair-mediated removal (A). 5-hmC in passive demethylation through DNA replication results in Cytosine (B)

and developmental responses, cellular processes and transport, and metabolic and redox regulation.

Physiological and developmental responses

Epigenetic changes during development can cause metabolic disorders like T2D [25] or CVDs [26]. Changes in the DNA methylation status of specific genes can also link T2D with CVD. In this section, we discuss the methylation changes affecting physiological and developmental responses that eventually cause T2D and CVD.

Diabetes induces the generation of reactive oxygen species (ROS) by non-enzymatic glycosylation reactions, electron transport chain, and membrane-bound NADPH oxidase in various tissues [27]. Oxidative stress-induced ROS leads to damage in the endothelial cells, affecting their structure and function. Thioredoxin interacting protein (TXNIP) is a marker associated with metabolism, oxidative stress, and inflammation, often elevated in cardiovascular diseases. It is thought to act as a potential link between metabolic processes and the cellular redox balance [28]. In the whole blood cells in the Pacific ethnic group of people residing in New Zealand, DNA methylation at cg19693031 within the TXNIP gene has been identified as being associated with T2D. This has also been shown to be a sensitive marker for T2D individuals experiencing acute coronary syndromes and is thus suggested to be a critical link between T2D and cardiovascular disease [29]. Hyperglycemic conditions can trigger the expression of TNFα in the cardiomyocytes, which in turn can cause irreversible changes in the DNMT activity, leading to the methylation of the promoter region of Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase 2 (SERCA2a) gene. The resultant downregulated expression of SERCA2a has been shown to cause an overload of calcium in the cardiomyocytes and diastolic heart failure later [30].

SRY-Box Transcription Factor 8 (SOX 8) is a gene involved in regulating development, fertility and metabolism. It orchestrates a complex interplay between lipid metabolism, redox balance, and iron homeostasis, ultimately promoting ferroptosis [31]. The SOX8 gene body has been shown to be hypermethylated in the peripheral blood cells of T2D patients [32], and SOX8 expression is upregulated in heart failure patients [33].

The Frizzled Class Receptor 5 (FZD5) gene, a key regulator of diabetic vasculopathy, has been implicated in cardiovascular complications associated with T2D. Elevated methylation levels of the FZD5 gene promoter have been observed in the peripheral blood cells of T2D patients with cardiovascular disease, suggesting a role for epigenetic modification contributing to vascular dysfunction. Aberrant methylation of FZD5 may disrupt Wnt signalling pathways, further exacerbating vascular complications in T2D. These observations together underscore the significance of FZD5 as a potential biomarker and therapeutic target for managing cardiovascular risks in diabetic patients [32, 34].

Gene polymorphism of TNFAIP3 Interacting Protein 1 (TNIP1) has been shown to be associated with an increased risk of coronary heart disease in the Chinese Han population, highlighting its potential role in cardiovascular pathology. In addition, a significant decrease in TNIP1 gene body methylation has been observed in the peripheral blood cells from T2D patients with cardiovascular disease, suggesting its contribution to the disease progression. TNIP1 is involved in regulating inflammatory responses and immune signalling pathways, which are critical in the pathogenesis of both T2D and cardiovascular disease. The interplay between genetic variations and methylation changes in TNIP1 may exacerbate chronic inflammation and endothelial dysfunction, key drivers of cardiovascular complications in diabetic patients [32, 35].

Elevated methylation levels of the Neurofilament Light Chain (NEFL) gene promoter have been observed in the peripheral blood cells from T2D patients with CVD, suggesting a role for epigenetic mechanisms contributing to cardiac complications. Consistently, a study by Yadi et al. demonstrated that the NEFL gene plays a role in the protective mechanisms against cardiac insufficiency, indicating its significance in maintaining cardiac function. Aberrant methylation of NEFL may impair its cardioprotective effects, thereby exacerbating cardiac dysfunction in T2D patients with CVD. These findings highlight the importance of NEFL as a potential biomarker for cardiovascular risk stratification and as a target for therapeutic strategies aimed at mitigating cardiac complications in T2D [32].

Cellular processes and transport

Cellular processes and transport mechanisms play a significant role in maintaining metabolic homeostasis and in intercellular communication. In T2D and related CVDs, several key genes and pathways involved in vesicular trafficking, ion exchange, glycosylation, and intracellular signalling have shown alterations in methylation. Methylation of the CpG (cg02711608) in the 1st exon encoding the 5' UTR region of Solute carrier family 1 member 5 (SLC1A5) in blood samples has been found to be associated with T2D [36], possibly contributing to the impaired insulin secretion. Glutamine metabolism also plays a critical role in endothelial cell (EC) function and angiogenesis, vessel sprouting, proliferation, and migration [37]. The expression of SLC1A5 is downregulated in heart failure [38].

The glucose-stimulated insulin secretion (GSIS) mediated by metabolic and hormonal signals helps maintain glucose homeostasis in mammals. Pancreatic β cells release insulin through an ATP-dependent process in response to rising blood glucose levels. Cellular glycolysis, the TCA cycle, and oxidative phosphorylation increase the ATP/ADP ratio in cells, which inhibits ATP-sensitive potassium (KATP) channels, leading to membrane depolarisation and activation of voltage-gated Ca^{2+} channels. The resulting Ca^{2+} influx triggers the release of insulin-containing granules [39]. In addition to glucose metabolism, pancreatic β cells leverage alternate metabolic pathways as an immediate source of energy. For instance, glutamine is processed by pancreatic β cells via the tricarboxylic acid cycle (TCA cycle) to produce the redox co-factor NADPH, which facilitates the exocytosis of insulin granules [40].

Phosphatase and tensin homolog (PTEN) plays a critical role in regulating insulin sensitivity, and its epigenetic regulation has been implicated in the pathogenesis of T2D [41]. In a study using the peripheral blood mononuclear cells from Uyghur patients with mild T2D, PTEN promoter methylation levels were found to be significantly lower compared to individuals with normal glucose tolerance (NGT), correlating with increased PTEN mRNA and protein expression. This hypomethylation was associated with reduced protein kinase B (AKT) levels, suggesting dysregulation of insulin signalling pathway. Two specific CpG sites (CpG 9 and CpG 21) within the PTEN promoter were identified to show significant differences in methylation between T2D and NGT groups. These findings identify PTEN promoter hypomethylation as a potential biomarker for T2D, offering insights into the epigenetic mechanisms underlying disease development in the Uyghur population [42]. PTEN also plays a pivotal role in regulating cardiomyocyte responses to cardiac stress by modulating the PI3K/AKT signalling pathway. It dephosphorylates PIP3, thereby negatively regulating processes such as hypertrophic growth, proliferation, and apoptosis in cardiomyocytes. Downregulation or inactivation of PTEN has been shown to improve heart function, promote cardiomyocyte proliferation, reduce cardiac fibrosis, and inhibit apoptosis, particularly following ischemic stress like myocardial infarction [43]. Thus, hypomethylation of CpG sites in the promoter region of PTEN in T2D patients may enhance CVDs. However, in smooth muscle cells (SMC), hypermethylation of the PTEN promoter region has been shown to lead to SMC dedifferentiation, inflammation, and atherosclerosis. A high-throughput screen has identified 5-azacytidine, a known DNA methyltransferase 1 (DNMT1) inhibitor, as a potent activator of the PTEN promoter. Treatment with 5-azacytidine reversed hypermethylation at the PTEN promoter region and restored its expression [44].

Phosphoglycerate dehydrogenase (PHGDH) is an enzyme involved in the serine synthesis pathway that regulates serine levels. Studies have shown that serine concentrations in the blood correlate with insulin secretion and sensitivity in humans [45]. A study using human

coronary artery smooth muscle cells (HCASMCs) grown in a calcifying medium showed that overexpression of PHGDH suppressed coronary artery calcification (CAC) [46]. Methylation at the CpG site, cg14476101, suppresses PHGDH expression and has been found in T2D patients in a T2D case cohort-study [36].

The mammalian Na+/H+ exchanger isoform one (NHE1) is a plasma membrane protein found in all human cells. It regulates intracellular pH by exchanging intracellular protons for extracellular sodium and plays a crucial role in heart disease. It is encoded by the gene Solute Carrier family 9A1 (SLC9A1) in humans [47]. NHE1 overactivation contributes to cardiomyocyte hypertrophy via MAPK pathways and induces oxidative stress, leading to heart failure [48]. Dysregulated NHE1 protein levels in cells lead to the increased intracellular concentration of Na+, impairment in insulin signalling and increased oxidative stress and inflammation [49]. Methylation at a CpG site (cg25130381) at the gene body of SLC9A1 has been found to be associated with T2D in humans based on blood sample analysis [36]. Furthermore, recent studies suggest that the cardioprotective effects of SGLT-2 inhibitors may be at least partly mediated through the regulation of NHE1 activity [50, 51]. SGLT-2 inhibitors have been shown to suppress NHE1 function indirectly, by reducing intracellular sodium and calcium levels, reducing myocardial stress, and thus improving the cardiac functions in both diabetic and non-diabetic patients [52].

Mannosidase Alpha Class 2A Member 2 (MAN2A2) encodes Golgi mannosidase, which is involved in the glycosylation of lipids and proteins in the Golgi body. Dysregulated expression of MAN2A2 leads to congenital disorders of glycosylation (CDGs). Lipid glycosylation plays a multifaceted role in cardiovascular diseases by promoting atherosclerosis, endothelial dysfunction, inflammation, oxidative stress, and thrombosis [53]. A DNA methylation cohort study using blood samples collected from women indicated a close relationship between methylation of MAN2A2 and myocardial infarction [54]. Methylation of MAN2A2 in whole blood cells has also been shown to be associated with the development of T2D [36]. Glycosylated lipids often alter the cell membrane structure and their properties and affect the signalling pathways. Glycosylation allows the glycosylated lipid to integrate into cell membranes, where it disrupts lipid metabolism and lipid-dependent signalling pathways and inhibits downstream signalling pathways by inhibiting the triggers of signalling, such as phosphorylation of the downstream targets or assembly of cascade proteins [55]. Advanced glycation end products (AGEs) are accumulated during diabetic conditions, which can lead to further complications, including CVDs [56].

A study using blood samples indicated that methylation at cg06397161, a CpG site within the gene body of the Synaptogyrin 1 (SYNGR1), a gene involved in exocytosis in the nervous system, has been found to highly correlate with T2D [36]. Given its role in vesicular transport, SYNGR1 could be involved in the secretion of pancreatic hormones. Dysregulation of SYNGR1 leads to an autoimmune disorder known as Sjögren's syndrome (SS) that predominantly affects the exocrine glands. Studies indicate that individuals with Sjögren's syndrome have a significantly higher risk of major adverse cardiovascular events, with reported rates between 34 and 46%, compared to the general population [57].

Patatin-like phospholipase domain-containing protein 6 (PNPLA6) is a member of the hydrolase family that primarily hydrolyses phosphatidylcholine (PC) and lysophosphatidylcholine (LPC), which may function as signalling messengers through membrane receptors. PNPLA6 is predicted to bind cAMP, a signalling molecule critical for regulating cardiac function. Differential methylation of the PNPLA6 gene can alter its expression, potentially disrupting lipid signalling and cAMP-mediated pathways, thereby affecting cardiovascular functions [32]. A recent study focusing on DNA methylation profiles in diabetic patients with and without cardiovascular problems revealed that hypomethylation of the genes, namely, VEGFB, PLGF, PLCB1, and FATP4, may serve as biomarkers for diabetic cardiovascular diseases. These genes, being integral components of the vascular endothelial growth factor receptor (VEGFR) signalling pathway, play a crucial role in endothelial function and angiogenesis. Alterations in DNA methylation patterns in these genes could contribute to endothelial dysfunction and, hence, enhance the progression of cardiovascular complications in diabetic patients [58].

Metabolic and redox regulation

Metabolic and redox regulation involves biochemical pathways that control energy production, lipid and glucose metabolism, and oxidative balance, and alterations, including changes in DNA methylations in the genes that modulate these metabolic processes, can contribute to the pathophysiology of T2D and CVD.

Obstructive sleep apnea (OSA) increases the risk of arterial hypertension (AH) and coronary heart disease (CHD). A study on genetic polymorphisms of genes associated with cardiovascular risks, which included 600 patients, found a correlation between the sterol regulatory element-binding transcription factor 1 (SREBF1), a protein that plays a crucial role in regulating lipid metabolism in the body and CHD. The SREBF1 gene functions primarily as a transcription factor that controls the expression of genes involved in the synthesis and uptake of cholesterol, fatty acids, triglycerides, and

phospholipids. Polymorphisms in the SREBF1 gene could thus be a good marker for predicting cardiovascular complications in OSA patients because the increased lipid uptake can eventually lead to cardiovascular complications [59]. SREBF1 also functions as a regulator of glucose metabolism and serum adiponectin levels [60]. DNA methylation at the cg11024682 in the SREBF1 gene has been found to increase the risk of T2D in the blood, liver, and visceral adipose tissue in humans [61].

Dysregulated lipid homeostasis often accompanies metabolic diseases. Dysregulated hepatic glucose production, impaired insulin secretion, and insulin resistance in T2D have been linked to the development of CVDs [62]. ATP Binding Cassette Subfamily A Member 1 (ABCA1) and ATP Binding Cassette Subfamily G Member 1 (ABCG1) are ATP-binding cassette transporters which play critical roles in the formation of high-density lipoprotein (HDL). They mediate the efflux of cholesterol from cells to apolipoproteins and HDL particles, respectively. ABCA1 helps in the initial transfer of cholesterol and phospholipids to apolipoprotein A-I (apoA-I), which forms naive HDL particles. Further, ABCG1 promotes cholesterol efflux to these naïve HDL particles, leading to their maturation into spherical HDL. Genotypic analysis of the participants from the Copenhagen City Heart Study (CCHS), which examined the associations of ABCG1 genetic variants with plasma HDL cholesterol, other lipids, and their predictive value for myocardial infarction (MI) and ischemic heart disease (IHD) over 34 years indicated a strong correlation between genetic variations in ABCG1 and myocardial infarction (MI) and ischemic heart disease (IHD) [63]. DNA methylation increase of the ABCG1 gene using peripheral blood samples was found to increase the risk of T2D. It had also been found that an increase of 1% methylation at CpG13 and CpG14 increased the T2D risk by 16%, and methylation gains ≥ 5% at CpG15 increased risk by 78% in rural Chinese populations [64].

Mutations in ABCA1 can lead to Tangier disease, characterised by extremely low HDL levels and increased cardiovascular risk [65–69]. Emerging research highlights ABCA1 methylation as a key epigenetic regulator influenced by diabetes, particularly GDM and T2D, impairing cholesterol transport and increasing CVD risk [70–72]. In diabetes, ABCA1 hypermethylation disrupts lipid handling in muscle and vascular tissues, exacerbating atherosclerosis and metabolic dysregulation. Genetic variations, such as the R219K polymorphism, further link ABCA1 dysfunction to premature coronary artery disease [73]. Additionally, microRNAs like miR-28-5p modulate ABCA1 expression, influencing plaque stability in conditions such as unstable angina [74]. These findings underscore ABCA1 methylation as a critical epigenetic mechanism linking diabetes to cardiovascular complications. CVD patients with coronary arterial disease show increased levels of CAC. Over time, microcalcifications grow larger and lead to arteriosclerosis.

Dysregulations in lipid synthesis, metabolism, and transport are often correlated with both diabetes and cardiovascular diseases [75–77]. A study using blood samples indicated that methylation at the 5'UTR region of Carnitine palmitoyl transferase 1a (CPT1a, cg00574958), a gene involved in the transport of long-chain fatty acids across the mitochondrial membranes, is associated with the development of T2D [36]. Additionally, CPT1a is upregulated in pathological cardiac remodelling, including heart failure (HF) and nonischemic cardiomyopathy (NICM) [78]. In mice, suppression of CPT1a has been found to worsen cardiac dysfunction and increase mortality, while overexpression improved heart function and reduced adverse cardiac remodelling [78]. Further, it was found that CPT1a regulates hypertrophic, profibrotic, and cell death gene programs independently of fatty acid oxidation via cytotoxic T-cell-mediated destruction of cells or by regulating apoptotic pathways through its interaction with the regulators of apoptosis. These findings highlight the role of CPT1a as an important cardioprotective adaptation to stress [78].

The peroxisome proliferator-activated receptor gamma (PPARG) is a nuclear receptor crucial for metabolic homeostasis, primarily expressed in adipose tissue, where it regulates adipocyte differentiation, lipid metabolism, and insulin sensitivity [79–81]. Activated by endogenous fatty acids and synthetic agents like thiazolidinediones, PPARG forms a dimer with the Retinoid X receptor to regulate gene transcription involved in glucose and lipid metabolism [82]. It has also been shown that PPARG hypermethylation, observed in insulin-resistant and diabetic models, reduces its expression and impairs its metabolic and anti-inflammatory functions [81, 83]. This dysfunction contributes to increased oxidative stress, endothelial cell dysfunction, and heightened cardiovascular risk in diabetic patients [84, 85]. Given its role in vascular health, therapies targeting PPARG activation, such as thiazolidinediones, are being investigated for their potential cardiovascular benefits in T2D.

Mitochondria are sites of energy metabolism and power generation in the cells. Aberrations in mitochondrial function can lead to metabolic disorders and CVDs. Impaired mitochondrial function can cause defective oxidative phosphorylation and abnormally high levels of ROS generation [86, 87]. Mitochondrial A-kinase anchoring proteins (MitoAKAPs), encoded by the Akap1 gene, are crucial for mitochondrial homeostasis and endothelial cell (EC) function. In Akap1 knockout mice, vascular impairments have been observed, including reduced blood flow recovery, capillary density, endothelial migration, proliferation, and survival. Under hypoxic

conditions, the Akap1 knockout endothelial cells showed mitochondrial dysfunction, increased oxidative stress, and apoptosis, highlighting mitoAKAPs' role in endothelial health [88]. CpG methylation at the CG site in the 5'UTR region of the Akap1 gene (cg05778424) was found to be correlated with T2D [36]. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) is a crucial enzyme that regulates glycolysis by enhancing the glycolytic flux. It achieves this by elevating the levels of fructose-2,6-bisphosphate, an activator of phosphofructokinase-1, the rate-limiting enzyme in the glycolytic pathway [89]. Enhanced glycolysis in the vascular tissues in the lungs has been found to correlate with pulmonary hypertension. Concordantly, the expression of PFKFB3 was also found to be upregulated in pulmonary hypertension and atherosclerosis. The increased glycolysis enhanced the production of growth factors and proinflammatory cytokines, promoting lung endothelial inflammation and proliferation of pulmonary arterial smooth muscle cells (PASMCs). Also, the elevated glycolytic metabolites stabilised HIF-2α, further driving the expression of proinflammatory and proliferative signals [90, 91]. PFKFB3 levels have also been observed to be upregulated in T2D patients. Hypermethylation at the CpG site (cg08994060) within the gene body of PFKFB3 in whole blood cells has been identified in T2D patients, which has been shown to regulate its expression [36]. Studies have identified the LMF1 gene as a key regulator of lipase activity, with evidence suggesting its involvement in triglyceride metabolism. Metformin has been shown to increase LMF1 expression in the heart, indicating that stimulation of LMF1 may contribute to its triglyceride-lowering effects. This is supported by a study that demonstrated that metformin activates AMP-activated protein kinase (AMPK) in brown adipose tissue, which subsequently enhances lipase activity and mitochondrial fatty acid oxidation, leading to accelerated clearance of VLDL-triglycerides from the plasma [92]. There is also evidence that metformin reduces VLDL-TG concentrations, potentially by enhancing Lipoprotein lipase (LPL)-mediated hydrolysis, a process in which LMF1 plays a critical role as a molecular chaperone [93]. Consistently, elevated methylation levels of the LMF1 gene promoter have been observed in T2D patients with cardiovascular disease, suggesting a role for DNA methylation in linking LMF1 dysregulation to cardiometabolic complications. These findings highlight the dual role of LMF1 in lipid regulation and cardiovascular disease, as well as its potential as a therapeutic target in T2D-related cardiac dysfunction [94].

The DNA methylation changes in T2D associated with CVD progression are shown in Fig. 3 and Table 1.

Methylation of genes involved in CVD contributing to T2D

Although rare, DNA methylation involved in the development of CVDs can contribute to the development of diabetes. Hypoxia-inducible factor 3A (HIF3A) is a dominant negative inhibitor of HIF1 and HIF2, which are responsible for inducing atrial inflammation and fibrosis. Hypermethylation of Hif3a and Ifltd1 genes and the

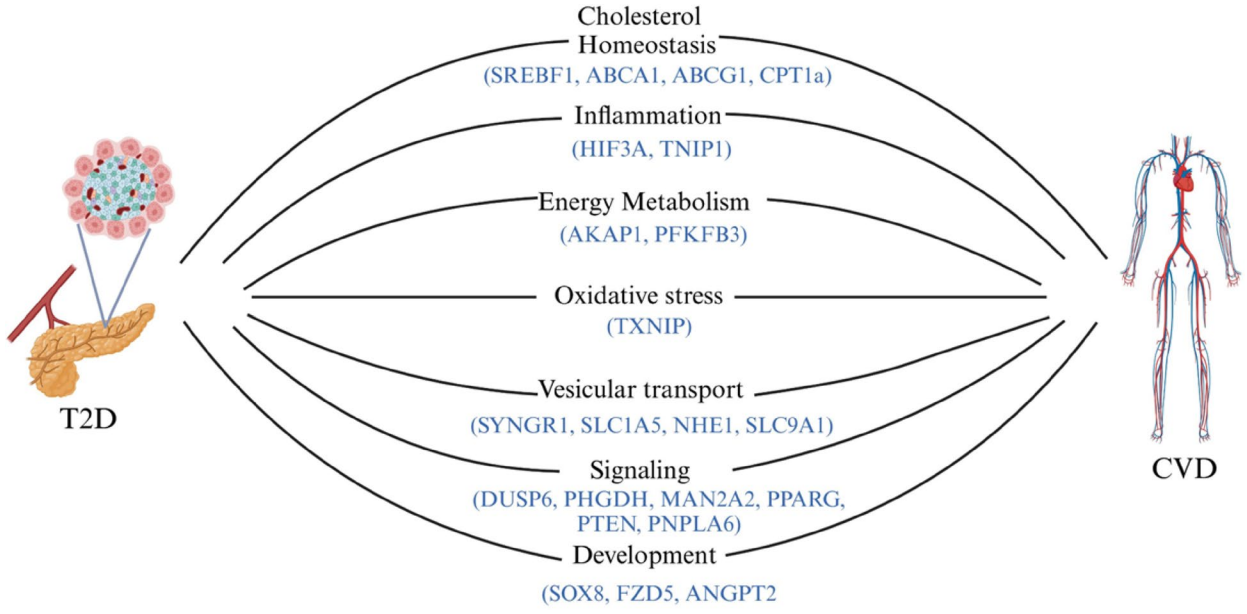


Fig. 3 Illustration of the physiological links between type 2 diabetes (T2D) and cardiovascular disease (CVD), highlighting key molecular pathways and genes influenced by DNA methylation. Epigenetic modifications, particularly DNA methylation, impact genes involved in cholesterol homeostasis, inflammation, energy metabolism, oxidative stress, vesicular transport, signalling and development, contributing to CVD progression in individuals with T2D. This figure was generated by using BioRender

Table 1 DNA methylations in T2D causing CVD

Gene	Function	Methylation	CVD	References
ABCA1	Lipid Metabolism		Premature Coronary Artery Disease	[68, 69, 70, 71, 72, 73]
ABCG1	Cholesterol Transportation	Cpg13, Cpg14 And Cpg15	Myocardial Infarction (MI) and Ischemic Heart Disease (IHD)	[63, 64]
Akap1	Mitochondrial Homeostasis And Endothelial Cell (EC) Function	Cg05778424	Vascular Impairments	[36, 88]
CPT1A	Transport Of Long-Chain Fatty Acids Across The Mitochondrial Membranes	Cg00574958	Heart Failure (HF) And Nonischemic Cardiomyopathy (NICM)	[36, 78]
FZD5	Development		Vascular Dysfunction	[32, 34]
LMF1	Lipid Metabolism		Cardiometabolic Complications	[92, 93, 94]
MAN2A2	Lipid Glycosylation		Myocardial Infarction	[53, 54, 55, 56]
NEFL	Development		Heart Failure	[32]
PFKFB3	Metabolism, Glycolysis, Inflammation	Cg08994060	Pulmonary Hypertension and Atherosclerosis	[36, 89, 90, 91]
PHGDH	Serine Synthesis	Cg14476101	Coronary Artery Diseases	[36, 45, 46]
PNPLA6	Signaling		Heart Failure	[32, 58]
PPARG	Metabolic Homeostasis		Endothelial Cell Dysfunction	[81, 83, 84, 85]
PTEN	Insulin Signaling	Cpg 9 And Cpg 21	Hypomethylation Can Cause Myocardial Infarction	[42, 43, 44]
SERCA2a	Secretion		Diastolic Heart Failure	[30]
SLC1A5	Insulin Secretion	Cg02711608	Heart Failure	[36, 37, 38]
SLC9A1	Insulin Secretion,	Cg25130381	Cardiomyocyte Hypertrophy, Heart Failure	[36, 47, 48, 49, 52]
SOX 8	Development		Heart Failure	[32, 33]
SREBF1	Regulation Of Fatty Acid And Cholesterol Synthesis	Cg11024682	Coronary Heart Disease	[59, 60, 61]
SYNGR1	Exocytosis	Cg06397161	Chronic Inflammation, Autoimmune Responses, and Endothelial Dysfunction	[36, 57]
TNIP1	Inflammation		Coronary Heart Disease	[32, 35]
TXNIP	Metabolism, Oxidative Stress, Inflammation	Cg19693031	Acute Coronary Syndromes	[28, 29]

corresponding downregulation of the expression of these genes have been found to have a strong correlation with arterial fibrillation in murine models of arterial fibrillation [95]. Studies also indicate that hypermethylation of the promoter region of HIF3a in the omental tissue has been associated with the development of GDM in humans [96].

DNA methylation changes in the key regulator of the apoptosis pathway, Fas Cell Surface Death Receptor (FAS), have been found to be associated with the pathogenesis of acute aortic dissection (AAD). In AAD patients, FAS was found to be hypomethylated, causing an increase in its expression levels by 1.78 times. Given that apoptosis contributes to vascular cell death, weakening of the aortic wall, and dissection progression [97], Fas plays a role in AAD development by promoting vascular smooth muscle cell apoptosis. Fas is known to induce β-cell apoptosis in the pancreas of diabetic patients, and thus, hypomethylation and the resultant enhancement of the expression of Fas in CVD patients could induce diabetes [98].

Angiopoietin-2 (ANGPT2) functions in blood and lymphatic vessel formation, remodelling, and vascular homeostasis. It is essential for the development and maintenance of the lymphatic vascular system. Hypomethylation at the promoter region of ANGPT2 and the resultant upregulation of its expression have been found to be associated with the development of AAD [97]. Endothelial complications caused by enhanced expression of ANGPT2 has been found to induce insulin resistance and eventually T2D [99].

Dual-specificity phosphatase 6 (DUSP6) is a phosphatase involved in the extracellular signal-regulated kinase 1/2 pathway (ERK 1/2). In mammals, a deficiency of DUSP6 has been shown to improve cardiac function [100]. Hypomethylation at the promoter region of DUSP6 has been seen in AAD patients [97]. However, a deficiency of DUSP6 leads to glucose intolerance and the development of insulin resistance [101].

DNA methylation plays an important role in atherosclerosis (AS)-associated inflammation, particularly in response to lipid oxidation. Oxidised low-density lipoprotein (oxLDL) formed during atherogenesis has been shown to upregulate DNMT1 in endothelial cells and lead to the methylation of the promoter region of the KLF2 gene, eventually silencing its expression. KLF2 expression is important in maintaining endothelial cell homeostasis and regulating anti-inflammatory and vaso-protective

Table 2 Methylations on genes involved in CVD contribute to T2D

Gene	Function	CVD	References
ANGPT2	Vascular Homeostasis	Acute Aortic Dissection	[97, 99]
BAZ1B	DNA Damage Repair And Mitosis	Cardiomyopathy	[105, 106, 107, 108]
DUSP6	ERK Signaling	Acute Aortic Dissection	[97, 100, 101]
Fas	Apoptosis	Acute Aortic Dissection	[97, 98]
HIF3A	Transcriptional Regulation, Adaptive Response To Low Oxygen	Arterial Fibrillation	[95, 96]

responses [102]. Studies using human umbilical vein endothelial cells (HUVECs) have shown that exposure to oxLDL reduces KLF2 expression through changes in DNA methylation [103]. However, this effect can be reversed by treatment with DNMT inhibitors such as 5-azacytidine, restoring KLF2 levels and restoring endothelial function.

Bromodomain adjacent to zinc finger domain 1B (BAZ1B), is a chromatin remodeler and transcriptional regulator which also functions in DNA damage repair and mitosis [104]. Recent studies have shown that alterations in the expression of BAZ1B can cause cardiomyopathy [105]. Altered methylation at cg07467649 at the promoter region of BAZ1B was shown to induce atrial fibrillation [106]. Studies on the genetic variants of BAZ1B have shown that certain genetic variants of BAZ1B cause dyslipidemia [107] and T2D [108].

The list of those known genes where methylations are involved in cardiovascular diseases, inducing T2D is given in Table 2.

Limitations, conclusions, and future perspectives

Diabetes affects millions of people worldwide, and CVD is the leading cause of mortality, with a high prevalence among individuals with diabetes. DNA methylation plays a crucial role in the pathogenesis of T2D and CVD. Many of the methylation changes associated with T2D affect cardiovascular health by altering pathways involved in inflammation, oxidative stress response, cholesterol biosynthesis, lipid homeostasis, energy metabolism, vesicular transport, insulin signalling, and development (Fig. 3). Despite extensive research on the molecular mechanisms underlying these conditions individually, the cross-talk between DNA methylation in T2D and its impact on CVD is only beginning to be explored. As DNA methylation is dynamic and reversible, understanding these epigenetic modifications provides valuable insights into disease mechanisms and opens the scope for novel diagnostic and therapeutic strategies.

Future studies should focus on longitudinal epigenome-wide association studies, including lifestyle parameters such as diet and exercise. Epigenetic risk scores integrating methylation data may enhance disease prediction models beyond traditional risk factors. DNA methylation signatures could serve as markers for T2D and early diagnostic biomarkers for CVD. Identification of methylation changes specific to individuals or subpopulations could enable precision medicine approaches. Although epigenetic drugs, including DNA methylation modulators, are still not used for metabolic diseases, this could be explored to target T2D and CVD-associated methylation patterns.

This review mostly addresses DNA methylation changes and excludes other critical epigenetic mechanisms such as histone modifications and the associated chromatin remodelling, which are known to play significant roles in both diabetes and CVD pathogenesis. Also, although DNA methylation is altered by factors such as diet, exercise, and medication, this review may not have addressed how such factors affect the DNA methylation relevant to the overlapping pathophysiology of diabetes and CVD.

Diabetes is a significant risk factor for CVD, and targeting this link could serve as a novel therapeutic strategy for preventing or mitigating CVD in diabetic patients. By bridging the gap between epigenetics and personalised medicine, the future of T2D and CVD management will likely be transformed, shifting towards more predictive, preventive, and precise healthcare solutions.

Abbreviations

T2D	Type 2 diabetes
CVD	Cardiovascular disease
Mets	Metabolic syndrome
IDF	International diabetes federation
GDM	Gestational diabetes mellitus
T1D	Type 1 diabetes
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
CpG	Cytosine-phosphate-Guanine
DNMT	DNA methyltransferase
RNAi	RNA interference
TDG	Thymine DNA glycosylase
MC	Methylcytosine
5hMC	5-Hydroxymethylcytosine
5FC	5-Formylcytosine5caC—5-carboxylcytosine
5caC	5-Carboxylcytosine
BER	Base excision repair
MMR	Mismatch repair
ROS	Reactive oxygen species
TXNIP	Thioredoxin-interacting protein
HDL	High-density lipoprotein
CCHS	Copenhagen city heart study
MI	Myocardial infarction
IHD	Ischemic heart disease
PHGDH	Phosphoglycerate dehydrogenase
HCASMC	Human coronary artery smooth muscle cells
AH	Atherosclerosis and hypertension
CHD	Coronary heart disease
SREBF1	Sterol regulatory element-binding transcription factor 1
OSA	Obstructive Sleep Apnea

CPT1a	Carnitine palmitoyltransferase 1A
HF	Heart failure
NICM	Non-ischemic cardiomyopathy
mitoAKAPs	Mitochondrial A-kinase anchoring proteins
EC	Endothelial cell(s)
PFKFB3	6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
PASMC	Pulmonary artery smooth muscle cell(s)
LMF1	Lipase maturation factor 1
SYNGR1	Synaptogyrin 1
GSIS	Glucose-stimulated insulin secretion
KATP	ATP-sensitive potassium channel
TCA	Tricarboxylic acid
SLC1A5	Solute carrier family 1 member 5
NHE1	Sodium-hydrogen exchanger 1
SGLT2	Sodium-glucose cotransporter 2
MAN2A2	Mannosidase alpha class 2a member 2
AGE	Advanced glycation end-product
PTEN	Phosphatase and tensin homolog
PI3K/AKT	Phosphoinositide 3-kinase/protein kinase B (AKT) pathway
PPARγ (PPARg)	Peroxisome Proliferator-Activated Receptor Gamma
SERCA2A	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2A
SOX8	SRY-box transcription factor 8
FZD5	Frizzled class receptor 5
TNIP1	TNFAIP3 interacting protein 1
NEFL	Neurofilament light chain
PNPLA6	Patatin-like phospholipase domain containing 6
LPC	Lysophosphatidylcholine
VEGFR	Vascular endothelial growth factor receptor
HIF3A	Hypoxia inducible factor 3 subunit alpha
AAD	Aortic aneurysmal disease
ANGPT2	Angiopoietin-2
DUSP6	Dual specificity phosphatase 6
ERK 1/2	Extracellular signal-regulated kinases 1 and 2
BAZ1B	Bromodomain adjacent to zinc finger domain 1B

Acknowledgements
Not applicable.

Author contributions
SK and B.S.E. conceived the idea and conducted a review of the literature, contributed to the design, and wrote the first draft of the review. LKY, MIKH., MZA, PS, JAK, MKSL, SS and SAA. contributed to the conception and final design of the review. All authors reviewed, edited the manuscript, and approved the final manuscript.

Funding
This work was supported by research grants from the United Arab Emirates University, UAEU Strategic Research Grants #12R110, #12R206, UAEU-AUA Joint Grant 12R120, and a grant from the Zayed Bin Sultan Charitable and Humanitarian Foundation (ZCHF), 2IM186. UPAR grant from the United Arab Emirates University to MZA (Grant No. G00004977, Fund No. 12M219). By ASPIRE, the technology program management pillar of Abu Dhabi's Advanced Technology Research Council (ATRC) via the ASPIRE Precision Medicine Research Institute Abu Dhabi (VRI-20-10).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anatomy, College of Medicine and Health Sciences, United Arab Emirates University, P.O. Box 15551, Al Ain, Abu Dhabi, United Arab Emirates
[2]A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore
[3]Program in Cancer and Stem Cell Biology, Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore
[4]Department of Internal Medicine, College of Medicine and Health Sciences, UAE University, P.O. Box 15551, Al Ain, United Arab Emirates
[5]Institute for Human Development and Potential (IHDP), Agency for Science, Technology and Research (A*STAR), 30 Medical Drive, Singapore 117609, Singapore
[6]Singapore Institute of Food and Biotechnology Innovation, A*STAR, Singapore, Singapore
[7]Department of Endocrinology, Tan Tock Seng Hospital, Singapore, Singapore
[8]Cardiovascular and Metabolic Diseases Program, Duke-NUS Medical School, Singapore, Singapore
[9]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
[10]Department of Biochemistry, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, Abu Dhabi, UAE
[11]Zayed Center for Health Sciences, United Arab Emirates University, P.O. Box 15551, Al Ain, Abu Dhabi, United Arab Emirates
[12]ASPIRE Precision Medicine, Research Institute Abu Dhabi, P.O. Box 15551, Al Ain, Abu Dhabi, United Arab Emirates

Received: 31 March 2025 / Accepted: 20 May 2025
Published online: 29 May 2025

References

1. Ambroselli D, Masciulli F, Romano E, Catanzaro G, Besharat ZM, Massari MC, Ferretti E, Migliaccio S, Izzo L, Ritieni A, et al. New advances in metabolic syndrome, from prevention to treatment: the role of diet and food. Nutrients. 2023;15(3):640.
2. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:943162.
3. Ashcroft FM, Rorsman P. Diabetes mellitus and the β cell: the last ten years. Cell. 2012;148(6):1160–71.
4. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33(Suppl 1):S62–9.
5. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241(19):2035–8.
6. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999;100(10):1134–46.
7. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. Int J Mol Sci. 2020;21(5):1835.
8. De Rosa S, Arcidiacono B, Chiefari E, Brunetti A, Indolfi C, Foti DP. Type 2 diabetes mellitus and cardiovascular disease: genetic and epigenetic links. Front Endocrinol (Lausanne). 2018;9:2.
9. Zhang TY, Meaney MJ. Epigenetics and the environmental regulation of the genome and its function. Annu Rev Psychol. 2010;61(439–466):C431-433.
10. Kaimala S, Kumar CA, Allouh MZ, Ansari SA, Emerald BS. Epigenetic modifications in pancreas development, diabetes, and therapeutics. Med Res Rev. 2022;42(3):1343–71.
11. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, Chen R, Dean C, Dinger ME, Fitzgerald KA, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023;24(6):430–47.
12. Kaimala S, Lootah SS, Mehra N, Kumar CA, Marzooqi SA, Sampath P, Ansari SA, Emerald BS. The long non-coding RNA obesity-related (Obr) contributes to lipid metabolism through epigenetic regulation. Adv Sci (Weinh). 2024;11(26):e2401939.
13. Kiselev IS, Kulakova OG, Boyko AN, Favorova OO. DNA Methylation as an epigenetic mechanism in the development of multiple sclerosis. Acta Nat. 2021;13(2):45–57.

14. Villeneuve LM, Reddy MA, Natarajan R. Epigenetics: deciphering its role in diabetes and its chronic complications. Clin Exp Pharmacol Physiol. 2011;38(7):451–9.
15. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013;38(1):23–38.
16. Kim M, Costello J. DNA methylation: an epigenetic mark of cellular memory. Exp Mol Med. 2017;49(4):e322.
17. Tóth DM, Szeri F, Ashaber M, Muazu M, Székvölgyi L, Arányi T. Tissue-specific roles of de novo DNA methyltransferases. Epigenetics Chromatin. 2025;18(1):5.
18. Kaimala S, Ansari SA, Emerald BS. DNA methylation in the pathogenesis of type 2 diabetes. Vitam Horm. 2023;122:147–69.
19. Prasad R, Yen TJ, Bellacosa A. Active DNA demethylation: the epigenetic gatekeeper of development, immunity, and cancer. Adv Genet (Hoboken). 2021;2(1):e10033.
20. Hackett JA, Sengupta R, Zylicz JJ, Murakami K, Lee C, Down TA, Surani MA. Germline DNA demethylation dynamics and imprint erasure through 5-hydroxymethylcytosine. Science. 2013;339(6118):448–52.
21. Shen JC, Rideout WM, Jones PA. The rate of hydrolytic deamination of 5-methylcytosine in double-stranded DNA. Nucleic Acids Res. 1994;22(6):972–6.
22. Kim M. DNA methylation: a cause and consequence of type 2 diabetes. Genom Inform. 2019;17(4):e38.
23. Kaimala S, Ansari S, Emerald BS. Risk factors which influence DNA methylation in childhood obesity. Hamdan Medical J. 2021;14(4):147–53.
24. Jeon JP, Koh IU, Choi NH, Kim BJ, Han BG, Lee S. Differential DNA methylation of MSI2 and its correlation with diabetic traits. PLoS ONE. 2017;12(5):e0177406.
25. Prabakaran AD, Karakkat JV, Vijayan R, Chalissery J, Ibrahim MF, Kaimala S, Adeghate EA, Al-Marzouqi AH, Ansari SA, Mensah-Brown E, et al. Identification of early indicators of altered metabolism in normal development using a rodent model system. Dis Model Mech. 2018. https://doi.org/10.1242/dmm.031815.
26. Abi Khalil C. The emerging role of epigenetics in cardiovascular disease. Ther Adv Chronic Dis. 2014;5(4):178–87.
27. Kaneto H, Katakami N, Matsuhisa M, Matsuoka TA. Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis. Mediat Inflamm. 2010;2010:453892.
28. Domingues A, Jolibois J, Marquet de Rougé P, Nivet-Antoine V. The emerging role of TXNIP in ischemic and cardiovascular diseases; a novel marker and therapeutic target. Int J Mol Sci. 2021;22(4):1693.
29. Gibbs S, Jones GT, Earle NJ, Poppe KK, Cameron VA, Fakahau PT, Frampton C, Rolleston A, Legget ME, Doughty R, et al. DNA methylation in the TXNIP gene is associated with type 2 diabetes in Pacific Peoples living in NZ. Eur Heart J. 2024;45:ehae666.2750.
30. Kao YH, Chen YC, Cheng CC, Lee TI, Chen YJ, Chen SA. Tumor necrosis factor-alpha decreases sarcoplasmic reticulum Ca^{2+}-ATPase expressions via the promoter methylation in cardiomyocytes. Crit Care Med. 2010;38(1):217–22.
31. Yang X, Gu C, Cai J, Li F, He X, Luo L, Xiao W, Hu B, Hu J, Qian H, et al. Excessive SOX8 reprograms energy and iron metabolism to prime hepatocellular carcinoma for ferroptosis. Redox Biol. 2024;69:103002.
32. He Y, Chen X, Liu M, Zuo L, Zhai Z, Zhou L, Li G, Chen L, Qi G, Jing C, et al. The potential DNA methylation markers of cardiovascular disease in patients with type 2 diabetes. BMC Med Genom. 2023;16(1):242.
33. Liu CF, Ni Y, Thachil V, Morley M, Moravec CS, Tang WHW. Differential expression of members of SOX family of transcription factors in failing human hearts. Transl Res. 2022;242:66–78.
34. Dai Y, Lu H, Wang S, Chang S, Li C, Huang Z, Zhang F, Yang H, Shen Y, Chen Z, et al. MicroRNA-216b actively modulates diabetic angiopathy through inverse regulation on FZD5. Gene. 2018;658:129–35.
35. Song Y, Yan M, Li J, Jin T, Chen C. Association between TNIP1, MPHOSPH6 and ZNF208 genetic polymorphisms and the coronary artery disease risk in Chinese Han population. Oncotarget. 2017;8(44):77233–40.
36. Cardona A, Day FR, Perry JRB, Loh M, Chu AY, Lehne B, Paul DS, Lotta LA, Stewart ID, Kerrison ND, et al. Epigenome-wide association study of incident type 2 diabetes in a British population: EPIC-Norfolk Study. Diabetes. 2019;68(12):2315–26.
37. Huang H, Vandekeere S, Kalucka J, Bierhansl L, Zecchin A, Brüning U, Visnagri A, Yuldasheva N, Goveia J, Cruys B, et al. Role of glutamine and interlinked asparagine metabolism in vessel formation. EMBO J. 2017;36(16):2334–52.
38. Kennel PJ, Liao X, Saha A, Ji R, Zhang X, Castillero E, Brunjes D, Takayama H, Naka Y, Thomas T, et al. Impairment of myocardial glutamine homeostasis induced by suppression of the amino acid carrier SLC1A5 in failing myocardium. Circ Heart Fail. 2019;12(12):e006336.
39. Lien EC, Vander Heiden MG. Pancreatic β cells put the glutamine engine in reverse. Cell Metab. 2021;33(4):702–4.
40. Zhang GF, Jensen MV, Gray SM, El K, Wang Y, Lu D, Becker TC, Campbell JE, Newgard CB. Reductive TCA cycle metabolism fuels glutamine- and glucose-stimulated insulin secretion. Cell Metab. 2021;33(4):804-817.e805.
41. Wong JT, Kim PT, Peacock JW, Yau TY, Mui AL, Chung SW, Sossi V, Doudet D, Green D, Ruth TJ, et al. Pten (phosphatase and tensin homologue gene) haploinsufficiency promotes insulin hypersensitivity. Diabetologia. 2007;50(2):395–403.
42. Yin L, Cai WJ, Chang XY, Li J, Zhu LY, Su XH, Yu XF, Sun K. Analysis of PTEN expression and promoter methylation in Uyghur patients with mild type 2 diabetes mellitus. Medicine (Baltimore). 2018;97(49):e13513.
43. Liang T, Gao F, Chen J. Role of PTEN-less in cardiac injury, hypertrophy and regeneration. Cell Regen. 2021;10(1):25.
44. Strand KA, Lu S, Mutryn MF, Li L, Zhou Q, Enyart BT, Jolly AJ, Dubner AM, Moulton KS, Nemenoff RA, et al. High throughput screen identifies the DNMT1 (DNA methyltransferase-1) inhibitor, 5-azacytidine, as a potent inducer of PTEN (phosphatase and tensin homolog): central role for PTEN in 5-azacytidine protection against pathological vascular remodeling. Arterioscler Thromb Vasc Biol. 2020;40(8):1854–69.
45. Vangipurapu J, Stancáková A, Smith U, Kuusisto J, Laakso M. Nine amino acids are associated with decreased insulin secretion and elevated glucose levels in a 7.4-year follow-up study of 5,181 Finnish men. Diabetes. 2019;68(6):1353–8.
46. Zou Y, Li D, Guan G, Liu W. Phosphoglycerate dehydrogenase overexpression inhibits ferroptosis to repress calcification of human coronary artery vascular smooth muscle cells via the P53/SLC7A11 pathway. Int J Gen Med. 2024;17:3673–87.
47. Fliegel L. Role of genetic mutations of the Na. Mol Cell Biochem. 2021;476(2):1221–32.
48. Fliegel L. Regulation of the Na(+)/H(+) exchanger in the healthy and diseased myocardium. Expert Opin Ther Targets. 2009;13(1):55–68.
49. Sun YM, Su Y, Li J, Tian Y, Wang LF. Role of the Na(+)/H(+) exchanger on the development of diabetes mellitus and its chronic complications. Biochem Biophys Res Commun. 2012;427(2):229–31.
50. Chen S, Wang Q, Bakker D, Hu X, Zhang L, van der Made I, Tebbens AM, Kovácsházi C, Giricz Z, Brenner GB, et al. Empagliflozin prevents heart failure through inhibition of the NHE1-NO pathway, independent of SGLT2. Basic Res Cardiol. 2024;119(5):751–72.
51. Deschaine B, Verma S, Rayatzadeh H. Clinical evidence and proposed mechanisms of sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction: a class effect? Card Fail Rev. 2022;8:e23.
52. Wichaiyo S, Saengklub N. Alterations of sodium-hydrogen exchanger 1 function in response to SGLT2 inhibitors: what is the evidence? Heart Fail Rev. 2022;27(6):1973–90.
53. Das D, Shruthi NR, Banerjee A, Jothimani G, Duttaroy AK, Pathak S. Endothelial dysfunction, platelet hyperactivity, hypertension, and the metabolic syndrome: molecular insights and combating strategies. Front Nutr. 2023;10:1221438.
54. Palou-Márquez G, Subirana I, Nonell L, Fernández-Sanlés A, Elosua R. DNA methylation and gene expression integration in cardiovascular disease. Clin Epigenetics. 2021;13(1):75.
55. Danker K, Reutter W, Semini G. Glycosidated phospholipids: uncoupling of signalling pathways at the plasma membrane. Br J Pharmacol. 2010;160(1):36–47.
56. Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol. 2014;18(1):1–14.
57. Su C, Zhu X, Wang Q, Jiang F, Zhang J. Causal associations of Sjögren's syndrome with cardiovascular disease: a two-sample Mendelian randomization study. Am Heart J Plus. 2024;47:100482.
58. Hu S, Chen L, Zeng T, Wang W, Yan Y, Qiu K, Xie Y, Liao Y. DNA methylation profiling reveals novel pathway implicated in cardiovascular diseases of diabetes. Front Endocrinol (Lausanne). 2023;14:1108126.
59. Bielicki P, Barnas M, Brzoska K. Genetic determinants of cardiovascular disease in patients with obstructive sleep apnea (OSA). Int J Obs. 2015. https://doi.org/10.1183/13993003.congress-13992015.OA13991751.
60. Felder TK, Oberkofler H, Weitgasser R, Mackevics V, Krempler F, Paulweber B, Patsch W. The SREBF-1 locus is associated with type 2 diabetes and plasma adiponectin levels in a middle-aged Austrian population. Int J Obes (Lond). 2007;31(7):1099–103.

61. Krause C, Sievert H, Geißler C, Grohs M, El Gammal AT, Wolter S, Ohlei O, Kilpert F, Krämer UM, Kasten M, et al. Critical evaluation of the DNA-methylation markers ABCG1 and SREBF1 for Type 2 diabetes stratification. Epigenomics. 2019;11(8):885–97.
62. Erion DM, Park HJ, Lee HY. The role of lipids in the pathogenesis and treatment of type 2 diabetes and associated co-morbidities. BMB Rep. 2016;49(3):139–48.
63. Schou J, Frikke-Schmidt R, Kardassis D, Thymiakou E, Nordestgaard BG, Jensen G, Grande P, Tybjærg-Hansen A. Genetic variation in ABCG1 and risk of myocardial infarction and ischemic heart disease. Arterioscler Thromb Vasc Biol. 2012;32(2):506–15.
64. Qie R, Chen Q, Wang T, Chen X, Wang J, Cheng R, Lin J, Zhao Y, Liu D, Qin P, et al. Association of ABCG1 gene methylation and its dynamic change status with incident type 2 diabetes mellitus: the Rural Chinese Cohort Study. J Hum Genet. 2021;66(4):347–57.
65. Wang S, Smith JD. ABCA1 and nascent HDL biogenesis. BioFactors. 2014;40(6):547–54.
66. Jacobo-Albavera L, Domínguez-Pérez M, Medina-Leyte DJ, González-Garrido A, Villarreal-Molina T. The role of the ATP-binding cassette A1 (ABCA1) in human disease. Int J Mol Sci. 2021;22(4):1593.
67. Wang S, Gulshan K, Brubaker G, Hazen SL, Smith JD. ABCA1 mediates unfolding of apolipoprotein AI N terminus on the cell surface before lipidation and release of nascent high-density lipoprotein. Arterioscler Thromb Vasc Biol. 2013;33(6):1197–205.
68. El Khoury P, Couvert P, Elbitar S, Ghaleb Y, Abou-Khalil Y, Azar Y, Ayoub C, Superville A, Guérin M, Rabès JP, et al. Identification of the first Tangier disease patient in Lebanon carrying a new pathogenic variant in ABCA1. J Clin Lipidol. 2018;12(6):1374–82.
69. Puntoni M, Sbrana F, Bigazzi F, Sampietro T. Tangier disease: epidemiology, pathophysiology, and management. Am J Cardiovasc Drugs. 2012;12(5):303–11.
70. Ding J, Reynolds LM, Zeller T, Müller C, Lohman K, Nicklas BJ, Kritchevsky SB, Huang Z, de la Fuente A, Soranzo N, et al. Alterations of a cellular cholesterol metabolism network are a molecular feature of obesity-related type 2 diabetes and cardiovascular disease. Diabetes. 2015;64(10):3464–74.
71. Ju Y, Shen T, Guo Z, Kong Y, Huang Y, Hu J. Identification of methylation-driven genes, circulating miRNAs and their potential regulatory mechanisms in gestational diabetes mellitus. Am J Transl Res. 2023;15(1):336–49.
72. Sterns JD, Smith CB, Steele JR, Stevenson KL, Gallicano GI. Epigenetics and type II diabetes mellitus: underlying mechanisms of prenatal predisposition. Front Cell Dev Biol. 2014;2:15.
73. Abd El-Aziz TA, Mohamed RH, Hagrass HA. Increased risk of premature coronary artery disease in Egyptians with ABCA1 (R219K), CETP (TaqIB), and LCAT (4886C/T) genes polymorphism. J Clin Lipidol. 2014;8(4):381–9.
74. Liu J, Liu Y, Sun YN, Li S, Liu XQ, Li J, Li CM, Tian W, Zhou YT, Shang XM. miR-28-5p involved in LXR-ABCA1 pathway is increased in the plasma of unstable angina patients. Heart Lung Circ. 2015;24(7):724–30.
75. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015;58(5):886–99.
76. Yan A, Xie G, Ding X, Wang Y, Guo L. Effects of lipid overload on heart in metabolic diseases. Horm Metab Res. 2021;53(12):771–8.
77. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol. 2018;17(1):122.
78. Carley AN, Maurya SK, Maurya CK, Wang Y, Webb A, Challa AA, Zhang Z, Zhu H, Heydemann A, Bedi KC Jr, Kyriakopoulos CP, Selzman CH, Drakos SG, Margulies KB, Lewandowski ED. Increased CPT1a expression is a critical cardioprotective response to pathological stress that suppresses gene programs for remodeling and enables rescue by gene transfer. bioRxiv; 2024.
79. Houseknecht KL, Cole BM, Steele PJ. Peroxisome proliferator-activated receptor gamma (PPARgamma) and its ligands: a review. Domest Anim Endocrinol. 2002;22(1):1–23.
80. Lehrke M, Lazar MA. The many faces of PPARgamma. Cell. 2005;123(6):993–9.
81. Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. Annu Rev Biochem. 2008;77:289–312.
82. Marion-Letellier R, Savoye G, Ghosh S. Fatty acids, eicosanoids and PPAR gamma. Eur J Pharmacol. 2016;785:44–9.
83. Fujiki K, Kano F, Shiota K, Murata M. Expression of the peroxisome proliferator activated receptor gamma gene is repressed by DNA methylation in visceral adipose tissue of mouse models of diabetes. BMC Biol. 2009;7:38.
84. Yin L, Wang L, Shi Z, Ji X, Liu L. The role of peroxisome proliferator-activated receptor gamma and atherosclerosis: Post-translational modification and selective modulators. Front Physiol. 2022;13:826811.
85. Kapadia R, Yi JH, Vemuganti R. Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists. Front Biosci. 2008;13:1813–26.
86. Krako Jakovljevic N, Pavlovic K, Jotic A, Lalic K, Stoiljkovic M, Lukic L, Milicic T, Macesic M, Stanarcic Gajovic J, Lalic NM. Targeting mitochondria in diabetes. Int J Mol Sci. 2021;22(12):6642.
87. Stamerra CA, Di Giosia P, Giorgini P, Ferri C, Sukhorukov VN, Sahebkar A. Mitochondrial dysfunction and cardiovascular disease: pathophysiology and emerging therapies. Oxid Med Cell Longev. 2022;2022:9530007.
88. Schiattarella GG, Cattaneo F, Carrizzo A, Paolillo R, Boccella N, Ambrosio M, Damato A, Pironti G, Franzone A, Russo G, et al. Regulates vascular function and endothelial cells behavior. Hypertension. 2018;71(3):507–17.
89. Rider MH, Bertrand L, Vertommen D, Michels PA, Rousseau GG, Hue L. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase: head-to-head with a bifunctional enzyme that controls glycolysis. Biochem J. 2004;381(Pt 3):561–79.
90. Cao Y, Zhang X, Wang L, Yang Q, Ma Q, Xu J, Wang J, Kovacs L, Ayon RJ, Liu Z, et al. PFKFB3-mediated endothelial glycolysis promotes pulmonary hypertension. Proc Natl Acad Sci U S A. 2019;116(27):13394–403.
91. Guo S, Li A, Fu X, Li Z, Cao K, Song M, Huang S, Yan J, Wang L, Dai X, et al. Gene-dosage effect of Pfkfb3 on monocyte/macrophage biology in atherosclerosis. Br J Pharmacol. 2022;179(21):4974–91.
92. Geerling JJ, Boon MR, van der Zon GC, van den Berg SA, van den Hoek AM, Lombès M, Princen HM, Havekes LM, Rensen PC, Guigas B. Metformin lowers plasma triglycerides by promoting VLDL-triglyceride clearance by brown adipose tissue in mice. Diabetes. 2014;63(3):880–91.
93. Green CJ, Marjot T, Walsby-Tickle J, Charlton C, Cornfield T, Westcott F, Pinnick KE, Moolla A, Hazlehurst JM, McCullagh J, et al. Metformin maintains intrahepatic triglyceride content through increased hepatic de novo lipogenesis. Eur J Endocrinol. 2022;186(3):367–77.
94. Dron JS, Hegele RA. Genetics of Hypertriglyceridemia. Front Endocrinol (Lausanne). 2020;11:455.
95. Abe K, Sasano T, Soejima Y, Fukayama H, Maeda S, Furukawa T. Hypermethylation of Hif3a and Ifltd1 is associated with atrial remodeling in pressure-overload murine model. Sci Rep. 2025;15(1):2699.
96. Zhang Y, Chen Y, Qu H, Wang Y. Methylation of HIF3A promoter CpG islands contributes to insulin resistance in gestational diabetes mellitus. Mol Genet Genom Med. 2019;7:e00583.
97. Chen Y, Xu X, Chen Z, Huang B, Wang X, Fan X. DNA methylation alternation in Stanford: a acute aortic dissection. BMC Cardiovasc Disord. 2022;22(1):455.
98. Savinov AY, Tcherepanov A, Green EA, Flavell RA, Chervonsky AV. Contribution of Fas to diabetes development. Proc Natl Acad Sci U S A. 2003;100(2):628–32.
99. Lim HS, Lip GY, Blann AD. Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis. Atherosclerosis. 2005;180(1):113–8.
100. Zhou X, Zhang C, Wu X, Hu X, Zhang Y, Wang X, Zheng L, Gao P, Du J, Zheng W, et al. Dusp6 deficiency attenuates neutrophil-mediated cardiac damage in the acute inflammatory phase of myocardial infarction. Nat Commun. 2022;13(1):6672.
101. Pfuhlmann K, Pfluger PT, Schriever SC, Müller TD, Tschöp MH, Stemmer K. Dual specificity phosphatase 6 deficiency is associated with impaired systemic glucose tolerance and reversible weight retardation in mice. PLoS ONE. 2017;12(9):e0183488.
102. Kumar A, Kumar S, Vikram A, Hoffman TA, Naqvi A, Lewarchik CM, Kim YR, Irani K. Histone and DNA methylation-mediated epigenetic downregulation of endothelial Kruppel-like factor 2 by low-density lipoprotein cholesterol. Arterioscler Thromb Vasc Biol. 2013;33(8):1936–42.
103. Yan Z, Deng Y, Jiao F, Guo J, Ou H. Lipopolysaccharide downregulates Kruppel-like factor 2 (KLF2) via inducing DNMT1-mediated hypermethylation in endothelial Cells. Inflammation. 2017;40(5):1589–98.
104. Tatu CA, Drugărin D, Stănescu DI, Păunescu V. DNA topology and V(D)J recombination: a tentative connection. Roum Arch Microbiol Immunol. 1993;52(4):255–60.
105. McIntosh B, Knutsen R, Levin M, Fu YP, Springer D, Kronquist E, Pai C, Heuckeroth R, Kozel B. Baz1b dosage influences cardiovascular function, predisposing to dilated cardiomyopathy. FASEB J. 2022;36(Suppl):1.
106. Carbonneau M, Li Y, Qu Y, Zheng Y, Wood AC, Wang M, Liu C, Huan T, Joehanes R, Guo X, et al. DNA methylation signatures of cardiovascular health provide insights into diseases. medRxiv 2024.

107. Kong X, Zhao Q, Xing X, Zhang B, Zhang X, Hong J, Yang W. Genetic variants associated with lipid profiles in Chinese patients with type 2 diabetes. PLoS ONE. 2015;10(8):e0135145.
108. Chidambaram M, Radha V, Mohan V. Replication of recently described type 2 diabetes gene variants in a South Indian population. Metabolism. 2010;59(12):1760–6.