

# Epigenetics and diabetes mellitus

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Epigenetic mechanisms were shown to be involved in the control of endocrine cell fate decision, islet differentiation,  $\beta$ -cell identity, proliferation, and mature function. The pathologic mechanisms involved in the development of type 1 diabetes may include DNA methylation, histone modification, microRNA, and molecular mimicry. These mechanisms may act through the regulation of gene expression.

## Keywords:

diabetes, epigenetic, gene expression

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## Epigenetics and diabetes mellitus

The number of people with diabetes worldwide has more than doubled during the past 20 years [1]. The prevalence of diabetes mellitus has reached epidemic proportions. In 2010, it was estimated that 6.4% of the adult population (285 million) has diabetes [2]. Diabetes mellitus causes chronic complications affecting the vasculature of various organs, risking patients for renal failure, vision loss, and heart failure [3]. In recent years, the incidence of type 2 diabetes has been steadily increasing among younger individuals [2]. One of the most worrying features is the emergence of type 2 diabetes in children and young adults [1]. The growing epidemic of type 2 diabetes mellitus and obesity is largely attributed to the current lifestyle of overconsumption and physical inactivity [4]. Type 2 diabetes is one of the most common chronic metabolic diseases characterized by insulin resistance and the decrease in insulin secretion [5–7]. Type 2 diabetes mellitus is a multifactorial disease, and its etiology involves a complex interplay between genetic, epigenetic, and environmental factors [8].

Type 1 diabetes mellitus is a chronic autoimmune disease resulting in immune destruction of  $\beta$ -cells in genetically susceptible individuals [9]. It is one of the most heritable common diseases, and, among autoimmune diseases, it has the largest range of concordance rates in monozygotic twins [10]. The mechanisms underlying the development of type 1 diabetes are not fully understood. However, a widely accepted point is that type 1 diabetes is caused by a combination of genetic and environmental factors [11]. Several mechanisms underlying the causes of  $\beta$ -cell failure have been reported, including decreased insulin signaling, endoplasmic reticulum stress, oxidative stress, and inflammation [12]. It has been proposed that  $\beta$ -cells are lost not only through

apoptosis, but also by dedifferentiating into progenitor-like cells [13].

## Developmental origins of health and disease

The concept of ‘Developmental Origins of Health and Disease’ has been widely accepted and it brings new insights into the molecular pathogenesis of human diseases [14]. The Developmental Origins of Health and Disease hypothesis holds that alterations to homeostasis during critical periods of development can predispose individuals to adult-onset chronic diseases such as diabetes and metabolic syndrome [15]. The rapid increase in the prevalence of noncommunicable diseases is probably the most important global health problem of the 21st century. Except Africa, noncommunicable diseases account for greater mortality compared with communicable, maternal, perinatal, and nutritional conditions combined [16]. Although modifiable lifestyle behaviors in adult life are the main risk factors, strong evidence now suggests that factors in early life also have a major role in the development of noncommunicable diseases. The mechanisms involved are not fully understood, including epigenetic changes and resetting of endocrine systems that affect energy metabolism and appetite [16].

Epigenetic changes are chemical modifications of DNA without changing DNA sequence. These chemical changes are enough to affect the genetic code expression. Epigenetic mechanisms were recently shown to be involved in the control of

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endocrine cell fate decision, islet differentiation,  $\beta$ -cell identity, proliferation, and function [17]. The mechanisms involved include DNA methylation, histone modification, microRNA, and molecular mimicry. These mechanisms may act through the regulation of gene expression, thereby affecting the immune system response toward islet  $\beta$ -cells [10,11]. Epigenetic modifications such as the reduction in histone acetylation and increase in methylation in the promoter region of the *Pdx1* gene (pancreatic and duodenal homeobox 1), which encodes an important transcription factor for pancreatic  $\beta$ -cell function, lead to the reduction in *Pdx1* expression levels [12].

This review provides an explorative reading of the relationship between epigenetic changes and diabetic patients even before birth. It explores several studies discussing the influence of surrounding environment, maternal and paternal effects, circumstances during pregnancy, and lifestyle during childhood and adolescence. This review specifically focuses on epigenetic changes in relation to diabetes: methylation-related changes, acetylation-related changes, microRNAs, effect of nutrition, maternal-fetal environment, maternal deficiencies, paternal factors, relations with diabetes complications, and the effect of exercise and environment.

#### **Epigenetic mechanisms, DNA methylation, histone modification, and microRNA**

##### *DNA methylation and development of diabetes mellitus*

Both lysine and arginine residues are known to be methylated. Methylated lysines are the best understood marks of the histone code, as specific methylated lysine match well with gene expression states. Histone H3 is one of the five main histone proteins involved in the structure of chromatin. H3 is involved with the structure of the nucleosomes of the 'beads on a string' structure. Histone proteins are highly post-translationally modified; however, H3 is the most extensively modified of the five histones. Histone methylation can be associated with either transcriptional repression or activation. Methylation of histone H3 at lysine 4 (H3K4me3) and H3K36 is correlated with transcriptional activation and are active marks for transcription, whereas trimethylation of histone H3 on lysine 27 (H3K27me3) is a mark of transcriptionally silent chromatin, and demethylation of histone H3 at lysine 9 (H3K9me2) is a signal for transcriptional silencing.

Lui *et al.* (2014) [18] investigated epigenetic changes that might orchestrate cell cycle and cell proliferation in

multiple organs during juvenile life. Lui *et al.* (2014) [18] performed chromatin immunoprecipitation-promoter tiling array to assess temporal changes in histone H3K4 and H3K27 trimethylation (me3) at promoter regions throughout the genome in the lung and kidney, comparing 1–4-week-old mice. They found extensive genome-wide shifts in H3K4me3 and H3K27me3 occurring with age in both the lung and the kidney. Gene analysis indicated that shifts in specific histone methylation marks were associated with developmental functions. Genes with decreases in H3K4me3 with age in both organs were strongly implicated in cell cycle and proliferation. The authors suggested that the common core developmental program of gene expression is associated with a common core developmental program of histone methylation. In particular, declining H3K4me3 is strongly associated with gene downregulation and occurs in the promoter regions of many growth-regulating genes, suggesting that this change in histone methylation may contribute to the genetic program that drives juvenile body growth deceleration [18].

#### **Methylation and development of type 2 diabetes mellitus**

The study of type 2 diabetes epigenetic networks provides a new way for understanding the pathogenic mechanism of type 2 diabetes caused by epigenetic disorders. In a study by Liu *et al.* (2014) [5], the weighted human DNA methylation network (WMPN) was constructed, and a type 2 diabetes-related subnetwork (TMSN) was obtained through related differentially methylated genes. It was found that TMSN had a diabetes-specific network structure and that nonfatal metabolic disease-causing genes were often located in the topological and functional periphery of the network. Combined with chromatin modifications, the weighted chromatin modification network (WCPN) was built, and a type 2 diabetes-related chromatin modification pattern subnetwork was obtained (TCSN). TCSN had a densely connected network community, indicating that TMSN and TCSN could represent a collection of type 2 diabetes-related epigenetic dysregulated subpathways. DNA methylation and chromatin modifications were identified; it was found that there existed genes with the variant expression level caused by the aberrant DNA methylation and (or) chromatin modifications, which might affect and promote the development of type 2 diabetes mellitus. Liu *et al.* (2014) [5] concluded that they have detected the potential interplay modules of DNA methylation and chromatin modifications for type 2 diabetes.

### Histone methylation in adipocytes

Jufvas *et al.* (2013) [19] analyzed the extent of methylation at lysine 4 and lysine 9 of histone H3 in primary human adipocytes from 43 individuals using modification-specific antibodies. Jufvas *et al.* (2013) [19] found that the level of lysine 9 dimethylation was stable, whereas adipocytes from type 2 diabetic and nondiabetic overweight patients exhibited about 40% lower levels of lysine 4 dimethylation compared with cells from normal-weight individuals. In contrast, trimethylation at lysine 4 was 40% higher in adipocytes from overweight diabetic patients compared with normal-weight and overweight nondiabetic patients. Jufvas *et al.* (2013) [19] defined genome-wide molecular modifications of histones in adipocytes that are directly associated with overweight and diabetes, and thus suggested a molecular basis for existing epidemiological evidence of epigenetic inheritance.

### DNA methylation in pancreatic islets

'CpG' are regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide in the linear sequence of bases along its length. 'CpG' is shorthand for '-C-phosphate-G-' - that is, cytosine and guanine separated by only one phosphate. Open Sea loci are isolated CpGs in the genome; CGI-shores are regions up to 2 kb distant from CGI island; and CGI-shelves are regions 2–4 kb from CGI island.

Several regions of the mRNA molecule are not translated into protein (untranslated regions). The three prime untranslated region (3'-UTR) or trailer sequence is found on the 3' side, and the 5'-UTR or leader sequence is found on the 5' side. 3'-UTR is the section of messenger RNA that immediately follows the translation termination codon. The 3'-UTR often contains regulatory regions that can influence polyadenylation, translation efficiency, localization, and stability of the mRNA.

Dayeh *et al.* (2014) [20] analyzed DNA methylation of CpG sites and the transcriptome in pancreatic islets from type 2 diabetes mellitus and nondiabetic donors. Genomic regions close to the transcription start site showed low degrees of methylation, and regions further away from the transcription start site, such as the gene body, 3'-UTR, and intergenic regions, showed a higher degree of methylation. Although CpG islands were hypomethylated, the surrounding 2 kb shores showed an intermediate degree of methylation, whereas regions further away (shelves and open sea) were hypermethylated in human islets,  $\beta$ -cells, and  $\alpha$ -cells. Dayeh *et al.* (2014) [20] provided new target genes with altered DNA methylation and expression in

type 2 diabetes mellitus islets that contribute to perturbed insulin and glucagon secretion.

### Methylation and development of type 1 diabetes mellitus

Stefan *et al.* (2014) [21] aimed to dissect the contribution of epigenetic factors, particularly DNA methylation, to the incomplete penetrance of type 1 diabetes mellitus. Stefan *et al.* (2014) [21] performed DNA methylation profiling in lymphocyte cell lines from three monozygotic twin pairs discordant for type 1 diabetes mellitus and six monozygotic twin pairs concordant for the disease using HumanMethylation27 BeadChip. Stefan *et al.* (2014) [21] identified 88 CpG sites displaying significant methylation changes in all type 1 diabetes mellitus-discordant monozygotic twin pairs. Functional annotation of the genes with distinct CpG methylation profiles in type 1 diabetes mellitus samples showed differential DNA methylation of immune response and defense response pathways between affected and unaffected twins [21].

In the study by Stefan *et al.* (2014) [21], integration of DNA-methylation data with genome-wide association study data that focuses on associations between genetic variants, typically single-nucleotide polymorphisms, and traits like major diseases mapped several known type 1 diabetes mellitus associated genes, HLA, gene encoding the preproinsulin precursor of insulin, interleukin-2 receptor subunit  $\beta$  (IL-2RB is involved in T-cell-mediated immune responses and in receptor-mediated endocytosis and transduction of mitogenic signals from interleukin-2), Cluster of Differentiation 226 (CD226: a protein that is expressed on the surface of natural killer cells, platelets, monocytes, and T cells and mediates cellular adhesion to other cells bearing its ligands), which showed significant differences in DNA methylation between affected and unaffected twins. Stefan *et al.* (2014) [21] suggested that abnormalities of DNA methylation patterns, known to regulate gene transcription, may be involved in the pathogenesis of type 1 diabetes mellitus.

### Acetylation-related changes

Khan and Jena (2014) [22] stated that recent pieces of evidence suggested that there is a link between diabetes and histone deacetylases (HDACs), because HDAC inhibitors promote  $\beta$ -cell development, proliferation, and function, as well as improve glucose homeostasis. Sodium butyrate (NaB) is a short-chain fatty acid having HDAC inhibition activity. Khan and Jena (2014) [22] aimed to investigate the protective role of sodium butyrate treatment in  $\beta$ -cell proliferation, function, and glucose homeostasis, as well as apoptosis

in juvenile diabetic rat. Plasma glucose and insulin levels, glycated hemoglobin (HbA1c), glucose tolerance, apoptosis, and expression of proliferating cell nuclear antigen, p38 (mitogen-activated protein kinases that are responsive to stress stimuli and are involved in cell differentiation and apoptosis), p53 (regulates the cell cycle and functions as a tumor suppressor, preventing cancer and conserving stability by preventing genome mutation), caspase-3 (caspase family is a family of cysteine-aspartic acid proteases that are essential in apoptosis, necrosis, and inflammation), extracellular signal-regulated kinase-1/2 (ERK-1/2), forkhead box protein O1 (FOXO1: a transcription factor that plays important roles in the regulation of gluconeogenesis and glycogenolysis through insulin signaling, and is also central to the decision for a preadipocyte to commit to adipogenesis), and insulin receptor substrate-1 (IRS-1) as well as histone acetylation were evaluated. Sodium butyrate treatment decreased plasma glucose, glycated hemoglobin, and  $\beta$ -cell apoptosis and improved plasma insulin level and glucose homeostasis through HDAC inhibition and histone acetylation in diabetic animal as compared with controls. Sodium butyrate treatment improved  $\beta$ -cell proliferation, function, and glucose homeostasis as well as reduced  $\beta$ -cell apoptosis in juvenile diabetic rat through the modulation of the apoptotic pathway and p38-mitogen-activated protein kinase (p38/ERK MAPK: participates in a signaling cascade controlling cellular responses to cytokines and stress) [22]. Sirtuins, belonging to class III HDAC family, have emerged as regulators of metabolism [23]. Preliminary findings suggest perturbations in a number of processes involved in cellular aging, such as changes in longevity-associated sirtuin activity, epigenetic regulation of key metabolic genes, and mitochondrial dysfunction [2].

#### **MicroRNAs and gene expression, silencing, and therapeutic intervention**

MicroRNAs (miRNAs) are a group of small, noncoding RNA molecules that regulate gene expression at the translational level by interfering with the 3' untranslated region of messenger RNAs [24]. MicroRNAs are interlaced within networks, which include transcriptional and epigenetic regulators as well, for continuous control of lineage-specific gene expression [25]. MicroRNAs regulate gene expression at the post-transcriptional level by inhibiting target messenger RNA translation. In disease states, the expression of microRNAs is often changed, resulting in altered expression (mostly overexpression) of downstream target genes [3].

Gene silencing through miRNA interference is one epigenetic mechanism impacting the development and

homeostasis of the organism. MiRNAs are critical for the regulation of several biological processes, cellular function, the cell cycle, differentiation, and apoptosis [24]. Deregulation of miRNAs was confirmed in several pathologies, including cancer (in lung cancer), chronic obstructive pulmonary disease, diabetes, and cardiovascular diseases [24].

MiR-1 is a miRNA precursor. There are two distinct miR-1 precursors that share an identical sequence; these are called miR-1-1 and miR-1-2. These microRNAs have pivotal roles in the development and physiology of muscle tissues, including the heart. MiR-1 is known to be involved in heart diseases such as hypertrophy, myocardial infarction, and arrhythmias. It regulates heart adaption after ischemic stress. MiR-1 is downregulated in myocardial infarcted tissue compared with healthy heart tissue where it is upregulated. Plasma levels of miR-1 can be used as a sensitive biomarker for myocardial infarction. The miR-17 microRNA precursor family includes miR-20a/b, miR-93, and miR-106a/b, and also includes members of the miR-19 and miR-25 families. Mir-126 is expressed in endothelial cells, throughout capillaries as well as larger blood vessels, and acts upon various transcripts to control angiogenesis. MiR-155 expression may inhibit malignant growth and viral infections and attenuates the progression of cardiovascular diseases. Mir-221 microRNA (and its paralogue, mir-222) prevents cell migration and proliferation in endothelial cells and is also involved in angiogenesis control.

In lung cancer, overexpression of several miRNAs (miR-155, miR-21, miR-17-92, and miR-221/222) and downregulation of let-7 (microRNA precursor), miR-1, miR-29, and miR-126 have been found. It has been shown that serum miRNA profile may be regarded as a potential tool for early, noninvasive lung cancer diagnosis, and it can be used for chemotherapy sensitivity prediction and prognosis [24]. Interestingly, restoring microRNA expression to normal levels can correct downstream effects and prevent diabetes-associated changes [3]. MiRNAs seem to represent a promising goal in the search for new biomarkers and may be considered as an interesting target for therapeutical intervention [24].

To determine whether microRNAs are involved in the pathogenesis of human type 2 diabetes mellitus, Kameswaran *et al.* (2014) [26] sequenced the small RNAs of human islets from diabetic and nondiabetic organ donors and identified a cluster of microRNAs in

an imprinted locus on human chromosome 14q32 that is highly and specifically expressed in human  $\beta$ -cells and markedly downregulated in islets from type 2 diabetes mellitus organ donors. The downregulation of this locus strongly correlates with hypermethylation of its promoter. Kameswaran *et al.* (2014) [26] identified disease-relevant targets of the chromosome 14q32 microRNAs that cause increased  $\beta$ -cell apoptosis upon overexpression in human islets. The results of Kameswaran *et al.* (2014) [26] support a role for microRNAs and their epigenetic control by DNA methylation in the pathogenesis of type II diabetes mellitus.

Epigenetic factors, when understood, could be used as early predictors of metabolic risk and for the development of drugs or diet-related treatments to delay these epigenetic changes and even to reverse them [27].

#### **The maternal–fetal environment**

Many maternal factors during pregnancy may increase the risk for diabetes of offsprings in later life, which include malnutrition, hyperglycemia, obesity, behavior (smoking, drinking, and junk food diet), hormone administration, and even stress [8]. Epigenetic modifications provide a potential link between the nutrition status during critical periods in development and changes in gene expression that may lead to disease phenotypes [28]. It is now well accepted that offspring exposed to maternal undernutrition, obesity, or gestational diabetes mellitus have an increased risk for chronic diseases later in life, supporting the theory of the early origins of chronic diseases [29].

#### **Effects of nutrition during pregnancy**

Epidemiological studies, including studies in identical twins and studies *in utero* during periods of famine, have provided strong correlations between low birth weight and subsequent risk for disease in later life, including type 2 diabetes and metabolic syndrome. These studies have suggested that the early environment, especially early nutrition, plays an important role in mediating these associations [30]. Nutrition is likely the most important environmental factor that influences the expression of genes involved in a variety of phenotypes associated with obesity and diabetes. During pregnancy, diet is a main factor that affects the organ developmental plasticity. Nutritional factors, including energy, fatty acids, protein, micronutrients, and folate, affect various aspects of metabolic programming [31].

#### **Maternal and neonate dietary and metabolic disorders in adults**

Epigenetic regulation of neuropeptide genes associated with central appetite control plays an important role in the development of nutritional programming. Pro-opio-melano-cortin (POMC) is a precursor polypeptide that is cleaved into multiple peptide hormones, and each of them is packaged in large vesicles that are released from the cells by means of exocytosis in response to appropriate stimulation. Although POMC is critical in appetite control, the molecular mechanism of methylation-related regulation of POMC is still unclear. On the basis of the report that the proximal specificity protein 1 (Sp1) binding site in POMC promoter is crucial for the leptin-mediated activation of POMC, the methylation of this site was investigated in a study by Zhang *et al.* (2014) [32] in both cultured cells and postnatal mice reared by the lactating dams with dietary supplementation of conjugated linoleic acids. The change in milk composition lead to an increase in food intake by offspring, suppression of POMC, attenuation of Sp1-promoter interaction, and the hypermethylation of cytosine guanine (CpG) dinucleotides at -100 and -103 within the Sp1 binding site of POMC promoter, which may be associated with the decrease in hypothalamic Sp1 and/or plasma S-adenosyl homocystein. In cultured cells, the methylation of the -100 CpG dinucleotides of the POMC promoter blocked the formation of Sp1-promoter complex and the leptin-induced activation of POMC. Adult metabolic changes like adult hyperglycemia and insulin resistance were observed, suggesting that this conjugated linoleic acid-mediated hypermethylation may contribute to the metabolic disorders [32].

#### **Maternal pregravid obesity effects**

Obesity is characterized as an excess accumulation of body fat resulting from a positive energy balance. It is the major risk factor for type 2 diabetes [33]. Obesity is a major health problem that is determined by interactions between lifestyle and environmental and genetic factors [34]. Maternal pregravid obesity combined with gestational diabetes mellitus leads to newborn hyperinsulinemia and increased offspring fat mass until week 6, whereas pregravid obesity without gestational diabetes mellitus does not. This strongly suggests the pivotal role of gestational diabetes mellitus in the adverse offspring outcome [35].

Attig *et al.* (2013) [36] stated that 20% of male and female inbred mice can cope with the obesogenic effects of a high-fat diet for 20 weeks after weaning,

remaining lean. However, the feeding of a control diet to diet-induced obesity mice during the peri-conceptual/gestation/lactation period led to sex-specific shift (17–43%) from susceptibility to resistance to high-fat diet, in the female offspring only. Adipose tissue displayed dysregulation of gene expression, with an upregulation of genes involved in lipid storage and adipocyte hypertrophy or hyperplasia in obese mice born to lean and obese mothers, respectively. Global DNA methylation, several histone marks, and key epigenetic regulators were also altered. Whether they were themselves lean (resistant) or obese (sensitive), the offspring of lean and obese mice clearly differed in terms of several metabolic features and epigenetic marks, suggesting that the effects of a high-fat diet depend on the leanness or obesity of the mother [36].

#### Effects of obesity during pregnancy

There is evidence that obese and diabetic people have a pattern of epigenetic marks different from nonobese and nondiabetic individuals [27]. Obesity during pregnancy is a threat to the well-being of the offspring in adulthood [36].

Nutrient excess causes metabolic and structural changes in adipocytes, which initiate transcriptional programs leading to the expression of inflammatory molecules and the subsequent recruitment of immune cells [37]. Schwenk *et al.* (2013) [33] stated that about 150 genetic loci identified in genome-wide association studies are linked with obesity and type 2 diabetes mellitus, each accounting for only a small proportion of the predicted heritability. However, the percentage of overall trait variance explained by these associated loci is modest (~5–10% for type 2 diabetes mellitus and ~2% for BMI). The lack of powerful genetic associations suggests that heritability is not entirely attributable to gene variations. Some of the familial aggregation as well as many of the effects of environmental exposures may reflect epigenetic processes [33].

#### Dietary interventions minimize metabolic costs for the next generation

Nicholas *et al.* (2013) [38] aimed to determine the effect of exposure to maternal obesity or to maternal weight loss around conception on the programming of hepatic insulin signaling in the offspring. Nicholas *et al.* (2013) [38] used an embryo transfer model in sheep to investigate the effects of exposure to either maternal obesity or to weight loss in normal and obese mothers preceding and for 1 week after conception on the expression of hepatic insulin-signaling and

gluconeogenic factors and key miRNAs involved in insulin signaling in the offspring. Nicholas *et al.* (2013) [38] found that exposure to maternal obesity resulted in increased hepatic miR-29b ( $P<0.05$ ), miR-103 ( $P<0.01$ ), and miR-107 ( $P<0.05$ ) expression, a decrease in insulin resistance ( $P<0.05$ ), phospho-Akt (protein kinase B: a serine/threonine-specific protein kinase that plays a key role in multiple processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration) ( $P<0.01$ ), and phospho-FoxO1 ( $P<0.01$ ) abundance, and a paradoxical decrease in 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD1, or 'cortisone reductase', is an NADPH-dependent enzyme that reduces cortisone to active cortisol) ( $P<0.05$ ), phosphoenol-pyruvate carboxykinase-C (PEPCK-C) ( $P<0.01$ ), and phosphoenol-pyruvate carboxykinase-M (PEPCK-M) ( $P<0.05$ ) expression in lambs (PEPCK is an enzyme in the lyase family that is used in gluconeogenesis metabolic pathway. It is found in two forms, cytosolic 'C' and mitochondrial 'M'). These changes were ablated by a period of moderate dietary restriction imposed during the periconceptual period. Maternal dietary restriction alone also resulted in decreased abundance of a separate subset of hepatic insulin-signaling molecules in the lamb. These findings highlight the sensitivity of the epigenome to maternal nutrition around conception and the need for dietary interventions that maximize metabolic benefits and minimize metabolic costs for the next generation [38].

#### Gestational diabetes mellitus

Gestational diabetes mellitus affects fetal DNA methylation and metabolic programming. Ruchat *et al.* (2013) [39] postulated that gestational diabetes mellitus exposure impacts the offspring's methylome and used an epigenomic approach to explore this hypothesis. They obtained placenta and cord blood samples from 44 newborns, including 30 exposed to gestational diabetes mellitus. Women were recruited at first trimester of pregnancy and followed up until delivery. The results suggested that gestational diabetes mellitus has epigenetic effects on genes preferentially involved in the metabolic diseases pathway, with consequences on fetal growth and development, and provided supportive evidence that DNA methylation is involved in fetal metabolic programming [39].

DNA methylation changes increase the risk for type 2 diabetes through their effects on  $\beta$ -cell function of the offspring of gestational DM mothers. Del Rosario *et al.* (2014) [40] investigated the potential role of DNA

methylation in mediating the increased risk of developing type 2 diabetes in offspring of mothers who had diabetes during pregnancy. Del Rosario *et al.* (2014) [40] collected peripheral blood leukocytes from nondiabetic Pima Indians who were either offspring of diabetic mothers or offspring of nondiabetic mothers. They found that pathway analysis of genes with differentially methylated promoters identified the top three enriched pathways as maturity onset diabetes of the young, type 2 diabetes, and Notch signaling (Notch signaling pathway is a highly conserved cell signaling system. It regulates embryonic development and has a major role in the induction of mesoderm and cell fate determination). Several genes in these pathways are known to affect pancreatic development and insulin secretion. These findings supported the hypothesis that epigenetic changes may increase the risk for type 2 diabetes through an effect on  $\beta$ -cell function in the offspring of mothers with diabetes during pregnancy [40].

Offspring of obese gestational diabetes mellitus mothers have higher cord insulin levels with higher fat mass compared with offspring of euglycemic lean and obese mothers. Maternal C-peptide and adiponectin levels in pregnancy are predictive for excess adipose tissue in newborns and could be indicative of obesity risk at later life. An analysis by Uebel *et al.* (2014) [35] revealed that a significantly positive relationship for maternal C-peptide levels and a significantly inverse relationship for high-molecular-weight adiponectin with infant preperitoneal adipose tissue at week 1 were identified.

#### **Mothers with polycystic ovary syndrome**

Midgestational amniotic testosterone levels are elevated in female fetuses with polycystic ovary syndrome compared with normal mothers and might influence fetal development. Such alterations likely program adult polycystic ovary syndrome by epigenetic modifications of genetic susceptibility of the fetus to polycystic ovary syndrome after birth. Understanding this phenomenon requires advanced fetal surveillance technologies and postnatal assessment of midgestational androgen exposure for new clinical strategies to improve reproduction in polycystic ovary syndrome women, optimize long-term health of their offspring, and minimize susceptibility of acquiring polycystic ovary syndrome in future generations [41].

#### **Maternal and infant deficiencies**

Variation in the quality or quantity of nutrients consumed by mothers during pregnancy, or by

infants during the first year of life, can exert permanent and powerful effects upon developing tissues. These effects are termed 'programming' and represent an important risk factor for noncommunicable diseases of adulthood, including the metabolic syndrome and coronary heart disease [42]. Poor maternal nutrition can prime a prediabetes phenotype, often manifest as insulin resistance, by very early stages of life. Early dietary challenges can accelerate the onset of metabolic disturbances, including insulin resistance, obesity, hypertension, and cardiovascular disease [2].

#### **Intrauterine growth retardation and low birth weight**

Intrauterine growth retardation leads to many disorders after maturation, such as obesity, glucose intolerance, and osteoporosis. Intrauterine growth retardation also reduces pancreatic/cell mass [12]. The association between low birth weight and risk of developing type 2 diabetes may involve epigenetic mechanisms, with skeletal muscle being a prime target tissue [43].

A comparison was made between DNA methylation in low birth weight and normal birth weight men with high-fat diet in a randomized crossover study by Jacobsen *et al.* (2014) [43]. They analyzed genome-wide DNA promoter methylation in the skeletal muscle of 17 young low birth weight men and 23 matched normal birth weight men after a control and a 5-day high-fat overfeeding diet. Jacobsen *et al.* (2014) [43] found DNA methylation levels to be similar in the low birth weight and normal birth weight groups during the control diet. However, widespread DNA methylation changes were observed in the normal birthweight group in response to high-fat overfeeding, whereas only a few methylation changes were seen in the low birth weight group. The results of Jacobsen *et al.* (2014) [43] indicated lower DNA methylation plasticity in skeletal muscle from low birth weight versus normal birth weight men, potentially contributing to understanding the link between low birth weight and increased risk for type 2 diabetes.

#### **Paternal prediabetes and father's diet can influence offspring health**

Father's diet can influence offspring's health through the sperm epigenome that includes heritable information such as DNA methylation [44]. Wei *et al.* (2014) [45] stated that, although the impacts of paternal impaired fasting blood glucose and glucose intolerance on the metabolism of offspring have been well established, the exact basis that mediates these

impacts remains unclear. Wei *et al.* (2014) [45] showed that paternal prediabetes increases the susceptibility to diabetes in offspring through gametic epigenetic alterations. They found that paternal prediabetes led to glucose intolerance and insulin resistance in offspring. Relative to controls, offspring of prediabetic fathers exhibited altered gene expression patterns in the pancreatic islets, with downregulation of several genes involved in glucose metabolism and insulin signaling pathways. Epigenomic profiling of offspring pancreatic islets revealed numerous changes in cytosine methylation depending on paternal prediabetes, including reproducible changes in methylation over several insulin signaling genes [45].

Lambrot *et al.* (2013) [44] hypothesized that the dietary supply of methyl donors may alter epigenetic reprogramming in sperm. In that study, male mice were fed either a folate-deficient or a folate-sufficient diet. Paternal folate deficiency was associated with increased offspring birth defects, which included craniofacial and musculoskeletal malformations. Genome-wide DNA methylation analysis identified differential methylation in the sperm of genes implicated in development and chronic diseases such as cancer and diabetes. This study suggested that adequate paternal dietary folate is essential for offspring health [44].

### Epigenetics and diabetes complications

#### *Diabetic vascular complications*

There is evidence demonstrating that factors that contribute to diabetic vascular complications include genetic variants, structural variants, and epigenetic changes [46]. A number of risk factors for atherosclerosis, including hyperlipidemia, diabetes, and hypertension, target the vascular endothelium by reprogramming its transcriptome. These alterations taking place on the chromatin depend on the interplay between sequence-specific transcription factors and the epigenetic machinery. The epigenetic machinery, in turn, tailor individual transcription events key to atherogenesis to intrinsic and extrinsic insults leading to the development of atherosclerotic lesions [47].

#### **Diabetic retinopathy**

Diabetic retinopathy is one of the most debilitating chronic complications. However, despite extensive research in the field, the exact mechanism(s) responsible for how the retina is damaged in diabetes remains vague [48]. Several studies have shown that tight glycemic control in diabetic patients does not immediately benefit the

progression of retinopathy, and the benefits of good control persist beyond the period of good glycemic control. This has led to the concept of persistent epigenetic changes [49]. The role of epigenetics in diabetic retinopathy is now an emerging area, and recent work has shown that genes encoding mitochondrial superoxide dismutase and matrix metalloproteinase-9 (MMP-9: proteases that are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, angiogenesis, bone development, wound healing, cell migration, as well as in pathological processes, such as arthritis, intracerebral hemorrhage, and metastasis) are epigenetically modified. Histone lysine demethylase 1 and DNA methyltransferase are increased, and the micro RNAs responsible for regulating nuclear transcription factor and vascular endothelial growth factor are upregulated. With the growing evidence of epigenetic modifications in diabetic retinopathy, better understanding of these modifications has potential to identify novel targets to inhibit this devastating disease [48].

#### **Diabetic nephropathy**

Diabetic nephropathy can progress despite subsequent glycemic control, suggesting a metabolic memory of previous exposure to hyperglycemia. Diabetes impacts transcription programs in target cells through activation of multiple signaling pathways and key transcription factors, leading to an aberrant expression of pathologic genes. These factors associated with the pathophysiology of diabetic complications and metabolic memory also might be influenced by epigenetic mechanisms in chromatin. Histone modifications and the related histone methyltransferases and acetyltransferases have been implicated in the regulation of inflammatory and profibrotic genes in renal and vascular cells under diabetic conditions [50].

Loss of nephrin integrity contributes to diabetic podocytopathy. MicroRNAs (miRs) modulate hyperglycemia-induced renal dysfunction. Lin *et al.* (2014) [51] investigated whether the regulation of HDAC actions and nephrin acetylation by miR-29 contribute to podocyte homeostasis and renal function in diabetic kidneys. In that study, it was found that overexpression of miR-29a was associated with attenuated HDAC4 signaling and restored nephrin acetylation, whereas knockdown of miR-29a promoted HDAC4 action, nephrin loss, podocyte apoptosis, and proteinuria in nondiabetic mice. Lin *et al.* (2014) [51] concluded that hyperglycemia impairs



miR-29a signaling that contributes to podocyte protein degradation and renal dysfunction, while increasing miR-29a action that may protect against diabetic podocytopathy.

#### Diabetic cardiac pathology

The underlying mechanisms of diabetic cardiac pathology are not well understood. Signaling disturbances involved in cardiac insulin resistance are linked to glucose handling abnormalities with hyperglycemia-induced modifications of extracellular and intracellular proteins either reversible [e.g.  $\beta$ -linked N-acetylglucosamine, a form of protein glycosylation (O-GlcNAc)] or irreversible [e.g. advanced glycation end products (AGEs)] involved in structural and functional changes in the diabetic heart [52].

Vecellio *et al.* (2014) [53] suggested that epigenetic interventions may reverse alterations in human cardiac mesenchymal cells (CMSC) in diabetic patients. In that study, diabetes-associated alterations in cardiac mesenchymal cells of nondiabetic (ND-CMSC) and type 2 diabetes patients (D-CMSC) were compared, identifying the histone acetylase activator pentadecylidenemalonate 1b (SPV106) as a potential pharmacological intervention to restore cellular function. D-CMSC were characterized by a reduced proliferation rate, diminished phosphorylation at histone H3 serine 10 (H3S10P), decreased differentiation potential and premature cellular senescence, and decreased acetylation on histone H3 lysine 9 (H3K9Ac) and lysine 14 (H3K14Ac), whereas trimethylation of H3K9Ac and lysine 27 significantly increased. Remarkably, treatment with SPV106 restored normal levels of H3K9Ac and H3K14Ac, and recovered D-CMSC proliferation and differentiation [53].

#### Exercise and epigenetics

Researchers have searched for molecular mechanisms explaining the health benefits of regular exercise, and it is well established that exercise alters the gene expression pattern in multiple tissues. Regular exercise can modify the genome-wide DNA methylation pattern in humans [54].

PGC1 $\alpha$  is a transcriptional coactivator that works as a central regulator of metabolism. PGC1 $\alpha$  is a regulator of mitochondrial biogenesis and respiration, adaptive thermogenesis, and gluconeogenesis. The expression of PGC1 $\alpha$  is highly inducible by exercise, cold, and fasting. PGC1 $\alpha$  is also a powerful regulator of reactive oxygen species (ROS) removal by increasing

the expression of numerous ROS-detoxifying enzymes. PGC1 $\alpha$ , by controlling both the induction of mitochondrial metabolism and the removal of its ROS byproducts, would elevate oxidative metabolism and minimize the impact of ROS on cell physiology.

Exercise has been shown to change DNA methylation of the promoter of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 $\alpha$ ) to favor gene expression responsible for mitochondrial biogenesis and function [4].

#### Maternal exercise protects the offspring

Laker *et al.* (2014) [55] investigated whether maternal exercise could protect offspring from adverse effects of a maternal high-fat diet. This study focused on the metabolic outcomes and epigenetic regulation of the peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  (PGC1 $\alpha$ ).

C57BL/6 mice is an inbred strain of laboratory mouse. It is the most widely used 'genetic background' for genetically modified mice for use as models of human disease.

Female C57BL/6 mice were exposed to high-fat diet, or an high-fat diet with voluntary wheel exercise for 6 weeks before and throughout pregnancy. Methylation of the PGC1 $\alpha$  promoter at CpG site -260 and expression of PGC1 $\alpha$  mRNA were assessed in the skeletal muscle of neonatal and 12-month-old offspring, and glucose and insulin tolerance tests were performed in the female offspring at 6, 9, and 12 months. Hypermethylation of the PGC1 $\alpha$  promoter caused by a maternal high-fat diet was detected at birth and was maintained until 12 months of age with a trend of reduced expression of PGC1 $\alpha$  mRNA and its target genes. Maternal exercise prevented high-fat-diet-induced PGC1 $\alpha$  hypermethylation and enhanced PGC1 $\alpha$  and its target gene expression, concurrent with improvement in metabolic dysfunction at 9 months of age in the offspring [55].

Santos *et al.* (2014) [56] stated that the increased PGC1 expression induced by exercise improves insulin sensitivity in skeletal muscle by increasing mitochondria density and glucose transporter expression (GLUT4: glucose transporter type 4 is an insulin-regulated glucose transporter found primarily in adipose tissues and striated muscle and is responsible for insulin-regulated glucose transport into the cell). Santos *et al.* (2014) [56] proposed that aerobic exercise

attenuates epigenetic modifications at PGC1 induced by high-energy diets and reduced physical activity, and that it leads to inhibition/delay of type 2 diabetic onset.

#### Smoking and DNA methylation

Dogan *et al.* (2014) [57] stated that smoking is associated with a variety of syndromes with prominent inflammatory components such as cancer, obesity, and type 2 diabetes. Heavy smoking is associated with changes in the DNA methylation of mononuclear cells. In younger smokers, inflammatory epigenetic findings are absent, which suggests that the inflammatory responses to smoking may be dose dependent. Dogan *et al.* (2014) [57] examined genome-wide DNA methylation, serum C-reactive protein, and interleukin-6 receptor levels and carried out bioinformatic analyses in a group of adult African American smokers to delineate possible pathways affected. Dogan *et al.* (2014) [57] found that DNA methylation analysis yielded 910 significant loci after Benjamini-Hochberg correction. The bioinformatic analyses showed that chronic smoking is associated with altered promoter DNA methylation of genes coding for proteins mapping to critical subnetworks moderating inflammation, immune function, and coagulation. Dogan *et al.* (2014) [57] concluded that chronic regular smoking is associated with changes in peripheral mononuclear cell methylation signature, which upset inflammatory and immune function pathways and may contribute to increased vulnerability for complex illnesses with inflammatory components.

#### In-vitro fertilization

The study by Feuer *et al.* (2014) [15] supported the vulnerability of preimplantation embryos to environmental disturbance and revealed that conception by in-vitro fertilization can reprogram metabolic homeostasis through metabolic, transcriptional, and epigenetic mechanisms with long-term effects for adult growth and fitness. Feuer *et al.* (2014) [15] assessed the effects of in-vitro fertilization on postnatal physiology in mice. They demonstrated that in-vitro fertilization and embryo culture, even under optimal conditions, alter postnatal growth, fat accumulation, and glucose metabolism in adult mice, with broad changes in metabolic homeostasis, characterized by systemic oxidative stress and mitochondrial dysfunction. Feuer *et al.* (2014) [15] identified thioredoxin-interacting protein (TXNIP), a key molecule involved in integrating cellular nutritional and oxidative states with metabolic response, as a marker for preimplantation stress and to demonstrate

tissue-specific epigenetic and transcriptional TXNIP misregulation in adult tissues.

#### Cellular reprogramming

Stem cell transplantation complexities and the difficulty in obtaining stem cells from adult cells is a major concern. The recent strategy of transcription-factor-based cellular reprogramming suggests that it is possible to reprogram any cell into functional  $\beta$ -cells. Among cellular reprogramming strategies, small molecule approach has better clinical results because it does not involve genetic manipulation. Several small molecules targeting certain epigenetic enzymes and/or signaling pathways have been successful in the induction of pancreatic  $\beta$ -cell specification [58].

Pennarossa *et al.* (2013) [59] aimed to investigate whether it is possible to achieve the direct conversion of an adult cell by exposing it to a demethylating agent immediately followed by differentiating culture conditions. Adult human skin fibroblasts were exposed for 18 h to the DNA methyltransferase inhibitor 5-azacytidine, followed by a three-step protocol for the induction of endocrine pancreatic differentiation that lasted 36 days. At the end of this treatment,  $35 \pm 8.9\%$  of fibroblasts became pancreatic-converted cells that acquired an epithelial morphology, produced insulin, and then released the hormone in response to a physiological glucose challenge *in vitro*. Furthermore, pancreatic-converted cells were able to protect recipient mice against streptozotocin-induced diabetes, restoring a physiological response to glucose tolerance tests [59].

#### Epigenetic explanation for metabolic memory

Miao *et al.* (2014) [60] aimed to assess whether epigenetic histone post-translational modifications are associated with the prolonged beneficial effects (metabolic memory) of intensive versus conventional therapy during the Diabetes Control and Complications Trial on the progression of microvascular outcomes in the long term (Epidemiology of Diabetes Interventions and Complications study). In that study, chromatin immunoprecipitation linked to promoter tiling arrays to profile H3 lysine-9 acetylation (H3K9Ac), H3 lysine-4 trimethylation (H3K4Me3), and H3K9Me2 were performed in blood monocytes and lymphocytes obtained from 30 (Diabetes Control and Complications Trial) conventional treatment group patients (mean HbA1c > 9.1% and progression of retinopathy or nephropathy by year 10 of follow-up) vs. 30 (Diabetes Control and Complications Trial) intensive treatment

patients (control patients: mean HbA1c level < 7.3% and without progression of retinopathy or nephropathy). Monocytes from the conventional treatment group had statistically greater numbers of promoter regions with enrichment in H3K9Ac (active chromatin mark) compared with control patients. Among the patients in both groups, monocyte H3K9Ac was significantly associated with the mean glycated hemoglobin level during the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications [60].

Nuclear factor- $\kappa$ B 'nuclear factor kappa-light-chain-enhancer of activated B cells' is a protein complex that controls transcription of DNA, and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized low-density lipoprotein, and bacterial or viral antigens. It plays a key role in regulating the immune response to infection; ' $\kappa$  light chains are critical components of immunoglobulins'. Incorrect regulation of NF- $\kappa$ B has been linked to cancer, inflammatory, and autoimmune diseases, septic shock, viral infection, and improper immune development.

The top 38 case hyperacetylated promoters included more than 15 genes related to the NF- $\kappa$ B inflammatory pathway and were enriched in genes related to diabetes complications. These results suggest an association between glycated hemoglobin level and H3K9Ac, and a possible epigenetic explanation for metabolic memory [60].

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## Conclusion

Diabetes mellitus is a multifactorial disease; its etiology involves a complex interplay between genetic, epigenetic, and environmental factors.

Alterations to homeostasis during critical periods of development can predispose individuals to adult-onset diabetes. The mechanisms involved epigenetic changes and resetting of endocrine systems that affect energy metabolism and appetite.

Epigenetic changes are chemical modifications of DNA without changing DNA sequence, including histone methylation, reduction of histone acetylation, microRNA, and chromatin modifications. These changes can affect the genetic expression. Epigenetic mechanisms were recently shown to be involved in the control of cell proliferation and function.

MicroRNAs are noncoding RNA molecules that regulate gene expression at the post-transcriptional level by inhibiting target messenger RNA translation. Deregulation of miRNAs was confirmed in diabetes. Restoring microRNA expression to normal levels can prevent diabetes-associated changes.

Through epigenetic modifications, many maternal factors during pregnancy may increase the risk for diabetes of offsprings in later life, including malnutrition, hyperglycemia, obesity, and behavior (smoking, drinking, and junk food diet). Gestational diabetes has epigenetic effects on genes involved in the metabolic diseases pathway, with consequences on fetal development. Poor maternal nutrition and intrauterine growth retardation can prime a prediabetes phenotype and often manifest as insulin resistance and obesity.

Moreover, epigenetically, the father's diet can influence the offspring's health through the sperm epigenome. The impacts of paternal abnormal glucose levels on the metabolism of offspring have been well established. Paternal prediabetes increases the susceptibility to diabetes in offspring.

Factors associated with the pathophysiology of diabetic complications and metabolic memory also might be influenced by epigenetic mechanisms. There is evidence demonstrating that factors contributing to diabetic vascular complications include genetic, structural, and epigenetic changes. It was suggested that epigenetic interventions may reverse alterations in human CMSCs in diabetic patients.

Regular exercise can modify the genome-wide DNA methylation pattern to favor gene expression responsible for mitochondrial biogenesis and function. Aerobic exercise attenuates epigenetic modifications induced by high-energy diets and leads to the delay of type 2 diabetic onset.

Recent strategy of cellular reprogramming suggests that it is possible to reprogram cells into functional  $\beta$ -cells. Small molecule approach has better clinical results because it does not involve genetic manipulation, targeting certain epigenetic enzymes and/or signaling pathways successful in the induction of pancreatic  $\beta$ -cell specification

Epigenetic factors, when understood, could be used as early predictors of metabolic risk and for the development of drugs or diet-related treatments to delay these epigenetic changes and even to reverse them.

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**Conflicts of interest**

There are no conflicts of interest.

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