Role of epigenetics in the pathogenesis and management of type 2 diabetes mellitus

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The need to reverse the growing incidence and burden of diabetes mellitus (DM) worldwide has led to more studies on the causes of the disease. Scientists have long suspected genetic and environmental factors in the pathogenesis of type 2 diabetes mellitus (T2DM). However, recent studies suggest that epigenetic changes may cause some cases of the disease. This review highlights the role of epigenetic modifications in the pathogenesis and management of T2DM. Peer-reviewed studies on the subject were retrieved from electronic databases such as PubMed, Google Scholar, SpringerLink, and Scopus. Most of the studies implicated epigenetic modifications in the pathogenesis of some cases of T2DM. DNA methylation, histone modification, and microRNAs mediated pathways are the main mechanisms of epigenetic changes. Certain environmental factors such as diets, microbial and pollutant exposure, and lifestyles, among others, may trigger these mechanisms prior to the onset of T2DM. Epigenetic changes can modify the expressions and functions of some genes involved in insulin biosynthesis and glucose metabolism, leading to hyperglycemia and insulin resistance. Fortunately, epigenetic changes can be reversed by blocking or activating the modulating enzymes. Thus, epigenetic reprogramming can improve some cases of T2DM. Medical practitioners are advised to employ epigenetic therapies for diabetic conditions with epigenetic etiology.

Electronic databases, including: PubMed, Google Scholar, SpringerLink, ResearchGate, Web of Science, and Scopus were searched for relevant information on the topic.

Search Terms

The following keywords used to retrieve information include: diabetes mellitus, hyperglycemia, insulin, epigenome, epigenetics, and epigenetic modifications. Other search terms used are type 2 diabetes mellitus, epigenetic mechanisms, epigenetic drugs, DNA methylation, histone modification, and insulin resistance.

Criteria for Inclusion of Studies

Research published in the English language.
Research that focused on the prevalence and pathogenesis of DM.
Research that focused on epigenetics of T2DM.
Studies that focused on epigdrugs of T2DM.
Studies that were published between 1990 and 2018.

However, the bulk of the information came from studies published...
between 2011 and 2018.

**Epigenetics in the T2DM**

The articles collected were screened for eligibility according to the PRISMA guidelines (21, 22). Criteria such as the study design, affiliation of the authors, and reputation of the journal hosting the articles, were considered in the article selection. Overall, none of the studies included in the review had major flaws to disregard the findings. Several studies agreed that epigenetic changes may initiate or contribute to the pathogenesis and burden of T2DM. DNA methylation, histone modification, and microRNA-mediated pathways are the main mechanisms by which epigenetic changes modify phenotypes, including disease presentations. Prior to epigenetic modification, environmental triggers interact with the genes through certain chemicals on the DNA.

**DNA Methylation in T2DM Pathogenesis**

DNA methylation is one of the epigenetic mechanisms in which a methyl group attaches to the DNA, causing a change of gene expression and function. Notable among DNA methylation processes is the covalent addition of a methyl group to the 5-carbon of the cytosine ring, resulting in 5-methylcytosine (5-mC) (23). After methylation, the methyl group protrudes inside the DNA and disrupts the transcriptional processes (24). 5-methylcytosine is present in about 1.5% of human genomic DNA (24). In somatic cells, 5-mC resides mostly near the CpG sites, except in the embryonic stem cells, which contain some 5-mC near the non-CpG sites (24). In the germ cells and around the promoters of normal somatic cells, the CpG sites are unmethylated, allowing gene expression to take place (25).

A class of enzymes known as DNA methyltransferases (DNMTs) mediates the pairing of methyl groups to DNA (26). Three DNMTs, namely DNMT1, DNMT3a, and DNMT3b, are necessary for the initiation and maintenance of DNA methylation processes (25). Two more enzymes, DNMT2 and DNMT3L, are equally important but perform more specialized tasks (25). DNMT1 maintains already methylated DNA, whereas DNMT3a and 3b modulate the creation of new or de novo DNA methylation processes (25). However, in diseased cells, the three enzymes, DNMT1, DNMT3a, and 3b interact and cause DNA over-methylation (25). Equally important as DNA methylation in epigenetic modification of organisms is DNA demethylation. The cellular process is the removal of a methyl group from DNA, which is necessary for reprogramming of methylated DNA and reversing disrupted gene expression. Demethylation can occur passively in which a DNMT1 inhibits the methylation of newly synthesized DNA strands during the replication stages (27). It can also occur actively wherein established patterns are demethylated by enzymatic removal of 5-methylcytosine through an enzyme called ten-eleven translocation (TET) (27).

In the last few decades, several studies have implicated DNA epigenome reprogramming in the development and pathogenesis of many chronic diseases, including T2DM. In one study, an examination of pancreatic beta cells of diabetics and non-diabetics showed altered DNA methylation in an enhancer molecule upstream of the PPARGC1A in the promoter of the ADRB3 gene in visceral adipose tissue causes abnormal waist-to-hip ratio and blood pressure in obese men (34). In addition, the PPARGC1A gene in subcutaneous adipose tissue showed altered DNA methylation after a high-fat diet (35). This finding again highlights the involvement of the PPARGC1A in epigenetic modulation of metabolic processes in several tissues, including adipose and skeletal muscle [36] and pancreatic islets (30). In a study, the visceral adipose tissue of the obese showed 3,258 methylated genes, indicating the role of epigenetic changes in obesity pathogenesis (37). A detailed genome-wide DNA methylation analysis of adipose tissue has also revealed evidence of over-methylation of tissue-specific molecules that regulate gene expression and susceptibility to metabolic disorders (38). Adipose tissues particularly showed altered DNA methylation in an enhancer molecule upstream of ADCY3 (39).

**Histone Modification in T2DM Pathogenesis**

Histones are the protein building blocks of chromatin - a mass of genetic material composed of DNA and protein - and form the backbones of the helical structure of the DNA. Modification of histones after being translated into protein can program the structural arrangement of chromatin (40). The resulting structure determines the transcriptional status of the associated DNA (40). Non-condensed chromatin is active and results in DNA transcription, whereas condensed chromatin (heterochromatin) is inactive and incapable of transcription (40).

Several mechanisms, namely acetylation, methylation, phosphorylation, and ubiquitylation, can modify histones; however, acetylation and methylation are the most frequently occurring mechanisms (41). Acetylation adds an acetyl group to the amino acid lysine in the histone, while methylation involves the addition of a methyl group (42). Acetylation typically occurs in non-condensed chromatin, while deacetylation often occurs in condensed chromatin (40). Histone methylation can occur in both forms of chromatin (40). For instance, methylation of a particular lysine (K9) on a specific histone (H3) represents inactive chromatin, while methylation of a different lysine (K4) on the same histone (H3) reveals active chromatin (40). Histone modification involves several enzymes, notably the histone deacetyltransferases (HDACs), which deacetylates amino-terminal lysine residues on histone ends (41). Thus, allowing the lysine residues to bind more tightly to the DNA (41). The genes in the more tightly bound regions become repressed because of the inaccessibility of the transcription factors into the promoters of the genes (41).
Studies have reported histone modifications in diabetic patients. For instance, histone acetyltransferases (HATs) and HDACs are linked to the altered expression of some genes in diabetics (43). One example is the SIRT family of HDACs: specifically, SIRT1 regulates several factors involved in metabolism, adipogenesis, and insulin synthesis (43). In an experiment, a high glucose treatment of monocytes in-vitro increased the production of the HATs CREB-binding protein (CBP) and P300/CBP-associated factor (PCAF) (43). This resulted in over-acetylation of histone lysine at the cyclooxygenase-2 (COX-2) and TNF-inflammatory gene promoters, causing over-expression of the genes (43). Similar over-acetylation of histone lysine at these gene promoters occurs in patients with T2DM compared with control (43).

MicroRNAs (miRNA) in T2DM Pathogenesis

Micro RNAs (miRNAs) are single-stranded transcribed RNAs between 19 and 25 nucleotide chains (44). They are a class of small, noncoding RNA molecules that mediate gene expression at the translational level by disrupting the 3' un-translated region of messenger RNAs (44). MicroRNAs interact with transcriptional and epigenetic modulators for the maintenance of lineage-specific gene expression (45). Specifically, MicroRNAs regulate gene expression at the post-transcriptional level by preventing the translation of target messenger RNA (46). However, in diseased individuals, the expression of microRNAs often changes, resulting in altered expression, mainly over-expression of the target genes (46). MicroRNAs are important in the maintenance of several biological processes, such as cell cycle control, cell differentiation, and apoptosis, among others (44). Studies have confirmed functional impairment of miRNAs in several pathologies, including cancer, respiratory diseases, heart diseases, and DM [44].

An experiment performed by Kameswaran et al. (47) investigated the involvement of microRNAs in the pathogenesis of T2DM. The scientists sequenced the microRNAs of islets obtained from individuals with T2DM and non-diabetics and found a mass of altered miRNAs such as GLUT4 that regulate glucose uptake in skeletal muscle (66). Exercise induces the expression of several factors involved in metabolism, adipogenesis, and insulin resistance (43). For instance, histone acetyltransferases (HATs) and HDACs are linked to the altered expression of some genes in diabetics (43). One example is the SIRT family of HDACs: specifically, SIRT1 regulates several factors involved in metabolism, adipogenesis, and insulin synthesis (43). In an experiment, a high glucose treatment of monocytes in-vitro increased the production of the HATs CREB-binding protein (CBP) and P300/CBP-associated factor (PCAF) (43). This resulted in over-acetylation of histone lysine at the cyclooxygenase-2 (COX-2) and TNF-inflammatory gene promoters, causing over-expression of the genes (43). Similar over-acetylation of histone lysine at these gene promoters occurs in patients with T2DM compared with control (43).

Physical Inactivity/Sedentary Life

Physical inactivity can influence the epigenome negatively, affecting several generations (55). Human physical activity has reduced drastically since the invention of technologies in the 19th century, resulting in the increasing overweight of people worldwide. Increasing physical inactivity has contributed immensely to the growing global burden of obesity, a risk factor of T2DM (56, 57, 58). Some mechanisms through which inactivity mediates diseases include mitochondrial dysfunction, changes in the composition of muscles, and insulin resistance, among others (59). Physical inactivity can also program the health of the offspring across several generations (60, 61, 62). Increased physical activity can help prevent, lessen, or reverse several health conditions, including T2DM (60, 61). Increased exercise was reported in the methylation of certain genes that predispose to some chronic diseases (63). For example, exercise causes demethylation of certain genes that promote the secretion of pro-inflammatory cytokines, reducing the risk of chronic diseases, including DM (63).

Several studies report genome-wide changes in DNA methylation in response to exercise. In one study, gene expression in muscle tissues following an exercise changed the efficiency of glucose metabolism by the muscle (63). Some studies which sought to know the amount of exercise needed to accomplish changes in DNA methylation of muscles reported it depended on exercise intensity (63). In obese individuals, exercise can modify the absorption of fats into the body. In a genome-wide adipose tissue methylation study of sedentary men, changes in about 18,000 CpG sites (encompassing 7,663 genes) occurred in the individuals after 6-month exercise (64).

The methylation occurred in obesity and T2DM predisposing genes such as TCF7L2 and KCNQ1, meaning that the exercise silenced these genes (64). In a study of skeletal muscles, 2,817 genes were methylated after 6-month exercise, but unlike the adipose tissue, most of the genes showed decreased levels of DNA methylation (65). Over-methylation of the skeletal muscle raised the expression of pro-inflammatory cytokines, which silenced some insulin-promoting genes (66). Exercise induces the expression of several genes, such as GLUT4 that regulate glucose uptake in skeletal muscle (67).
Exercise may also induce histone modifications. When a human is at rest, MEF2 interacts with HDAC5 in the nucleus, leading to deacetylation of the GLUT4 gene at the histone end (68). This creates condensed chromatin, repressing GLUT4 expression (68). During exercise, AMP-activated protein kinase phosphorylates HDAC5, splits from MEF2, and migrates to the cytosol from the nucleus (69). MEF2 may then interact with PPARGC1A and HATs in the nucleus (68). This leads to acetylation of the GLUT4 gene histone, which enhances the expression and transcriptional activity of the gene (69). Ca/calmodulin-dependent protein kinase (CaMK) may also modulate the MEF2 activity through histone acetylation after exercising for a short duration (70, 71).

Nutrition Choices

The epigenetic effects of diets are the most studied and understood of all the environmental triggers of epigenetic changes. Nutrients undergo a series of metabolic reactions to become molecules the body can use. One of these reactions creates methyl groups (72). Nutrients that induce methyl-making include folic acid, B vitamins, some drugs, etc. (73). Diets rich in these compounds can alter gene expression, especially during early development, when the epigenome is young (74). The diet of a mother during pregnancy and the baby’s diet can program the baby’s epigenome for life (72).

Experiments in mice have demonstrated the role of a mother’s diet in shaping the epigenome of offspring. For instance, when a mammalian gene called agouti was completely unmethylated in mouse, its skin turned yellow and became obese, predisposing it to DM (72). When the agouti gene was methylated like normal mice, the skin color turned brown and reduced its disease risk (72). Fat yellow mice and skinny brown mice are genetically identical, but modification exists in the epigenome of the fat yellow mice (72). When the yellow mice ate a methyl-rich diet, most of their newborns were brown and were healthy throughout life. These results show that the intrauterine environment can influence adult health (72).

The diet of a dad can also influence his child’s epigenome. Records showed that the amount of food consumed at ages 9 to 12 by some Swedish paternal grandfathers affected the lifespan of their grandchildren (75). Shortage of food relates to the increased lifespan of the grandchildren, while abundant food, mediated by either DM or heart disease, shortens their lifespan (75). Epigenetic mechanisms could have programmed the nutritional information of the grandfathers and transmitted it to subsequent generations (75).

Energy-dense diets can also induce profound epigenetic modifications. High-fat diets can influence the gut microbiota to increase body accumulation of fat (76) and program the epigenome of a developing embryo. This implies that frequent consumption of fat-laden diets such as western diets may cause multi-generational programming of obesity (56). A paternal high-fat diet can cause trans-generational metabolic traits such as weight and fat gain, glucose intolerance, among others (77). These conditions are caused by abnormal methylation of certain regions and genes in the sperm cells, such as adiponectin, leptin, IGF2, MEG3, SGCE/PEG10, MEG3-IG and H19 DMRs (78, 79). Maternal high-fat diets also relate to altered gene expression, DNA methylation, and obesity risk (80). In a rat experiment, maternal high-fat diets increased obesity risk in the high-fat-fed daughters, increasing their body weight, fat accumulation, and serum levels of leptin as adults (80).

Apart from high-fat diets, adverse intrauterine environments such as inflammation and endoplasmic reticulum stress may epigenetically program for childhood obesity involving several genes. The programming may even switch the preference of a child to energy-dense foods, leading to over-nutrition and obesity (81, 82, 83). Childhood reduced DNA methylation of LINE1 and increased methylation of some genes, including CASP10, CDKN1C, EPHA1, HLDAB83, IGF, etc., occurred in individuals predisposed to childhood obesity (84, 85). Over-nutrition during childhood increases the risk of developing obesity in childhood through to adulthood (86).

The fruits and vegetables in a human’s diet may also influence both his/her epigenome with heritable effects. Eating too few fruits and vegetables may cause low serum levels of methyl-donating minerals and vitamins, which are important regulators of the epigenome during intrauterine life (56). For example, folate, choline, and betaine metabolism generate S-adenosyl methionine, which can influence DNA and histone methylation by supplying methyl groups to DNA and histone methyltransferases (87). A deficiency of these compounds may lead to widespread altered DNA methylation at 57 CpG loci in the offspring (88). About 4 % of the 1, 400 CpG islands examined in a study had altered methylation status, 88 % of which were hypo-methylated relative to controls (88).

Whole-grains (unrefined grains) reduce the risk of T2DM (89) and metabolic syndrome (90). However, in the bid to make whole-grains more tasteful, technological advancement has introduced a lot of refined grains into the market with less fiber and nutritional content. Refined grains are energy dense and have a high glycemic index, thus causing higher glycemic and insulin responses following consumption, with increased risks of developing T2DM (91). Rice, in particular, is the staple food of half of the world population and is increasingly being consumed worldwide (92). Some scientists suspected ancestral epigenetic programming towards a preference for rice consumption. However, refined white rice with characteristics of high glycemic index and low fiber content contributes to the global explosion of T2DM. In a study, feeding of white rice to female rats for eight weeks prior to pregnancy and throughout pregnancy and lactation showed significant differences in metabolic indices compared with brown rice feeding (93). These indices relate to insulin resistance and insulin signaling genes in hepatic, adipose, and muscle cells (93).

Starvation around conception time and early gestation is another factor that can influence the epigenome of humans. Starvation during fetal development causes either hypo-methylation or hyper-methylation of many genes, including the insulin receptor (INSR) gene, which is important in insulin synthesis and metabolism during adulthood. The placenta modulates the exchange of molecules, including nutrients between the mother and fetus; thus, this function makes the placenta the target of epigenetic changes during starvation (94). Starvation can modify placenta epigenome through gene methylation or modification of miRNAs associated with genes necessary for fetal development, nutrient transfer, and disease prevention (94). In an experiment, mice short of food during pregnancy produced first-generation diabetic offspring and predisposed second-generation offspring (95). Normally, the body removes most of the methyl groups upon the formation of an embryo except for methyl groups on a few genes (95). Nutrient starvation in the mother may also alter normal methylation patterns in the sperm cells (95). In an experiment, scientists observed reduced methylation of 111 genomic regions in the offspring of starved mothers compared with the controls. In the study, over-methylated 55 regions also occurred in the DNA of the offspring of the starved mothers (95). In another study, children born to starved mothers showed differential methylation of IFG2 and other T2DM-related genes, which further proved epigenetics as a mechanism linking prenatal nutrition and
Chemical exposure influences the epigenetic programming of some diseases. For instance, smoking during pregnancy directly affects the fetus, causing health conditions such as low birth weight and increased risk for several diseases, such as T2DM (97). Maternal cigarette smoking during pregnancy related with altered DNA methylation and disrupted microRNA expression (98). These conditions were thought to result from some toxic chemicals in tobacco, but some evidence points to the involvement of epigenetic alterations (98). Thus, besides the direct effects of tobacco smoking, epigenetic alterations induced by its chemicals can modulate some smoking-related risks of developing many diseases, including T2DM (98). Some of these epigenetic changes areheritable; thus smokers may produce offspring with tobacco-smoke related problems lasting long until adulthood (56).

In a study, tobacco smoke induced long-term lymphocyte DNA methylation changes in several CpG sites and genes, increasing the risks of some diseases, including T2DM (99). These conditions persisted for at least three decades, indicative of multi-generational consequences of smoking (99). Findings suggest that there are a variety of placental dysfunctions linked to prenatal exposure to cigarette smoke, including alterations to the development and function of the placenta (100). In a research by Wilhelm-Benartzi et al. (101), differential methylation of repetitive molecules on placenta DNA relates to birth weight and maternal smoking during pregnancy (101). In another study, men who smoked around 11 years of age showed massive epigenetic changes in the genes imprinted on the Y chromosome (102). These men produced overweight male offspring by age 9. This means the sons of men who smoke before puberty will be at higher risk for obesity and other health problems well into adulthood (102). Methylation of germine or placenta may transmit these effects across many generations (96, 98). Thus, widespread smoking and inhalation of second-hand smoke may affect smokers and nonsmokers across many generations through epigenetic reprogramming (103). This underscores the involvement of tobacco in the global upsurge of several chronic diseases beginning from the 19th century (56). Similarly, alcohol addiction can cause or worsen several health problems. If consumed in excess during pregnancy, alcohol can cause fetal alcohol syndrome, such as low birth weight, impaired cognitive and neuropsychological functions (104). Alcohol interferes with folate metabolism and reduces overall methylation levels in mice exposed to alcohol in utero (105). Alcohol can induce extensive DNA methylation of the germine of a man and transmit the epigenetic changes to his offspring via conception. Alcohol-induced placental epigenetic changes are also heritable via the female germine (104). Alcohol addiction by men can increase the chances of alcoholism in male offspring (106). Thus, children exposed to alcohol prenatally already have epigenetically predetermined increased risks of some diseases, including T2DM, subsequent consumption of alcohol only worsens the epigenetic programming (56).

Pollutant exposure is another burden with serious effects on the health of humans. Evidence abounds that prenatal exposure to some toxic pollutants can increase the risk of multi-generational transmission of some diseases (56). For example, maternal and paternal exposure to dichlorodiphenyltrichloroethane (DDT) increases the obesity risks of future generations through epigenetic alterations in obesity-related genes in both male and female germ lines (107). Some other chemicals, including bisphenol-A (BPA), bis (2-ethylhexyl) phthalate (DEHP), and dibutyl phthalate (DBP) can also increase the risk of epigenetic transgenerational inheritance of adult metabolic diseases (108). Embryonic exposure to BPA generates metabolic disturbances later in life, such as obesity and DM (108). BPA and other endocrine disruptors can alter fat tissue development and growth by disrupting the production of functional adipocytes and their differentiation (108). Several studies showed that BPA-induced multi-generational effects, such as obesity may involve epigenetic mechanisms (108). Other pollutants, including pesticides, agrochemicals, among others, can also induce transgenerational extensive epigenetic changes with a consequent increase in the risk of adult diseases (109).
In addition, some dietary substances such as vegetables, fruits, whole-grains, among others, have HDAC inhibiting properties comparable to pharmacological HDACIs without side-effects (118).

In DM management, some HDACIs improve diabetic conditions by reversing the cytokine-induced damage of pancreatic beta cells (123, 124, 125). Other HDACIs promote insulin secretion and performance and increase beta cell mass (126, 127, 128). However, as a precautionary measure, high doses of HDACIs must be avoided as they are cytotoxic (125).

MicroRNA (miRNA) Inhibitors

The maintenance of the normal functioning of the body is in part regulated by certain miRNAs, which are often disrupted in diseased individuals. Scientists have demonstrated that by restoring affected miRNAs to the normal state, its associated diseases can be prevented or reversed. microRNAs restoration can be achieved either by normalizing the expression of repressed miRNAs using miRNA mimics or disrupting the activity of overexpressed miRNAs using miRNA inhibitors (129). MicroRNA inhibitors are antisense oligonucleotides (129) designed based on the molecular properties of the target miRNA to bind to it and activate the target gene. Some proven miRNA inhibitors include locked nucleic acid (LNA) anti-miRs, antagonors, and morpholinos (130, 131). LNA anti-miRs are exceptionally efficient, less toxic, and great therapeutic potential (132). LNA anti-miR-122 reduces plasma cholesterol with no sign of toxicity in mice (133). The antisense oligonucleotide 2'O-methyl-miR-375 normalizes insulin secretion in-vitro by boosting the expression of 3'-phosphoinositide-dependent protein kinase-1 (PDK-1) (122). Some epidrugs like Byetta, Victoza, Trulicity, Januvia, Onglyza, and Tradjenta modify over-expressed miR-204 in the beta cells of diabetics (134). This activates glucagon-like peptide 1 receptor, or GLP1R, assisting the beta cell to synthesize more insulin (134).

Conclusion

T2DM is a multifactorial disorder, and so its development in an individual is multifaceted. However, several studies reviewed showed that epigenetic changes, starting from intrauterine life to adulthood, may play a critical role in the pathogenesis of some cases of the disease. Some environmental factors such as diet choice, pollutant, and microbial exposure, and lifestyles may trigger epigenetic changes in individuals prior to the onset of T2DM. Fortunately, epigenetic changes are reversible, so health care providers can use epigenetic modifications to reverse or treat DM induced by epigenetic changes. Several epigenetic drugs are in use; however, most of the drugs need improvement to achieve the desired results.

Conflict of interest

The authors declare no conflict of interest.

Authors’ contributions

TY and EO wrote the manuscript, US and MA revised the manuscript. All authors have read and approved the final document.

References


Table 1. Reference numbers by subjects.

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