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A Review on epigenetics alternations in high fat diet induced diabetes

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Abstract:
T2DM is complicated, with irreversible risk factors such as age, genetic, race, and ethnicity, as well as reversible risk factors like as food, physical activity, and smoking, with eating habits and sedentary lifestyle being the key contributors for fast growing incidence. Chronic

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exposure to HFD promotes liver damage, poor glucose homeostasis, hyper insulinemia, late pancreatic β-cell failure to generate insulin due to cell fatigue and resultant hyperglycemia, which are the key hallmarks of T2DM. Metabolic diseases such as T2DM have been linked to epigenetic changes that occur without changes in the DNA sequence, such as cytosine methylation of DNA, histone posttranslational modifications, and microRNA, which provide links between genes and environmental factors such as diet, smoking, and other lifestyle factors. T2DM affects insulin gene expression and beta cell differentiation via both histone modifications and DNA methylation in diabetic islets, which plays a vital role in regulating mitochondrial genes and in diabetes regulation. As a result, we provide existing evidence on epigenetic changes in high fat diet-induced diabetes. Metabolic diseases such as T2DM have been linked to epigenetic changes that occur without changes in the DNA sequence, such as cytosine methylation of DNA, histone posttranslational modifications, and microRNA, which provide links between genes and environmental factors such as diet, smoking, and other lifestyle factors. T2DM affects insulin gene expression and beta cell differentiation via both histone modifications and DNA methylation in diabetic islets, which plays a vital role in regulating mitochondrial genes and in diabetes regulation. In this review, we provide existing evidence on epigenetic changes in high fat diet-induced diabetes.

Key words: Epigenetics, high fat diet, diabetes, insulin resistance

Background:

Type 2 diabetes mellitus (T2DM) is one of the most frequent illnesses in the world. The etiology of T2DM is complex, with irreversible risk factors such as age, genetic, race, and ethnicity, as well as reversible risk factors such as diet, physical activity, and smoking, with dietary habits and sedentary lifestyle being the major factors for the rapidly rising incidence of T2DM in developing countries (**Figure 1**) **[1]**. Indians as mentioned earlier, role of diet in the etiology of T2DM was observed that the disease was almost confined to rich people who consumed oil, flour, and sugar in excessive amounts **[2]**. Obesity results from an imbalance of food intake, basal metabolism, and energy expenditure is a major risk factor for various metabolic syndromes such as insulin resistance, type 2 diabetes and non-alcoholic fatty liver disease **[3,4]**. Changes in the epigenome that occur without changes in the DNA sequence, such as cytosine methylation of DNA, histone posttranslational modifications, and microRNA, have been linked to metabolic disorders. Epigenetics can provide some insights into the relationships between genes and environmental settings (diet, inactivity, smoking, etc.) to help understand genetic foetal programming, monozygotic twin differences, and chronic disease onset in adults, all of which interact with dietary intake and nutritional processes **[5]**. Such chronic diseases in response to earlier transient experiences has led to the suggestion that developmental programming may have an epigenetic component such as DNA methylation or histone tail modifications could provide a persistent memory of earlier nutritional states.DNMT1, DNMT3a and DNMT3b are the groups of DNA methyl transferases which are responsible for pattern between cell generations during replication and de novo methylation of DNA. The core histones are densely packed; their NH2-terminal tails can be modified by histone modifying enzymes, resulting in acetylation, methylation, phosphorylation and ubiquitination. These modifications are important for determining the accessibility of the DNA to the transcription machinery as well as for replication, recombination, and chromosomal organization which reflects the impact of epigenetics on the pathogenesis of type 2 diabetes **[6-7]**. These pathways, along with other transcriptional regulatory processes, will be reviewed to determine how they eventually govern gene activity and expression in high fat diet-induced T2DM.

High fat diet model:

Although the etiology of obesity and T2DM is complicated, dietary variables, particularly the intake of a high-fat (HF) diet, are thought to be risk factors for its development **[8]**. A high-fat diet in mice results in increased body weight gain and over time a stable hyperglycemia but a progressively increased hyper insulinemia, indicating progressive worsening of insulin resistance **[9,10]**. These diets rich in saturated fat promote weight gain by expansion of white adipose tissue (WAT), altering lipid homeostasis, adipocyte differentiation and survival. Subsequently to these alterations promote an inflammatory state and leucocyte infiltration **[11, 12]**. Chronic HFD exposure causes liver damage [13], altered glucose homeostasis, compensatory hyper insulinemia to maintain normal glycemia (in the early stage), late pancreatic -cell failure to generate insulin owing to cell fatigue, and consequent hyperglycemia, all of which are hallmarks of T2DM [14]. As a result, a high-fat diet (HFD) is frequently employed as an experimental method to establish obesity and T2DM in mice, replicating an environmental impact on these animals' metabolism **[15].**

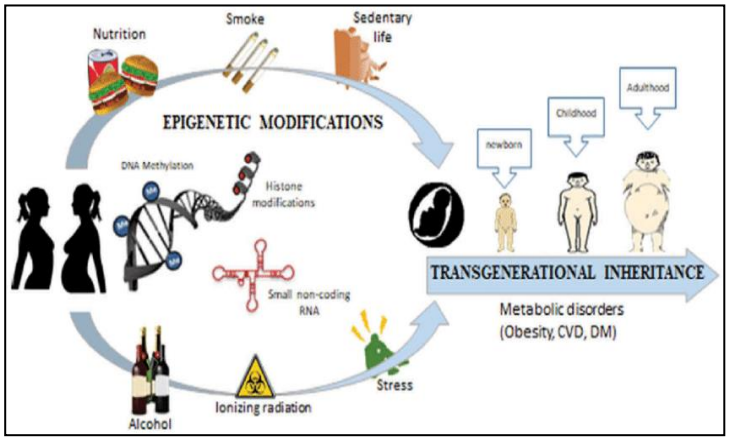

Figure 1: Epigenetic changes caused by diet, hyperglycemia, smoking, radiation, psychological stress, alcohol intake, and other factors might result in a variety of long-term metabolic abnormalities in offspring **[1].**

High fat diet induced epigenetic alternations

DNA methylation, histone alterations, and non-coding RNAs are the most common epigenetic changes. Environmental factors can influence gene expression through epigenetic alterations. DNA methylation is characterized as the insertion of a methyl group to a cytosine, commonly in CpG islands **[16, 17]**. DNA methylation at CpG-rich promoters or gene regulatory regions is normally associated with the inhibition of gene expression. These epigenetic changes in key metabolically important tissues following high-fat feeding between lean and obese animals and by human studies which showed epigenetic changes in obesity and T2DM candidate genes in obese/diabetic individuals **[18]**.The level of DNA methylation in HFD exposure, are also suggested to contribute to long-term changes in adipokine secretion [19,20] has been consistently linked in DNA methylation near the genes Leptin and Pparg2 (the adipocyte-specific isoform 2 of Pparg) **[21]**. The adipokine Leptin is a critical signaling component regulating food intake, energy homeostasis, and exhibits potent immuno modulatory functions **[22]** and Pparg2 is a master regulator of adipogenesis and is involved in adipocyte differentiation and maturation as well as fat storage and glucose metabolism **[23]**. Zhang et al. [24] found that a high fat maternal diet paired with a high fat offspring feeding produced hyperglycemia and insulin resistance in male pups. Male pups exposed to the maternal high fat diet displayed hyperglycemia and glucose intolerance even after switching to the control diet. A hyper methylated insulin receptor substrate 2 (Irs2) genes and a hypo methylated mitogen-activated protein kinase kinase 4 (Map2k4) gene were found in the livers of pups fed a high fat maternal diet. In pups exposed to a high fat maternal diet, the expression of the Irs2 gene dropped while that of Map2k4 rose. Changes in GLUT1, GLUT4, and IRS-1 expression levels, as well as GLUT4 membrane translocation, were reported in insulin-resistant people and animal models' adipose tissue **[25]**. Thus, both indirect/secreted and direct/cell contact-mediated macrophage factors regulate insulin sensitivity in adipocytes, indicating that pro inflammation control is important in high fat diet-induced diabetes.

Diabetic epigenetic complications:

Diabetes is linked to various severe microvascular consequences such as nephropathy, retinopathy, and neuropathy, as well as macro vascular disorders such as atherosclerosis and stroke, which are linked to epigenetic changes that occur without changes in the DNA sequence. Diabetes is linked to various severe microvascular consequences such as nephropathy, retinopathy, and neuropathy, as well as macro vascular disorders such as atherosclerosis and stroke, which are linked to epigenetic changes that occur without changes in the DNA sequence **[26].** As previously stated, causal and correlative linkages between HFD-induced inflammation and the establishment of insulin resistance decrease insulin production from b cells and peripheral insulin action via hypothalamic inflammation **[28].** In turn, Pro-inflammatory cytokines produced by b cells due to macrophages accumulation in islets may further block B cell function **[27-29].** T2D caused by Pdx1 epigenetic silencing, a critical transcription factor that controls insulin gene expression and beta cell development via histone modifications and DNA methylation. **[30]**. Another study found that the promoter of the peroxisome proliferator-activated receptor-(PPAR) and co-activator 1 gene (PPARGC1A) had enhanced DNA methylation in diabetic islets, which plays a vital role in regulating mitochondrial genes and modulating diabetes **[31,32]**. Insulin resistance, a key determinant of T2DM and its complications, is defined as an insufficient metabolic response of target tissues to insulin stimulation and is associated with a variety of pathological conditions or long-term anti-inflammatory treatments, such as obesity, infections, polycistic ovary, lipo dystrophy, and steroid therapy in the liver, skeletal muscle, and adipose tissue. Obesity is a major risk factor for T2DM and is characterized by ectopic fat accumulation, enhanced lipolysis, and secretion of inflammatory cytokines by enlarged and supernumerary adipocytes. These factors promote insulin resistance both at the systemic and adipose tissue level, thus causing T2DM **[33-34].** Hyperglycemia increases promoter H3K4me1 (Histone H3 lysine 4 methylation) and p65 expression in aortic endothelial cells, retinal pericytes and endothelial cells, or renal mesangial cells, tubules, and podoctyes that are involved in common diabetic complications, retinopathy and nephropathy, suggesting that transient high glucose or metabolic control can lead to epigenetic changes **[35,36]**.

Conclusion:

Data shows that nutrigenetics and epigenetics in diabetes can give critical information and insights in this condition. Further interventional and longitudinal research studies are needed to broaden understanding in this topic.

Conflict of interest:

None declared.

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Shyamaladevi Babu requested for the removal of her name post publication for unknown reasons