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IMPACT OF EPIGENETIC MODIFICATIONS ON DIABETES MELLITUS AND ITS COMPLICATIONS

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Abstract

The current review outlines the imprint of epigenetic changes on the development of diabetes mellitus (DM) and its comorbidities. Diabetes mellitus includes T1DM and T2DM, which are chronic disease associated with hyperglycemia due to insulin deficiency or insulin resistance. DNA methylation and histone modification along with microRNA and small interfering RNA have been established to participate in diabetes regulating the gene related with insulin production, secretion and glucose metabolism. It has been established that, the methylation of DNA in functional genes such as PDXI and IGF2 is associated with the abnormal functioning of beta-cells and insulin resistance in T2DM. Histone modifications also have crucial roles: histone acetylation is involved in modulation of insulin secretion and sensitivity. Also, microRNAs and long intergenic non-coding RNAs, which comprise a diverse group of molecules, are involved in the management of beta-cell action as well as glucose utilization. Genomic imprinting is involved not only in the development of diabetes but also in its complications as diabetic nephropathy, neuropathy, and cardiovascular diseases. These may be used as intervention points for the prophylaxis and treatment of diabetes besides its complications. New knowledge being generated in understanding the epigenetic role in diabetes will add areas of therapeutic intervention to reduce mortality and morbidities in patients with diabetes.

Keywords: Epigenetic changes**,** Hyperglycemia, Diabetic nephropathy, Neuropathy, Cardiovascular diseases

1. Introduction

Diabetes mellitus is a long-term condition, which affects metabolism and is caused by high blood sugar levels. It can be due to insufficient insulin production (T1DM) or when the body is not able to use the insulin in the correct way (T2DM) (American Diabetes Association). T1DM is an autoimmune disease; the body's immune system destroys insulin-secreting cells in the pancreas, called pancreatic β-cells. T2DM which is more prevalent is resultant of insulin resistance and it is predisposed by such factors as obesity and lack of exercise and poor diet (Holt et al., 2017).

The diabetes-related complications are numerous and depriving, for instance microvascular where the damage results in neuropathy, nephropathy and retinopathy, while macrovascular complication include cardiovascular diseases (Brownlee, 2005). These complications have led to increased morbidity and mortality, hence early diagnosis and proper management is advisable.

Epigenetics is defined as changes in the rate at which a gene is used to make a protein that can be passed down to the next generation without change in the sequence. Such polygenic changes are normally controlled by environmental aspects and can alter the access to genetic information (Fig 1) which in turn can influence diverse cellular activities (Jaenisch & Bird 2003).

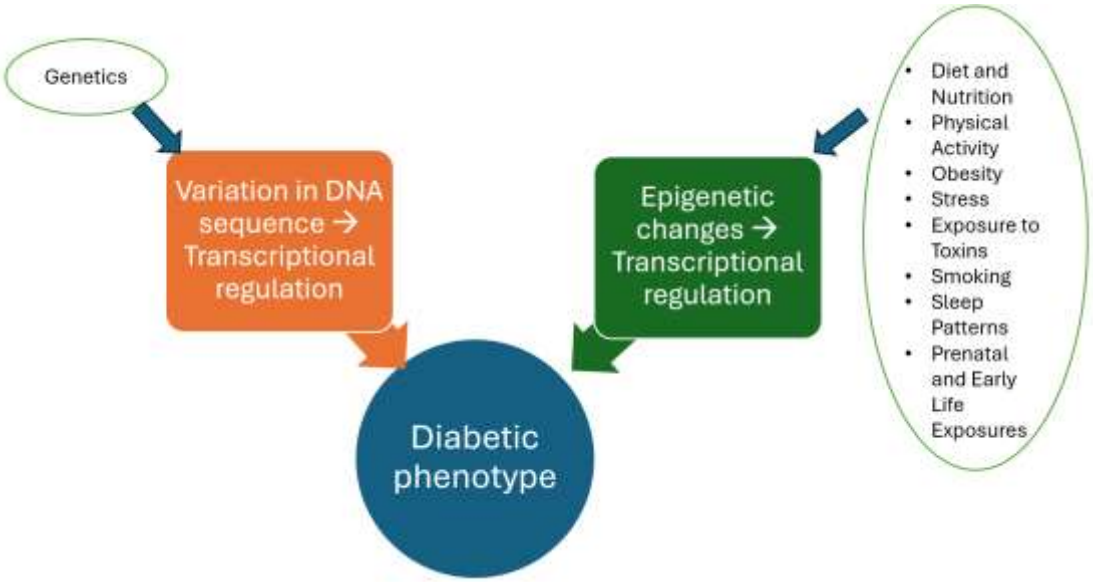

Figure 1: Factors influencing the expression of diabetic phenotype.

2. Rationale for Review

Epigenetic modification in DM has emerged as an area of interest in the recent past and been found to play a part in the development of the disease. Since epigenetic modifications are generally reversible, they present potential therapeutic targets (Zhang et al., 2015). The knowledge of these modifications on insulin synthesis and secretion, glucose homeostasis, and course of diabetic complications can help in searching new therapeutic approaches. This review seeks to summarize the contemporary understanding of epigenetics in DM and the way in which it influences the disease.

3. Epigenetic Mechanisms in Diabetes Mellitus

3.1 DNA Methylation: This is a process by which a methyl group – consisting of one carbon and three hydrogen atoms – is attached to the 5-carbon of cytosine particularly in the CpG islands which are part of DNA sequences containing cytosine and guanine nucleotides. This process is mediated by DNA methyltransferases (DNMTs) and usually, is associated with gene suppression due to inhibition of the access by the transcription apparatus (Bird, 2002). As for DM, changes in DNA methylation have been reported to occur in genes associated with insulin biosynthesis and sensitivity. For instance, down regulation of PDX1 gene that is imperative to the correct functioning of pancreatic β-cell has been linked to low insulin generation in T2DM patients (Yang et al., 2011) (Table 1). In the same way, decreased DNA methylation at the IGF2 gene has been associated with higher levels of insulin resistance (Burdge et al., 2007). Another gene involved in insulin resistance is the inflammatory cytokine TNF-alpha for which there are differences in methylation profiles in diabetic patients (Gupta et al., 2012).

3.2 Histone Modifications: Chromatin restructuring is the major regulatory mechanism at the chromosomal level, and such changes include acetylation, methylation, and deacetylation of histones. Histone acetylation that is catalyzed by histone acetyltransferases (HATs) generally enhances gene expression by chromatin remodelling, conversely, histone deacetylation by histone deacetylases (HDACs) inhibits gene expression through chromatin compaction (Kouzarides, 2007). Concerning DM, it has been established that histone modifications can regulate glucose homeostasis and also β-cells (Table 1). For example, the acetylated histone structure at the promoter site of genes responsible for secretion of insulin for example GLP1R is observed to improve on gene expression and

consequently insulin sensitivity (Haumaitre et al., 2008). HDAC inhibitors in animal models have demonstrated to effect modification in insulin sensitivity and could therefore be a promising approach in diabetic therapy (McKinsey 2011).

3.3 Non-coding RNAs: Small non-coding RNA, which includes microRNA (miRNAs) are involved in controlling gene expression at post-transcription level by binding to target mRNAs for degradation or repression of translation. In DM, some miRNAs are considered as the modulators of insulin sensitivity and β-cell function or death. For instance, miR-375 has been found to negatively regulate insulin secretion by targeting MYOT and PDK1 and on the other hand miR-29 has been associated with insulin resistance through modulation of genes that are involved in glucose metabolism mainly through regulating their expression (Latreille et al., 2014). lncRNAs are also involved in the regulation of glucose metabolism, including insulin sensitivity and glucose homeostasis; H19 is one of the lncRNAs of significance in this aspect.

Table 1: Role of Epigenetic Modification in Diabetes

Epigenetic Modification	Mechanism	Role in Diabetes	Citations
DNA Methylation	Methylation of CpG islands such that methyl groups are attached to the cytosine in the DNA molecule.	Influences genes related to insulin synthesis and tissue sensitivity (for example *PDX1, IGF2*). Implicated in beta-cell dysfunction.	Reddy et al., (2012); Yuan et al., (2016)
Histone Acetylation	Acetylation of histones, rendering chromatin less compact, and increasing the expression of genes.	Improve the level of some genes involved in the exchange of glucose and its effective use based on insulin. Reduced in T2DM and obesity.	Crider et al., (2012); Christensen et al., (2011)
Histone Deacetylation	Removal of acetyl groups from histones, for compaction of chromatin and silence of the genes.	Involved in the development of insulin-resistant and inflammation in diabetes. HDAC inhibitors hold promise for enhancing the survival of beta-cells.	Sasaki et al., (2015); Christensen et al., (2011)
Histone Methylation	Addition of methyl groups to histones, which can either activate or repress gene expression depending on the site.	Altered in diabetes and implicated in processes concerning the beta cells and the glucose metabolism. Possible candidate for pharmacological treatment.	Dayeh & Ling, (2015)
microRNAs (miRNAs)	Small non-coding RNAs that plays a role of negative regulators of gene expression by binding to mRNA molecules.	Regulate the removal of beta cells connected to the degree of insulin sensitivity. Several miRNAs, for instance, miR-375 is up/down regulated in diabetes mellitus.	Reddy et al., (2012); Egger et al., (2004)
Long Non-Coding RNAs (lncRNAs)	Long non-coding RNAs that modulate gene expression through chromatin remodelling and protein and mRNA binding.	Effect on the response of beta-cells and insulin sensitivity. H19 and other lncRNAs have been reported to associate with diabetes.	Yuan et al., (2016); Liu et al., (2016)

4. The Epigenetics to Type 1 Diabetes Mellitus

4.1 Genetic vs. Environmental Triggers: Type 1 Diabetes Mellitus (T1DM) is mainly genetic but often brought about by changes that are usually environmental which include infection, diet and stress which are known to precipitate epigenetic changes (Knip & Simell, 2012). For example, the changes in DNA methylation have been observed in immune system linked genes due to early life viral infection and such changes might contribute to autoimmune destruction of β-cells (Pugliese, 2013).

4.2 Autoimmunity and Epigenetics: Thus, the epigenetic changes are involved in the regulation of autoimmune reactions in T1DM pathogenesis. Abnormal DNA methylation patterns have been

reported in immune-related genes, including FOXP3 which is essential for regulatory T-cells, these changes have been found to be instrumental in the disruption of immune tolerance and destruction of beta cells (Mazzone et al., 2019). The same epigenetic changes may be targeted using either demethylating agents or HDAC inhibitors which might be a useful therapeutic intervention for perhaps putting off or halting the development of T1DM by protecting β-cell function (Jerram et al., 2017).

5. Epigenetics in Relation to Type 2 Diabetes

5.1 Insulin Resistance and Epigenetics: Epigenetic changes are on the forefront of dysregulation of insulin signalling a key pathophysiologic feature of T2DM. Insulin resistance is when the cells in muscles, fat, and the liver fail to respond to the insulin hormone hence causing high levels of blood sugar (Boucher et al., 2014). The PI3K/AKT molecular pathway is one of the key pathways that are involved in the regulation of insulin signalling and by the mediates the transport of glucose transporter 4 (GLUT4) to the cell membrane. Abnormality of DNA methylation and histone modifications can affect this signalling pathway. For instance, hypermethylation of the promoter of the GLUT4 gene has as its effect the low level of this gene expression, and this is a cause of insulin resistance (Barres et al., 2013).

Furthermore, there is evidence that LPS influence the epigenome depending on the diet and exercise regimens and their subsequent impacts on T2DM. The current research has shown that high-fat diet can cause DNA methylation to genes involved in adipogenesis and insulin signal transduction; the genes include PPARG and ADIPOQ. On the other hand, physical activity positive epigenetic marks by physically training have been shown to lead to hypomethylation of genes that we promote insulin sensitivity including PIK3CA and PPARGC1A (Loh et al., 2019). These research studies indicate that epigenome is rather plastic and immediately reacts to environmental alterations and is an essential factor in the pathogenesis of T2DM.

5.2 Beta-cell Dysfunction and Epigenetics: A key characteristic of T2DM is an impairment of the beta-cell function and a subsequent inability of the cells to secrete insulin under high blood glucose (Ashcroft & Rorsman, 2012). Epigenetic changes in pancytokeratin positive cells in the islets of Langerhans of the pancreas can deteriorate the capacity of beta cells to function and also play a role in the progression of the disorder. Abnormal DNA methylation has also been established in genes whose products are crucial for the function of beta cells, for instance PDX-1, which is mandatory for the expression of insulin genes (Yang et al., 2011). The ability of PDX1 to drive expression of insulin and other beta-cell genes depends on its DNA binding to the promoter region: however, hypermethylation of the promoter region of PDX1 also decreases its activity, which in turn decreases insulin secretion and results in the failure of beta-cells (Yang et al., 2011).

Various changes in the histone proteins have been known to be involved in the dysfunction of beta-cells. For instance, histone acetylation at the promoter region of the INS gene is required for insulin gene transcription and, low histone acetylation has been linked to impaired beta-cell function and T2DM (Crider et al., 2012). HDACs, which has been implicated in the removal of acetyl groups from histones, are often over expressed in T2DM, hence resulting in chromatin remodeling and gene repression. Modulators of chromatin function which include HDAC inhibitors have been demonstrated to improved beta–cell function through the course of histone acetylation and enhancement of insulin release (Christensen et al., 2011).

6. Epigenetics and Diabetic Complications

6.1 Diabetic Nephropathy: Diabetic nephropathy is one of the discouraging complications of diabetes, it implicates the harm of the kidneys and the gradual loss of renal function. Among epigenetic mechanisms, DNA methylation has been a focus of interest in the context of diabetic nephropathy. Another study revealed that elevated hypermethylation of promoter region of RAGE gene is directly related with high expression of this receptor of advanced glycation end products which plays significant role in renal inflammation and fibrosis (Kan et al., 2018). In addition,

hypomethylation has been reported to be global in the patients with diabetic nephropathy and this was associated with enhanced expression of TGF-beta1 and COL4A1.
Epigenetic modification of histones has also been implicated in the progression of renal fibrosis in DN. Histone methylation is seen as a higher level at the promoter regions of pro-inflammatory and pro-fibrotic genes that, in turn, is associated with increased transcriptional activity in kidney cells (Yuan et al., 2016). The strategies involving epigenetic alterations with the use of HMT or HDAC inhibitor have been suggested to provide a therapeutic approach to diabetic nephropathy (Yuan et al., 2016).

6.2 Diabetic Neuropathy: Diabetic neuropathy (DN) is a complication that causes damage to nerve fibres and changes in the perception of pain making patient feel tingling, numbness or pain in the extremities. There is evidence that epigenetic factors are involved in the development of DN, DNA methylation in particular, as well as histone changes. Another discovered showed that there was upregulation of DNA methylation at SCN9A gene which codes for sodium channel that is associated with pain transmission and reduced its expression and nerve functionality (Guo et al., 2019). Epigenetic modification also occurs in diabetic neuropathy where there is a decrease in the acetylation of histones in the sensory neurons that thereby leads to the decrease in gene expression and subsequent impaired neuronal function (Bansal & Pinney, 2017).
Other ncRNAs that are also associated with DN are miRNAs. For example, miR146a has been implicated in the regulation of inflammation in the nervous system and dysregulation of this miRNA in diabetes produces increased inflammation and nerve injury. Entire lines of drugs may be developed targeting miRNAs and other epigenetic factors, which can result in the new treatment of diabetic neuropathy.

6.3 Cardiovascular Complications: Diabetes is well known to carry a high risk for cardiovascular disease and epigenetic changes have been linked to diabetic cardiovascular disease. DNA methylation of genes that regulate genes in the endothelium is believed to be involved in the endothelial dysfunction, atherosclerosis and vascular inflammation in diabetic individuals and Patients with diabetes also experience histone modifications on genes in the vascular endothelium. In one of the studies, hypermethylation of eNOS promoter was reported to down regulate the endothelial nitric oxide synthase (eNOS), consequently prejudiced the nitric oxide production and the endothelial derogation (Turgeon et al., 2014).
Like examples of DNA methylation, other changes have also been observed to impact on vascular inflammation and atherosclerosis in diabetes, including post-translational modifications for instance increased histone acetylation at the promoter of genes that produce inflammatory cytokines. Other types of ncRNA molecules such as miRNA are involved in the modulating of vascular inflammation and endothelial function. For instance, miR-126 has been implicated in endothelial cell homeostasis, and there is research evidence that its levels are altered in diabetes to impact on vascular inflammation and atherogenesis (Yuan et al., 2016).

7. Epigenetic Therapeutic Approaches

7.1 Current Epigenetic Drugs: Due to the positions that epigenetic changes play in the occurrence of diabetes, epigenetic drugs appear to be good prospects in the management of the condition. Two groups of drugs that are currently being used in various cancer therapies are Histone deacetylase inhibitors and DNA methyltransferase inhibitors are of special interest for use under diabetic conditions.
Valproic acid and suberoylanilide hydroxamic acid (SAHA) are examples of HDAC inhibitors because they inhibit the deacetylation of histones that make the chromatin structure more open and consequent increase in the expression genes. Clinical investigations also revealed that HDAC inhibitors can increase insulin signalling and preserve and prevent apoptosis of the pancreatic beta cells besides decreasing inflammation in diabetes (Halban et al., 2014). Likewise, DNMT inhibitors which include azacitidine and decitabine inhibit the addition of methyl group to DNA that may

potentially relieve hypermethylation of genes that have roles in insulin synthesis and metabolic glucose (Yuan et al., 2016).
Nonetheless, such outcomes have not become the basis of extensive clinical utilization of these drugs in diabetes treatment, which is still in its experimental phase. Newer epigenetic drugs pose a difficulty of being non-selective and may affect expression of other genes besides those of diabetes type and so has side effects (Egger et al., 2004). This has therefore called for the need to create other more specific epigenetic drugs.

7.2 Epigenetic Diets and Lifestyle Modifications: It is well known that many medications can alter their expression and diet, and lifestyle can also impact on the whole epigenome meaning that it may be possible to reverse or prevent such epigenetic modifications of diabetes. Other micronutrients like folate, vitamin B12 and the other methyl donors can influence DNA methylation and histone modification hence gene expression (Barua et al., 2014). For instance, methyl donors like foods from the leafy greens, nuts and seeds can enhance the DNA methylation of the genes that are involved in glucose metabolism may lower down the onset of T2DM (Crider et al., 2012).
Exercise also has huge epigenetic implications, particularly in conditions associated with metabolic syndrome such as diabetes. Loh et al, (2019) found that physical activity has the ability to decrease DNA methylation of gene relating to glucose metabolism and insulin sensitivity, which improved the metabolic fitness of an individual. These studies imply that perhaps there is potential of using lifestyle alteration in the prevention of or in slowing the downhill process of diabetes through genomic modification.

7.3 Epigenetic therapies: future directions: As for new techniques that can be used for the epigenetic manipulation in diabetes therapy, the most promising of them seems to be the CRISPR/Cas9-based epigenetic editing. Crispr/cas9 as a tool to modulate epigenetic signals is different from the conventional epigenetic drugs which have some drawbacks of acting on cells without their specificity (Xie et al, 2018). For instance, modifying a gene known as PDX1 through CRISPR-based demethylation could return the gene's activity to normal in the beta cells used for T2DM, thereby rejuvenating the execution of the beta cells (Xie et al, 2018).
However, there are various disadvantages, mainly in relation to the application of the CRISPR-based systems to certain tissues and the possible off-target effects of the mentioned innovative therapies. Moreover, with regard to the problem of introducing genetic modifications within diseases in humans, especially with heritable effects, there stays the question of ethics which also should be solved before clinical trials (Lanphier et al., 2015).

8. Challenges and Knowledge Gaps

8.1 Epigenetics - Some Methodological Problems: On of the most complex issues of epigenic studies is tissue specificity and this adds on to epigenic complexity. Epigenetic changes can maybe differ by tissues therefore when elaborating data obtained in one tissue to another tissue, different picture is obtained. For instance, epigenetic alterations that have been reported in leukocytes may not necessarily reflect alterations in pancreatic beta cells or in adipose tissue that are more directly implicated in diabetes development (Keating et al., 2016).
Another issue is the, often, small number of participants included in epigenetic studies, which reduces the sensitivity to measure meaningful effects and raise the chances of type I errors. Moreover, generalisability of epigenetic observations is further confounded by about measurability issue in studying epigenetic marks including DNA methylation and histone modifications (Rakyan et al., 2011). To address these limitations, we are required to use methodological standardization, and have to perform larger cohorts' studies.

8.2 Unresolved Questions: However, several issues need further clarification in terms of an etiology of epigenetic changes in diabetes, including the following: For example, although there are studies that have shown that certain EP would be responsible for insulin resistance or beta-cell dysfunction or diabetic complications, one cannot really tell as to whether these EP are initiators of the disease or

simply biomarkers of the epithetic. Epigenetic modifications are dynamic and require follow up of subjects through time to determine the temporal relationship between such changes and the onset of diabetes (Dayeh & Ling, 2015).
In addition, although large numbers of epigenetic modifications have been catalogued, the consequences of these modifications are often uncertain. For instance, what role of histone modifications or any non-coding RNAs that are involved in the complexion of this complexity of insulin biosynthesis and glucose homeostasis are still unfolded.

9. Conclusion

The present review focuses on the involvement of epigenetic changes in the development of diabetes mellitus and its complications. DNA methylation, histone modifications, and micro/RNA play an integral role in the regulation of such processes as insulin signaling, and beta cell function and the development of diabetic complications. Epigenetic changes can therefore be controlled genetically and also by diseases related factors like diet and lifestyle. By meditating in on these changes, there are potential treatments for diabetes. Overall, it is possible to describe the contribution of epigenetic modifications in diabetes and suggest the further development of individualized medicine. For instance, discovering epigenetic markers of insulin resistance or impaired beta-cell function would allow defining subjects at risk of developing diabetes. Furthermore, application of HDAC and DNMT targeting drugs, with the possibilities of the CRISPR tool for gene editing, can be applied to shift or even eradicative epigenetic changes relating to the progression of diseases.

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