

DIABETES – EPIGENETICS A OVER VIEW

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ABSTRACT:

Diabetes has reached epidemic proportions throughout the world. It is undoubtedly one of the most challenging health problem in the 21st century. Worldwide it was estimated that the prevalence of diabetes among adults was 366 million in 2011; by 2030 this will have risen up to 552 million. Type 2 diabetes is the predominant form and accounts for at least 90% of cases. 80% of people with diabetes live in low- and middle-income countries; the greatest numbers of people with diabetes are between 40 to 59 years of age. Many recent research evidence suggests that complex interactions between environment and genes might play a major role in the pathogenesis of this multifactorial disease and its complications, and this might be a result of the involvement of epigenetic factors. Many recent studies shows that epigenetic factors, including histone modification and DNA methylation may affect the susceptibility for type 2 diabetes and progression of their complications. However, molecular mechanisms linking environmental factors and type 2 diabetes still remains limited.

Key Words: Diabetes, Epigenetics, Metabolic Disorder, Environment, Insulin.

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INTRODUCTION:

Type 2 diabetes mellitus (T2DM) is a polygenic metabolic disease characterized by elevated blood sugar levels due to pancreatic beta-cell functional impairment and insulin resistance in tissues such as skeletal muscle, adipose tissue and liver [1]. Millions of people around the globe are diagnosed with diabetes, and its incidence is estimated to double by

2030. It has become one of the most challenging public health issues in 21st century and the fifth leading cause of death worldwide [2]. The American Diabetes Association (ADA) estimates that 1.7 million Americans are diagnosed with diabetes every year, which means about 4,660 new diagnoses of diabetes daily [3]. In United States 30 million people who currently have diabetes mellitus, about 90% have T2DM. While the onset of T2DM is known to be the consequence of a multifactorial interplay with a strong genetic component, emerging research has demonstrated the additional role of a variety of epigenetic mechanisms in the development of this disorder. This chronic disease process is accompanied by complications in various vital organs and can be associated with a higher risk for neurological changes, cardiovascular events, osteoporosis, kidney impairment, dementia and cognitive impairment (CI) [4]. Though diabetes has a strong genetic component, as it tends to run in families, environment also has a significant role in triggering this condition. The notable risk factors for developing diabetes are obesity, advance in age, and sedentary lifestyle with lack of physical activity. However, many people with these risk factors do not develop diabetes and research studies indicate that complex interaction between genes and environment through epigenetic modifications makes a person susceptible to develop diabetes [5]. Epigenetic mechanisms and their role in the development of diabetes and diabetic complication of an individual is presented in this article.

OVER VIEW ON EPIGENETIC:

It described as changes in gene expression that occurs not by changing in the DNA sequence this is due to modification of DNA methylation and remodelling chromatin. Epigenetic is study of the processes by which the genotype gives rise to phenotypes through programmed changes during the development. There is a heritable changes in gene expression but not any alteration in DNA sequence [6]. (OR) It has been well defined as the “study of stable genetic modification that result in changes in gene expression and function but without any changes in DNA sequence”.

This mechanism encompasses all the deploying genetic program for the many processes operating during the life span of a cell. But this epigenetic modification is stable, it can be modulated by many factors, including pathological, physiological and by environmental factors [7,8]. By understanding this epigenetic mechanism have established them as key players in several cellular process including cell aging, differentiation, DNA replication and repair [9,10, 11 and 12]. Type II diabetic people have epigenetic changes on

their DNA but healthy people do not have. Many research finding says that epigenetic changes of a large number of genes that contribute to reduced insulin production.

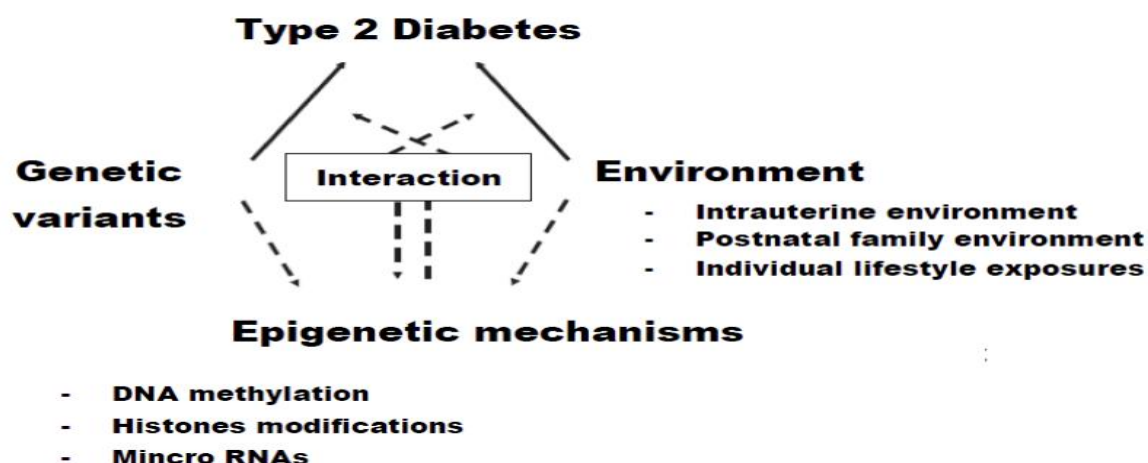
BASIC PRINCIPLES OF EPIGENETICS:

The human genome contains nearly 23, 000 genes that must be expressed in specific cells at precise time. Cells can manage the gene expression by wrapping DNA around cluster of globular histone proteins to form nucleosomes [13]. These nucleosomes of DNA and histones are organized in to chromatin. Any changes in structure of chromatin influence the gene expression. When chromatin is condensed, genes are inactivated, they are expressed when chromatin is open [14]. These dynamic chromatin states are controlled by reversible epigenetic pattern of DNA methylation and histone modification. Many enzymes are involved in this process including histone deacetylase, histone acetylase, DNA methyl transferase, histone methyl transferase and methyl binding domain protein. Alteration in these normal epigenetic patterns can deregulate patterns of gene expression which result in profound and diverge clinical outcome [15].

But epigenetic modifications can be passed from one cell generation to the next generation. This was well established in the plant system [16]. Regarding with animals, having only limited information about the inheritance of epigenetic traits between the generation [5, 17]. Environment also play a major role in epigenetic mechanism, making them potentially important pathogenic mechanism in complex multifactorial disease such as diabetes, especially type –II diabetes. The epigenetic factors include histone modification, DNA methylations and Micro RNAs they can help in to explain how the cells of identical DNA can differentiate in to different cell types with different phenotype. Among other types of epigenetic changes, DNA methylation is the best known epigenetic modification and has a critical role in the control of gene expression and the architecture of the cell nucleus [18].

EPIGENETIC CHANGES IN TYPE 2 DIABETES:

Regarding with epigenetic changes and research in type II diabetes is still very young field. The role of epigenetic mechanism in the etiology of these disorder and related metabolic abnormalities and hypertension, obesity, dyslipidaemia is not well elucidated. In the year 2012, over than 150 genetic loci have been conclusively implicated in the development of syndromic, monogenic forms of diabetes and obesity [19].



Several research evidence point to a substantial epigenetic components to the development of Type –II Diabetes and also obesity. From foetal origin the hypothesis established the notion of “ metabolic programming” during in early stage of life their nutritional and other exposures generate a long term changes that , later predispose to type II diabetes and other disease like cardiovascular disease. This hypothesis establish a strong epidemiological data linking early life to disease risk in late life [20].

EPIGENETICS AND DIABETIC COMPLICATION:

Diabetes and metabolic disorders are leading causes of micro- and macro vascular complications such as hypertension, nephropathy, retinopathy, neuropathy and atherosclerosis. One major event in the progression of diabetic complications is vascular inflammation with increased expression of inflammatory genes. Some research studies says that severe dyslipidaemia, oxidative stress and hyperglycaemia have also been suggested to influence the development of diabetic complications [21].Among other disease ,cardiovascular disease is remains the major causes of morbidity and mortality in diabetic population. This may be due to that exposure to high glucose is the major factor leading to these complications. Many recent research proposed that hyperglycaemia may induce epigenetic modification especially hyperglycaemia induced DNA methylation of genes involved in vascular inflammation [22, 23].

DIBETEIC NEPHROPATHY:

Diabetic nephropathy represents the major cause of end stage renal failure in Western societies [24]. Clinically, it is characterized by the development of proteinuria with a subsequent decline in glomerular filtration rate, which progresses over a long period of time,

often over 10–20 years. For the untreated cases the resulting uraemia is fatal [25]. In diabetic nephropathy (DN) tubule interstitial fibrosis was observed it is due to increased expression of extracellular matrix proteins such as collagen and fibronectins is initiated and sustained by a number of different factors including the Transforming Growth Factors Beta (TGF β) family. This inflammatory mediators are aberrantly expressed in metabolic memory, implicating TGF β as a major mediator of epigenetic events in diabetic nephropathy [26, 27].

DIABETIC RETINOPATHY:

In diabetic retinopathy a spectrum of lesions was observed with in the retina and is the leading causes of blindness among adult aged in 20- 74 years [28,29]. The changes including vascular permeability, capillary micro aneurysms, excessive formation of blood vessels, capillary degeneration. The neural retina is also dysfunctional with death of some cells, which alters retinal electrophysiology and result in an inability to discriminate between the colors. The epigenetic mechanisms in pathogenesis of diabetic retinopathy observed that the matrix metalloproteinase MMP2 and MMP9 causes mitochondrial DNA damage and degeneration of mitochondrial membrane in retinal capillary cells. This will induce apoptosis of the same [28]

DIABETIC NEUROPATHY:

More than half of all individual's with diabetes eventually develop neuropathy [30]. Diabetic neuropathy which encompasses the somatic and autonomic division of the peripheral nervous systems. There is growing appreciation was observed that, it causes damage to the spinal cord [31] and also in central nervous system. Neuropathy is a major factor in the impaired wound healing, cardiovascular dysfunction and erectile dysfunction was observed in diabetes.

CONCLUSION:

The use of genome-wide technologies to study gene expression and genetic variation in patients with type 2 diabetes has increased rapidly over the recent years, generating long lists of new type 2 diabetes candidate genes. However, the use of global techniques to study epigenetic modifications in these same patients has been limited. Epigenetic changes associated with type 2 diabetes are therefore still poorly understood. Nevertheless, epigenetics may play an important role in the growing incidence of type 2 diabetes, and over the next few years, it will be a great challenge to dissect the role of histone modifications and DNA methylation in the pathogenesis of the disease and its complications. Two additional important questions are whether the epigenetic changes induced by today's sedentary lifestyle can be inherited by coming generations and whether these changes are reversible. Currently,

several epigenetic drugs are being tested in clinical trials or are already being used (e.g., anticancer or antiepileptic drugs); it may thus be possible to test epigenetic drugs as putative novel drugs for the treatment of diabetes and its complications.

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