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Epigenetics and chronic non-communicable diseases: a new preventive approach

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Abstract: The prevention of chronic non-communicable diseases with high prevalence around the world, such arterial hypertension, diabetes mellitus, cardiovascular diseases and cancer, represents a health priority. The new perspective given by epigenetics on the intrauterine origin of the diseases that will affect the human being during the postnatal stage, forces us to reconsider a new preventive vision which must begin from the prenatal period of life. With the aim of structuring the theoretical references that support the relevance of a new preventive approach to chronic non-communicable diseases, based on modifying interventions of unfavorable epigenetic profiles during the prenatal stage of the human development, an updated search on the subject was conducted, consulting 28 bibliographic references. Maternal conditions during pregnancy, such as malnourishing, stress, toxic habits and obesity, constitute factors that cause unfavorable epigenetic modifications, which will be transmitted to future generations and will increase in them the risk of disease during the post-natal stage of life. It is concluded that the interventions carried out during the prenatal period of human development can contribute to the prevention of chronic non-communicable diseases, to which epigenetics provides a new approach in the prevention of this important health problem.

Key words: epigenetics; chronic non-communicable diseases; intrauterine origin of diseases; prevention

1 Introduction

Chronic non-communicable diseases currently represent a major public health problem, constituting the leading causes of death worldwide. In Cuba, there is a high prevalence of these diseases and a growing incidence of some of them—a situation also common in many more highly developed countries. For this reason, addressing this group of diseases is a high-priority strategic objective for Cuban public health [1].

The risk factors for these diseases have been extensively studied due to their global magnitude and trends, with toxic habits, obesity, a sedentary lifestyle, and poor dietary habits, among others, identified as the main factors affecting human health [1,2]. Addressing modifiable risk factors for the development of so-called "diseases of modern life"—such as high blood pressure, diabetes mellitus, cardiovascular diseases, and cancer—has been the main pillar of prevention in recent decades [2], which is why preventive health care is a fundamental tool in medical practice [3].

Maintaining a healthy body weight, engaging in regular physical activity, eliminating harmful habits, receiving proper nutrition education regarding a diet with a balanced energy intake (providing health-promoting micronutrients), and managing stress are some of the measures aimed at preventing these diseases [4,5].

Derived from the Latin word "praeventio", prevention is the action taken in advance to ensure that potential harm does not occur. The concept is associated with care or caution and encompasses three levels related to health or illness: primary, secondary, and tertiary. Primary prevention (prevention and health promotion) involves implementing targeted measures to ensure that "healthy individuals" do not become ill [6].

In the authors' view, a preventive approach is based on preserving, caring for, and restoring health, resulting in an undeniable reduction in healthcare costs and human suffering. Prevention seeks the greatest possible protection; its goal is to avoid any adverse health consequences and to prevent the onset, development, and progression of diseases. Therefore, efforts should be made to promote the maintenance of health and to establish barriers against all factors that determine or contribute to the occurrence of diseases.

It is therefore worth asking: At what point in life do chronic diseases arise? When should prevention begin? How does individual experience induce changes in gene expression and trigger these diseases?

In light of the most recent findings on epigenetics and its relationship to human diseases, the timing of the onset of the most common chronic conditions affecting humans has been reevaluated, with numerous authors recognizing their intrauterine origin [7–10].

This new conception of the prenatal origin of diseases that will affect humans during the postnatal stage of life would also imply a new preventive approach, one that traces its origins back to the embryonic and fetal stages of human development. In the prevention of chronic non-communicable diseases, this approach represents an immense and exciting challenge for 21st-century medicine.

Research question: What are the current theoretical frameworks that support the relevance of a new preventive approach to chronic non-communicable diseases, based on interventions to modify unfavorable epigenetic profiles during the prenatal and early postnatal stages of human development?

The objective of this study is to outline the current theoretical frameworks that support the relevance of a new preventive approach to chronic noncommunicable diseases, based on interventions aimed at modifying unfavorable epigenetic profiles during the prenatal stage of human development.

2 Materials and methods

The literature review was conducted by searching the Infomed Virtual Health Library, specifically the Medline Complete, PubMed Central, Clinical Key, SciELO Regional, and SciELO Cuba databases. The search terms "chronic diseases," "prevention," "epigenetics," and "intrauterine origin" were used.

The search was conducted between June and November 2022 and was limited to the last five years.

Original studies and literature reviews on epigenetics and chronic diseases, prevention, and the intrauterine origin of disease were selected; a total of 102 studies were reviewed, of which 28 were chosen based on their quality and relevance to the research objective.

The data were processed using the Microsoft Office 2007 software suite.

3 Discussion

3.1 Prevention of chronic non-communicable diseases: a health priority

Non-communicable chronic diseases (NCDs) represent a major public health problem affecting most nations; they are considered by the World Health Organization (WHO) to be a "pandemic" that threatens countries' economic and social development, as well as the lives and health of millions of people. They are currently among the leading causes of morbidity and mortality worldwide [1,2,11].

Some NCDs, such as cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases, are the leading

causes of morbidity and mortality — especially among older adults — not only globally but also in the Americas. They continue to account for three out of every four deaths in the Americas. Cardiovascular diseases cause 1.9 million deaths annually; cancer, 1.1 million; diabetes, 260,000; and chronic respiratory diseases, 240,000. The burden of premature deaths from NCDs is particularly concerning: 1.5 million people die each year before the age of 70, which has negative consequences for both socioeconomic development and the health-disease continuum [12,13].

In Cuba, according to the 2020 Statistical Yearbook of Health, the highest mortality rate is associated with chronic non-communicable diseases. Heart disease ranks first among causes of death, with a rate of 267.3 per 100,000 inhabitants, followed by death from malignant tumors, with a rate of 232.6. Cerebrovascular diseases rank third, with a rate of 96.6 per 100,000 inhabitants [14].

Rapid urbanization and industrialization, the decline in the fertility rate, increased life expectancy—with the resulting aging of the population—changes in lifestyles, and greater access to and effectiveness of health services are factors that, both in Cuba and in other nations, have made NCDs the leading causes of death and will continue to do so in the future [2,13]. In fact, the progressive aging of the population and the steady rise in NCDs will lead to a significant increase in the demand for curative services. If the projected increase in the burden of NCDs materializes, and the demand for health services resulting from this burden rises, countries in Latin America, the Caribbean, and Cuba could face serious human and financial resource constraints, which could jeopardize the improvement of the health sector [2,15]. In addition, the economic consequences of premature mortality and disability will fall on the economically active population [15].

In the authors' view, an appropriate health policy that is consistent with the current reality in Latin America and the Caribbean cannot be based on the approach adopted by developed countries to address NCDs (which relies predominantly on high-tech clinical management), but rather on the urgent need to launch prevention programs and interventions for these diseases, which are relatively low-cost and offer substantial benefits.

Strengthen public communication regarding the prevention of and education about NCDs and their risk factors; advocate for strengthening measures related to legislation and policies in other sectors that affect population health; and educating the public to better understand the behaviors and measures necessary to prevent or delay the onset of NCDs—by taking responsibility for their own health and taking action to control the risk factors that endanger it—are, without a doubt, a health priority.

3.2 Epigenetics: an opportunity that cannot be postponed

Derived from the Greek prefix epi- ("on" or "in"), the term "epigenetics," which means "beyond the genes," was first introduced into the literature in 1940, by the Scottish biologist, geneticist, and embryologist Conrad Hal Waddintong (1905–1975), to refer to the interactions between genes and the environment that give rise to the phenotype, highlighting two characteristics of epigenetic mechanisms: plasticity and stability, stemming from the possibility that the organism's adaptive response to the environment can be fixed without the need for mutation—that is, without modifying the structure of DNA [16,17].

This means that the change can be stable and, consequently, inherited. Therefore, according to Waddintong, epigenetic mechanisms provide the organism with the ability to react rapidly to environmental contingencies through molecular changes that alter gene expression. These changes take place in the physical substrate of DNA, which is precisely chromatin. These are, therefore, mechanisms in which gene function is altered—often silencing the genes—which is reflected in the phenotype, without modifying the DNA base sequence [17,18].

Simply put, epigenetics can be defined as the study of heritable changes in gene expression that occur without modifications to the DNA sequence and may be reversible. Epigenetic processes, therefore, can be understood as the

mechanisms that regulate gene expression, determining not only whether a gene is expressed or silenced, but also where, when, and to what extent it is expressed [16,18].

There is evidence that these epigenetic processes can be modified by physical, chemical, nutritional, and even psychosocial factors. Thus, the environment in which an individual lives and their lifestyle habits can modify gene expression through epigenetic mechanisms. Among the environmental factors that lead to epigenetic changes, prenatal and postnatal factors stand out, such as malnutrition, smoking, alcoholism, and drug use during pregnancy, as well as abuse or stress [16,18,19].

The epigenetic perspective has revolutionized biological, social, and medical concepts, placing great importance on education and the environment [16,20].

Epigenetic mechanisms consist primarily of: DNA methylation, histone modification with chromatin remodeling, and non-coding microRNAs, which play a major role in regulating gene activation and silencing; among their most significant characteristics is the possibility of being reversible. This opens up significant possibilities regarding their treatment and prevention or, conversely, their inheritance—as they may be long-lasting and thus transmitted to subsequent generations [16,17].

DNA methylation involves the attachment of methyl groups to cytosine bases. This methyl group serves as a beacon, indicating that the DNA segment should be silenced. The more methylated a DNA segment is, the less likely it is that the information it contains will be expressed [16,17].

Histones, which form the structure of chromatin and are responsible for winding and unwinding DNA, are the target of another epigenetic mechanism that attaches various types of molecules to them to modify their behavior. When the corresponding DNA segment can relax or become compacted, revealing or concealing the information [21,22].

MicroRNAs are short RNA sequences that interfere with the translation of a gene into a protein, acting to silence certain genes by interrupting the translation of complementary DNA [21,22].

It is now known that epigenetic modifications are involved in a significant number of processes, such as the acquisition of immunological memory by T lymphocytes, the neurobiological basis of memory and learning, and the stress response mediated by the hypothalamic-pituitary-adrenal axis [16,22].

The interaction between genes and the environment occurs throughout life and is particularly critical during three specific stages: pregnancy, the early years of life, and periods of hormonal change. Therefore, events that occur during these stages will have lasting consequences for humans [22].

Environmental factors—particularly intrauterine factors—and experiences during the early years of life can lead to epigenetic changes that increase an individual's susceptibility to neurodevelopmental disorders, as well as to diseases such as cancer, obesity, high blood pressure, diabetes mellitus, schizophrenia, depression, behavioral disorders, intellectual disability, and substance use disorders [16–18, 20].

From an existential perspective, the authors argue that it is not only the determinism of one's genetic makeup at birth that matters, but also the decisions made by one's parents and, later, by the individual themselves, which contribute to shaping one's health, personality, and, ultimately, one's life.

Genes are expressed throughout an individual's life, and they do so based on genetic programming and the personal and social circumstances in which that life unfolds and with which the genes interact; this explains the enormous differences between individuals and among different species, accounting for the unique nature of each person's life [16].

Epigenetic mechanisms regulate gene expression; therefore, in the authors' view, the study of genetics is inseparable from the study of epigenetics, and vice versa. The authors of this article agree with the opinion recently expressed on the

subject by the Matanzas-based embryologist Blanco Pereira: "Genes write the course of ontogeny, but epigenes rewrite it; from this perspective, genetics has ceased to be a matter of fate to the same extent that epigenetics reemerges as an opportunity: there is an urgent need to take advantage of it" [22].

3.3 Prenatal period: its impact on the development of the disease

Human development is a continuous process that begins with fertilization and ends with death. Birth is a pivotal event in this development, at which a change in environment occurs that divides human development into two major stages or periods: [23,24]

- Prenatal stage (before birth): This stage comprises the pre-embryonic stage (first week of life), the embryonic stage (second through eighth week), and the fetal stage (ninth week through birth) [23,25].
- Postnatal stage (after birth): Begins at birth and ends at death. It is characterized by numerous sub-stages: childhood, adolescence, adulthood, and aging [23,24].

Experiences during the prenatal stage of life are critical for the postnatal stage and affect both cognitive ability and behavioral characteristics; various maternal factors—such as smoking, alcoholism, nutrition, stress, and endocrine disorders, among others—are considered to have a significant influence on postnatal health [25].

Epigenetic changes associated with diseases occur throughout life. However, the lability of the epigenetic state during the early stages of development leads to the hypothesis that the association between adverse events early in life and predisposition to disease is mediated by epigenetic mechanisms [22,25].

There are numerous events that occur during the prenatal stage of human development that are associated with a predisposition to certain chronic diseases [17,25]. Poor maternal nutrition, for example, is associated in the short term with intrauterine growth restriction and, in the long term, with certain chronic diseases in adulthood, such as diabetes mellitus, obesity, and cardiovascular disorders. In these cases, epigenetic modifications such as DNA methylation and histone modifications have been detected; these mechanisms may constitute the molecular basis for the predisposition to these diseases [17,22,26].

Other adverse events, such as maternal stress and depression during pregnancy, have been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, particularly with alterations in autonomic responses, leading to an altered stress response in the long term among children of affected mothers. One mechanism that could explain these alterations in children is the methylation of the NR3C1 gene (glucocorticoid receptor), which is sensitive to the mother's mood [20,22].

In the authors' view, prenatal development has direct consequences that affect human health in the short and long term; therefore, positively influencing the healthy development of embryonic and fetal processes will undoubtedly help prevent long-term sequelae. The development of strategies in obstetric and prenatal healthcare will contribute not only to improving birth outcomes but also to mitigating long-term postnatal outcomes, hence the importance of health professionals involved in maternal and child care understanding this topic.

3.4 Barker's theory or the intrauterine programming effect

Changes in the course of intrauterine growth and development, as well as during the first years of life, lead to functional changes that, in adulthood, result in an increased risk of cardiovascular disease, diabetes mellitus, obesity, dyslipidemia, asthma, and other conditions. This process results from disruptions in the natural balance of environmental factors, which, in the case of the developing fetus, originate from the intrauterine environment and from signals that the pregnant mother (as a result of her diet, environmental exposure, pollution, drugs, stress, etc.) transmits to her child through the placenta [20,22,25].

The placenta is an organ that regulates the unidirectional transfer of nutrients and metabolic products—including oxygen—from the maternal circulation to the fetal circulation and vice versa [23,25]. This transfer depends directly on the mother's own nutritional status, the fetus's genetic makeup, and the growing fetus's requirements. A growing body of evidence suggests that, at the cellular level, epigenetic mechanisms are involved in this "programming" process during an individual's early development. These mechanisms involve a series of chemical modifications to DNA and the proteins that interact with it, which shape and regulate gene expression in the short and long term without altering the genetic code [16,22].

The identification of epigenetic markers of vascular and metabolic programming, as well as the underlying mechanisms, is currently at the forefront of research in this field known as the developmental origins of chronic diseases (DOHaD, an acronym for Developmental Origins of Health and Disease) [22].

The notion that the interaction between genetic and environmental factors—such as the mother's diet and physical activity—constitutes a risk factor for the development of chronic non-communicable diseases has its origins in the work pioneered by Dr. David Barker in England. Based on epidemiological observations, Barker and his colleagues identified an association between the risk of cardiovascular and metabolic diseases in the United Kingdom during the 1980s and the developmental conditions in the same areas studied at the beginning of the 20th century [22,26].

This hypothesis, originally termed "fetal programming," is now known as "developmental origins of health and disease," due to the growing certainty that the effect on an individual's health is present from before conception through the first years of life [27].

Furthermore, current evidence shows that not only does low birth weight predispose individuals to a higher risk of developing chronic diseases in adulthood, but so does excessive fetal growth (macrosomia), as occurs in the case of children born to obese or diabetic mothers [28]. Thus, the prepregnancy obesity and excessive weight gain during pregnancy are thought to be involved in the so-called trans-generational vicious cycle of obesity [27,28].

According to Barker's theory, fetal adaptations cause permanent changes in the body's structure and physiology, which ultimately lead to the development of diseases in adulthood; therefore, the authors believe that creating the right conditions for a healthy pregnancy is an essential starting point for the trans-generational prevention of chronic diseases.

Furthermore, the authors believe that promoting healthy lifestyles among pregnant women—including proper nutrition, stress management, physical activity, and avoiding toxic habits and environmental pollutants—will have a positive influence on the epigenetic mechanisms that determine the onset of chronic diseases, making prenatal prevention an urgent necessity.

4 Conclusion

The prevention of chronic non-communicable diseases is a health priority, with epigenetics offering a novel preventive approach in 21st-century medicine. Maternal conditions during pregnancy—such as malnutrition, stress, toxic habits, and obesity—cause adverse epigenetic changes that increase the risk of disease during the postnatal stage of life. Epigenetic alterations are potentially reversible; therefore, interventions during the prenatal period could modify adverse epigenetic profiles, helping to prevent chronic diseases in susceptible populations from such an early stage.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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