Special Article: Dietetics

Nutritional Epigenetics and Its Relevance in the Prevention of Obesity and Derived Non-Communicable Chronic Diseases

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Received: February 15, 2024 **Accepted:** March 29, 2024 **Published:** April 05, 2024

Introduction

The prevalence of non-communicable chronic diseases such as obesity, diabetes, Cardiovascular Diseases (CVD), neurological disorders, and some cancers is increasing at a rate that cannot be solely explained by genetic factors and is responsible for around 34 million deaths per year. It is deduced that the most likely driver of this significant increase is environmental factors and lifestyles. Considering the global obesity rate, it is logical to consider that our genes are programmed to store as much excess energy as possible, in the form of fat. However, due to the global improvement in living standards, along with easy ac-

International Journal of Nutritional Sciences Volume 9, Issue 1 (2024) www.austinpublishinggroup.com Cristina A © All rights are reserved

Summary

Introduction: The prevalence of obesity and other non-communicable chronic diseases is increasing at a rate that cannot be explained by genetic factors alone, leading to the conclusion that environmental factors are the most likely driver. Epigenetics is one of the mechanisms that link environmental factors with altered genetic activity and thus a connection between the rapid change in dietary habits and the observed obesity phenotypes. This discipline studies the changes in gene expression not determined by the DNA sequence per se, but by chemical modifications that occur on the DNA, such as DNA methylation.

Objective: To identify the importance of epigenetics in the study and treatment of obesity and non-communicable chronic diseases to provide personalized intervention.

Method: A review of scientific articles was conducted using the databases of Scielo, Medline Plus, PubMed, and Google Scholar, selecting articles in Spanish and English that had free access to the full text in PDF from the last 5 years.

Main Results: Recent studies have shown that different dietary patterns, nutrients, and food components have been linked to epigenetic processes that can contribute to increased susceptibility to the development of obesity and other metabolic disorders. Poor nutrition during gestation can lead to metabolic dysregulation later in life, which has been associated with cardiovascular diseases, obesity, or hyperglycemia; as well as other dietary patterns during adulthood, are capable of inducing hypermethylation in organs leading to various pathologies.

Conclusions: Epigenetics is a recent discipline, but its study can allow nutrition professionals to design personalized dietary intervention strategies that reduce the risk of disease in individuals with a higher predisposition to them.

Keywords: Epigenetics; DNA methylation; Obesity; Non-communicable chronic diseases

cess and abundance of food, it is quite clear the challenge that our bodies must go through to adapt to the new environment [13,18,21]. Epigenetics studies the changes in gene expression that are not determined by the DNA sequence itself, thus epigenetic mechanisms are mitotic and/or meiotic hereditary modulations of genetic function; DNA cannot determine the biological functionality of a phenotype, and it is environmental factors such as nutrition, inflammation, and stress that modulate the phenotype. Epigenetic mechanisms are an important source of interindividual variability as they contribute to cel-

Citation: Milena S, Cristina A, Alberto B. Nutritional Epigenetics and Its Relevance in the Prevention of Obesity and Derived Non-Communicable Chronic Diseases. Int J Nutr Sci. 2024; 9(1): 1086.

lular plasticity throughout life, which can increase the risk of chronic diseases. Epigenetic modifications are typically divided into three categories: DNA methylation, non-coding RNAs, and histone modifications [3,6,7,11,16].

Method

A review of 60 scientific articles on nutritional epigenetics published in the last 5 years was conducted, from which 20 articles related to nutritional epigenetics and its relevance in obesity prevention were selected.

Development

In recent years, various relationships have been identified between different dietary patterns, nutrients, and food components, and epigenetic processes. These links can potentially increase susceptibility to the development of obesity and other metabolic disorders. The epigenetic system's sensitivity to nutritional factors is most pronounced during developmental transition phases, as epigenetic marks undergo critical modifications during this period. Thus, inappropriate dietary practices and nutrient deficiencies during pregnancy and lactation can have long-term repercussions on offspring health. Poor nutrition during early and mid-gestation can result in metabolic dysregulation in later life stages, associated with cardiovascular diseases, obesity, or hyperglycemia [23,24].

Protein Intake

The protein composition of the father's diet influences the metabolism of the offspring. In mouse studies, it is observed that when fathers are fed a low-protein diet, the offspring show a greater propensity for glucose intolerance, metabolic and cardiovascular dysfunctions, as well as skeletal development issues and alterations in bone mineral deposition.

Moreover, male pups from fathers on this diet tend to be heavier, while females are lighter compared to control pups. Alterations in the offspring's vascular function and an increased risk of breast cancer in female offspring are also reported. An alteration in the gene expression of the offspring, especially in genes related to cholesterol and lipid synthesis pathways, is detected. The father's low-protein diet negatively affects the gene expression of several AMPK pathways in blastocysts [5].

Maternal protein malnutrition has also been linked to the development of metabolic diseases in adult offspring, including obesity, insulin resistance, and diabetes. In a mouse model, male offspring of mothers exposed to a low-protein diet during gestation and lactation showed a reduced body weight and a loss of methyl groups in the promoter of the leptin gene in adipose cells, which coincided with decreased mRNA levels of leptin.

Since leptin regulates appetite and body weight, the alterations caused by the maternal diet suggest that these changes would not prepare the individual for an environment with excess food, thus increasing the risk of obesity.

Another study, using a porcine model, investigated the epigenetic changes associated with the low-protein maternal diet; in this case, mothers were fed a low-protein diet one month before fertilization and during pregnancy; the epigenetic regulation of Glucose-6-Phosphatase (G6PC), which plays a crucial role in glucose regulation and the risk of hyperglycemia, was examined, revealing that the G6PC promoter was hypomethylated in male offspring, along with an increase in H3K4 methylation at the G6PC promoter in the liver, indicating that the low-protein diet during pregnancy activated the G6PC gene in males, which was associated with the development of hyperglycemia and diabetes in adulthood [19].

Fat Intake

High-fat diets during early life have been shown to induce epigenetic changes at the whole-genome level and at specific gene loci (e.g., genes associated with obesity, insulin resistance, and type 2 diabetes), and can modify the expression of certain miRNAs related to obesity and lipid metabolism [1]. Several animal studies have shown that offspring of parents consuming high-fat diets exhibit indicators of obesity, heart disease, and type 2 diabetes. These effects originate from epigenetic changes in the sperm of the parents. If unhealthy intake persists across several generations, overweight and sperm-linked epigenetic changes accumulate [26]. Research has shown that the lack of polyunsaturated omega-3 fatty acids (n-3 PUFA) has a significant impact on diet-induced obesity, as it reduces energy expenditure. In experiments with mice, perinatal exposure to a diet high in n-6 fatty acids for four generations (linoleic acid: alpha-linolenic acid ratio of approximately 28:1) causes a gradual increase in fat mass in the offspring, without an increase in food intake. This phenomenon mimics the condition of developing obesity in humans [2]. Another study showed that rodent parents fed a high-fat diet could transmit pancreatic β-cell dysfunction and glucose intolerance to their female offspring and an altered insulin response in male offspring [5].

Recent research with pregnant mice has explored the effects of maternal high-fat diets on epigenetic alterations in the adipose tissue and liver of the offspring. One study showed that offspring of mothers on this type of diet exhibited increased acetylation and decreased methylation of histone H3K9 at the adiponectin promoter and increased methylation of histone H4K20 at the leptin gene, resulting in decreased adiponectin and increased mRNA expression of leptin in adipose tissue, epigenetic modifications associated with the presence of hypertension, insulin resistance, and hyperlipidemia in the offspring. As for the transgenerational impact of obesity, the accumulation of epigenetic modifications contributes to increased lipogenesis across multiple generations and the development of obesity. These effects of maternal high-fat feeding are reversed in the offspring only after feeding a standard diet for three consecutive generations [19,22].

Excessive Sugar Intake

The consumption of fructose has alarmingly increased in recent years due to its addition to processed foods. Several studies on the high-fructose diet of parents have shown that it induces an increase in hepatic triacylglycerol concentration, hypercholesterolemia, hypertriglyceridemia, and an alteration in glucose metabolism with hyperinsulinemia in both mothers and fathers. In the case of their children, a decrease in adiponectin concentration, an increase in leptin level, as well as increases in blood pressure, uricemia, and genital fat are observed when the mother or father, or both, are exposed to a high-fructose diet. The situation worsens when both parents follow a highfructose diet, manifesting more severe effects on the offspring's hepatic metabolism, accompanied by an increase in inflammatory markers. Other studies have suggested that a high-sugar diet by the father could be linked to a disturbance in the energy homeostasis of the offspring [19].

Intake of Methyl Donors

Carbon metabolism depends on the methyl donors present in the diet, and the availability of folate, methionine, betaine, or choline during this phase can influence DNA methylation. Methylation reactions are imparted during embryonic and fetal development; and it has been shown that the levels of dietary methyl donors in the mother's diet affect the configuration of the DNA methylation profile in the fetus, having adverse metabolic effects during infancy and childhood. For example, maternal folate deficiency has been associated with higher levels of inflammatory mediators (interleukins, TNF- α , and monocyte chemoattractant protein-1), as well as with an increased risk of cardiovascular diseases, obesity, and insulin resistance in the offspring [19,23].

In vivo studies in rats involving a folic acid supplement administered to mothers during pregnancy revealed that nutritional imbalance generated widespread DNA hypermethylation in the cortex of adult offspring. Since the cortex is associated with cognitive functions, decision-making, and memory, modifications in DNA methylation in this brain region could trigger brain disorders such as Alzheimer's disease and bipolar disorder. Another study, the administration of folic acid supplements (5 mg/day) during pregnancy in rats resulted in a significant decrease in DNA methylation in the mammary glands of adult offspring, indicating that elevated levels of folate during pregnancy and lactation are associated with an increased risk of breast cancer in the offspring. A study with a mouse embryonic stem cell culture model aimed to examine the impacts of limited folate supplementation (0.5 mg/L of folate) in the early stages of development revealed hypomethylation in the promoter domain of the long interspersed nuclear element-1 (LINE-1) and an increase in LINE-1 expression, phenomena associated with defects in neural tube development [19,24]. In another study, rodents were fed a diet lacking methyl donors for a month before conception, gestation, and lactation, leading to myocardial hypertrophy, with cardiomyocyte enlargement, alteration of mitochondrial alignment, decreased respiratory activity of complexes 1 and 11, and increased concentrations of triglycerides in weaning offspring, alterations caused by imbalanced methylation and acylation of PGC1- $\!\alpha$ and SIRT1 genes (mitochondrial metabolism regulators) [21].

Emerging evidence suggests that folate intake by the father can also influence health and disease onset in his offspring. A recent study highlighted that offspring of rats with paternal folate deficiency are more prone to develop anxious and depressive traits; and a low intake of folate by the father during the periconceptional period alters the sperm epigenome, linking to adverse pregnancy outcomes, such as a reduction in the pregnancy rate after implantation and abnormal placentas. Other studies reported that paternal folate deficiency affects placental folate transport, DNA methylation, mutations, and the level of expression of Igf-2 in the fetal brain in rodents. In humans, folate status affects reproductive health, especially the duration of gestation when intake is 4 mg/day [5].

Parental Non-Communicable Chronic Diseases (NCDs)

Studies have shown that children of parents with NCDs have a higher risk of developing these diseases in their adult life. This is due to a combination of genetic, epigenetic, and environmental factors. For example, obesity in parents has been associated with an increased risk of obesity and metabolic disorders in their children [12]. NCDs in parents not only increase the risk of chronic diseases in their children but can also negatively affect child development. Studies have found correlations between gestational diabetes in mothers and the development of type 2 diabetes in the offspring [23].

The prevention and management of parental NCDs require a comprehensive approach that includes lifestyle changes, health education, and regular medical follow-up. Promoting healthy diets and regular physical activity are fundamental to reducing the risk of NCDs in families [20].

Transgenerational Epigenetics

Epigenetics, as mentioned, is influenced by environmental stimuli such as diet, nutrition, chemicals, and stress, consequently altering gene expression and generating changes in the phenotype. For several years, it was considered that epigenetic markers from previous generations were completely eliminated or "reset" during gametogenesis to convert the cells into a "naive" state, however, recent evidence suggests that the removal of epigenetic markers is not complete in certain loci during critical stages of embryonic development, causing permanent changes in the epigenetic genome of germ cells, and these markers can be inherited transgenerationally to the offspring through mitosis and meiosis [10,15,25].

The first studies that evidenced a connection between the prenatal environment and modifications in the epigenetic profiles of the offspring were carried out in the offspring of mothers pregnant during the "Dutch Hunger Winter" (World War II). Initially, researchers identified an increased risk of obesity in young men whose mothers experienced pregnancy during the famine, and subsequent studies demonstrated alterations in DNA methylation that persisted up to six decades later, highlighting the preconceptional period and early pregnancy as critical moments for exposure to famine. These changes in blood methylation were associated with genes linked to growth, increasing the risk of metabolic diseases in both male and female offspring [10,14,25].

Another of the earliest examples of transgenerational inheritance occurred in 19th century Scandinavia, in the rural town of Överkalix, Sweden, where residents' lives depended largely on the success of crops for food. Fluctuations in crops, with periods of famine followed by abundance, provided valuable epidemiological data. This context marked some of the earliest examples of epigenetic inheritance, especially transgenerational, establishing patterns of non-genetic inheritance. Studies in Överkalix revealed that the nutrition of boys aged 9 to 12 years, during times of food surpluses, was associated with a decrease in the lifespan of their grandchildren. The grandchildren of paternal grandparents exposed to food surpluses presented higher rates of mortality from metabolic diseases (diabetes) and cardiovascular diseases. Although a father-to-son response (intergenerational inheritance) was observed, the most significant influence on longevity was the nutrition of the paternal grandfather [9,26].

Prevention of Non-Communicable Chronic Diseases Using Epigenetics

The prevention of Non-Communicable Chronic Diseases (NCDs), such as cardiovascular diseases, diabetes, cancer, and neurodegenerative disorders, has become an area of growing interest in modern medicine. Epigenetics, which studies how environmental influences can alter gene expression without modifying the DNA itself, offers a promising approach to the prevention of these diseases.

Epigenetics plays a crucial role in the regulation of genes related to NCDs. Factors such as diet, exercise, stress, and exposure to environmental toxins can cause epigenetic modifications that affect the expression of genes associated with the development of these diseases. For example, DNA methylation and histone modifications can activate or repress genes involved in metabolic processes and the inflammatory response.

According to GARCÍA-CALZÓN et al., [8], Diet and Nutrition is a significant epigenetic factor. Foods rich in folate, vitamin B12, and other nutrients can influence DNA methylation patterns. The Mediterranean diet, rich in fruits, vegetables, and omega-3 fatty acids, has been shown to have protective effects against cardiovascular and neurodegenerative diseases through epigenetic mechanisms.

Conclusions

In conclusion, nutritional epigenetics provides a deeper understanding of the interaction between diet and genes, offering new strategies for the prevention and treatment of obesity and NCDs. Research in nutritional epigenetics has demonstrated that certain dietary patterns and specific nutrients can activate or silence genes related to metabolism, inflammation, and cell proliferation. For example, DNA methylation, one of the most studied epigenetic modifications, can be influenced by levels of folate, vitamin B12, methionine, and other methyl donors present in the diet. These epigenetic changes can have lasting effects and, in some cases, be heritable, underscoring the importance of nutrition not only for individual health but also for future generations.

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