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Maternal Diet and Epigenetic Modifications at the Start of Life: Repercussions on the Development of Obesity

Matheus Santos de Sousa Fernandes[1]*, Camila Tenório Calazans[2], Gabriela Carvalho Jurema Santos[3]

1 Neuropsyquiatry and Behavior Science Postgraduate Program, Federal University of Pernambuco - UFPE, Recife, PE, Brazil

2 Physical Education Postgraduate Program, Universidade of Pernambuco - UFPE, Recife, PE, Brazil

3 Nutrition Postgraduate Program, Universidade Federal de Pernambuco - UFPE, Recife, PE, Brazil

***Corresponding author:**
Matheus Santos de Sousa Fernandes

matheus.sfernandes@ufpe.br

Neuropsyquiatry and Behavior Science Postgraduate Program, Federal University of Pernambuco - UFPE, Recife, PE, Brazil

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Abstract

Objectives: Thus, the objective of the study was to evaluate the repercussions of the maternal diet and epigenetic changes in early life and its repercussions on the development of obesity.

Methods: For this, a narrative review of a descriptive character was developed using the following descriptors: “Maternal diet”, “epigenetics” and “obesity”. The articles published between the years 2015 to 2020 were selected from the databases: Scientific Electronic Library Online (Scielo), National Library of Medicine (PubMed) and Virtual Health Library of the Ministry of Health (VHL).

Results: It was observed that the intake of maternal high-fat diets promotes the appearance of epigenetic changes that favor the appearance of diseases, such as diabetes mellitus, in addition to increasing food intake, and consequently increasing body weight.

Conclusions: Thus, the importance of healthy eating is observed during critical periods of development to prevent the onset of cardiometabolic diseases.

Keywords: Nutrigenomics; High-fat diet; Chronic non-communicable diseases; Genetic; Epigenomics

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Introduction

Obesity is characterized by an increase in body fat and it is a public health problem that occurs on a large scale. Worldwide, between 1980 and 2013, there was an increase in overweight from 28.8% to 36.9% in men and 29.8% and 38% among women [1]. With the increase in obesity, there is also an increasing advance in the appearance of cardiometabolic diseases [2]. In a recent study, it was observed that 33.3% of individuals with grade III diabetes obesity had diabetes, 66.7% had hypertension and 40.3% had dyslipidemia [3]. In other study, abdominal obesity was a risk factor for the development of hypertriglyceridemia and a reduction in LDL cholesterol [4].

Among the main etiological factors of obesity, the consequences of the nutritional transition stand out, such as an increase in sedentary behavior in response to technological advances and changes in food consumption, based on palatable foods rich in sugar, fat and calories [5]. During the perinatal phase, which includes pregnancy and lactation, the consumption of hyper caloric/hyper lipidic foods has a negative impact on the health of the offspring [6]. In an experimental study, it was observed that the consumption of a high-fat diet by rats during pregnancy and lactation caused an increase in visceral and subcutaneous fat in the puppies. In addition, there was an increase in insulin, leptin and adiponectin levels [7].

Nutrients are also responsible for regulating gene expression by several mechanisms, such as changes in DNA transcription, DNA methylation and post-translational modifications of histones [8]. When these changes occur early in life, metabolic programming is characterized [9]. Metabolic programming occurs when trans generational effects cause changes in organ growth and differentiation and epigenetic changes causing obesity and cardiometabolic diseases [9]. In an experimental study, consumption of a cafeteria diet during pregnancy and lactation caused greater expression of the PI3K subunit P110ß (PIK3CB) (47%) and AKT2 (23%) mRNA in visceral adipose tissue, which plays an important role in insulin resistance [10].

Since there is an increase in cases of obesity associated with

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the consumption of hyper caloric/hyper lipidic foods, especially during critical periods of development, such as growth and development, the aim of the study was to evaluate the repercussions of the maternal diet and epigenetic changes in early life and its repercussions on the development of obesity. For this, a narrative review of a descriptive character was developed using the following descriptors: "Maternal diet", "epigenetics" and "obesity". The articles published between the years 2015 to 2020 were selected from the databases: Scientific Electronic Library Online (SciELO), National Library of Medicine (PubMed) and Virtual Health Library of the Ministry of Health (BVS).

Epigenetics

Mechanism of epigenetic regulation

The term epigenetics is the branch of biology that studies the interaction between the genotype and the phenotype [11]. This term was introduced in the literature by Conrad Waddington in 1940 and can be defined by changes that occur in gene expression that do not modify the sequence of the genetic code [12]. These changes can occur at any stage of life and can continue for future generations. However, these changes are dynamic and modifiable depending on the lifestyle, so they can be reversed [13]. Epigenetic modifications involve the addition or removal of methyl or acetyl groups through enzymes such as DNA methyltransferases, histone acetyltransferases, histone deacetylases, and histones methyltransferases [14]. DNA methylation can be defined as adding or subtracting a methyl group to a cytosine nucleotide in a DNA sequence [15]. Methylation is controlled by the enzymes DNA methyltransferases and occur in the CpG islands, which are promoter regions present in the genome where they present cytosine sequences from guanine [15]. The hypermethylation of the CpG islands promotes the transcriptional silencing of the gene, resulting in reduced gene expression [15].

In histones, protein components of chromatin that extend outside of DNA, methylation, acetylation, phosphorylation and ubiquitination can occur [15]. However, the most studied alteration is acetylation. Histone acetylation occurs in the lysine residue and is associated with transcriptional activation and is performed by the enzyme histone acetyltransferases [15]. On the other hand, deacetylation is related to transcription repression, resulting in reduced gene expression, and occurs through histone deacetylases [15].

Epigenetic changes and development of cardiometabolic diseases associated with obesity in puppies through the consumption of a maternal high-fat diet

Hypermethylation of DNA is also associated with the development of cardiometabolic diseases [16,17]. Animal studies and diet administration have been used in studies with changes in the proportion of lipids during pregnancy and lactation. In the study by Khurana et al the species Psammomys obese was used in the animal model and a low-fat diet (10% kcal/fat) was administered. It was observed that 1447 genomic regions were methylated in the hypothalamus in the offspring that came from mothers who were fed a low-fat diet [18]. Among the methylated genes, ABCC8 stands out, this gene is responsible for providing instructions for the production of sulfonylurea receptor 1 (SUR1) protein [16]. The SUR1 protein is an ATP-sensitive potassium channel subunit found in the cell membranes of pancreatic beta cells [16]. Thus, the methylation of the ABCC8 gene reduces gene expression, causing a reduction in the control of insulin secretion, resulting in the appearance of Diabetes Mellitus [16].

Unlike the previous study, Schellong et al used the Wistar model and a high-fat diet (34% kcal/fat). The consumption of a high-fat diet by mothers who consumed a high-fat diet during pregnancy and lactation caused hypermethylation of IRNF1 [17]. This gene is responsible for controlling the expression of INSR which is responsible for controlling the insulin receptor in several types of cells [19]. Thus, when IRNF1 hypermethylation occurs, there is a reduction in the activity of insulin receptors, favoring the appearance of hyperinsulinemia and insulin resistance [17]. Still on the epigenetic changes in DNA, Wankhade et al investigated quantitative changes in the methylation of liver DNA in puppies in which mothers were fed a high-fat diet (45% kcal/fat) for 12 weeks. It was observed that offspring of mothers who consumed a high-fat diet showed altered methylation patterns of genes that play important roles in liver fibrosis and lipid accumulation, including Ppargc1β (receptor-activated peroxisome proliferator γ co-activator 1-beta), Fgf21 (Factor of growth of fibroblasts 21), Ephb2 (Ephrin type B receptor 2) and VWF (von Willebrand factor) [20]. Thus, depending on the gene, hypermethylation or hypomethylation of DNA due to the consumption of high-fat diets are responsible for causing the development of metabolic diseases that are generally associated with obesity, such as diabetes mellitus and liver diseases. Just as epigenetic changes in DNA are capable of promoting the development of metabolic disorders, histone hyperacetylation or hypoacetylation is also capable of causing these problems [21]. In the study by Masuyana et al, the reduction in histone acetylation in the H3K9 region of puppies in which their mothers consumed a high-fat diet (62% kcal/fat) for four weeks caused less expression of the hormone adiponectin, responsible for regulating and blood glucose and fatty acid catabolism. In contrast, Panchenko et al observed that the consumption of a diet with 59.9% fat in its composition during pregnancy and lactation caused an increase in histone acetylation, increasing the expression of Kat3a, favoring the development of diabetes mellitus [22].

Epigenetic changes and control of food intake through the consumption of maternal high-fat diet

The hypermethylation of DNA in specific regions of CpG zones in puppies caused by the consumption of maternal hyperlipidemic diet (34% kcal/fat) was responsible for the reduction in leptin-mediated activation of POMC (pre-opiomelanocortin). On the other hand, the hypomethylation of promoter regions responsible for the activation of AgRP (protein related to the agouti gene) was observed [23]. The hormone leptin, responsible for signaling to the hypothalamus of adipose reserves, through signaling via neurons AgRP and POMC, regulates body weight and food intake. POMC is responsible for reducing food intake, while AgRP

causes the opposite effect [24]. Similarly, the hypermethylation of histones in the H4K20 region provided a reduction in leptin expression, favoring an increase in food consumption [21].

In another study, consumption of a high-fat diet (60% kcal/fat) by Wistar rats caused hypomethylation and hyperacetylation of histones in the H2K27 region of puppies [25]. This epigenetic alteration alters the levels of Mc4r (melanocortin 4), which when inactivated favors the development of obesity, increased food intake, hyperinsulinemia, and, consequently, hyperglycemia [26]. Thus, epigenetic changes caused by maternal consumption of a high-fat diet are responsible for causing changes in the control of food intake, which directly favors overweight and obesity.

Epigenetic changes and body weight control through the consumption of maternal high fat diet

In addition, to controlling through food consumption, body weight is mediated by intrinsic factors, such as neural and biochemicals, which interact with the environment and determine the phenotype. The hypomethylation of DNA in the ZFP423 gene (promoter of the digital zinc protein 423), which is responsible for the control of adipogenesis, increased its expression, reducing the expansion capacity of adipose tissue and resulting in metabolic dysfunction [27,28]. This epigenetic change was mediated by the maternal consumption of a 45% lipid diet that was offered to rats of the C57BL / 6 line, four weeks before mating [28].

On the other hand, the hypermethylation of DNA in the NR4a1 gene (Subfamily of nuclear receptors 4 Member of group 1) reduced its expression. Thus, causing the reduction of AMPk activation and control of homeostasis [29]. Thus, maternal obesity demonstrates long-term effects on the adipogenic capacity of progenitor cells in the offspring adipose tissue, demonstrating a programming effect on development.

The increase in histone acetylation due to the ingestion of maternal high fat diet is also related to the increase in lipogenesis and gluconeogenesis. This was demonstrated in the study by Pancheko et al. In this study, the hyperacetylation of histones in puppies of rats that consumed a 59.9% fat diet, caused an increase in HDAC2 in the liver, which increased the expression of Kat3b (lysine acetyltransferases), which has an important role on metabolism [22]. Similarly, H3K4ME3 histone hyperacetylation was associated with metabolic stress, cardiac dysfunction, diabetes mellitus, and increased body fat [30].

Conclusions

With the increasing advance of obesity, identifying possible etiological factors can assist in the design of prevention, control, and treatment of its comorbidities. Thus, in the present review, it was observed that the maternal diet has an important role in cardiometabolic development due to the increase in food consumption and, consequently, an increase in body weight through an epigenetic mechanism. Thus, the adoption of healthy eating habits during critical periods of development, such as pregnancy and lactation, can be a strategy to prevent the onset of cardiometabolic diseases in the offspring.

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Disclosure statement

The authors report no conflict of interest.

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