International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn22104

Programming of obesity and pediatric metabolic syndromes: a review in light of epigenetic modulation

Liana Carla Albuquerque Peres Martinho[1,2]*

[1] State Department of Health - Center for Comprehensive Child Care (Secretaria Estadual de Saúde – Centro de Atenção Integral à Criança (CAIC), Dr Afrânio Soares, Manaus, Amazônia, Brazil.
[2] Martinho Clinic, Manaus, Amazônia, Brazil.

Corresponding Author: Dr. Liana Carla Albuquerque Peres Martinho, State Department of Health - Center for Comprehensive Child Care (CAIC), and Martinho Clinic, Manaus, Amazônia, Brazil.
E-mail address: lianacapm@hotmail.com
DOI: https://doi.org/10.54448/ijn22104
Received: 09-14-2021; Revised: 11-21-2021; Accepted: 12-22-2021; Published: 01-04-2022; IJN-id: e22104

Abstract

Obesity is a multifactorial health problem characterized by the excessive accumulation of fat in the body and affects approximately 338 million children and adolescents worldwide. For this reason, this study consisted of a literature review to investigate how the causes and treatments of pediatric obesity are being addressed in light of epigenetic modulation as a factor in metabolic programming. For this, preferentially original articles published in English between the years 2017 to 2021 in the PubMed and Scholar Google databases were searched using the epigenetics descriptors; epigenetic modulation; child obesity; metabolic syndrome, combined with each other. A total of 54,000 articles were returned to searches in PubMed and 16,107,000 in Scholar Google. Fewer than 500 studies jointly addressed epigenetics and aspects of obesity or metabolic syndromes in childhood. Only 14 works matched the search criteria. The most discussed epigenetic mechanism in the literature is DNA methylation, whose rates observed mainly in CpG islands of promoter regions in several genes contribute to the prevention and early diagnosis of obesity and other pediatric comorbidities even before birth, based on the correlation between the epigenetic marks, maternal and paternal health and anthropometric indices. Although experimental studies on infant metabolic programming are scarce, existing knowledge suggests that environmental, nutritional, and energy expenditure changes are capable of modulating the epigenome and reversing marks that induce susceptibility to metabolic comorbidities.

Keywords: DNA methylation. miRNAs. Epigenetic programming. Metabolic comorbidities. Adiposity.

Introduction

Obesity is considered, according to the World Health Organization, as a multifactorial health problem, characterized by the abnormal or excessive accumulation of fat in the body, which involves psychosocial, socioeconomic, biological, environmental, cultural, and political aspects. It is widely debated as an epidemiological issue as it affects approximately 672 million adults and 338 million children and adolescents worldwide **[1]**.

In children and adolescents, obesity is being driven by the increased consumption of processed foods and the decrease in natural foods. Individuals in this age group are more vulnerable to the influence of advertising and advertising of foods such as fast food, among other foods high in fat and low in nutrients. Furthermore, with technological advances, children are being conditioned to sedentary routines with little or no physical activity. The combination of these habits contributes to the increasing increase in obesity at this stage of life **[2]**.

Overweight or obese children and adolescents have increasingly presented early stages of chronic diseases such as metabolic and cardiovascular disorders **[3]**. They are also much more likely to become obese as adults compared to non-obese children, which can contribute to greater susceptibility to comorbidities in adulthood and reduced life expectancy **[3]**. By convention, a person is considered obese when their

BMI is BMI>30 kg/m2 (Body Mass Index) is one of the commonly used tools to measure obesity (BMI =weight in kg/height in m2) **[1]**. However, this index should be used as an approximate measure, since it does not pay attention to the distribution of adipose tissue **[4]**.

Understanding the distribution of adipose tissue is important as it is directly associated with some aspects of the body's functioning, for example, visceral adipose tissue is related to the high incidence of free fatty acids in the bloodstream, and the release of adipokines that act on the modulation of metabolic processes such as perception of hunger or satiety **[4]**. However, some of these adipokines are pro-inflammatory associated with metabolic complications (e.g. insulin resistance; type 2 diabetes; hepatic steatosis; atherosclerosis; hypertension) and cardiovascular problems **[4]**.

The interaction of factors such as bad routine habits (inadequate diet, sedentary lifestyle) and genetic propensity is commonly listed as a causal factor for obesity. Currently, there is the knowledge that the environment and the behavior patterns of individuals can influence gene expression, consequently narrowing the relationship of habits with genetic tendencies and obesity **[5]**. The mechanisms that act on gene expression involve factors associated with histone modifications (decreased affinity of histones for DNA allowing gene expression), the action of non-coding RNAs, and direct DNA methylation (prevents the association of transcription factor with the promoter region inhibiting gene expression). These mechanisms make up an important aspect of organisms called epigenetics, which broadly can be defined as the dynamic regulation of gene expression by mechanisms that do not depend on the alteration of DNA nucleotide sequences and provide a heritable majority for daughter cells through mitosis or meiosis **[6]**.

Since mechanisms of functioning of organisms, such as the physiological processes of obesity, for example, depend on signals that order their activity and these orders of functioning can be relaxed by epigenetic factors, which in turn are susceptible to interference from the environment and the behavior **[6]**, how can epigenetic modulations be used in the treatment and prevention of childhood obesity? To answer this question, this study consisted of a literature review carried out to identify how the causes and treatments of childhood obesity are being addressed in the light of epigenetic modulation as a factor in metabolic programming.

Methods

Articles published in English were searched, concerning the theme of the objective of this study in a time window corresponding to the years 2017 to 2021. The databases used were PubMed and Scholar Google. The survey was carried out between March and May 2021, using the descriptors: epigenetics; epigenetics modulation; child obesity; metabolic syndrome, combined. Only articles referring to clinical trials or controlled and randomized tests (original studies) were selected for the preparation of this study. Analytical literature reviews were used when pertinent. Some of the references of the articles found were also explored. Finally, the results were discussed in terms of the epigenetic aspects of metabolism associated with obesity throughout the stages of human development.

Results and discussion

This study consisted of a literary survey on how aspects of epigenetic programming are associated with metabolic syndromes and childhood obesity and how the available studies contribute to these conditions being alleviated. A total of 54 thousand (fifty-four thousand) articles were returned to searches in PubMed and 16,107 thousand (sixteen thousand one hundred and seven) in Scholar Google. However, less than 500 (five hundred) studies jointly addressed epigenetics and aspects of obesity or metabolic disorders in childhood, and among the articles that corresponded to the scope of the proposed theme, 13 (thirteen) were original works, while one was an analytical review of the literature.

As a result of the search, it was found that various stages of human development can be influenced by the environment on the epigenetic mechanisms of metabolism, starting with the health and nutritional habits of the parents before the fetus is conceived, the nutritional quality of the mother in the pre-natal and postnatal, lifestyle habits, nutritional aspects in the first years of life until adolescence. Regarding the main epigenetic mechanisms involved in metabolic programming, DNA methylation is the most widely studied. The methylations of promoters or regions close to some genes associated with the expression of metabolic phenotypes can be used as epigenetic markers of obesity and diabetes in childhood or the susceptibility of its development throughout life.

The health and life habits of parents impact the epigenetic programming of their children's metabolism

Some aspects of life history, for example, an individual's epigenetic mechanisms can be largely determined even before conception. This is

demonstrated in studies in which different expression levels were observed in the circulating micro RNAs miR-155, miR-181 a, and miR-221 between infants of women with normal pre-gestational weight and women with pre-gestational obesity **[7]**. The researchers argue that changes in microRNA expression may interfere with fetal epigenetic programming of metabolic disorders related to weight gain, diabetes, and cardiovascular problems, particularly in the offspring of obese women.

Pre-gestational obesity as a major factor in epigenetic programming is widely debated in the literature, as maternal overweight is often correlated, especially with variations in DNA methylation rates across the genome of the offspring **[8,9]**. Studies by Martin et al. **[9]** demonstrate that most of the loci in the genome that have high rates of differentiation due to DNA methylation correspond to regions that act on structures responsible for protein processing and lipid transport, which can result in differential variations in blood price and of adiposity rates among individuals of different sexes throughout life. Furthermore, the increase in CD4 T cells, B cells, and granulocytes in females also demonstrate an association with DNA methylation influenced by maternal health.

Also, Noor et al. **[10]** state that paternal health and physical status is a factor that greatly contributes to the epigenetic programming of the individual's physiology before conception. In a cohort study of 429 parent-infant triads, these researchers found that birth weight and genome-wide DNA methylation patterns in children under the age of the first decade of life are strongly correlated with mass index. paternal body in periods close to the moment of conception, and that, in addition to the propensity to obesity, this factor can result in cardiometabolic and even cognitive complications throughout the children's lives. These results also suggest that inherited epigenetic marks can be quite persistent.

Other studies had already observed this portion of paternal contribution on birth weight and also included it as one of the several aspects responsible for the susceptibility to the development of diabetes mellitus throughout development **[8]**. According to Dunford and Sangster **[8]**, the influence of maternal and paternal health and life habits on epigenetic marks of offspring metabolism is even more evident when one observes that the methylation rates in regions responsible for the insulin and adiposity response are minor in children of non-obese parents or those who underwent weight-loss processes before conception.

As well as parental obesity, exposure in utero to gestational diabetes mellitus (GDM) is capable of providing changes in DNA methylation in individuals in the first years of life. Some of the changes in this epigenetic mark at various loci throughout the genome (mainly those expressing transcription factors, protein kinase, and methyltransferases), associated with GDM, may cause an increase in childhood adiposity rates and diabetes risk, since children with a history of exposure to GDM while in utero have different methylation indices in genes such as PTPRN2 and E2F6 that act on the physiology of obesity, as well as on glycemic metabolism, than children of metabolically healthy mothers **[11]**.

Metabolic programming in the first years of life can also be influenced by exposure to nutritional deficiency during pregnancy **[8]**. Children who have been through this condition at some point in their pregnancy have a considerably high birth weight, in addition to being more susceptible to insulin resistance. The researchers argue that possibly nutritional deprivation influences the activation of food compensation mechanisms, implying a high possibility of later obesity.

Epigenetic marks and metabolic programming in children and adolescents

Preschool-age children with obesity have shortened leukocyte telomeres and a negative association with body mass index. The methylated fractions in various regions of the TERT promoter (the gene responsible for the expression of telomerase reverse transcriptase) are significantly increased in obese children compared to normal-weight children. Likewise, erythrocyte lauric acid, total saturated fatty acids (SFAs), linoleic acid, and polyunsaturated fatty acids (total PUFAs) indices are higher, while docosahexaenoic acid (DHA) is decreased in obese children compared to non-obese children. The length of telomeres is responsible for changes in the SFAs and DHA indices, as well as the ratio of arachidonic acid (AA) to docosahexaenoic acid in these children **[12]**.

Although in this specific case Liu et al. **[12]** have not observed a statistical association between TERT methylation and DHA variations, the increase in rates of this epigenetic mark occurs along with weight gain. Other studies show that the variation in the DNA methylation rate along the genome of obese children is associated with deficiencies in physiological functions and structural aspects **[13]**. For example, Rzehak et al. **[14]** in studies carried out using blood tissue from preschool-age children demonstrated strong associations between specific variants of DNA methylation with anthropometric measures such as BMI, fat mass index, absolute fat mass index, free mass index fat, and absolute fat-free mass index.

This study provides strong evidence that this epigenetic marker is largely responsible for a large part of the variations in the expression of genes associated with the programming of physiological processes such as inflammation, metabolic alterations of lipids and glucose (SEND1; KLHL6; WDR51A; CYTH4-ELFN2; ZNF643; ST6GAL1; C3orf70; LOC101929268), size and body composition (CYTH4-ELFN2; CFLAR; PRDM14; CILP2) in children. The differentiation in epigenetic signatures between fat mass and fat-free mass levels demonstrates that DNA methylation in these genes varies strongly as a function of physical status, and elucidates that self-yielding DNA methylation matrices obtained from blood cells can very efficiently illustrate the existence of genes with potential action on various biological functions with roles in the regulation and programming of childhood obesity.

Evidence of the importance of epigenetic signatures for metabolism and pediatric obesity is supported by Samblas et al. **[15]** who analyzed variations in DNA methylation at 734 loci associated with the regulation of a variety of cellular processes (cell growth, cell differentiation, mitotic cycle, oncogenic transformation) and other physiological aspects such as the circadian cycle of obese children in comparison with non-obese children. Information such as these suggests that epigenetic alterations at different stages of children's lives may be related to the onset of obesity, and according to the authors, dietary factors can modify these marks since the methylation rate in the same regions is low. altered in individuals who change habits such as eating and exercising.

Variations in the patterns of epigenetic mechanisms as a function of lifestyle habits have also been addressed recently **[16]**. In this investigation, significant changes in DNA methylation were detected throughout the genome of prepubertal children after twelve months of changes in nutritional behavior and adherence to physical exercise.

Variations in the percentage of DNA methylation were significant in the genes of lipid metabolism and inflammation. According to the researchers, the entire prepubertal population participating in the study showed strong correlations between methylation of metabolism genes, anthropometric parameters, energy and food intake, and energy expenditure, clearly demonstrating that epigenetic marks can be modulated by diet and practice of activities physical. The information collected by the authors also reinforces the knowledge that the epigenetic variations of obesity and metabolic factors can occur differently between the sexes, with greater susceptibility to weight gain and inflammatory metabolic changes among women **[17]**.

Arguing the need for studies on the epigenetic mechanisms of adolescent health when compared to the number of investigations involving only children or individuals with comorbidities, He et al. **[18]** analyzed the correlation of DNA methylation with the percentile of BMI in obese adolescents without metabolic diseases. It was observed by the researchers that individual alterations in the methylation of associated genes energy homeostasis and lipid metabolism (SMI 1, CPE, and ADRB3 respectively) showed weak correlations with body mass indices when evaluated in isolation, however, this correlation becomes highly significant when changes in methylation occur together. Changes in methylation at some of these loci may also contribute to the emergence of cardiometabolic complications in adulthood.

Another gene that has a well-established relationship with adiposity in adolescents is FTO, on which studies indicate that methylation is strongly associated with BMI, waist circumference, and with the absolute fat mass and percentage of fat mass indices. In addition, methylation rates in some regions of the gene are higher in children and adolescents with obesity and insulin resistance. According to the study's developers, greater methylation in the gene's promoter region implies the inhibition of mechanisms responsible for controlling weight and keeping it at an adequate level, contributing to a greater probability of developing obesity and other associated complications at some stage of life **[18]**.

Epigenetic markers of obesity and metabolic syndrome

Epigenetics has immense potential to predict obesity predispositions and metabolic disorders throughout development, mainly through methylation in specific genes related to these physiological characters **[13,19,20]**. Studies imply that differentiation in CpG island methylation rates in various gene sets such as IRS1 is correlated with obesity and comorbidities associated with regulation of cancer suppression and adipocyte differentiation **[19]**. Variations in methylation rates in these genes are variable depending on the severity of obesity, age, and gender, which makes it promising to be used as a signaling agent for various aspects of health and susceptibility to comorbidities associated with levels of obesity. The ability to identify methylation alterations in specific genes allows directing the focus to particular elements of the epigenome and their involvement in the mechanisms of metabolic activities as well as their therapeutic potential for childhood obesity.

Experimental investigations demonstrate

considerable contributions from the environment in the early stages of life to the possibility of obesity through epigenetic processes. It was observed that DNA methylation of perinatal tissues (such as umbilical cord and placenta) at important loci for the function of ANRIL (a long non-coding RNA) can be used as an efficient marker of posterior adiposity, thus providing extremely efficient support for the evaluation of epigenetic processes in mediating long-term consequences of the environment for human health in early life **[20]**.

The authors also noted that CpG methylation increased binding to an estrogen response element within the ANRIL promoter, which is possibly associated with later obesity susceptibility in females. Furthermore, an association between ANRIL methylation and adiposity was also observed in three additional populations at different stages of development; in neonatal birth tissues, in peripheral blood of adolescents, and adipose tissue of adults. The differentiated rates of ANRIL methylation demonstrate that this RNA can be an important marker for the subsequent nutritional and metabolic health of the offspring, indicating a different risk of obesity between sexes and age groups.

Studies carried out from adipose tissue strongly suggest that the CPA3 gene is a potential marker of inflammation with the ability to associate obesity with dysfunctions of glycemic metabolism in children **[13]**. The research developers came to this conclusion after observing that hypomethylated regions in its transcription group, GATA1 are highly associated with increased expression in the body of obese children. This phenomenon is highly correlated with the incidence of obesity and diabetes in childhood or the risk of developing these diseases in the future.

Conclusion

Epigenetics has provided significant contributions to the understanding of predispositions to adiposity and metabolic syndromes even before conception and throughout development through the study of epigenetic inheritance associated with parental health. Experimental epigenetic studies applied directly to reprogramming or metabolic programming as methods of combating childhood obesity are still scarce, according to the searches of this review, whose most articles accessed have an exploratory character, focusing on the identification of relationships between epigenetics and obesity and other metabolic disorders that may occur throughout life. However, although pediatric epigenetic research is a relatively young field, its current technical and theoretical framework can be directed towards the prevention of metabolic diseases in pre-pregnancy, gestational, childhood, and adolescence periods, to the diagnosis of susceptibility to these diseases from epigenetic biomarkers and, finally, the metabolic programming of children with obesity or other associated comorbidities.

Acknowledgement

I thank my husband Paulo Sérgio and my children Isabela and Rafael for their unconditional support during the development of this study.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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