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REVIEW ARTICLE

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The employment of the nutrigenomic tool in the prevention and reduction of obesity problems: a review

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Abstract

Introduction: The use of the nutrigenomics tool in the prevention and reduction of obesity problems. **Objective:** To discuss, through the literature, the interaction between genes, nutrient, and their association with obesity, to convey to the health professional a broader and more detailed and understandable view of the advantages of using nutrigenomics in the prevention or aggravation of this morbidity condition. **Methods:** Exploratory bibliographic research for its development, articles found in the scientific electronic databases Scielo, Medline, Bireme, and Latin American Literature in Health Sciences (LILACS) in the area of nutrigenomics indexed in the years 2012 to 2018 were selected. **Results:** Concerning obesity, several studies prove that the control of the need for food intake is affected by polymorphisms in genes encoding peripheral signaling peptides, such as insulin, leptin, and adiponectin. In addition, it is also affected by energy homeostasis that involves changes in PLIN and UCPs genes. Diets based on nutritional needs, nutritional status, and genotype are factors in the prevention and control of obesity and several chronic diseases. **Conclusion:** Nutrigenomics represents the latest in nutrition science. Health professionals need to know and scientifically debate this new science, showing the health benefits it grants and directing actions that enable the future insertion of this practice in the context of population programs based on public policies for the construction of new paradigms related to the treatment of obesity.

Keywords: Gene. Genome. Obesity. Nutrigenomics.

Introduction

Obesity is characterized as the excessive accumulation of body fat, in the form of adipose tissue, and its cause is attributed to an energy imbalance between spent and consumed calories **[1]**. The agency points out that the main triggering factors of this growing epidemic are the increased intake of foods rich in fats, salt, and sugars, and poor in vitamins and minerals, together with the decrease in physical activity, resulting from the growing process of a sedentary lifestyle. It is also known that the etiology of obesity is multifactorial, with both environmental and genetic aspects involved in its genesis.

In this sense, obesity is now considered one of the main health problems of the world's population, with its prevalence rate increasing dramatically in several countries. In prospective estimates, in the world, approximately 2.3 billion people were diagnosed with overweight or obesity in the year 2015. These data become alarming since this condition is considered a risk factor for several diseases, such as physical disability, endocrine, metabolic, cardiovascular, pulmonary diseases, and some types of cancer **[2]**.

The diagnosis of overweight/obesity has been carried out using the body mass index – BMI, (calculated by dividing weight in kg by height in meters squared, kg m^{-2}). The classification adopted by the WHO is divided into: <18.5 kg m^{-2}. Thin or underweight; 18.524.9 kg m^{-2} Normal or eutrophic; 25-29.9 kg m^{-2} Overweight or pre-obese; 30-34.9 kg m^{-2} Obesity; 30-39.9 kg m^{-2} Moderate obesity; ≥40.0 kg m^{-2} Severe obesity **[3]**.

Concerning anthropometric methods, skinfold thickness measurements and bioimpedance (BIA) are frequently used in the assessment of body composition, while waist/hip ratio (WHR) and waist circumference

(WC) is used to assess the abdominal concentration of body fat and the risk of developing non-transmissible chronic diseases **[4,5]**.

Genetic factors play an important role in weight maintenance since there are genes involved in the regulation of energy expenditure, appetite, lipid metabolism, thermogenesis, cell differentiation, and synergies. The study of nutrients in gene expression is called nutrigenomics and can be explored in two ways: food can influence gene activity, and genes can influence the need for certain nutrients. This provides a genetic understanding of how common dietary components may affect the balance between health and disease, thereby altering the expression and/or structure of an individual's genetic makeup **[6]**.

Nutrigenomics (or Nutritional Genomics) emerged in the context of the Human Genome Program and aims to study how food, nutrients, and other ingested bioactive compounds influence the genome. It identifies over time the influence of diet on the structure and expression of genes, favoring health or disease conditions. Genetic data from healthy or sick individuals are related to their diet to reach conclusions about the interference of diet in the structure and genetic expression. The subdivisions of Nutrigenomics are highlighted as **[7]**:

a) Transcriptomics: analyzes the transcription products, the messenger RNA, and its alterations against a nutrient or bioactive;

b) Proteomics: analyzes the set of proteins and the alterations suffered when in the presence or absence of nutrients and bioactive;

c) Metabolomics: analyzes how the transport of a certain nutrient and metabolite is controlled in its biochemical route.

In this sense, nutrigenomics makes it possible to gather information on how nutrients and other compounds in food interact with genes, model their expression, and establish the best individual dietary recommendations for reducing the risk of obesity and diseases related to metabolic syndrome, aiming at promoting health **[7]**.

It is important to study the effect of nutrients on gene expression, because, according to the particular pattern of genetic variation, personalized advice can be generated with recommendations on diet and lifestyle, becoming an important instrument in promoting wellfounded health. in individualized interactions, therefore more effective **[6,7]**.

Therefore, this study aimed to discuss, through the literature, the interaction between genes and nutrients and its association with obesity, to convey to the health professional a broader and more detailed understandable view of the advantages of using the nutrigenomic in prevention or aggravations of this morbidity condition.

Methods

Study Design

Exploratory research of the literature review.

Literature Search Strategy and Sources

To search for important works for the development of the study, the following descriptors were used: Nutrigenomics, obesity, gene, and genome in the databases of PubMed, Medline, BDENF, and Latin American Literature in Health Sciences (LILACS), from January to March 2022.

The question that guided the search for articles in this review was: What is the interaction between gene and nutrients and their association with obesity? After refining the search, 109 articles were found in the databases, and after reading the abstracts of the productions, twenty-seven (27) were selected, as they effectively responded to the search and inclusion criteria: works available in full, published in the languages Portuguese and English, from 2010 to 2018.

Works that mentioned the subject only as a secondary part of the text, incomplete articles, or theses and monographs were excluded. For the analysis of the selected material, reading techniques were used, the main analysis strategy in bibliographical research such as exploratory and selective readings to determine the adequate material for the construction of the fundamental theoretical argumentation of the research, taking into account the quality, temporality, and reliability. In sequence, an analytical reading was carried out for ordering and summarizing the information contained in the sources. In the last stage, an interpretative or synthetic reading was carried out to integrate the ideas expressed in the works. The discussion was categorized into two main thematic chapters: 1) Obesity and Genetics, Nutrigenomics, and 2) Prevention of obesity problems.

Results and Discussion

Obesity and Genetics

Obesity is a chronic disease that affects approximately 205 million men and 297 million women worldwide. Among the risk factors associated with the disease, those of behavioral, environmental, neuroendocrine, and genetic origin stand out **[4]**. The discovery of the functionality of adipose tissue and associated genetic alterations considerably expanded

the scope of the investigation of mechanisms and risk factors. Despite the socio-behavioral influence on the development of this disease, the genetic component constitutes an important factor and a risk element for the pathophysiology. The increase in its prevalence in almost all countries during the last few years seems to indicate that there is a genetic predisposition or susceptibility to the development of overweight/obesity in the population **[8]**.

Genetic studies have contributed significantly to understanding the physiology of body mass regulation, through animal models and the investigation of genetic factors related to rare and common forms of human obesity. Since the mapping of the human genome (1990 – 2003), several single nucleotide polymorphisms (SNPs) of genes have been associated with excess weight, such as FTO (associated fat mass and obesity), MC4R (melanocortin-4 receptor), LEP (leptin) and LEPR (leptin receptor). These genes have been frequently studied because they are involved in central or peripheral pathways controlling energy intake and expenditure **[9]**.

Polymorphisms are genetic variants in the sequence of alleles, in the sequence of nucleotide bases, or in the chromosomal structure, which occurs with a frequency greater than 1% in the population. The type of polymorphism in evidence in the literature is the single-base polymorphism, known as Single Nucleotide Polymorphism (SNP), which consists of a variation in the identity of a single nucleotide at a particular site in the genome and which are associated with the overweight **[10]**.

The FTO (fat mass and obesity-associated) gene is expressed in the nucleus of the hypothalamus and plays a role in controlling food intake and caloric burning. Although the functions and pathways of the FTO gene are unknown, analysis of its structure demonstrates that it is involved in post-translational modification, repair of deoxyribonucleic acid (DNA, which protects the genome from damage that leads to mutations), and the metabolism of fatty acids, having been identified for the first time as an obesity-susceptible gene by two genomewide studies **[11]**.

Gene MC4R (melanocortin) controls a protein in the hypothalamus, an area of the brain that regulates sleep, body temperature, appetite, and satiety. The melanocortin system is a key pathway in the regulation of energy balance, often associated with obesity through modulation of the hypothalamic response **[12]**. MC4R is widely expressed in the CNS, namely in the hypothalamus, hippocampus, thalamus, and spinal cord. The direct involvement of MC4R in the regulation of energy homeostasis was tested in knockout mice for this gene. The animals tested, which have the mutation in this receptor and which do not have the two alleles, that is, MC4R -/-, showed increased food intake, severe obesity, hyperinsulinemia, and hyperleptinemia.

One of the most obvious polymorphisms related to obesity is in the leptin receptor gene (LEPR), for which positive associations were found between genetic variants and increased risk of developing overweight/obesity **[8]**. Leptin is a hormone produced primarily by adipose tissue cells known as fat cells that act through receptors in the hypothalamus to regulate food intake, body temperature, energy expenditure, and cardiac function. Studies indicate that a mutation in the leptin gene can lead to excessive food consumption and consequently to obese phenotypes.

The contribution of polymorphisms in the leptin receptor (LEPR) and the leptin gene (LEP) in the pathophysiology of obesity, reinforces the idea that obesity can result from both interactions: gene-gene and gene-environment **[13]**. The decrease in leptin production or the inability of the hypothalamus to exert its effects are two mechanisms related to the development of obesity, as well as environmental factors, such as a hypercaloric diet in the presence of the polymorphism, potentiate the development of this clinical condition, resulting in increased measures anthropometric and biochemical, in the presence of genetic mutation **[8,14]**.

Of particular importance in this context are also PLIN, the most abundant phosphoproteins around fat droplets in adipocytes. PLIN plays a key role in lipid storage and TG lipolysis and, depending on the body's energy state, whether fed or fasting, can limit or facilitate, respectively, the lipolysis of stored TG **[15]**.

The finding of monogenic obesity has contributed a lot to unravel the mysteries that still permeate obesity. The fraction of these disorders in the global context of obesity is still small (5% of cases), but it has provided us with important lessons to understand the role of some metabolic pathways that are critical for weight control, such as the leptin-melanocortin system, within from which most monogenic disorders have been described **[13]**.

Today we know for sure that some genetic diseases are influenced by nutrition, even though they belong to the class of monogenic diseases, which are those caused by mutations in a single gene, such as, for example, galactosemia and phenylketonuria. Both are rare characteristics that, due to enzymatic defects, lead, respectively, to the accumulation of galactose and phenylalanine in the blood, increasing the risk of mental retardation and neurological damage if not diagnosed and treated early. A nutritional way to treat these

monogenic diseases is based on a diet restricted in galactose and lactose, for galactosemia, and with a low protein content for phenylketonuria **[16]**.

Studies of twins adopted individuals, and families have shown that obesity is heritable and the familial risk for obesity (the risk ratio for obesity for an individual if a first-degree relative is obese compared to individuals in a population that has only first-degree relatives with normal weight) ranges from 1.5 to 5 depending on the severity of obesity **[17]**. Estimated inheritance ranges from 16 to 85% for BMI; from 37 to 81% for waist circumference; from 6 to 30% for waist/hip ratio and from 35 to 63% for body fat percentage.

Longitudinal studies demonstrate that the estimated inheritance tends to increase from childhood to pre-adolescence and from adolescence to adolescence, mirroring the increasing exposure to obesogenic environments that tend to affect individuals with a genetic propensity. Likewise, longitudinal changes in BMI from adolescence to young adulthood are a heritable trait, and genetic factors that modulate BMI levels are only partially explanatory of those modulatory changes in BMI and changes in BMI **[17]**.

Genetic and environmental determinants are not antagonistic. Obesity is determined by several factors, and they act together in the clinical determination of the disease. Therefore, the result would be the product of the combination of genetic and environmental factors, suggesting that genetic influences are specifically more important to determine the distribution of body fat, with a special influence on the predisposition of visceral fat deposits **[18]**.

Technological advances in recent years have enabled the development of molecular tools that allow examining the intervention of genes in maintaining stable weight and body fat over time, through their participation in the control of efferent pathways (leptin, nutrients, nervous signals, among others). others), central mechanisms (hypothalamic neurotransmitters), and afferent pathways (insulin, catecholamines, autonomic nervous system (ANS). Thus, energy balance, in which energy intake and energy expenditure participate, seems to depend on approximately 40% of genetic inheritance, which may affect both parts of the energy equation (appetite and expenditure) **[19]**.

Nutrigenomics and the Prevention of Obesity Diseases

Obesity is a condition that can be determined by a specific gene mutation, in the case of monogenic obesity, or it can also be related to multifactorial inheritance, represented by polygenic obesity. This is conditioned by the interaction of environmental characteristics, with an important influence of genetic factors **[20]**.

Monogenic obesity is the rarest, produced by mutation or alteration in the DNA sequence of a single gene, obesity being the most likely phenotype. The discovery of genes involved in the monogenic form of obesity has been of great value for recognizing obesity as a medical disorder, in addition to providing effective therapies **[21]**.

Monogenic forms of obesity can be divided into three broad categories. The first is obesity caused by mutations in genes that play a physiological role in the leptin-melanocortin hypothalamic energy balance system. These include congenital leptin deficiency, leptin receptor deficiency, complete POMC (pro-opiomelanocortin) deficiency, and mutations in melanocortin type 4 receptor (MC4R). Its inefficiency is one of the main factors responsible for inhibiting the feeling of satiety **[17]**.

The second category is obesity resulting from mutations in genes necessary for hypothalamic development (SIM1, BDNF, and NTRK2). The mechanisms by which these genes regulate body weight are not yet known. These mechanisms tested in animals involve the development of an inflammatory process in the hypothalamus and eventually neuronal injury, resulting in local resistance to the action of leptin and insulin. In humans, there are also indications, although indirect, that similar alterations are present in obesity **[21]**.

The third category is obesity, presenting itself as part of a complex syndrome caused by mutations in genes whose functional relationship with obesity is still unclear (eg Prader-Willi Syndrome (PWS). Prader-Willi Syndrome (PWS) is the most frequent syndrome that has obesity as one of its characteristics, with an incidence of 1:25,000 births. It is characterized by neonatal hypotonia with sucking difficulty, neuropsychomotor developmental delay (NPMD), hyperphagia, obesity, short stature in adolescents, small hands and feet, hypogonadism, sleep disorders, dysmorphic facial features, mild to moderate intellectual disability, obsessivecompulsive behavior **[22]**.

However, only a small fraction of cases of severe obesity are due to single gene mutations. For the vast majority of the population, variation in adipose mass results from complex interactions between many genetic variants and environmental factors **[23]**. Common obesity is a polygenic disorder resulting from a complex interaction between genetic and environmental factors, it is suggested that genetic factors contribute from 40 to 70% in the susceptibility of developing obesity and, in this context, Single Nucleotide Polymorphisms (SNPs) in

genes FTO (Fat mass obesity-associated), TMEM18 (transmembrane protein 18) and ADIPOQ (Adiponectin) were shown to be related to changes in anthropometric and biochemical parameters **[19]**.

Also, obesity causes functional disability, reduced quality of life, reduced life expectancy, and increased mortality. Chronic conditions such as kidney disease, cancer, T2DM, sleep apnea, non-alcoholic fatty liver disease (NAFLD), SAH, and cardiovascular disease. Many epidemiological studies have confirmed that weight loss improves these diseases, reducing risk factors and mortality **[3]**. The Federal Council of Medicine - CFM published Resolution nº 2.131/15 that obesity is an increasingly common disease in Brazil whose prevalence already reaches epidemic proportions in our country, being a high risk for diseases such as diabetes, cardiovascular diseases, and some types of cancer **[3]**.

It should be noted that individuals affected by the disease need to treat it throughout their lives, as it is considered a member of the group of Chronic Noncommunicable Diseases (NCDs), with a generally slow, prolonged, and permanent clinical course. Therefore, the treatment of obesity is a challenge for specialists in the areas of health, since the great difficulty is maintaining weight in the long term, which requires changes in eating habits and lifestyle, as well as the perception of the risks involved. in the disease **[24]**.

Also, nutrigenomic science enables personalized nutritional strategies according to specific individual needs to promote health and prevent disease. The important objectives of nutrigenomics are to study the effect of foods and their nutrients on gene expression, in addition to identifying and investigating interactions between the genome and bioactive compounds in foods **[25]**.

Besides, a nutrigenomics-based diet can be a very useful tool to help the individual achieve optimal nutrient content and increase motivation and maintenance of long-term lifestyle changes. Based on all this knowledge, it may be possible to create a personalized diet to reduce the genetic predisposition to certain diseases. A personalized DNA-based diet represents a very promising alternative for establishing more targeted and effective nutritional recommendations for health promotion **[26]**.

The long-term goal of nutrigenomics is to try to understand how the whole body responds to food, using an integrated approach called "systems biology". Systems biology is a buzzword in modern biology, used to describe all aspects of a biological system. The key principle is that a whole-organism perspective will provide a more accurate view than the sum of the parts, based on the idea that a complex system has intrinsic properties that cannot be derived directly from the additive effects of the elements. its components **[27]**.

The advancement of nutrigenomics has as its purpose the perspective of prescription and elaboration of personalized diets according to the individual genetic composition, expanding the strategies available in the system of health promotion and prevention and treatment of NCDs such as obesity, T2DM, cancer, and inflammatory bowel disease **[15]**.

As discussed in this work, several genes responsible for a series of physiological functions, often in different metabolic pathways, are involved in the obesity process. For understanding how genes affect transcription factors, protein expression, and metabolite production are advanced methods of analysis, in addition to bioinformatics that can generate recommendations on diet and lifestyle, customizing interventions by adjusting and selecting food according to the genetic variability of the metabolic profile of each individual **[26,27]**.

Conclusion

Nutrigenomics is a contemporary science and represents an approach to the interaction between diet and genes, seeking to unravel the complex relationship between nutrients, genetic polymorphisms, and the biological system as a whole, aiming to improve health through the establishment of personalized diets. Current knowledge about the influences of dietary factors on the human genome is expanding, and it certainly is a promising approach to improving population health. Nutritional strategies based on nutritional needs, nutritional status, and genotype (personalized diets) can be tools that help physicians and nutrologists to act in disease prevention and health promotion. Health professionals need the training to know and scientifically debate this new science, showing the health benefits it grants and directing actions that enable the future insertion of this high-cost practice in the context of population programs based on public policies for the construction of new paradigms related to obesity.

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Ethical Approval

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Conflict of interest
The authors declare no conflict of interest.

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