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PROTEIN RESTRICTION IN THE PERINATAL PERIOD AND THE EMERGENCE OF METABOLIC DISORDERS

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Abstract: During the gestational period, it is necessary for the pregnant woman to have a balanced diet so that the fetus has a favorable environment for its development. Thus, this study aims to understand the adverse effects on the fetus of an unbalanced diet during pregnancy through a literature review in databases and journals. It is believed that a low-protein diet during pregnancy induces the fetus to adapt to a non-conforming intrauterine environment, optimizing its energy expenditure for the benefit of its survival. However, at birth, the individual has low weight and is subject to "catch-up", a risk factor for obesity and type 2 diabetes mellitus. In pregnant women who received a low-protein diet, the fetus presents functional and structural, such as changes in insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF). These substances are of paramount importance for the maturation of the pancreas. Dysfunctional or at reduced levels in the pancreatic islets, these factors lead to reduced differentiation, proliferation and functioning of beta cells.
Keywords: Protein restricted diet. Fetal programming. Type 2 diabetes mellitus.

INTRODUCTION

In the 1960s, Neel launched the "thrifty genotype hypothesis", explaining that some populations were more prone to insulin resistance, both by natural selection and by genetic factors. The theory explained that a random mutation would lead the individual to develop insulin resistance, which could be adaptive and beneficial for those who suffered from some kind of food shortage. Thus, it would generate natural selection and, consequently, there would be the transmission of the character to subsequent generations. However, recent studies of gene-environment interactions have shown that uniquely genetic and environment-independent effects do not have a true biological correlate.[1,2].

Based on information published by Neel, David Barker and his colleagues developed the sparing phenotype hypothesis, which suggested that adverse conditions during intrauterine life and childhood increase the risk of cardiovascular disease. To confirm the validity of this proposal, the researchers correlated birth weight and environmental conditions throughout childhood with the cardiovascular health of adults born in the early 20th century in Hertfordshire, England. In studies, it was shown that people born with low birth weight, unlike those with adequate weight, had higher blood pressure and would be more likely to develop type 2 diabetes mellitus (DM2). In addition, other findings – such as plasma lipid pattern, reduced bone density, differentiated stress responses, less elastic arteries, specific hormone secretion patterns, and a higher incidence of depression – also correlated with low birth weight.[1,3-5].

In parallel to Barker's studies, an independent group of researchers observed that preterm newborns (NB) subjected to different types of dairy diet had different outcomes. However, contrary to the concept of the sparing phenotype, these neonates did not have adaptations with immediate objectives, but metabolic adjustments that ensured long-term adaptations in order to guarantee their survival at least until the reproductive period. In this context, to adapt the term to the events, they proposed the use of the word "metabolic programming", referring to the process in which there are nutritional and/or hormonal changes, which occur in a critical period of development, such as pregnancy, lactation, puberty or adolescence, promoting lasting morphological, metabolic and functional adjustments, which determine a greater predisposition to pathological states in adult life[1,6].

Among the nutritional imbalances, the low-

protein diet during pregnancy (so classified when pregnant women have an intake of less than 71 g of protein per day) leads the fetus to adapt to an adverse intrauterine environment and develop several structural and functional changes that contribute for energy optimization in favor of their survival, but with lower birth weight. Such changes can be temporarily reversed by "catch-up growth", a phenomenon characterized by a compensatory growth mechanism of weight or height due to a period of slow growth, characteristic of food restriction. Thus, this rapid weight gain of the individual has gained prominence in the literature for influencing the development of the child's metabolism, and may be a risk predictor for obesity, DM2 and other metabolic disorders.[1,7-9].

Among some disorders that can occur in individuals subject to metabolic programming, DM2 is a multifactorial disease that occurs due to the inability of insulin to correctly exert its effects, due to the decrease in tissue sensitivity to this hormone. Insulin, produced by the beta cells of the pancreatic islets, is responsible for maintaining glucose metabolism. The lack of its action in the body, due to conditions that provide insulin resistance (such as obesity), leads to the installation of DM2, also called Non-Insulin Dependent Diabetes Mellitus (DMNDI)[10-12].

According to the guidelines of the Brazilian Society of Diabetes (SBD), DM is an important and growing public health problem worldwide. In 2017, the International Diabetes Federation presented an estimate pointing out that 8.8% of the world's population aged between 20 and 79 years of age (i.e. 424.9 million people) were living with diabetes. If current trends persist, the estimated number of people with diabetes must exceed 628.6 million in 2045. Brazil ranks fourth in the ranking of the main countries with the highest number of patients with diabetes in the world, with 12.5 million of people in 2017 and with a projection of 20.3 million in 2045[13].

According to the current Human Development Index (HDI) report, there are still 41 countries, mainly in Africa and Asia, with a low development index (HDI < 0.500). The HDI is calculated based on factors such as health, education and standard of living. A low HDI value is associated with poor social groups in the population – and this poverty inevitably implies a protein-deficient diet[14].

Due to the exponential growth in the number of patients with DM2 and the nutritional imbalance caused by the difficult access to protein consumption, the objective was to understand if the low-protein diet during pregnancy interferes with the embryological formation of the fetal pancreas and predisposes it to developing type 2 diabetes mellitus. in the adult stage.

METHODOLOGY

The project carried out consists of a literature review related to the main metabolic changes in the fetus, which can result in the imbalance of pancreatic functions and cause disorders of glucose metabolism, as a result of a low-protein diet during pregnancy. The search was carried out seeking clinical studies, systematic reviews and meta-analyses published in English and Portuguese, in the PubMed, LILACS, UpToDate, Scielo databases, and in the CAPES Periodicals Portal from 2020 to 2022. Thus, as inclusion criteria, were Scientific articles were used that met the previously established publication limit, which addressed the objectives outlined, the guiding question raised in this study in Portuguese and English. The exclusion criteria were scientific articles not available in full, materials not corresponding to the theme of the work, works with very old publication dates. In addition, works found in a general search were used in the same bases with the

same keywords, but addressing their use in titles and abstracts.

DEVELOPMENT

Food is fundamental in the history of human evolution, as it provides the energy necessary for the proper physiological functioning of the body. However, the lack or excess of it can lead to important adaptive consequences, in a way that will determine the success or failure of the maintenance of the offspring and, consequently, the perpetuation of the species. The loss of homeostasis, as for example by maternal-fetal malnutrition, leads to prioritization of brain development to the detriment of other visceral organs, aiming at the survival of the fetus in adverse conditions. Among some of the observable consequences are the structural loss of important cells, such as nephrons, cardiomyocytes and beta cells, in addition to a decrease in fetal size and a lower birth weight.[38,39].

To investigate the effects of malnutrition on fetal development, the researchers analyzed a variety of historical, clinical and epidemiological data obtained during times of war or famine. One of the studies was on women in the prenatal period during the second world war, in the winter of the Dutch famine (1944-1945). These women received a daily diet of 1,800 kcal, which was gradually reduced until reaching 400 kcal at the height of hunger. According to Garner (2021)[40], most women in the last two trimesters of pregnancy need between 2,200 and 2,900 kcal/day. Thus, in this period of famine, maternal malnutrition generated children with low birth weight and glucose intolerance, who were more likely to develop DM2 and obesity in adulthood, when compared to newborns whose intrauterine period occurred one year earlier. or after hunger[14,40].

Associated with the extreme inequality that already exists in most countries, including Brazil, the covid-19 pandemic can cause catastrophes of unimaginable dimensions. According to the United Nations (UN), the number of hungry people could double, reaching 265 million people by the end of 2020. In humans, malnutrition before the age of 2 is known to be associated with various deficits, including behavioral and cognitive deficits. Even if after this period such individuals receive nutritional rehabilitation for up to 20 years immediately after the event, these deficiencies may remain. Thus, both the fetus and the baby can respond to this unbalanced nutrition by modifying their pattern of growth and development. This event is known as metabolic programming, which led to the emergence of the theory of "fetal origins of adult disease". This theory explains that changes in fetal nutrition and endocrine status would permanently provoke adaptations in the development of offspring, thus altering their morphology, physiology and metabolism. Thus, these individuals would be predisposed to several diseases in adulthood, such as metabolic, endocrine and cardiovascular diseases.[41-43].

This individual, who was malnourished in the prenatal period and adapted to a scarce environment, may trigger the catch-up-growth mechanism after having their nutrition normalized in the first two years of life. In this case, the organism begins to present a compensatory mechanism of accelerated growth in an attempt to reach the ideal size for the age, sex and degree of maturation. Despite being beneficial for neurodevelopment and contributing to greater resistance to infections, this phenomenon can condition children to obesity, especially central obesity, with consequent insulin resistance. In an attempt to repair these changes, greater insulin secretion occurs, leading the individual to have a greater chance of developing DM2 in adulthood.[5,44].

Barker (1998)[45] found that this rapid weight

gain in childhood leads to a higher incidence of cardiovascular disease, T2DM, and high blood pressure. This is associated with the genetic-environmental component; that is, maternal nutrition directly influences fetal epigenetic programming. However, when associated with an unhealthy lifestyle (sedentary lifestyle and high caloric intake), maternal nutrition makes the individual more likely to have chronic diseases. This environmental influence was seen mainly after the industrial revolution, when there was a greater devaluation of work by the hands of man and subsistence food and an overvaluation of machines, fast foods and body image. The consequences involved two aspects: in the first, there is the consumption of high-calorie foods since childhood; in the second, there are anorexic or bulemic people, exalting aesthetics more than their own health[38,45].

Among the essential energy substrates, proteins perform crucial functions in our organism, highlighting the regulation of cell development through growth factors. Thus, some of the fetal consequences of protein malnutrition would be changes in insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF), both involved in pancreas maturation. Frantz (2012)[14] explains that IGF is an important survival factor, as it potentiates the growth, maturation and functioning of beta cells. However, the author also reports that malnourished offspring have a lower expression of IGF-2 in the pancreatic islets, so that beta cell proliferation becomes less, due to a longer G1 phase and increased apoptosis. VEGF is expressed in the developing pancreas, and its function is related to the differentiation and functioning of beta cells. Thus, when an individual is in contact with a protein-poor environment, vascular dysfunction occurs associated with a reduced expression of VEGF in the fetal islets, so that, if the normoprotein diet is introduced after birth, the vascular network in the endocrine pancreas may recover in adulthood; however the beta cells suffer an irreversible deficit[14,46,47].

In view of the need to verify the veracity of theories related to metabolic programming in practice, studies were carried out in rodents, due to similarities in embryology, anatomy and physiology. However, in order to carry out studies in rodents, it is necessary to meet the dietary guidelines of the American Institute of Nutrition. This organ indicates that a normoproteic diet during pregnancy and development periods must contain 19.3% of proteins; but when the level reaches 5%, it is considered severe protein restriction. In animals exposed to poor nutritional environments, evidence of the economic phenotype hypothesis proposed by Barker was verified, in which the animal is born with a reduced body and pancreatic mass, reflecting in metabolic alterations and predisposing the individual to develop the triad of metabolic syndrome in the adult, such as hypertension, insulin resistance, and obesity[46].

The phase of body development in which the protein-nutritional insult is applied can generate different effects in the adult life of the offspring. In mouse models, when the insult is applied from conception to weaning, a series of changes have been observed. Among them, the main ones were: (1) phenotypic changes and post-implantation embryonic stem cell and endodermal tissue deficit; (2) during pancreatic embryogenesis, changes occurred in the development of endocrine precursor cells; (3) the islets, once defined, showed insufficient growth; (4) deficient vascularization and angiogenesis, as they are not sufficient to supply the pancreatic beta cell mass, which increases significantly shortly before birth[48]. In addition, at 70 days, adult phase, rats with a low-protein diet showed hypoproteinemia and hypoalbuminemia, characteristic of child malnutrition of

the Kwashiorkor type. Furthermore, over exposure to protein deficit, the pancreatic islets undergo a progressive atrophy, reducing the volume and number of beta cells per islet. Thus, after the administration of several doses of glucose, malnourished animals show a deficient insulin secretion response.[49].

CONCLUSION

With the present study, it was possible to verify that the gestational period is sensitive to maternal nutrition. In pregnant women who received a low-protein diet, the fetus ended up with functional and structural damage, such as changes in IGF and VEGF. These substances are of paramount importance for the maturation of the pancreas, since when they are dysfunctional or in reduced levels in the pancreatic islets, they lead to less differentiation, proliferation and functioning of beta cells. The growing social inequality and the implications of the covid-19 pandemic can accentuate the number of pregnant women with unregulated diets, increasing the exponential number of patients with metabolic diseases.

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