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REVIEW

Metabolic programming interference in the development of obesity and its comorbidities

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Abstract
Objective: To investigate the potential interference of metabolic programming in the development of obesity and its comorbidities. Method: It was consulted the MEDLINE and LILACS databases, including articles published between 2004-2014 in Portuguese, English and Spanish, using the descriptors fetal development, obesity and chronic disease. Results: Of the 19 articles identified, five were excluded. The search for references from 14 studies analyzed resulted in the inclusion of 38 new articles. Conclusion: There is evidence that intrauterine and postnatal nutrition and lifestyle can interfere in the health programming and the future risk of obesity and chronic diseases.

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Introduction

The prevalence of obesity in children and adults has exponentially increased over the past two decades, thus becoming a major worldwide public health issue[1] due to its association with comorbidities in childhood and the increased risk of premature death in adulthood[2]. This condition indicates the need to prioritize the adoption of public policies to prevent overweight and obesity in childhood, a nutrition situation involved in the genesis of cardiovascular diseases.[1]

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide and they are associated with the atherosclerosis process, which may begin in childhood and early manifest throughout life. Risk factors such as dyslipidemia, hypertension, and insulin resistance - associated or not with obesity -, accelerate the atherosclerosis process and increase the risk of cardiovascular diseases.[3] Therefore, the early identification of overweight risk factors, their comorbidities as well as the establishment of primary prevention measures are unquestionable to the control of this serious global public health issue. [4]

Studies have shown the effects of early nutrition and lifestyle on the long-term health programming and on the future risk of obesity and chronic diseases such as type 2 diabetes mellitus, hypertension and cardiovascular diseases. [5-7] These transgenerational effects are explained by mutations at the epigenetic machinery level and they may establish plausible associations between intrauterine and post-natal nutrition and the development of chronic non-communicable diseases in adulthood.[8-10]

The phenomenon known as "programming" refers to stimuli that, when applied during the first moment of life, may lead to permanent changes that persist throughout life. This phenomenon is not limited to the intrauterine environment, but it extends to childhood, during which different organs and systems keep adapting to different stimuli. This concept was described by David Baker, in 1986, and became popular as a fetal-origin hypothesis on adult diseases, which is based on the development of plasticity in which a single genotype can give rise to different phenotypes influenced by environmental stimuli or intrauterine insults. Such adaptations prepare the fetus to extrauterine life. However, these changes may not be compatible with the external environment, thus causing an imbalance that may lead to increased risk of diseases in adulthood.[7,11] The current review aims to check the knowledge on metabolic programming and its potential interference in the development of obesity and its early and late comorbidities.

Method

Electronic databases such as the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Latin American and Caribbean Literature on Health Sciences (LILACS) were consulted. The survey included articles published between 2004 and 2014 in Portuguese, English and Spanish, using the following MESH (Medical Subject Headings) terms: fetal development, obesity chronic disease; searched on the website http://www.ncbi.nlm.nih.gov/mesh.

The search strategy adopted in MEDLINE/PUBMED database was: (("Fetal Development"[Mesh]) AND "Obesity"[Mesh]) AND "Chronic Disease"[Mesh], whereas the strategy adopted in LILACS was: "Fetal Development" AND "Obesity" AND "Chronic Disease". Nineteen (19) articles have been identified in the databases; however, five were excluded due to their publication period (prior to 2004 N = 03), language (French N = 01) and type of study (experimental: N = 01). Thus, 14 articles were included, all of them review articles, 13 (92.9%) were published in the MEDLINE/PUBMED database and one (7.1%) in LILACS. The search for the references mentioned in the 14 analyzed studies resulted in the inclusion of 38 new articles.

Results

The synthesis of the articles on metabolic programming and its potential interference in the development of obesity and its comorbidities is described in Table 1.

Chart 1 - Summary of manuscripts analyzed in the period from 01/01/2004 to 12/01/2014, in the databases MEDLINE / PUBMED and LILACS.

REFERENCE	CONCLUSION
Gluckman *et al.*[12]	Incompatibility between the fetal expectation of their postnatal environment and the actual postnatal environment contributes to the future risk of chronic diseases.
Gluckman, Hanson[13]	The development of genetic plasticity in response to stimulus / signal in the intrauterine environment, if the induced phenotype differs from the postnatal environment may be associated with the risk of disease in adults.
Uauy *et al.*[14]	Specific patterns of pre and postnatal growth are crucial determinants for the development of obesity and chronic diseases in adulthood.
Nair *et al.*[15]	Intrauterine malnutrition can cause permanent changes in the structure and function of the body fetus predisposing to future non-communicable chronic diseases.
Joss-Moore, Lane[16]	Intrauterine growth restriction is associated with an increased risk of metabolic and non-metabolic diseases in adulthood.
Langley-Evans, McMullen[17]	Consuming inadequate quantity and quality of nutrients during pregnancy can cause lasting effects on fetal development that will predispose to future chronic diseases.
Calkins, Devaskar[7]	Stimuli or signals at critical periods of fetal development have a profound impact on disease risk in adults.
Fall[18]	Unfavorable environmental conditions during fetal and post-natal development may predispose to the development of chronic diseases by activating epigenetic mechanisms.
Durnwald, Landon[19]	Fetal exposure to a metabolically altered intrauterine environment increases the risk of obesity and chronic diseases in adulthood.
Lewis *et al.*[20]	Children of obese and diabetic mothers are at increased risk of being born with excess body fat, suggesting an effect of intrauterine environment on placental function.

Brenseke *et al.*[11]	Poor or excessive supply of nutrients during intrauterine life causes permanent changes in the fetus that can lead to future development of metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease.
Briozzo *et al*.[21]	Activation of epigenetic mechanisms during fetal life and early infancy can increase the risk of future chronic diseases, especially in situations greater social vulnerability.
Tarantal, Berglund[22]	Maternal obesity has negative effects on fetal development and may be associated with the development of chronic diseases that will lead to increased demand for health care in the future.
Ferguson[23]	Understanding the role of the modern diet in the genesis of obesity and other chronic diseases at various stages of human development, it can be useful to clarify effective interventions for prevention of this epidemic.

Discussion

Nutrition during pregnancy may affect the health status of future generations and these transgenerational effects appear to be explained by mutations in the epigenetic machinery, with associations between intrauterine nutrition and the development of chronic non-communicable diseases in adulthood. [8-10,22] The effects of nutrition and lifestyle during childhood on the programming of unfavorable nutritional evolution and the risk of chronic diseases are demonstrated in several studies. [5-7,11,17]

Recently, three hypotheses have been proposed to explain the effects of nutrition on the programming of obesity and its comorbidities. The first hypothesis suggests that the intrauterine exposure to excess nutrients, especially glucose, causes permanent changes in the fetus that lead to obesity in post-natal life. Scientific evidences suggest that maternal obesity and excessive weight gain during pregnancy are independently associated with the risk of obesity in childhood, thus corroborating the first hypothesis. [24]

The mother's nutritional status influences the quantity and quality of nutrients coming to the fetus, thus representing a potential determinant of the child's metabolic programming and body composition. [17,20,25] Accordingly, the presence of obesity or diabetes mellitus during pregnancy was associated with fetal hyperinsulinemia, increased perinatal morbidity and mortality, increased body fat, future development of obesity, glucose intolerance, hypertension, dyslipidemia and metabolic syndrome.[9,26-27] Therefore, improving glycemic control and reducing insulin resistance during pregnancy through balanced diet and regular exercise may change fetal growth and reduce the risk of obesity in childhood.[28]

Maternal obesity has also been linked to changes in the metabolism and in the transport of fatty acids across the placenta, without affecting fetal growth. However, these changes may alter fetus metabolism thus affecting the formation and distribution of adipose tissue and its predisposition to develop future cardiometabolic diseases. [20,22,29]

A study showed that the dietary advice given to the mothers during pregnancy and breastfeeding were not associated with the serum lipid levels found in their children between one and four years of age. On the

other hand, the consumption of monounsaturated fatty acids by these children is correlated with apolipoprotein A-I values. There is also negative correlation between the consumption of polyunsaturated fatty acids and apolipoprotein B, thus indicating the diet intervention at the different stages of life.[30]

The second hypothesis suggests the association between the rapid weight gain in childhood and the increased risk of future obesity and associated diseases.[31] There are indications that the increased protein intake contributes to increased plasma and tissue levels of insulin-releasing amino acids, insulin and insulin-like growth factor-1, leading to increased weight gain and adipogenic activity. [32] This hypothesis is reinforced by the fact that breastfed children have approximately 20% less risk of developing future obesity in comparison to those feeding on infant formula. This protective effect may be associated with the lower protein content in human milk, in comparison to that found in conventional infant formulas.[33]

In addition, there is evidence of the beneficial effects of exclusive breastfeeding in reducing the risk factors for cardiovascular diseases such as dyslipidemia, hypertension, type 2 diabetes mellitus, glucose intolerance and excessive weight. [34-36] Exclusive breastfeeding until six months also promotes optimal growth, neurocognitive development and resistance to infections, and it is associated with cardiovascular health in childhood and in adulthood. [37]

On the other hand, inadequate feeding practices in early life may lead to malnutrition, growth retardation, increased risk of infant morbidity and mortality and, hence, to increased future risk of chronic non-communicable diseases.[38] Inadequate complementary feeding practices and their socio-demographic and cultural determinants were associated with higher energy consumption and greater weight by height index in children, with potential effect on the modulation of the risk of childhood obesity.[39]

Huh et al.[40] found that the introduction of complementary food in children under four months was associated with six times greater obesity risk at the age of three. It was also observed the association between breastfeeding duration, early introduction of solid foods and the increased risk of obesity in childhood.[41]

The proper distribution of macronutrients derived from the complementary food introduced at six months of age should potentiate the proper growth from childhood to adolescence and prevent the risk factors for the development of chronic non-communicable diseases in adulthood. [25] The intake of 4 to 5 g/kg protein/day by children from eight to 24 months of age is associated with the increased risk of future overweight. [42] Similarly, the excessive sodium intake during infancy may lead to the late development of cardiovascular disease. [43] No evidence of association between fat intake and subsequent weight gain and body adiposity was found in children;[44] however, the consumption of high energy density food may induce excessive weight gain.[45]

The last hypothesis suggests that the incompatibility between the suboptimal pre- and post-natal development and the obesogenic environment in childhood are related to greater predisposition to obesity and other future comorbidities. This association may be attributed to a stimulus or an insult occurring at a critical developmental period, in which the fetus produces the most appropriate phenotype for its survival. This fact leads to the development of irreversible anatomical, endocrine and/or metabolic adaptations with late consequences that may manifest in childhood or in adulthood[5,12-13] especially within a social context of greater vulnerability. [21]

Changes in tissues' cellular composition, which are induced by suboptimal intrauterine conditions, may influence the post-natal physiological function. Evidence suggests that the liver may be a target organ for metabolic programming, undergoing epigenetic, functional and structural changes after the exposure to an unfavorable intrauterine environment, which may increase the risk of future cardiometabolic diseases.[46]

Newborns small for their gestational age and with height déficit in childhood run increased risk of developing cardiovascular disease later in life, especially when the height déficit is

followed by increased weight gain.[47] Thus, the linear growth routine assessment and weight gain monitoring in the first two to three years of life are potential strategies to control child obesity and to prevent chronic non-communicable diseases, including, the cardiovascular ones.[14]

Similarly, the correlation between birth weight and risk factors of cardiovascular disease has been studied in the recent decades. The low birth weight was associated with the later development of a number of disorders including abdominal adiposity, arterial hypertension, dyslipidemia, insulin resistance, hyperinsulinemia, glucose intolerance, type 2 diabetes mellitus, metabolic syndrome and cardiovascular disease.[15,48-50] Fetal macrosomia was also associated with the later development of obesity, type 2 diabetes mellitus and dyslipidemia.[51]

The genetic mechanisms involved in the genesis of obesity are still not fully understood; however, the main goals of the epigenetic research on obesity include: a) seeking epigenetic markers to predict future health problems or to detect individuals at higher risk; b) understanding the environmental factors associated with obesity that are able to modulate gene expression, thus affecting epigenetic mechanisms; c) studying new therapeutic strategies based on nutritional or pharmacological agents able to change epigenetic marks. [52]

Thus, studies show that intrauterine and post-natal nutrition as well as lifestyle may affect health programming and the future risk of obesity and chronic diseases. These current evidences should be taken under consideration in the formulation of public policies to reverse the increasing obesity rates and other early and late comorbidities. Further studies are necessary to assess the impact of infant feeding and, especially, breastfeeding, complementary feeding and the composition of infant formula in reducing the risk of obesity and other related diseases in future generations.

Similarly, one should consider the policy guidelines related to quality pre-natal care in order to prevent intrauterine insults as well as the appropriate follow-up in the peri- and post-natal care period to identify and to correct risks associated with chronic non-communicable diseases in adulthood.

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