REVIEW ARTICLE

Cardiometabolic Disease in Latin America: The Role of Fetal Programming in Response to Maternal Malnutrition

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Latin America is experiencing an epidemic in cardiovascular disease and type-2 diabetes mellitus. The rise in life-expectancy and increasingly rapid urbanization have resulted in a greater prevalence of overweight, obesity, and metabolic syndrome. In Latin America, there is a high level of susceptibility to the development of insulin resistance and low-grade inflammation at relatively low levels of abdominal obesity. This susceptibility is associated with the adaptive response of the fetus to deficient fetal nutrition, which results in a loss of anatomical structures such as nephrons, cardiomyocytes and pancreatic beta cells. These adaptations may prove detrimental if food becomes abundant again after birth. In Latin America, the high prevalence of maternal and fetal malnutrition could mean that the resulting fetal adaptations may contribute to an increased risk of cardiometabolic disease. The socioeconomic differences that exist between developed and underdeveloped countries may be reflected in different biological adaptations, which could invalidate the diagnostic criteria and preventive and therapeutic approaches that have been recommended on the basis of research carried out in populations with different characteristics. Clinical studies are needed to evaluate the effectiveness of interventions recommended for preventing and aiding recovery from cardiometabolic disease in Latin America.

Key words: *Cardiovascular disease. Maternal malnutrition. Fetal programming.*

Enfermedades cardiometabólicas en Iberoamérica: papel de la programación fetal en respuesta a la desnutrición materna

Iberoamérica sufre una epidemia de enfermedades cardiovasculares y diabetes mellitus tipo 2. El aumento en la expectativa de vida y el acelerado proceso de urbanizacion dan origen a un aumento en la prevalencia de sobrepeso, obesidad y síndrome metabólico. Iberoamérica presenta una mayor susceptibilidad a la aparición de resistencia a la insulina e inflamacion de bajo grado a menores niveles de obesidad abdominal, relacionada con una respuesta adaptativa del feto a una nutricion fetal deficiente, que resulta en una pérdida de unidades estructurales como nefronas, cardiomiocitos y células beta pancreáticas. Estas adaptaciones resultan perjudiciales si en la vida extrauterina la alimentación se vuelve abundante. En Iberoamérica, por la alta frecuencia de desnutrición maternofetal, estas adaptaciones pueden contribuir a un mayor riesgo de enfermedades cardiometabólicas. Las diferencias socioeconómicas entre el primero y el tercer mundo se reflejan en comportamientos biológicos adaptativos diferentes, por lo que no son necesariamente válidos los criterios diagnósticos, las medidas preventivas y las intervenciones terapéuticas recomendadas con base en investigaciones realizadas en poblaciones con características diferentes. Son imprecindibles estudios clínicos que evalúen la eficacia de intervenciones para la prevención y recuperación de enfermedades cardiometabólicas en Iberoamérica.

Palabras clave: *Enfermedades cardiovasculares. Desnutrición materna. Programación fetal.*

INTRODUCTION

Latin America is experiencing an epidemic of cardiovascular disease and type-2 diabetes mellitus (DM2), which between them are responsible for 46% of all recorded deaths.[1] This increase in cardiometabolic diseases is a general phenomenon in developing countries, to the extent that, in 2001, 79% of all deaths associated with chronic diseases in the whole world occurred in such countries.[2] The increase in life expectancy in Latin American countries is one of the reasons behind the epidemic in cardiometabolic diseases. For example, in Colombia, life expectancy for both sexes increased

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on average from 55 years in 1955 to 72.2 years in 2005.[3] In addition, the acceleration in migration to urban environments in these countries and the spread of western lifestyles among all social classes have lead to an increase in the number of individuals who have overweight or obesity, hypertension, metabolic syndrome, DM2, and cardiovascular disease.[3,4]

Changes in diet and levels of physical activity are the most noteworthy characteristics associated with the accelerated economic transition experienced by developing countries in recent years. Migration to urban areas is responsible for a change from diets rich in vegetable fiber in rural environments to a diet rich in processed flours and sweet drinks.[3,5] While these changes are drastic, changes related to energy expended in daily activities due to mechanization in the urban environment are more so. Mechanization is particularly marked in leisure activities, especially in children, where traditionally active games with high energy requirements are giving way to sedentary games in front of the television and mechanical games.[4,6] A number of studies have shown a relationship between the level of physical fitness during childhood and adolescence and the risk of cardiovascular disease in adults. The AVENA study (acronym in Spanish for Diet and Assessment of the Nutritional Status in Adolescents) performed in 2859 Spanish adolescents showed that a low level of physical fitness was associated with a higher-risk lipid-metabolic profile.[7,8] The authors suggested that an improvement in physical fitness, particularly aerobic capacity in boys and muscle strength in girls, may help protect against cardiovascular risk in adolescents. The results of the AVENA study reflect the need to improve physical fitness in children and adolescents. It is likely that poor physical condition and changes in diet are the reasons why the increase in overweight and obese children and adolescents has become a public health problem in developing countries, and particularly in Latin American countries,[9] given that it has been observed that the populations of these countries show a greater predisposition to insulin resistance and low-grade inflammation at lower levels of abdominal obesity than those reported in developed countries.[3,4] There is a range of evidence to support this hypothesis. For example, the results of the most recent National Health and Nutrition Examination Survey in the United States showed a higher prevalence of overweight and obesity in children from minority Hispanic groups compared to Caucasian ones, suggesting that Hispanic children in the United States are more predisposed to weight gain.[10] These results support the hypothesis—formulated some years ago and known as the "thrifty phenotype"[11]—that suggests that when fetal nutrition is poor due to poor maternal nutrition, the developing fetus undergoes an adaptive response allowing growth of certain key organs at the expense of others, leading to an altered postnatal metabolism. According to this proposal, the fetal adaptive mechanism aims essentially at increasing the chances of postnatal survival in conditions of chronic malnutrition. It has been shown that inadequate intrauterine nutrition results in loss of structural units such as nephrons, cardiomyocytes, and β-pancreatic cells during the development of the fetal organic system.[12] These adaptations during fetal programming and development may be harmful if food is more abundant in the postnatal perdiod.[12] This suggestion has been reinforced by the series of studies conducted in individuals conceived during the period of hunger in Europe after the Second World War. Thus, at the age of 50 years, individuals conceived and born during the transient period of hunger showed higher rates of obesity, glucose intolerance, and coronary artery disease than individuals matched according to age, sex, ethnic origin, and place of residence who were not exposed to that period of hunger.[13-15] These observations provide solid support for the idea that nutritional deficiencies during critical periods of ontogenic fetal development may have a long-term influence through the expression of several genes by interaction with epigenetic mechanisms—which affect the conformation of chromatin and, therefore, the expression of certain genes (overexpression or silencing)—and also with changes in the accessibility of transcription factors.[16,17] These mechanisms result in increased or decreased synthesis of proteins such as angiotensin II, leptin, and adiponectin.[16] Currently, an increasing body of evidence lends support to the hypothesis that, in addition to inheriting the "thrifty genotype," individuals with metabolic syndrome experience an altered "epigenetic programing" during fetal development and in the postnatal period as a result of an inadequate maternal nutrition. After birth, this is translated into metabolic disorders characteristic of metabolic syndrome, such as insulin resistance and low-grade inflammation, if individuals are exposed to nutritional excesses.[17] These individuals may also suffer "transgenerational effects" as a result of the inheritance of epigenetic changes mainly experienced by their parents and/or grandparents.[17]

These observations may explain why, in developing countries, the frequency of maternal-fetal malnutrition and/or restriction in placenta growth and placenta function due to the high incidence of

diseases such as preeclampsia[18] result in epigenetic adaptations that increase the chances of fetal survival, although they may, in the future, contribute to the proven association between intrauterine malnutrition and the increased risk of hypertension, metabolic syndrome, DM2, and cardiovascular disease in adult life because, as mentioned earlier, the aggressive imposition of the western lifestyle in developing countries is contributing to a high intake of energy-rich foods, animal and vegetal fats, and refined sugars.[18,19]

The impact of this transition of dietary habits and lifestyles on the risk of acute myocardial infarction in Latin America has been demonstrated recently in the worldwide study of risk factors for acute myocardial infarction known as INTERHEART.[20,21] This study has identified risk factors associated with the presentation of a first acute myocardial infarction and has determined the population attributable risk (PAR). Although the new risk factors identified (changes in lipid profile, smoking, hypertension, abdominal obesity, psychosocial stress, changes in glucose metabolism, lack of physical activity, insufficient intake of fruit and vegetables, lower consumption of alcoholic drinks) explain more than 90% of the PAR in both men and women throughout the world, there was an important difference in the South American countries included (Chile, Colombia, Brazil, and Argentina). In those countries, abdominal obesity was the most important (48.5%)—a much higher figure than in the rest of the world (30.2%). In addition, in a similar population-based study in Costa Rica,[22] the PAR for acute myocardial infarction in 889 individuals without a history of DM2 who had not received any drugs, abdominal obesity was the most important risk factor (PAR, 29.3%), particularly among women (PAR, 35%). These results highlight the importance of abdominal obesity among the Latin American population as the chief risk factor for acute myocardial infarction, a very worrying finding given the epidemic of overweight and obesity in these countries.[23] Although there are no population-based studies on the prevalence of metabolic syndrome in Latin America, several studies in specific populations[24,25] show that prevalence lies between 25% and 40% for the adult population. These levels are similar to those published for Spain.[26-28]

ACUTE LOW-LEVEL INFLAMATION DEPENDENT ON BODY FAT

Recently, in a representative sample of school children in Bucaramanga, Colombia, we selected 325 school children (mean age, 10 years) and demonstrated a positive correlation between body mass index (BMI), systolic blood pressure, and C-reactive protein (CRP).[29] This finding confirms in children the correlation previously demonstrated in Colombian adults,[3] and reinforces the idea that there is a link between adipocyte content, particularly in visceral regions, and increased plasma concentrations of inflammatory markers such as CRP.

Several studies have assessed CRP concentrations in school children in developed countries.[30-33] Cook et al[33] measured CRP concentrations in a representative sample of the population of England and Wales that included 699 children aged 10 to 11 years. That study showed that serum concentrations of CRP correlated positively with BMI, heart rate, systolic blood pressure, fibrinogen, and high-density lipoproteins, but not with other lipid fractions. Interestingly, it was found that a small number of children of South-Asian origin had CRP levels 2.04 times larger than those of age-, sex-, and BMI-matched children (95% confidence interval [CI], 1.23-3.36). Ford[30] analyzed the results of the National Health and Nutrition Examination Survey of the United States (NHANES, 1999-2000), in which 2486 boys and girls aged between 3 and 17 years participated. A multiple linear regression analysis showed that BMI was the best predictor of CRP plasma concentration. This study also found differences related to ethnic origin in boys aged 8 to 17 years and girls aged 8 to 11 years. Specifically, they observed a higher CRP concentration in children of Mexican-American origin (geometric means of 0.60 and 0.76 mg/L; P=.023 and P=.015) in comparison with Caucasian-American children (geometric means of 0.35 and 0.39 mg/L). In Colombia, we found a significant positive correlation between BMI and CRP and, as a result, higher levels of CRP among boys and girls in the upper tercile of BMI. It is important to note that the concentrations of CRP that we encountered in the second terciles of BMI of both sexes in our population were as high as those registered in Caucasian-American children and European children of a similar age who were overweight or obese.[34,35]

Despite the possible differences in methodology for quantification of CRP in the different studies, and on the basis of data from our study in children and previous studies in our adult population,[24,36,37] is it attractive to suggest that the hypothesis that the Latin American pediatric population and children in southern Asia share a predisposition to greater inflammatory response at lower body fat levels than those reported for Caucasian populations. This ethnic predisposition had been demonstrated in Latin

American adults, who have a greater propensity to insulin resistance, low-grade inflammation, and greater cardiovascular risk with a lower abdominal circumference than that reported for the Caucasian population.[38,39]

In the study performed in Colombia, CRP concentrations were 25% higher in girls than in boys; however, this difference was not statistically significant. In adults, several studies have shown that the concentration of CRP is higher in women, and the correlations between BMI and CRP concentration are stronger than in men.[38,39] Ford[30] reported similar observations in adolescents in the United States. In the NHANES 1999-2000, it was reported that women aged 16 to 19 years had higher CRP concentrations than men of the same age. In a representative sample of young people in the province of Quebec, Canada, Lambert et al[40] found that CRP concentrations were greater in girls aged 9 to 16 years than in boys of the same age.

These variations in PCR concentration associated with BMI and sex among different ethnic groups and individuals of the same ethnic group living in countries with different durations of exposure to western lifestyles and marked socioeconomic differences support our hypothesis that certain populations and social classes may have a particular predisposition to insulin resistance, low-grade inflammation, and higher cardiovascular risk. This hypothesis may have important implications not only in the diagnostic criteria used to define entities such as metabolic syndrome and prediabetes but also in approaches to prevention and treatment (Figure).[3,18]

We recently undertook an analysis of the published results of 3 important studies aimed at determining the effectiveness of lifestyle interventions and the use of metformin in the prevention of progression of prediabetes to DM2 in subjects with abnormal fasting blood-glucose levels or with an abnormal response to glucose loading, in 3 different populations with ethnic and socioeconomic differences.[41] The Finnish study for diabetes prevention included 522 participants; the intervention group (n=257) received tailored nutritional advice aimed at reducing body weight and total intake of fats and saturated fats and increasing intake of vegetable fiber and physical activity.[42] The mean duration of follow-up was 3.2 years.[42] The Diabetes Prevention Program in the United States was a double-blind, placebo-controlled study that included 3234 American individuals.[43] The mean duration of follow-up was 2.8 years. The Indian Diabetes Prevention Program was not a placebo-controlled, blinded study, but the principal investigators were blinded to the outcomes.[44] The mean duration of follow-up was 30 months. The mean age was 55 years in the case of prediabetic Finns, 50 years in the American study, and 45 years in the Indian study. The Finns had a mean BMI of 31, abdominal circumference of 101 cm, and fasting glucose of 110 mg/dL, which increased to 159 mg/dL at 2 hours after loading. The Americans had a mean BMI of 34, abdominal circumference of 105 cm, and fasting glucose of 106 mg/dL, which increased to 165 mg/dL at 2 hours after loading. Finally, the Indians had a mean BMI of 25, abdominal circumference of 90 cm, and fasting glucose of 98 mg/dL, which increased to 153 mg/dL at 2 hours after loading. The rate of progression from glucose intolerance to full DM was very high in the Indian study—with an annual incidence of 18.3%—whereas the annual incidence was 6% in the Finnish population and 11% in the American population. Metformin at low doses (500 mg/d) was much more effective at reducing the rate of progression from glucose intolerance to full DM in the Indian population (14.5%) than in the American population (7.2%), in which the dose used was 1700 mg/d. This difference also reflects the small number needed to treat to avoid a new case of DM. This number was 6.9 in the Indian Diabetes Prevention Program and 13.9 in the American Diabetes Prevention Program.

These observations are a good example of how the socioeconomic differences present in the developed and developing world are also reflected in poorly defined epigenetic differences that determine a different adaptive biological behavior. In addition, these results support the hypothesis that diagnostic criteria, preventive measures, and therapeutic interventions recommended by the academic institutions of the developed world are not necessarily valid according to the results of research performed in populations with the different socioeconomic characteristics seen in developing countries.[3] Performing studies that identify the specific weight of each of the risk factors and assess the impact of preventive measures and therapeutic interventions in the conditions unique to populations in developing countries is an obligation for all parties involved in public health, that is, ministries, universities, scientific societies, and research institutes.

Latin America needs well-designed clinical trials to be conducted that assess the efficacy of interventions aimed at the prevention and treatment of cardiovascular and metabolic diseases. Studies of this type should preferably be coordinated and sponsored by the national science and technology organizations and be free of any commercial conflicts of interest and show an impact in medical practice and public health policies.

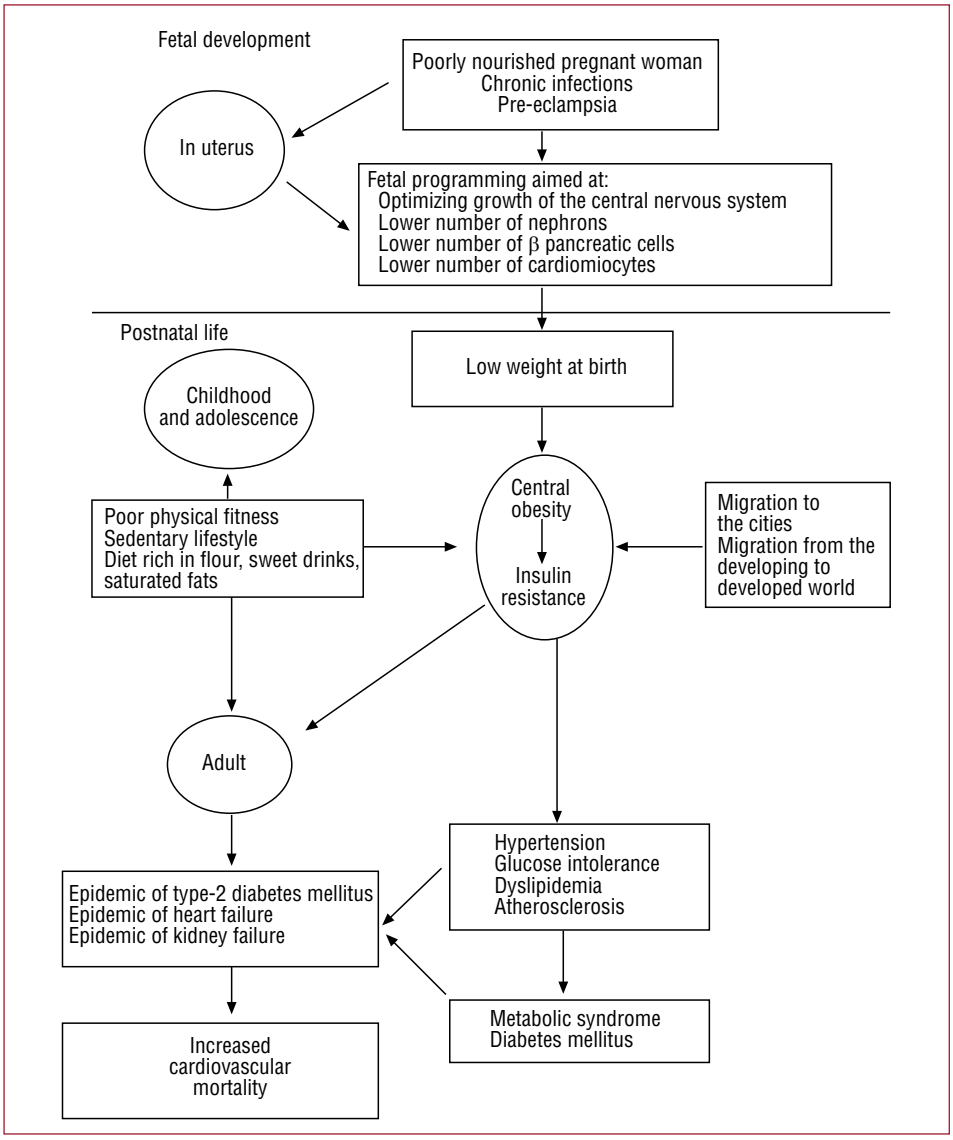

Figure. Maternal malnutrition and fetal programming associated with greater cardiovascular risk in adult life.

In addition, recent migration en masse of Latin American citizens to Spain where they subsequently adopt lifestyles different to those in their countries of origin suggests that there is a population group with a high risk of abdominal obesity, metabolic syndrome, DM2, and cardiovascular disease. This situation demands a strict epidemiological control on the part of the Spanish health system.

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