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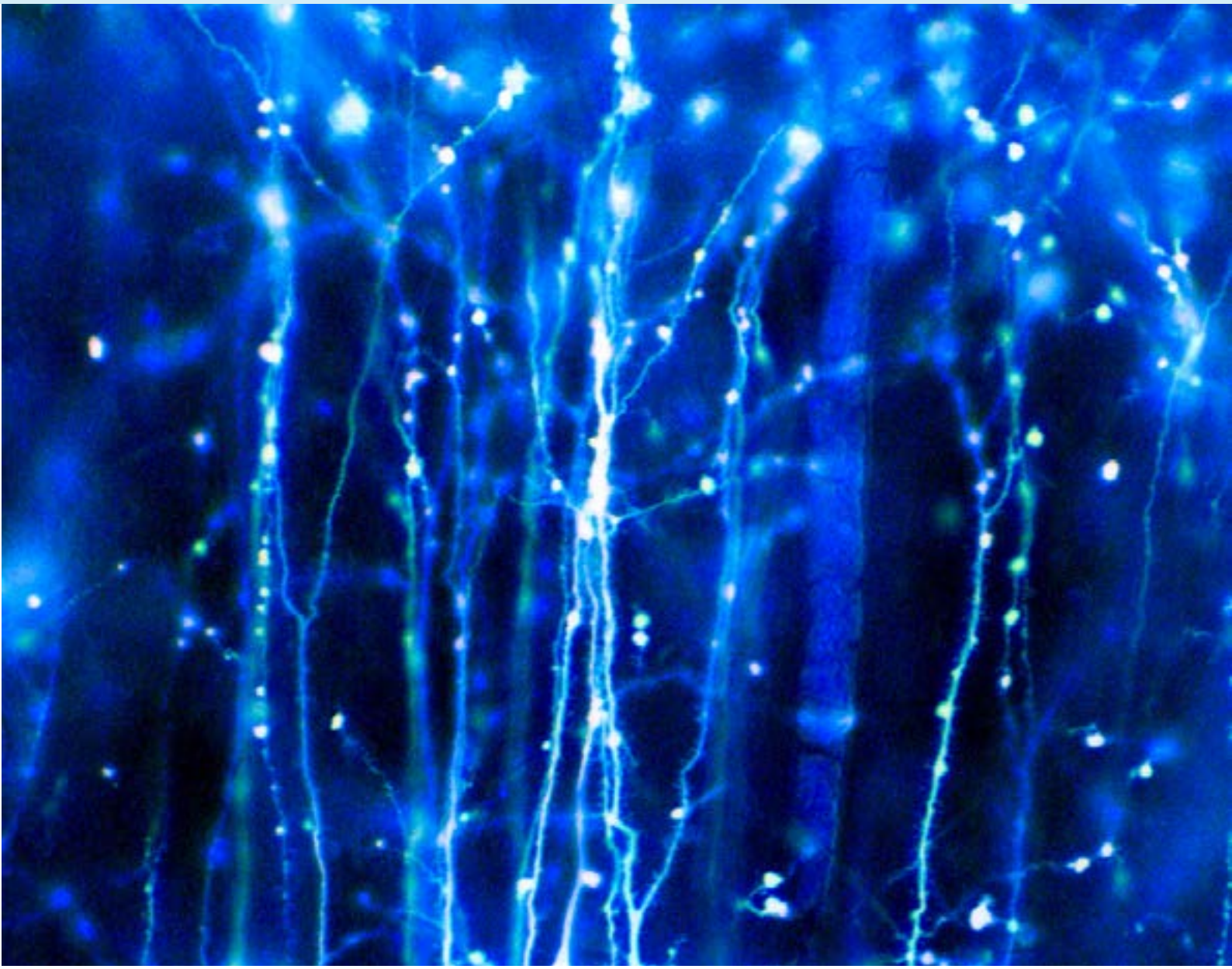

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DEVELOPMENTAL ORIGINS OF CARDIOVASCULAR, METABOLIC AND RENAL DISEASES IN ADULTHOOD INDUCED BY MICRONUTRIENT DEFICIENCIES

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ABSTRACT
Inadequate intake of minerals and vitamins during growth has become a major health problem in developed and developing countries, particularly in pregnant women, infants and children who have an unbalanced diet.
Studies in humans and animals have shown that micronutrient deficiency during development may be responsible for *in utero* programming of cardiovascular, metabolic and renal diseases in adulthood. Zinc deficiency is now widely recognized as a leading risk factor for morbidity and mortality since it is an essential trace element required for growth, reproduction, development of multiple organs and regulation of glucose and lipid metabolism. This micronutrient is also a catalytic, structural and regulatory component of enzymes and has antioxidant, anti-apoptotic and anti-inflammatory properties.
This work is an updated review of the association between micronutrient deficiency during fetal and postnatal life and the development of cardiovascular, renal and metabolic diseases in adulthood. The effects induced by zinc deficiency during prenatal and postnatal life are described in greater depth.
Keywords: developmental programming, micronutrients, zinc deficiency, cardiovascular, renal and metabolic diseases

RESUMEN
La ingesta inadecuada de minerales y vitaminas durante el crecimiento se ha convertido en un problema de salud importante en los países desarrollados y en desarrollo, particularmente en mujeres embarazadas, bebés y niños que tienen una dieta desequilibrada.
Los estudios en humanos y animales han demostrado que la deficiencia de micronutrientes durante el desarrollo puede ser responsable de la programación *in útero* de enfermedades cardiovasculares, metabólicas y renales en la edad adulta. La deficiencia de zinc es ampliamente reconocida como un factor de riesgo de morbi-mortalidad, ya que es un oligoelemento esencial requerido para el crecimiento, la reproducción, el desarrollo de múltiples órganos y la regulación del metabolismo de la glucosa y los lípidos. Este micronutriente es también un componente catalítico, estructural y regulador de las enzimas y tiene propiedades antioxidantes, antiapoptóticas y antiinflamatorias.
Este trabajo es una revisión actualizada de la asociación entre la deficiencia de micronutrientes durante la vida fetal y postnatal y el desarrollo de enfermedades cardiovasculares, renales y metabólicas en la edad adulta. Los efectos inducidos por la deficiencia de zinc durante la vida prenatal y postnatal se describen con mayor profundidad.
Palabras claves: Programación durante el desarrollo, micronutrientes, deficiencia de zinc, enfermedades cardiovasculares, renales y metabólicas.

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Introduction

Inadequate intake of micronutrients during critical periods of growth has become a major health problem in developed and developing countries, particularly in pregnant women, infants and children who have an unbalanced diet. This nutritional disorder includes minerals and vitamins such as zinc, copper, iron, calcium, vitamin A and vitamin D, which are needed in small quantities for biochemical and metabolic processes. Micronutrient deficiency, also known as hidden malnutrition, can occur in individuals with adequate, low or high body mass index [1].

Vitamins and minerals are essential for human health and development, since they participate in numerous biochemical functions. Trace elements, such as zinc and selenium, are part of transcription factors and are also involved in the modulation of enzymatic activity as cofactors or as part of prosthetic groups. On the other hand, vitamins and their metabolites are involved in complex biochemical reactions required for intermediate and energy metabolism. Finally, many vitamins (vitamin E, A, C, β-carotenes) and minerals (zinc, copper, manganese and selenium) have antioxidant properties by modulating the activity of antioxidant enzymes (superoxide dismutase and glutathione peroxidase), inducing the synthesis of metallothioneins, protecting the sulfhydryl groups of proteins and glutathione from oxidation and inhibiting NADPH oxidases [2].

Inadequate supply of trace elements can cause fetal development abnormalities and predispose children to disorders later in life. In recent years, numerous epidemiological and experimental studies have shown that metabolic and nutritional imbalances during a critical time window in development have persistent effects on the health of the offspring and may be responsible for *in utero* programming of diseases such as obesity, diabetes and high blood pressure in adulthood [3, 4].

The aim of the current work is to carry out an updated review about the association between micronutrient deficiency during fetal and postnatal life and the development of cardiovascular, renal and metabolic diseases in adulthood. The effects induced by zinc deficiency during prenatal and postnatal life are described in greater depth.

Developmental programming of chronic diseases in adult life

Barker DJ et al. were the first to describe that low birth weight was associated with an increased risk of death from cardiovascular diseases [5]. Afterwards, multiple epidemiological and experimental studies found associations between the quality of pre and/or postnatal growth and the increased risk of developing chronic diseases, such as diabetes type II, high blood pressure, obesity, insulin resistance and metabolic syndrome [4, 6].

The fetal programming hypothesis suggests that an injury during fetal life, which leads to restricted intrauterine growth, not only results in low birth weight but also sets in motion adaptive responses that can lead to the loss of structural units (nephrons, cardiomyocytes, β pancreatic cells, skeletal muscle cells) in order to maintain the development of other organs, such as the brain. These adaptive changes can bring immediate advantages by increasing perinatal survival in a poor nutritional environment, but they program in individuals a lower morphological and functional capacity for their life. Moreover, it was proposed that these adaptive responses could be more harmful when those individuals who have a minor morphological and functional capacity face a postnatal environment with greater metabolic demands. These findings are supported by studies in humans suggesting that low birth weight

followed by accelerated postnatal growth is associated with an increased risk of death from cardiovascular disease [6, 7].

Different experimental models in rats, sheep, rabbits and pigs have been used to induce an adverse fetal environment and resemble intrauterine growth restriction conditions in humans (Figure 1). Micronutrient deficiency during pregnancy can affect fetal development through multiple mechanisms and induce fetal adaptations during critical periods of organogenesis that determine the functional capacity of the cardiovascular, renal and metabolic systems. Within these mechanisms are epigenetic changes, morphological alterations, activation of apoptotic and inflammatory processes and hormonal and metabolic alterations [7].

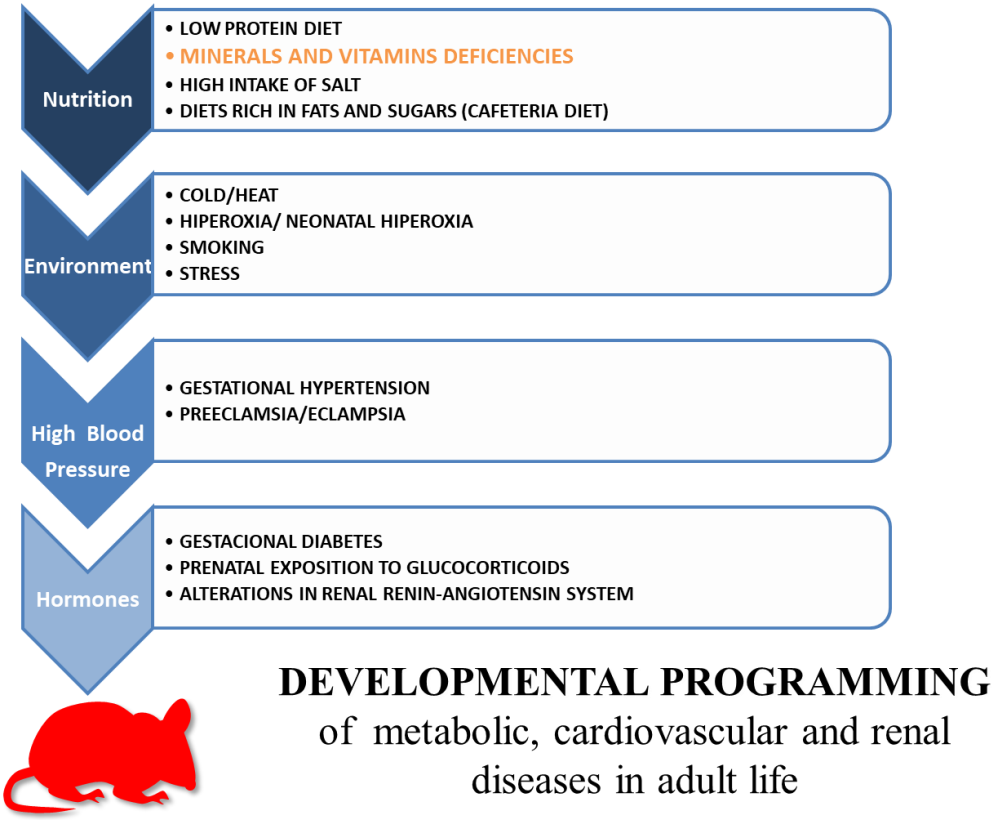

Figure 1. Animal models used to induce an adverse fetal environment.

Zinc deficiency is now widely recognized as a leading risk factor for morbidity and mortality. Approximately 17.3% of the world's population are at risk of inadequate intake of absorbable zinc and the global mortality burden due to zinc deficiency stands at 116,000 deaths per year, only second to that of vitamin A deficiency among micronutrient deficiencies [8].

Zinc deficiency is usually due to inadequate zinc intake or absorption, increased losses of zinc from the body, or increased zinc requirements. Zinc is found in a wide variety of foods. Red meat, poultry, whole-grain cereals, beans, nuts, certain types of seafood, and dairy products provide the highest concentrations of zinc. However, bioavailability of zinc from legumes, grains, and plant foods is lower than that from animal foods because they contain high amounts of phytates that bind zinc and inhibit its absorption. Therefore, vegetarians are at risk of this deficiency. Moreover, the body has only limited zinc stores that are easily depleted and cannot compensate for longer periods of zinc deficiency [9].

Zinc is an essential trace element required by all living organisms for many physiologic functions, including growth, reproduction and development of multiple organs, including the brain, lungs, skeleton, kidneys, and heart. Over 300 enzymes have been shown to contain zinc, either directly involved in catalysis as a cofactor or for structural stabilization. Nitric oxide synthase (NOS) is a family of metalloenzymes involved in blood pressure regulation and in cardiovascular and renal functions that use zinc as a cofactor. This micronutrient is also involved in the reduction of oxidative stress and in the inhibition of apoptosis and inflammation (Figure 2). Therefore, there is increasing interest in the possible involvement of zinc deficiency, during different periods of life, in the pathogenesis of cardiovascular, metabolic and renal diseases [10, 12].

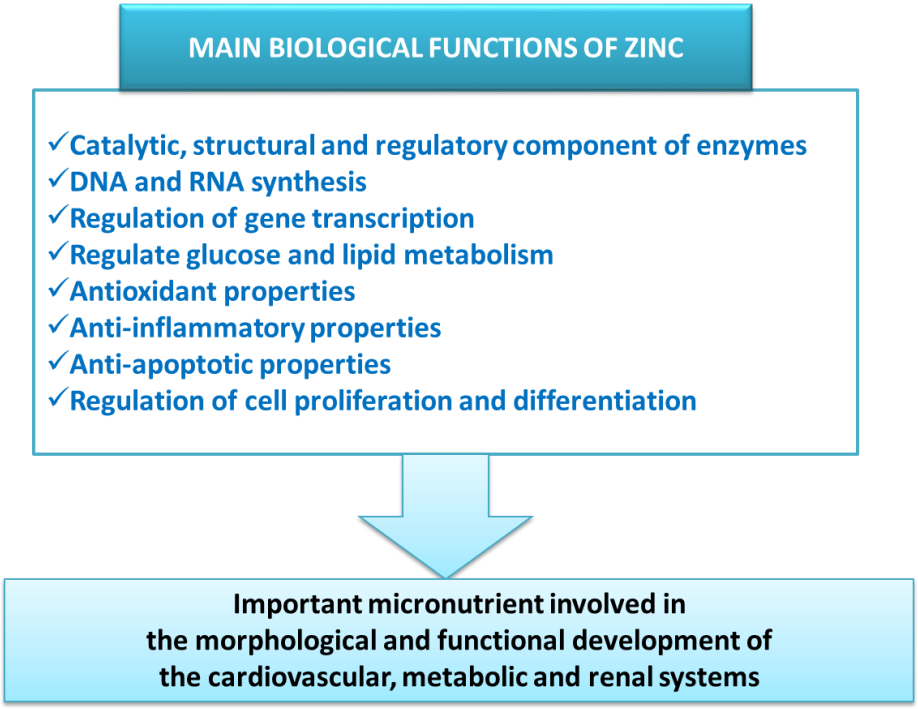

Figure 2. Main biological functions of zinc.

Cardiovascular, renal and metabolic alterations induced by zinc deficiency during prenatal and postnatal life.

Moderate zinc deficiency during intrauterine and postnatal growth in rats is a developmental programming model of cardiovascular, metabolic and renal diseases in adult life (Figure 3). Dietary zinc restriction during fetal life and lactation induces growth delay in male and female offspring and increases systolic blood pressure (SBP) only in adult males [13, 14]. In this regard, zinc can stimulate cell proliferation by up-regulating gene expression of the DNA synthesizing enzyme deoxythymidine kinase [15] and by stimulating synthesis of the growth hormone and insulin-like growth factors [16]. These results are in agreement with other experimental and clinical studies showing that different insults during early stages of development are associated with low birth weight and the onset of hypertension in adult life [17, 18]. On the other hand, the sex differences observed in SBP are consistent with findings across other developmental programming animal models showing that female offspring exhibit a protected status regardless of the species or specific fetal insult [19].

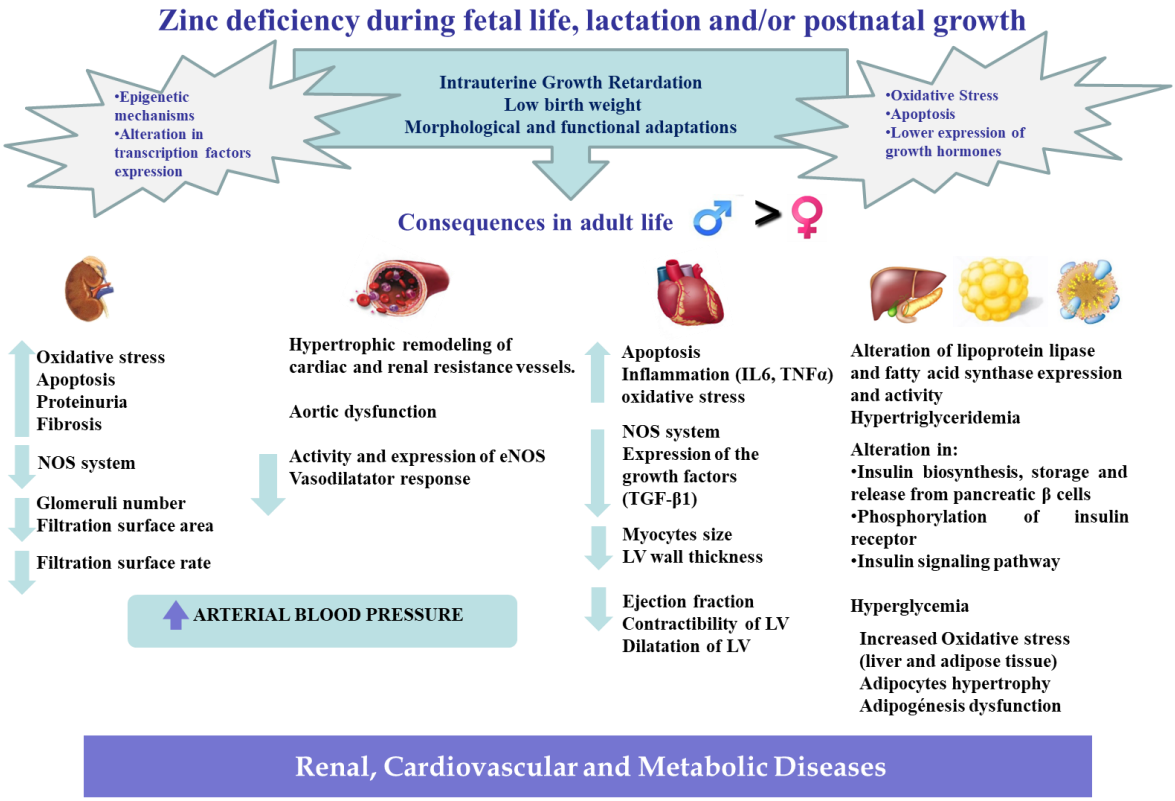

Figure 3. Cardiovascular, renal and metabolic consequences of zinc deficiency during fetal life, lactation and/or postnatal growth.

Moderate zinc restriction during prenatal and postnatal development results in the programming of the morphological and functional capacity of the kidney in adult life. In this regard, it has been reported a decrease in glomerular filtration rate associated with a reduction in the number of nephrons and glomerular filtration surface, an increase in renal oxidative stress, activation of apoptotic and fibrotic processes, proteinuria and a decrease in the activity of the renal nitric oxide (NO) system. In addition, restitution of adequate zinc content in the diet after weaning cannot correct the alterations observed in SBP, glomerular filtration rate, NO system activity and renal morphology. On the other hand, similarly as other models of fetal programming, animals exposed to zinc deficiency during fetal life have a lower birth weight which correlates negatively with the lower number of nephrons and the higher levels of SBP in adult life [20, 21].

Moreover, our findings show that dietary zinc restriction during fetal life, lactation and/or post-weaning growth alters vascular function in adult male and female offspring, programming lower endothelial-dependent relaxant responses to Acetylcholine (Ach) in thoracic aortic rings [14]. The smooth muscle relaxation induced by ACh depends on NO produced in the endothelial cells. However, we did not observe significant changes in the smooth muscle relaxation response to a NO donor, like sodium nitroprussiate, among the studied groups. These results suggest a preserved action of NO in smooth muscle, and that a lower endothelial production or bioavailability of NO could be responsible for the lower vasodilator response to ACh. In this regard, the aortas of zinc-deficient male and female offspring show lower endothelial NOS (eNOS) activity at early periods of postnatal life that persisted until adulthood. The decrease in NO system activity is observed even when these

animals were fed an adequate zinc diet during post-weaning life, suggesting that this fetal injury can program the functional capacity of the NO system in adulthood.

Moreover, when evaluating vascular oxidative state, we did not observe changes in NAPDH oxidase activity or in thiobarbituric acid reactive substances (TBARS) levels in adult male or female rats exposed to this nutritional deficiency. Thus, it could be postulated that the lower vasodilator response to ACh would be caused mainly by a decrease in NO production by eNOS rather than a decrease in NO bioavailability. Moreover, adult female rats exhibit a higher protected status than males since they show higher eNOS activity and/or expression in aortic tissue[14]. These could be associated to the protective effect of estrogens and progesterone that can increase eNOS-derived NO production in vascular tissue [22].

In addition, zinc deficiency during fetal and postnatal life programs a lower contractile response to Angiotensin II (AngII) and caffeine in thoracic aorta rings of adult male and female offspring, associated to a lower mobilization of calcium from the sarcoplasmic reticulum to the cytosol during smooth muscle contraction [14].

On the other hand, cardiac development may be particularly sensitive to zinc deficiency. In rats, the high incidence of fetal heart abnormalities has been associated with a decrease in the expression of specific cardiac genes that contain zinc-finger transcription factors. Moreover, apoptosis constitutes an important mechanism during embryonic development. However, zinc deficiency can induce changes in apoptosis patterns that can result in morphogenesis alterations. Lopez et al. have reported that maternal zinc deficiency induces excessive embryonic death in regions and tissues populated by neural crest cells that are essential for normal morphogenesis of the heart [23].

The consequences of this micronutrient imbalance on the developing fetus would induce adaptive responses of cardiac myocytes in early postnatal life which would become manifest later in adulthood. In males, this nutritional injury decreases myocytes sizes, left ventricular (LV) wall thickness, ejection fraction and contractility, which would not allow the heart to compensate the higher levels of blood pressure that these animals show in adult life. Moreover, zinc-deficient male rats showed hypertrophic remodeling of coronary arteries architecture associated with the chronic increase in arterial blood pressure. On the other hand, females would be less sensitive to this micronutrient deficiency since they exhibit no significant structural or functional heart alterations. Moreover, adequate zinc content in the diet during postnatal life could reverse some of the detrimental effects of this earlier micronutrient deficiency on cardiac tissue[13]. Diverse biological zinc-dependent cardiac processes could contribute to the onset of these morphological and functional cardiac alterations. In this regard, adult zinc deficient rats show lower expression of growth factors like transforming growth factor beta 1 (TGF-β1), a decreased NO system activity, an increase in apoptotic and inflammatory processes and an activation of oxidative stress [25].

Zinc deficiency during pregnancy and lactation would also play an important role in the programming of metabolic alterations. In fact, zinc deficiency is known to be a common phenomenon in diabetic patients. On the other hand, low and chronic zinc intake is associated with a reduction in insulin secretion and tissue resistance and with an increase in circulating glucose [26].

Zinc is an essential trace element directly involved in the physiology and action of insulin, since it is crucial for insulin biosynthesis, storage forming complexes with zinc and release from β cells of the pancreas. In addition, zinc has been considered as a mimetic insulin factor since it acts as a second messenger, activating cellular signaling pathways that generate insulin-like effects on the metabolism of carbohydrates and lipids. In this regard, zinc favors

the actions of insulin in target tissues increasing phosphorylation of its receptor and proteins involved in the insulin signaling pathway, as protein-kinase B [27, 28].

Our findings show that dietary zinc restriction during fetal life, lactation and post-weaning growth induces an increase in glycemia after a 12-hour fasting and at 180 minutes post-glucose overload. These alterations would reflect a lower glucose tolerance programmed by zinc restriction during fetal life and lactation in male rats. Moreover, we demonstrated that an adequate zinc diet during post-weaning life could revert most of these metabolic alterations [29]. However, other studies showed that maternal zinc restriction can irreversibly modulate insulin synthesis in adulthood. Padmavathi et al reported a decrease in fasting plasma insulin levels and after glucose overload, without changes in glucose tolerance, in adult rats exposed to zinc deficiency during fetal life [30].

Moreover, zinc plays a key role in lipids and lipoproteins metabolism since it is important for the expression and activity of lipoprotein lipase and fatty acid synthase [31]. Chronic zinc restriction also induces a rise in serum triglycerides concentration without changes in the concentrations of total cholesterol, HDL cholesterol and non-HDL cholesterol in adult male rats[29]. This result is relevant since hypertriglyceridemia contributes significantly to cardiovascular risk and the associated mortality, independent of cholesterol levels [32].

The metabolic disturbances induced by zinc restriction could be associated with alterations in retroperitoneal adipose tissue (RPAT) since white adipose tissue constitutes an energy deposit, an endocrine organ and is one of the main target organs of insulin [31]. In our experimental model, male rats exposed to zinc deficient diet during prenatal and postnatal life show adipocyte hypertrophy, lower adipose tissue mass and an increase in lipid peroxidation associated with a decrease in the activity of antioxidant enzymes [29]. Chronic zinc deficiency would affect the adipogenesis process, since a large part of the transcription factors involved in this process have zinc finger motifs [33]. Female zinc deficient offspring do not exhibit alterations in intermediate metabolism and RPAT. Furthermore, female rats showed higher levels of HDL cholesterol and lower values of Castelli's risk index, suggesting a reduced cardiovascular risk compared with males [29]. This could be due, at least in part, to the protective effect of estrogens. It has been reported that estrogens exert antioxidant protection, increase insulin sensitivity and prevent inflammation and lipid accumulation on different tissues and cells, like skeletal muscle, adipose tissue, liver and immune cells [34].

Conclusion

Micronutrient undernutrition during critical periods of growth has become an important health issue in developing and developed countries, particularly among pregnant women and children having an imbalanced diet. The current economic crisis, the unhealthy lifestyle and the increased consumption of processed foods based on flours, sugars and fats in developed countries, has been the main impulse for this hidden malnutrition.

Experimental studies suggest that moderate zinc deficiency during critical periods of prenatal and postnatal development programs cardiovascular, renal and metabolic diseases in adulthood. Moreover, as in many developmental programming models, we found that male and female offspring exhibit different phenotypes in response to this nutritional injury.

The fact that even seemingly minor influences, such as composition of diet during pregnancy, lactation, and postweaning growth can have major consequences in adult life, underscores the critical importance of perinatal care optimization for better management and prevention of adult diseases.

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Trabajos publicados (2018-2020)

-Cardiac changes in apoptosis, inflammation, oxidative stress and nitric oxide system induced by prenatal and postnatal zinc deficiency in male and female rats. Juriol L, Gobetto MN, Mendes Garrido F, Dasso M, Pineda G, Güttlein L, Carranza A, Podhajcer O, Toblli J, Elesgaray R, Arranz C, Tomat AL. Eur J Nutr. 2018 Mar;57(2):569-583.

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