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Review

Zinc restriction during different periods of life: Influence in renal and cardiovascular diseases

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ABSTRACT

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. Zinc is a widely studied microelement in infant feeding because it is a component of several enzymes involved in intermediary metabolism ranging from growth to cell differentiation and metabolism of proteins, carbohydrates, and lipids.

Human and experimental studies have reported an association between zinc deficiency and the etiopathogenesis of cardiovascular and renal diseases like hypertension, atherosclerosis, congestive heart failure, coronary heart disease, and diabetes. The main links between the development of these pathologies and zinc deficiency are multiple mechanisms involving oxidative stress damage, apoptosis, and inflammation.

A substantial body of evidence suggests that a poor in utero environment elicited by maternal dietary or placental insufficiency may "programme" susceptibility in the fetus to later development of cardiovascular, renal, metabolic, and endocrine diseases. Zinc deficiency in rats during intrauterine and postnatal growth can also be considered a model of fetal programming of cardiovascular and renal diseases in adult life. Dietary zinc restriction during fetal life, lactation, and/or postweaning induces an increase in arterial blood pressure and impairs renal function in adult life.

This review focuses on the contributions of experimental and clinical studies to current knowledge of the physiologic role of zinc in the cardiovascular and renal systems. Moreover, this review examines the relationship between zinc deficiency during different periods of life and the development of cardiovascular and renal diseases in adult life.

Introduction

Micronutrient undernutrition during critical periods of growth has become an important health issue in developing and developed countries, particularly among pregnant women, infants, and children having an imbalanced diet. This nutritional disorder includes deficiency of minerals and vitamins, such as zinc, iron, calcium, vitamin A, and vitamin D, that are essentially required in small quantities for metabolic and biochemical processes. Accordingly, these micronutrient deficiencies, known as hidden malnutrition, are not only present in undernourished people but also in individuals with a normal or higher body weight [1,2].

Global recognition of the importance of zinc nutrition in public health has expanded dramatically in recent years. Deficiency of zinc in low-income populations is not a new phenomenon. However, zinc deficiency is now widely recognized as a leading risk factor for morbidity and mortality [3,4]. The recent *Lancet* series on maternal and child undernutrition concluded that zinc deficiency is responsible for ~4% of child mortality and disability-adjusted life-years [3]. Moreover, the Food and Agricultural Organization estimates prevalence of inadequate zinc intake to be as high as 20.5% worldwide [5]. Zinc deficiency is usually due to inadequate zinc intake or absorption, increased losses of zinc from the body, or increased zinc requirements [6–8]. Therefore, the Steering Committee of the International Zinc Nutrition Consultative Group reexamines the latest information about strategies that have been developed to enhance zinc nutrition and recommended supplementation,

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fortification, and dietary diversification to control zinc deficiency [9].

Zinc is an essential trace element required by all living organisms for many physiologic functions, including growth and reproduction, and its deficit can affect the development of multiple organs, including the brain, lungs, skeleton, kidneys, and heart [10,11]. Therefore, there is increasing interest in the possible involvement of zinc deficiency, during different periods of life, in the pathogenesis of cardiovascular and renal diseases.

This review focuses on the contributions of experimental animal models and clinical studies to current knowledge of the physiologic role of zinc in the cardiovascular and renal systems. Moreover, this review examines the relationship between zinc deficiency during different periods of life and the development of cardiovascular and renal diseases.

Zinc requirements and zinc deficiency

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. Moreover, the body has only limited zinc stores that are easily depleted and cannot compensate for longer periods of zinc deficiency [6,12–14].

Although severe zinc deficiency has been described in infants and children, it is rare and is usually found only in children with acrodermatitis enteropathica, a genetic disorder of decreased capacity for intestinal zinc absorption, by prolonged used of zinc-free intravenous nutrition, or in breastfed infants of mothers with low milk zinc [6,15].

In contrast, marginal and moderate zinc deficiency is believed to be prevalent in pregnant women, infants, children, and elderly people worldwide, primarily owing to low zinc intake or low dietary zinc bioavailability [7–9,16]. Physiologically, the zinc serum level declines during pregnancy, mainly due to hemodilution and decreased albumin levels. Moreover, intestinal absorption is not increased during pregnancy and thus the additional zinc requirements of fetal and placental tissues must be covered by increased intake and from maternal tissues [17]. Moreover, breast milk is the only dietary source of zinc for exclusively breastfed infants until 6 months and it remains a potentially important source of zinc for older infants and young children who continue breastfeeding beyond early infancy. Milk zinc concentration declines rapidly during the first few months postpartum and more slowly thereafter. Therefore, lactation can also deplete maternal zinc stores [18]. Consequently, insufficient intake further aggravates the physiologic drop in zinc during pregnancy and lactation.

On the other hand, several physiologic, social, psychologic, and economic factors may contribute to zinc deficiency in many elderly people [16]. Moreover, recent literature suggests that bariatric surgery patients are at risk of micronutrient deficiencies like zinc and should receive daily multivitamin and multitrace mineral supplements. It was recommended that bariatric surgery patients take an additional supplement of 6.5 mg of zinc per day. This would be especially important in pregnant women who have undergone bariatric surgery in order to prevent maternal and fetal complications [19]. Collectively, these data support the concept that suboptimal zinc status is common in many stages of life.

Serum or plasma zinc concentration, assessment of the adequacy of zinc intakes, and the prevalence of stunting in children are important ways of evaluating the risk of zinc deficiency in a population. The main prevalence of zinc deficiency is observed in developing countries of Africa, Asia, and Central America as well as in Andean countries [7]. A national survey of nutrition and health conducted by the National Maternal and Child Health, between 2004 and 2005 in Argentina, showed that 11.6% of infants (6 to 23 mo), 4.2% of children (2-5 y), 33.5% of women (10-33 y), and 52% of pregnant women ingest inadequate amounts of zinc. Moreover, this study showed that 8% of children aged between 6 mo and 5 y are stunted according to WHO curves [20].

A systematic review of relevant supplementation trials in infants and prepubertal children performed in developing countries indicates that zinc supplementation induces a reduction in child mortality and increases linear growth and weight gain in previously stunted or underweight children [21,22]. A recent nutritional study performed in western India demonstrated that the lactovegetarian diets of adolescent girls were deficient in energy, protein, and micronutrients including zinc compared with the recommended dietary intakes of India. Moreover, this study showed that dietary interventions in the form of cereal-based recipes with high bioavailability have the potential to alleviate the deficiencies of zinc and other micronutrients in adolescents [23]. Therefore, zinc supplementation programs should be considered for children in countries with an elevated risk of zinc deficiency to reduce morbidity and mortality and to enhance child growth.

Physiologic roles of zinc in the cardiovascular and renal systems

Maintenance of discrete subcellular pools of zinc is critical for the functional and structural integrity of cells. Zinc plays a role in gene expression and is essential for cell division, differentiation, and development of multiple organs, including the kidneys and heart [10,11].

Over 300 enzymes have been shown to contain zinc, either directly involved in catalysis as a cofactor or for structural stabilization [6,11]. 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 [24].

The NOS are a family of enzymes that catalyze the synthesis of nitric oxide (NO) and L-citruline from L-arginine in the presence of NADPH, O_2, and cofactors. The NOS family consists of three isoforms: neuronal, endothelial (eNOS), and inducible (iNOS), which are expressed in many tissues, including endothelium and vascular smooth muscle, heart, and kidney. It is well known that NO is an important factor in the regulation of blood flow, arterial blood pressure, glomerular filtration rate, sodium and water renal excretion, myocardial contractility, and heart rate in mammals [25–28]. All three isoforms of NOS show a zinc thiolate (ZnS_4) cluster. This zinc center is considered to play an essential role in the catalytic activity of this enzyme by maintaining stability of the dimer interface and integrity of the tetrahydrobiopterin binding site [29].

This micronutrient is also involved in the reduction of oxidative stress and in the inhibition of apoptosis and inflammation. Zinc limits the extent of damage induced by free radicals and thereby suppresses some of the signaling pathways leading to caspase activation and apoptosis. Moreover, it directly inhibits certain apoptotic regulators, principally caspase 3, 6, 9,

and calcium-magnesium-dependent endonuclease. Figure 1 describes the possible mechanisms by which zinc can exert antioxidant, antiapoptotic, and antiinflammatory actions [30,31]. On the other hand, Prasad has reported that zinc supplementation to normal healthy and elderly subjects, for 6 months, lowered the oxidative stress markers and the production of C-reactive protein, inflammatory cytokines, and adhesion molecules in macrophages and monocytes [32].

Therefore, generation of oxidative stress, apoptosis, and inflammation processes in tissues are consequences of zinc deficiency that can contribute to the development and/or maintenance of several chronic diseases such as atherosclerosis and related vascular diseases, congestive heart failure, coronary heart disease, renal insufficiency, hypertension, diabetes mellitus, cancer, immunologic disorders, and neurodegeneration.

Impact of zinc deficiency on the development of cardiovascular and renal diseases: clinical and experimental studies

There is increasing interest in the possible involvement of zinc in the pathogenesis of cardiovascular and renal diseases. Many human studies have reported an association between the changes in zinc metabolism that lead to zinc deficiency and the etiopathogenesis of cardiovascular diseases like primary arterial hypertension [33,34]. Moreover, Chiplonkar et al. have shown that zinc intake and erythrocyte membrane-zinc were negatively correlated with blood pressure in a traditional Indian lactovegetarian population with a great risk of developing mild zinc deficiency [35].

However, until now, there were no systematic reviews or meta-analyses that evaluate the relationship between zinc deficiency and/or supplementation programs in different periods of life and the incidence of cardiovascular and renal diseases, in developing and developed countries.

On the other hand, experimental studies have shown that severe zinc deficiency during adult life does not change blood pressure in normotensive rats [36], but it can aggravate hypertension in spontaneously hypertensive rats [37].

Furthermore, zinc may play a role in the preservation of renal function. Kurihara et al. showed that severe zinc deficiency in adult rats induced a decrease in glomerular filtration rate and renal blood flow, and increased renal vascular resistance. These alterations were associated with an enhanced formation of superoxide anion through low Cu/Zn SOD activity in the kidneys of zinc-deficient rats [38].

However, the role of zinc in renal function seems to be more crucial in diseased animals than in healthy ones. Yanagisawa et al. reported that zinc deficiency would aggravate tubulointerstitial nephropathy and glomerular hemodynamics in adult rats with unilateral ureteral obstruction through an increment in the biological action of the vasoconstrictors angiotensin II and endothelin [39].

Moreover, zinc deficiency may also play a role in the progression of renal failure. The predominant effect of renal insufficiency on zinc homeostasis is hypozincemia due to

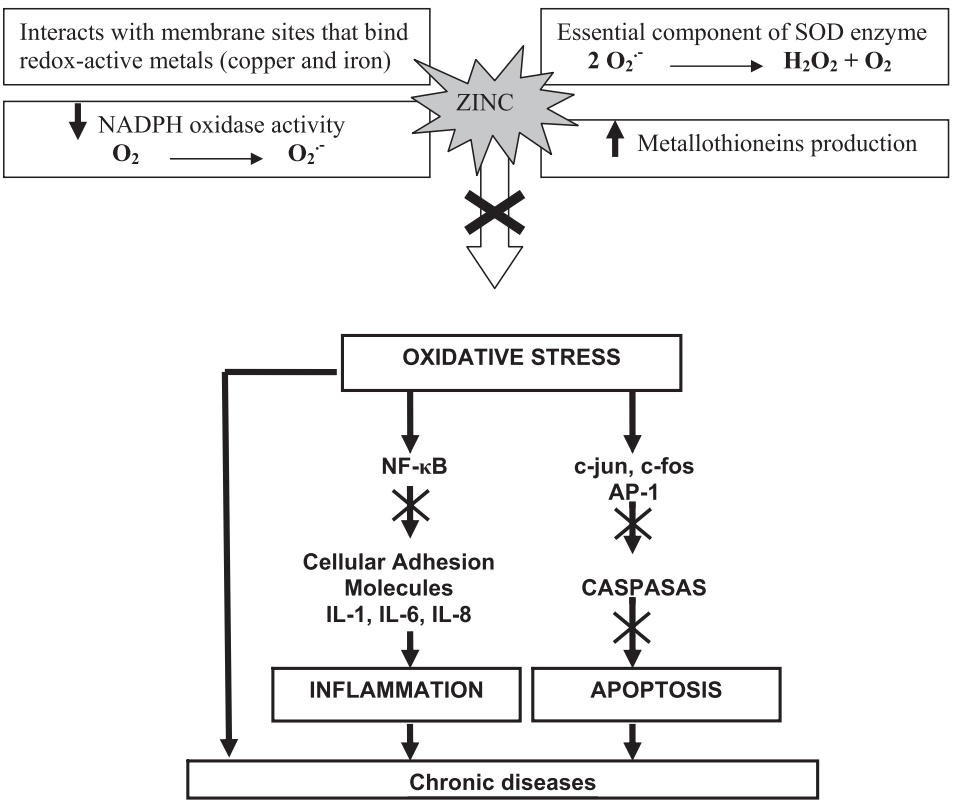

Fig. 1. A schematic diagram illustrating the antioxidant, antiapoptotic, and antiinflammatory properties of zinc. Zinc interacts with membrane sites that might otherwise bind copper and iron that catalyze the production of radical hydroxyl. It is an inhibitor of NADPH oxidases that catalyze the production of superoxide anion (O_2^-) from oxygen (O_2) and is an essential component of superoxide dismutase (SOD) enzyme that catalyzes the dismutation of the O_2^- to hydrogen peroxide (H_2O_2). It also induces the production of metallothioneins, which are scavengers of free radicals. Zinc can reduce the production of inflammatory interleukins (IL) and adhesion molecules in macrophages and monocytes by inhibiting the nuclear transcription factor kB (NF-kB) activation through the decrease in reactive oxygen species. Zinc suppresses the signaling pathways involving c-jun and c-fos genes and AP-1 transcriptor factor leading to caspase activation and it directly inhibits caspase 3, 6, 9, and calcium-magnesium-dependent endonuclease. Bold cross bars represent pathways possibly inhibited by zinc.

increased urinary zinc excretion. Moreover, many clinical studies have reported that patients undergoing hemodialysis exhibit zinc deficiency [40].

Because environmental factors such as diet during postnatal growth may be of great importance in determining blood pressure and renal function in adults, we studied the effects of moderate zinc restriction during postweaning growth on the cardiovascular and renal system. In our earlier works, we reported that animals exposed to low zinc intake during growth exhibited an increase in arterial blood pressure levels and a decrease in glomerular filtration rate from day 30 after weaning up to the end of dietary treatment (adulthood) (Fig. 2). These alterations were related to a decrease in the vascular and renal NO system, an increase in systemic and renal oxidative stress, and activation of apoptosis in the renal cortex that provoked a decrease in the filtration surface area of cortical and juxtamedullary nephrons [41,42].

The decrease in NO system activity reported in this model was associated with a lower activity in NOS activity and to a decrease in NO bioavailability [41,42]. It is probable that zinc deficiency could reduce zinc labile pools required to create the zinc tetrathiolate center at the NOS dimer interface that has structural and catalytic functions [24,29]. On the other hand, the increase in oxygen free radicals such as superoxide anions in vessel walls and kidneys of zinc-deficient rats would cause a decrease in the action of NO through the formation of peroxinitrite. Therefore, the enhanced oxidative stress condition would contribute to the development of higher levels of blood pressure through an impaired vasodilator tone and renal function, presumably by decreasing NO bioavailability [41–43]. In addition, anionic oxidants such as peroxinitrite could disrupt the zinc-thiolate cluster of NOS, oxidizing the coordinated thiols in the processes of releasing zinc. This should result in the uncoupling of the enzyme and generation of more oxidant species like superoxide anion [24,44].

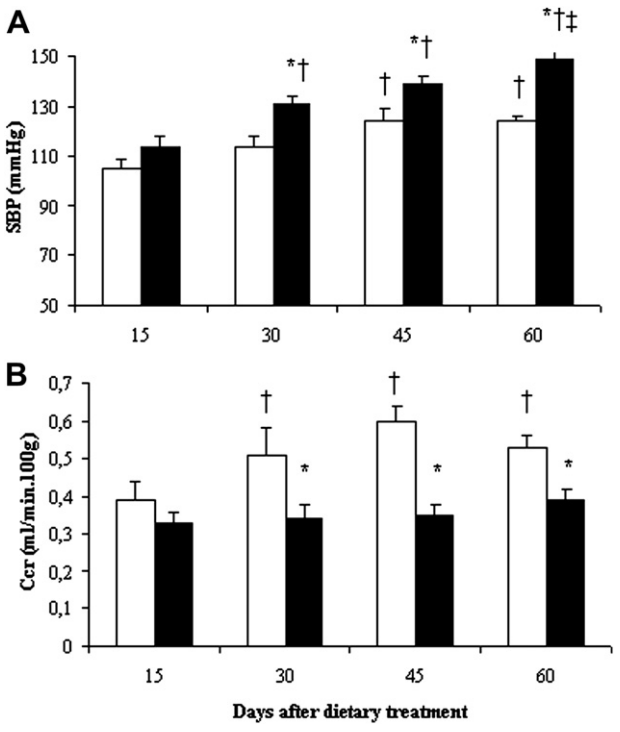

Fig. 2. (A) Systolic blood pressure (SBP), measured by tail-cuff technique, and (B) creatinine clearance (C_{cr}) determined at 15, 30, 45, and 60 d of the dietary treatment in the control (□, C, $n = 12$) and the zinc-deficient diet group (■, ZD, $n = 12$). Values are means ± SEM. Data were analyzed by two-way ANOVA, followed by a Bonferroni multiple-comparison post-hoc test. Factor treatment (diet): significant effect ($P < 0.001$), Factor time: significant effect ($^{\dagger}P < 0.05$ versus day 15; $^{\ddagger}P < 0.001$ versus day 30), Interaction treatment × time no significant effect. Mean differences between C and ZD rats at one time ($^{*}P < 0.05$).

However, controversial information about NOS activity and NOS isoforms expression in different tissues of adult animals exposed to zinc deficiency is found in the literature. Some studies have shown an increased expression of iNOS in the lung of rats exposed to severe zinc deficiency and it has been suggested that NO produced by iNOS would have a central role in inflammatory processes observed in these tissues [45,46]. On the other hand, Sato et al. found that severe zinc deficiency during adult life does not change NOS activity and aortic eNOS expression in normotensive rats [36], but it enhances the expression of eNOS mRNA and protein in the thoracic aorta of spontaneously hypertensive rats [37].

The exact mechanism whereby zinc deficiency acts in the pathogenesis of cardiovascular and renal diseases is still unknown. However, the main links between the development of these pathologies and zinc deficiency would be multiple mechanisms involving oxidative stress damage, apoptosis, inflammation, and metabolic alterations.

Zinc deficiency during intrauterine and postnatal growth: a model of fetal programming of cardiovascular and renal diseases in adult life

A substantial body of epidemiologic and experimental evidence suggests that a poor in utero environment elicited by maternal dietary or placental insufficiency may “programme” susceptibility in the fetus to later development of cardiovascular, renal, metabolic, and endocrine diseases. The developmental origins hypothesis proposes that when an insult, such as undernutrition, occurs in utero at a critical period of development, the resulting adaptative responses may lead to permanent and long-term changes in organ growth, structure, function, and metabolism. Fetal or perinatal responses may include loss of structural units such as nephrons, cardiomyocytes, or pancreatic β-cells within the developing organ system that confer on individuals an immediate adaptative benefit for survival, but result in the programming of a reduced functional capacity of an organ system for life [47–49].

Moreover, epigenetic mechanisms would also be involved in the programming of metabolic, endocrine, neuronal, renal, and cardiovascular diseases in adult life. Many nutrients, such as zinc, are considered essential for the epigenome because they control methylation reactions and are structural components of enzymes that epigenetically modify DNA and histones (DNA methyltransferases, histone lysine methyltransferases, and histone deacetylases enzymes) [47,50,51].

A large number of models in rats, mice, and sheep have been used in the study of the effects of maternal nutrition on fetal development, including global dietary restriction, low protein diets, chronic hypoxia, placental insufficiency, glucocorticoid exposure, and high fat diets [47,52–55]. Even though experimental and human studies have found that zinc deficiency early in development affects all tissues [56], there are few studies reporting its effects on the programming of adult pathologies [57–60].

Our group was, to our knowledge, the first to demonstrate that moderate zinc deficiency in rats during intrauterine and

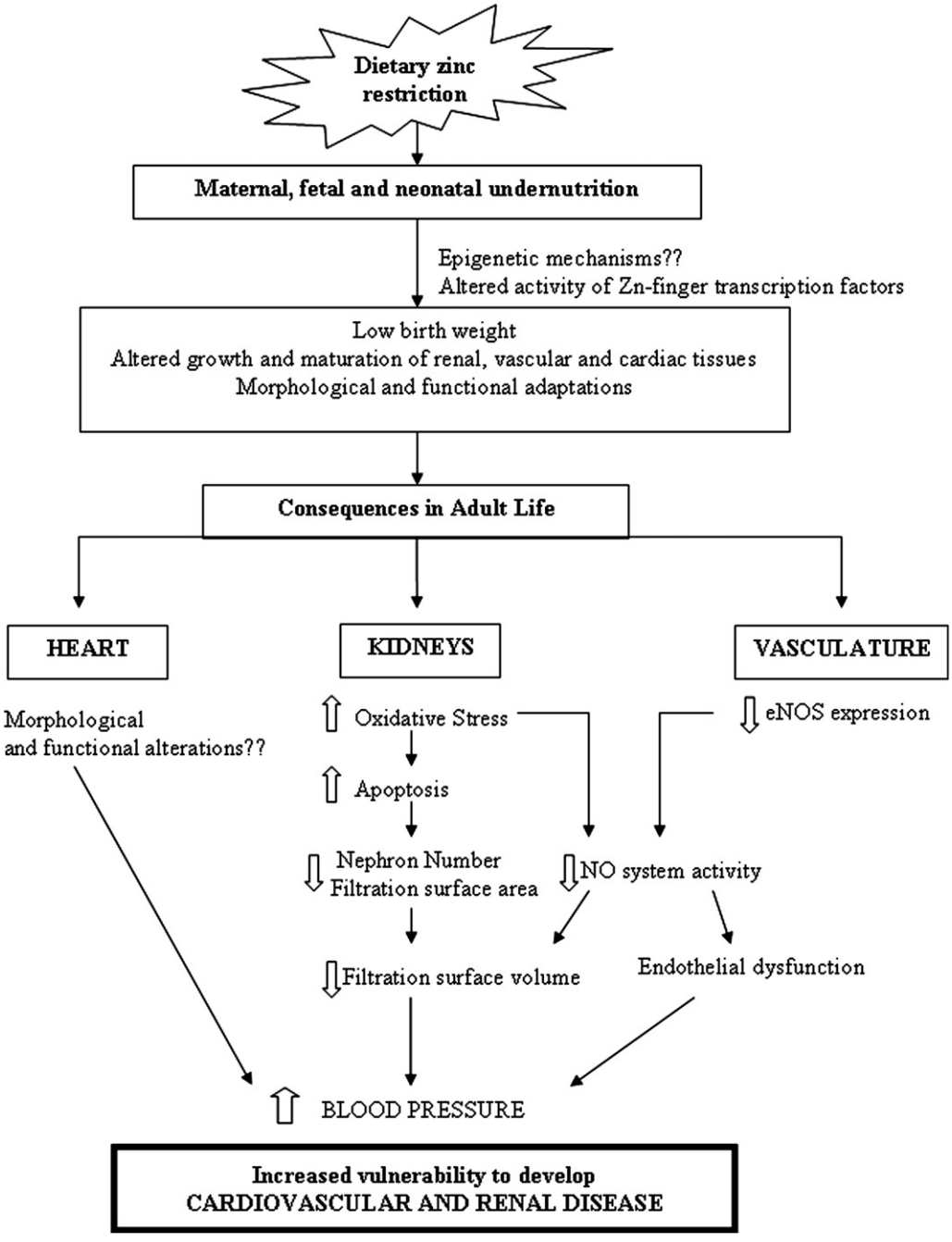

Fig. 3. Effects of dietary zinc restriction during fetal and neonatal life on cardiovascular and renal systems in adulthood.

postnatal growth is also a model of fetal programming of cardiovascular and renal diseases in adult life. Dietary zinc restriction during fetal life and lactation induces an increase in arterial blood pressure and impairs renal function in adult life. Among renal alterations, zinc-deficient rats showed a decrease in glomerular filtration rate associated with a reduction in nephron number and glomerular filtration surface areas, an activation of renal apoptosis and fibrosis, proteinuria, and a decreased activity of the NO system. Furthermore, one of the mechanisms which may underlie these morphologic and functional changes is the increase in renal oxidative stress. Our study demonstrated that moderate zinc deficiency during pre- and/or postweaning growth induced an increase of lipid peroxidation, a reduction in glutathione levels, and a decrease in glutathione peroxidase and catalase activities in the kidney [57,58].

Moreover, in these studies, a control diet during postweaning growth did not totally overcome renal oxidative stress damage, apoptosis, and fibrosis induced by zinc deficiency before weaning. In addition, restitution of zinc content in the diet from weaning did not correct arterial blood pressure levels, glomerular filtration rate, NO system activity, and renal morphometric parameters [57,58]. It thus appears that, when nephrogenesis is compromised, alterations in renal function and morphology are observed. This is likely to contribute to the development of hypertension in adult life.

As in other models of fetal programming, animals exposed to moderate zinc deficiency during fetal life showed lower body weight at birth, which was negatively correlated with nephron number and systolic blood pressure in adult life [48,49,57,58]. Low birth weight is considered a marker of an altered development of organ structure and/or function due to a poor intrauterine environment. These results are in accordance with much epidemiologic and experimental research that found the links between low birth weight and later cardiovascular and renal adult diseases [49,61–63].

The role of maternal zinc status on pregnancy outcome is still unclear. Experimental studies conducted in animals and observational studies in human populations have also reported that low zinc levels during pregnancy is associated with an increased risk of low birth weight and preterm delivery [59,60], although other studies did not find evidence for such an association [64,65]. The evidence from maternal zinc supplementation trials in less developed countries indicates benefits with regards to preterm delivery, neonatal immune system, early neonatal morbidity, and infant infections, but does not support the hypothesis that it promotes intrauterine growth and infant birth weight [64–66].

On the other hand, human and experimental studies of fetal programming have also demonstrated considerable association between low birth weight and endothelial dysfunction [67,68]. In accordance with these reports, zinc restriction during fetal and early postnatal life induced vascular and renal NO system impairment in adult life. The reduction in vascular NOS activity was associated with a lower protein expression of the eNOS isoform [57]. Therefore, the lower eNOS-derived NO production in conduit arteries would impair vascular smooth muscle relaxation and would not allow the response to increases in flow and in shear stress, inducing a decrease in arterial compliance.

On the other hand, the heart development can be particularly sensitive to zinc deficiency. Therefore, the heart is also an important target of fetal programming of cardiovascular diseases in adult life. In rats, severe maternal zinc deficiency has been associated with a high incidence of fetal heart anomalies, which were speculated to result in part from a reduced expression of heart-specific genes that contain zinc-finger transcription factor binding sites in their promoter sequence [69,70]. Furthermore, apoptosis is an integral component of embryonic development. However, zinc deficiency can induce a disruption of apoptotic timing or pattern that results in dysmorphogenesis. It was reported that excessive embryonic cell death after maternal dietary zinc deficiency occurred, specifically in regions and tissues populated by neural crest cells that are essential to support normal heart morphogenesis [70].

Therefore, these findings suggest the possible mechanisms by which dietary zinc restriction during fetal and neonatal life could program cardiovascular and renal diseases in adulthood (Fig. 3). However, more experimental and epidemiologic studies are needed to further support the associations among zinc deficiency, low birth weight, and later life hypertension and cardiovascular and renal disease.

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.

Zinc is a widely studied microelement in infant feeding because it is a component of several enzymes involved in intermediary metabolism ranging from growth to cell differentiation and metabolism of proteins, carbohydrates, and lipids.

Moreover, 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 cardiovascular and renal diseases. Therefore, it would be important to conduct systematic assessment of population zinc status and to develop and mainstream interventions to control zinc deficiency in the context of existing health and nutrition programs.

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