REVIEW

Impact of Zinc Deficiency During Prenatal and/or Postnatal Life on Cardiovascular and Metabolic Diseases: Experimental and Clinical Evidence

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ABSTRACT

This review summarizes the latest findings, from animal models and clinical studies, regarding the cardiovascular and metabolic consequences in adult life of zinc deficiency (ZD) during prenatal and early postnatal life. The effect of zinc supplementation (ZS) and new insights about sex differences in the phenotype and severity of cardiovascular and metabolic alterations are also discussed. Zinc has antioxidant, anti-inflammatory, and antiapoptotic properties and regulates the activity of enzymes involved in regulation of the metabolic, cardiovascular, and renal systems. Maternal ZD is associated with intrauterine growth restriction and low birth weight (LBW). Breast-fed preterm infants are at risk of ZD due to lower zinc uptake during fetal life and reduced gut absorption capacity. ZS is most likely to increase growth in preterm infants and survival in LBW infants in countries where ZD is prevalent. Studies performed in rats revealed that moderate ZD during prenatal and/or early postnatal growth is a risk factor for the development of hypertension, cardiovascular and renal alterations, obesity, and diabetes in adult life. An adequate zinc diet during postweaning life does not always prevent the cardiovascular and metabolic alterations induced by zinc restriction during fetal and lactation periods. Male rats are more susceptible to this injury than females, and some of the mechanisms involved include: *1*) alterations in organogenesis, *2*) activation of oxidative, apoptotic, and inflammatory processes, *3*) dysfunction of nitric oxide and renin-angiotensin-aldosterone systems, *4*) changes in glucose and lipid metabolism, and *5*) adipose tissue dysfunction. Safeguarding body zinc requirements during pregnancy, lactation, and growth periods could become a new target in the prevention and treatment of cardiovascular and metabolic disorders. Further research is needed to elucidate the efficacy of ZS during early stages of growth to prevent the development of these diseases later in life. *Adv Nutr* 2022;00:1–13.

Statement of significance: This review focuses on the latest clinical and experimental findings studying the effects of zinc deficiency during prenatal and early postnatal life on the developmental programming of cardiovascular and metabolic diseases in adult life. The regulation of zinc homeostasis during pregnancy, lactation, and postweaning growth could become a new target in the prevention and treatment of cardiovascular and metabolic disorders in adult life.

Keywords: zinc deficiency, zinc supplementation, developmental programming, cardio-reno-vascular alterations, obesity, diabetes, hypertension, metabolic syndrome, sex differences

Introduction

The fetal programming hypothesis suggests that an injury during fetal life, which leads to intrauterine growth restriction (IUGR), not only results in low birth weight (LBW) but also causes adaptive responses that can lead to the loss of structural units (nephrons, cardiomyocytes, pancreatic β cells, skeletal muscle cells) to maintain the development of other organs, such as the brain (1, 2). These changes can bring immediate advantages by increasing perinatal survival in a poor nutritional environment. However, these adaptive responses decrease morphological and functional capacity in later life. Moreover, it has been proposed that these adaptive responses could be more harmful when these individuals face a postnatal environment with greater metabolic demands. These findings are supported by clinical studies suggesting that LBW followed by accelerated postnatal growth is associated with an increased risk of death from cardiovascular disease. Moreover, it was reported in developmental programming studies that male and female offspring can exhibit different phenotypes following nutritional injuries, as

well as differences in the severity of cardiovascular, renal, and metabolic diseases (2, 3).

One of the nutritional problems that mainly affect children and pregnant women is what WHO and UNICEF have defined as hidden hunger, or micronutrient deficiencies: a set of specific micronutrient deficiencies that are highly prevalent and important in children's growth and development, including zinc, iron, vitamin A, group B vitamins, folates, and/or essential fatty acids (4–6). Micronutrient deficiencies coexist with overweight and obesity or diet-related diseases within individuals, households, and populations of all social classes (7, 8). Many children eat high-calorie but micronutrient-poor diets, and the result of hidden malnutrition is a paradox: children of short stature but overweight (9).

It has been estimated that 17.3% of the world's population has an inadequate intake of zinc (10). Zinc deficiency (ZD) appears to be a public health concern in low- and middle-income countries, irrespective of the recommended indicators used for assessment (plasma zinc concentration, dietary zinc adequacy, and stunting prevalence) (11, 12).

Nowadays, cases of severe ZD are uncommon, whereas moderate deficiency has been widely reported. The most affected population groups, of any social stratum, are children, women during pregnancy and lactation, and elderly people (13). Moreover, ZD during fetal and early postnatal life can affect intrauterine and postnatal development through multiple mechanisms and induce fetal adaptations during critical periods of organogenesis that determine the functional capacity of different organs and systems. Epigenetic changes, morphological, hormonal, and metabolic alterations, and activation of oxidative, apoptotic, and inflammatory processes are involved. Additionally, nitric oxide (NO) and renin-angiotensin-aldosterone system (RAAS) dysfunction contributes to developmental programming of cardiovascular and metabolic diseases in adult life (2, 14–17) (**Figure 1**).

Considering that moderate ZD is a frequent and poorly studied hidden malnutrition in pregnant women and children, the aim of this review is to summarize the latest evidence, from experimental animal models and clinical studies, regarding the cardiovascular and metabolic consequences in adult life of ZD during prenatal and postnatal life. The effect of zinc supplementation (ZS) and new insights about sex differences in the phenotype and severity of cardiovascular and metabolic alterations are also discussed.

Current Status of Knowledge

Zinc: an essential micronutrient

The ubiquitous distribution of zinc in the organism and its physicochemical properties, including its stable association with macromolecules, determine the essentiality of this micronutrient. The cytosolic free zinc ion concentration is maintained at low picomolar to nanomolar concentrations by zinc-transporting proteins, metallothioneins (MTs), and specific storage sites such as zincosomes (cytoplasmic vesicles that accumulate zinc). Cells express zinc transporters, which are divided into 2 major families: ZNT (Zinc transporter) transporters (numbered 1 to 10) decrease cytosolic zinc concentrations by promoting the passage of zinc out of the cell or into organelles or vesicles, whereas ZIP (Zrt-/Irt-like protein) proteins (numbered 1 to 14) increase cytosolic zinc concentrations by favoring the entry of zinc from the extracellular fluid or its exit from organelles and vesicles (18, 19). The expression of zinc transporters and MTs is tissue-dependent and is modulated by concentration of zinc in the diet, hormones, cytokines, and free radical species (20, 21). However, cytosolic zinc concentrations can transiently and locally increase through release from proteins and organelles, enabling zinc to affect gene expression, enzymatic activity, and cell signaling (22) (**Figure 2**).

Between 3% and 10% of human genes encode proteins with zinc-binding domains. Zinc controls gene expression because it is a component of transcription factors such as nuclear receptors for steroids, thyroid hormones, and vitamin D (23). It is an essential micronutrient for organ development and growth. Zinc stimulates cell proliferation by upregulating gene expression of enzymes involved in DNA synthesis such as deoxythymidine kinase. Additionally, zinc enhances production of tissue growth factors and the pituitary growth hormone 1 receptor signaling pathway (24).

Moreover, zinc has antioxidant (25, 26), anti-inflammatory (27, 22), and antiapoptotic effects (28, 29) (Figure 2). It has also been shown that zinc is essential for the activity of >300 enzymes involved in the use of energy, protein synthesis, and intermediate metabolism (30). Regarding cardiovascular and renal systems regulation, zinc can determine the activity of endothelial nitric oxide synthase (NOS3). Endothelial NO produced by NOS3 can act on different cells producing vasodilation and inhibiting platelet aggregation, smooth muscle cell (SMC) proliferation, leukocyte adhesion, and apoptosis in endothelial cells (31). NOS3 has a zinc-thiolate cluster that plays an essential role in the catalytic activity of the enzyme by maintaining dimeric stability and integrity of the tetrahydrobiopterin cofactor binding site. Molecular dynamics studies suggest that the absence of zinc disrupts the zinc-thiolate cluster, preventing L-arginine from entering the catalytic site and leading to loss of tetrahydrobiopterin from the active site. Destabilization of the dimeric structure induces enzyme decoupling and

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Abbreviations used: AGTR1, angiotensin II receptor type 1; AngII, angiotensin II; AZ, adequate zinc diet; AZGP1, adipokine zinc-α2-glycoprotein; IUGR, intrauterine growth restriction; LBW, low birth weight; MT, metallothionein; NO, nitric oxide; NOS3, endothelial nitric oxide synthase; NOX, NADPH oxidase; $O_2^{\bullet}$, superoxide anion; RAAS, renin-angiotensin-aldosterone system; *SLC29*, solute carrier family 29; SMC, smooth muscle cell; SNP, single nucleotide polymorphism; TGFB1, transforming growth factor β 1; ZD, zinc deficiency/deficient; ZIP, Zrt-/Irt-like protein; ZNT, Zinc transporter; ZS, zinc supplementation.

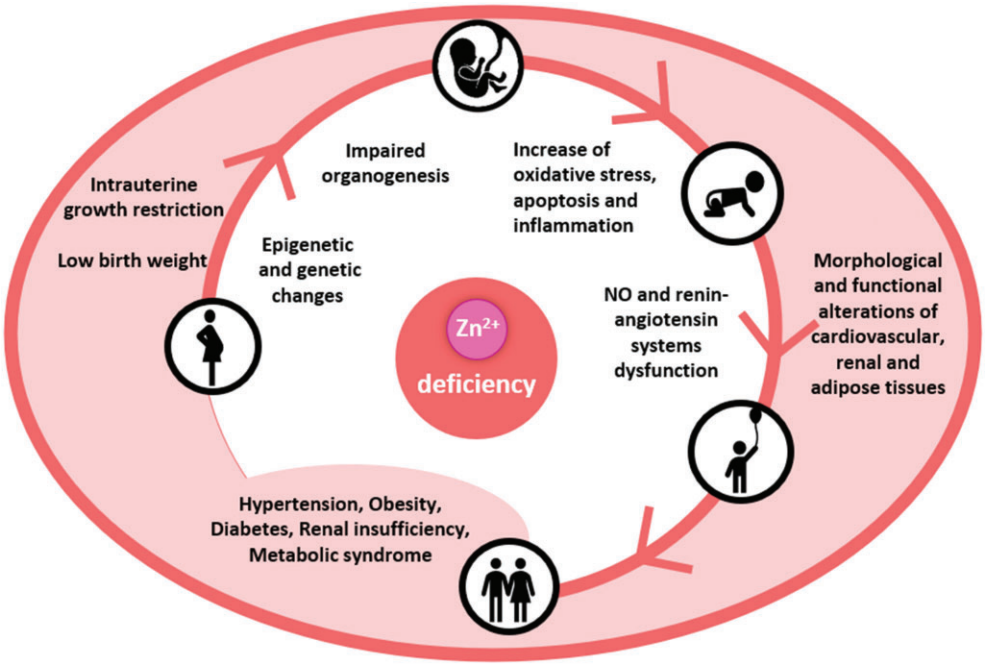

FIGURE 1 Zinc deficiency and developmental programming of adult diseases. Zinc deficiency during prenatal and early postnatal life programs cardiovascular, renal, and metabolic alterations in adult life by different mechanisms, such as: *1*) increased oxidative stress, apoptosis, and inflammation; *2*) dysfunction of nitric oxide and renin-angiotensin systems; and *3*) epigenetic and genetic changes.

the production of superoxide anion ($O_2^{\bullet}$) instead of NO (32–34).

ZD in pregnancy and childhood

ZD can be due to different causes, which can be related or coexist, such as decreased intake (protein malnutrition, parenteral nutrition without supplementation), an increase in the body's requirements (growth, pregnancy, lactation), increased excretion (diabetes mellitus, prolonged diarrhea, treatment with diuretics), genetic diseases [mutation in the solute carrier family 29 member 4 (*SLC29A4*) gene, which encodes the ZIP4 transporter in the duodenum and jejunum leading to acrodermatitis enteropathica; mutation in the *SLC30A2* gene, which encodes the ZNT2 transporter, leading to low zinc concentration in breast milk), or a decrease in intestinal absorption (35).

Risk factors for ZD also include bariatric surgery, smoking, alcoholism, and a vegetarian diet with a high content of phytates that inhibit zinc absorption (36). Zinc is found in a wide variety of foods including red meat, poultry, wholegrain cereals, beans, nuts, and certain types of seafood (37).

Maternal serum zinc concentration decreases until 35 wk of gestational age, due to hemodilution, hormonal changes, increased zinc uptake by maternal tissues and the fetus, and higher urinary zinc excretion. Therefore, the daily dietary requirements of zinc are higher in pregnant women (11 mg/d) compared with nonpregnant women (8 mg/d) (38).

Moreover, zinc uptake by the fetus increases in the third trimester of pregnancy. Zinc stored in the fetal liver, mostly associated with MTs, can provide an endogenous source of this micronutrient for early postnatal life. Therefore, preterm infants are at risk of ZD (39).

In pregnancy, ZD is associated with an increased risk of hypertension, pre-eclampsia, abortion, difficulties in labor and delivery, fetal malformations, IUGR, and alterations in fetal development (39, 40). A population-based birth cohort study demonstrated that maternal ZD (serum zinc concentration $<56\ \mu$g/dL) increases the incidence of small for gestational age and LBW (41). Moreover, a meta-analysis showed a correlation between cord and maternal blood zinc concentrations and reported that cord serum zinc concentration is lower in LBW neonates (42). However, a meta-analysis that included 21 randomized controlled trials showed that although ZS in pregnancy reduces the risk of preterm births by 14% compared with placebo in women in low-income settings, it does not improve fetal growth (43). But, increased neonatal growth was seen in a Peruvian clinical trial of maternal ZS (15 mg/d) (44).

A high zinc concentration is found in breast milk particularly during the first 3 mo of life. However, breast-fed preterm infants have an increased risk of ZD because of the lower capacity of gut absorption (45). In a recent review, Brion et al. (39) summarized the results from 18 observational studies and 4 randomized controlled trials of ZS in neonates. They concluded that ZS is most likely to increase growth in preterm infants and survival in LBW infants in countries where ZD is prevalent (India, Iran, and Egypt).

In children, ZD can contribute to multiple alterations including stunting, decreased head growth, periorificial

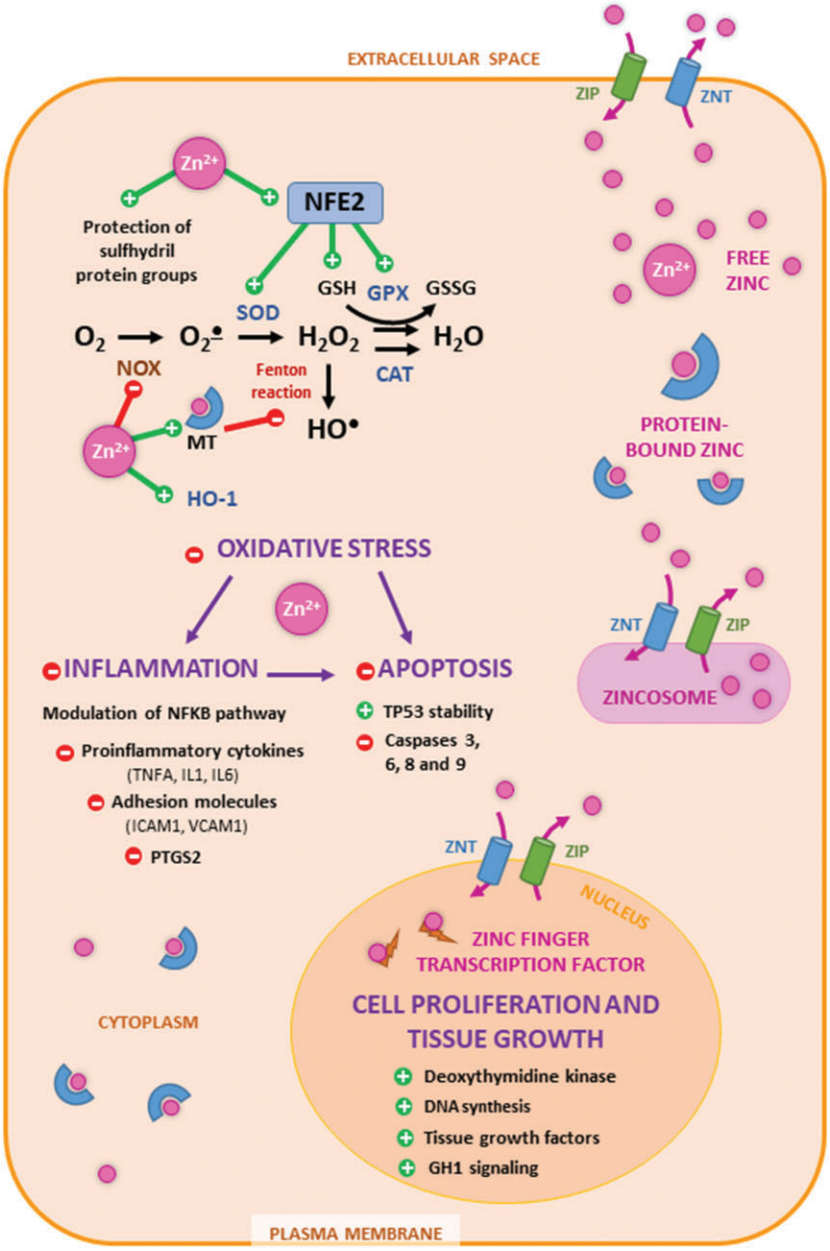

FIGURE 2 Role of zinc in cell biology. Cells express zinc transporters, which are divided into 2 major families: ZNT transporters decrease cytosolic zinc concentrations by favoring the passage of zinc out of the cell or into organelles or vesicles, whereas ZIP proteins increase cytosolic zinc concentrations by favoring the entry of zinc from the extracellular fluid or its exit from organelles and vesicles. Inside the cell, zinc is present as free zinc ions or protein-bound zinc. Zinc is present in numerous transcription factors that have zinc-finger motifs. This micronutrient contributes to cell proliferation by: *1*) upregulating deoxythymidine kinase, enhancing DNA synthesis; *2*) increasing production of tissue growth factors; and *3*) promoting GH1 signaling pathway. Zinc acts as an antioxidant and membrane-stabilizing agent because it: *1*) interacts with membrane sites that could be occupied by other metals that catalyze the Fenton reaction; *2*) inhibits NOX; *3*) protects the sulfhydryl protein groups and GSH from oxidation (GSSG) by forming strong but reversible complexes; *4*) is an essential component of intracellular and extracellular SOD; *5*) induces the synthesis of HMOX1, an antioxidant enzyme, and MTs, which act as free radical scavengers; and *6*) increases NFE2 concentrations, critical for gene expression of SOD and GPx enzymes and nonenzymatic antioxidants (GSH). Zinc has anti-inflammatory properties by modulation of the NF-κB pathway: *1*) it reduces proinflammatory cytokine production; *2*) it inhibits PTGS2 activity; and *3*) it reduces adhesion molecule expression (VCAM1 and ICAM1). Zinc reduces apoptosis because: *1*) it inhibits caspases 3, 6, 8, and 9; *2*) it contributes to the structural stability of TP53; *3*) its effects on inflammatory process and/or oxidative stress impact apoptosis as well. CAT, catalase; GH1, pituitary growth hormone; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; HMOX1, heme oxygenase; $HO^{\bullet}$, hydroxyl radical; ICAM1, intracellular adhesion molecule 1; MT, metallothionein; NFE2, nuclear factor (erythroid-derived 2)-like 2; NOX, NADPH oxidase; $O_2^{\bullet}$, superoxide anion; PTGS2, cyclooxygenase 2; SOD, superoxide dismutase; TP53, tumor suppressor protein 53; VCAM1, vascular adhesion molecule 1; ZIP, Zrt-/Irt-like protein; ZNT, Zinc transporter.

lesions, delayed wound healing, hair loss, diarrhea, immune deficiency, cognitive impairment, and alteration of gut physiology and microbiota composition (46, 47). A review of randomized clinical trials in children aged 6 mo to 12 y indicated a positive effect for ZS in reducing all-cause and infectious disease mortality, and a small positive impact on linear growth (48). Similar results were observed in a clinical trial in full-term infants in India receiving placebo or 5 mg zinc daily (49). However, further research should determine the optimal supplement dose.

ZD limits intrauterine and postnatal growth and consequently can program alterations in the morphology and function of different organs. In this regard, we applied an experimental protocol in which pregnant Wistar rats were randomly fed either a moderately ZD diet (8 mg/kg) or an adequate zinc diet (AZ) (30 mg/kg, control group) during the pregnancy and lactation periods (50–52). After weaning, offspring born of control mothers were fed a control zinc diet (30 mg/kg), whereas offspring of ZD mothers were fed a low-zinc (8 mg/kg) or control zinc diet for 60 d (young adults). In agreement with other clinical studies, male and female offspring exposed to moderate ZD showed lower body, heart, and kidney weights at 6, 21, and 81 d. Moreover, an AZ diet (30 mg/kg) during postweaning life could not always normalize these growth markers (50–52).

Cardiovascular consequences in adult life of ZD during prenatal and postnatal life

Hypertension and renal alterations.

Several experimental and clinical studies have reported an association between ZD and the development of renal, cardiovascular, and metabolic diseases, including metabolic syndrome (53–55).

Hypertension is one of the most important risk factors for the development of cardiovascular diseases, heart and renal failure, or stroke (56, 57). The prevalence of hypertension in adults is 31.1% worldwide, including >1.39 billion people (58). Primary, idiopathic or essential is the most prevalent type of hypertension and is not related to renovascular disease, renal failure, or endocrine alterations. Essential hypertension progresses in the presence of different factors such as obesity, high salt intake, and a sedentary lifestyle. Moreover, hypertension can be programmed by different injuries during fetal and early postnatal life (59–61). Several mechanisms like insulin resistance, oxidative stress, endothelial dysfunction, overactivation of the sympathetic nervous system, and the pressor arm of the RAAS contribute to fetal programming and development of hypertension in adulthood (62).

Different clinical studies have demonstrated a relation between zinc status and blood pressure levels. A recent Mexican study revealed that ZD, determined by serum zinc concentrations <74 μg/dL in men and <70 μg/dL in women, is associated with the presence of prehypertension in apparently healthy subjects (63). In addition, a recent meta-analysis of 25 studies involving 9129 cases and 11,888 controls assessed the association between serum zinc concentrations and hypertension risk, and it showed that serum zinc concentrations in hypertensive patients are significantly lower than in normotensive individuals (64).

Experimental studies support that ZD can be a risk factor for the development of hypertension. Our research group described the effects of ZD during prenatal and/or postnatal life on adult blood pressure levels. A moderately ZD diet (8 mg/kg) during fetal life and lactation (8 mg/kg) programs an increase in systolic blood pressure in 81-d-old male rats that cannot be reversed by an AZ diet (30 mg/kg) during postweaning growth (52). Systolic blood pressure levels in male ZD rats were >140 mmHg, and it has been demonstrated that a rise of this magnitude increases the risk of cardiovascular events (65). Conversely, adult female rats exhibited normal levels of systolic blood pressure. These sex differences 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 (66, 67). Sex differences can be due to differences in genetic, transcriptional, and morphological patterns, or in timing of development, and can be influenced by steroid hormone exposure during intrauterine and postnatal life (17) (**Figure 3**).

The increase in blood pressure in 81-d-old male rats exposed to dietary zinc restriction (8 mg/kg) during fetal life, lactation, and/or postweaning growth is mainly due to renal and vascular alterations. Adult ZD rats showed a reduction in glomerular filtration rate associated with a lower nephron number, renal fibrosis, and proteinuria (50, 68, 69). These renal changes were related to a decrease in NO bioavailability due to lower NOS3 activity and higher oxidative stress, activation of apoptotic processes, and an increase in renal RAAS pressor arm. Eighty-one-day-old and 6-d-old rats exposed to a moderately ZD diet (8 mg/kg) during prenatal and postnatal growth showed higher renal angiotensin II (AngII) concentrations and AngII/angiotensin-(1-7) ratio, and an increase in angiotensin II receptor type 1 (AGTR1) protein expression (15, 51). Moreover, Williams et al. (70) described that ZD induces hypertension by stimulating renal sodium retention by the distal convoluted tubule via upregulation of the sodium-chloride cotransporter in mice. However, ZD during early stages of life did not produce alterations in renal function or RAAS in female rats. We suggest this sexual dimorphism could be due to variations in genetic and transcriptional patterns and/or sex-dependent epigenetic modifications. In this regard, other fetal programming models have also found sex differences in renal RAAS expression in early stages of life (71) (Figure 3).

Cardiovascular alterations.

Zinc restriction during prenatal and postnatal growth programs vascular alterations, like lower NO system activity, contributing to an increase in peripheral resistance and blood pressure (14).

Rats of both sexes exposed to dietary zinc restriction (8 mg/kg) during prenatal and lactation periods showed lower aortic NOS activity, aggravated by higher oxidative

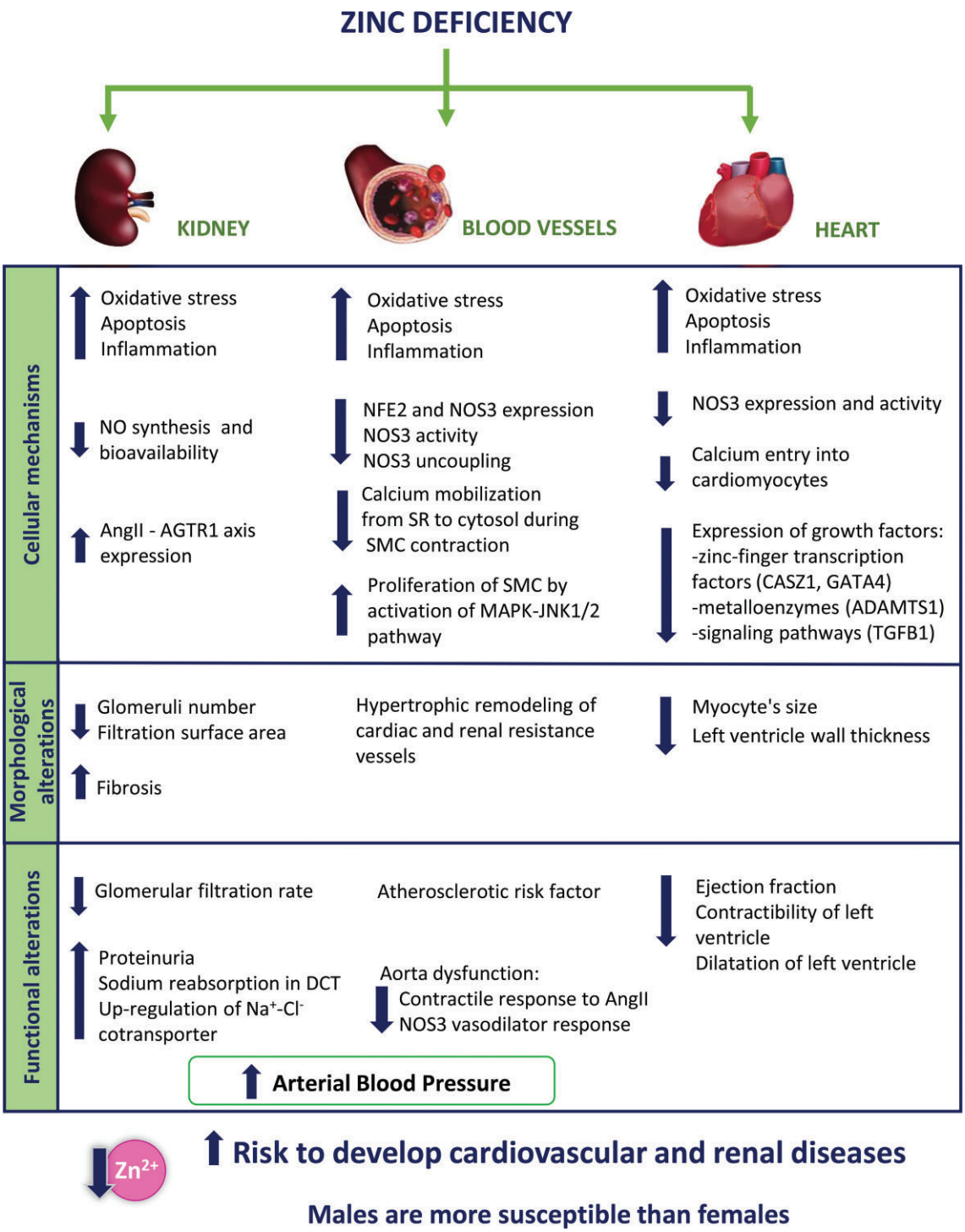

FIGURE 3 Impact of ZD on the cardiovascular and renal systems. ZD during different stages of life induces morphological and functional alterations of the cardiovascular and renal systems by different molecular mechanisms that involve an increase in oxidative stress, inflammation, and apoptosis, as well as alterations in the expression of growth factors, calcium mobilization, NO, and RAAS systems. ADAMTS1, ADAM metallopeptidase with thrombospondin type 1 motif 1; AGTR1, angiotensin II receptor type 1; AngII, angiotensin II; CASZ1, castor zinc finger 1; DCT, distal convoluted tubule; GATA4, GATA binding protein 4; JNK1/2, c-Jun N-terminal kinases 1/2; MAPK, mitogen-activated protein kinase; NFE2, nuclear factor (erythroid-derived 2)-like 2; NO, nitric oxide; NOS3, endothelial nitric oxide synthase; RAAS, renin-angiotensin-aldosterone system; SMC, smooth muscle cells; SR, sarcoplasmic reticulum; TGFB1, transforming growth factor β1; ZD, zinc deficiency.

stress, at 6 d of life. The lower NO production in early stages could have consequences in adult life because it is important for vascular development (72). This alteration persisted until adulthood (81-d-old rats), and it could not be reversed by an AZ diet (30 mg/kg) during postweaning growth. In this regard, zinc restriction during intrauterine growth and lactation programmed a lower activity and protein expression of NOS3, as well as a lower NOS3-dependent vasodilator response in aorta of adult rats of both sexes (14). In addition, zinc restriction during early life programmed a lower contractile aortic response to AngII due, at least in part, to lower calcium mobilization from the sarcoplasmic reticulum to the cytosol in SMC (14) (Figure 3).

Regarding clinical studies, a Polish study reported a positive correlation between blood zinc concentration and NO concentrations in coronary arteries (73). However, there are no clinical studies evaluating the vascular effects of ZD during prenatal and postnatal growth.

Endothelial dysfunction associated with atherosclerosis leads to a focal inflammatory process in the intima and to the accumulation of lipids in plaques, hyperplasia of SMC, increased vascular collagen deposits, elastin fiber rupture, and arterial calcification (74). Zinc is crucial for endothelium and vascular SMC integrity. In addition, 6-d-old and adult male ZD rats (diet with 8 mg/kg zinc) showed a hypertrophic inward remodeling in renal arteries that could be associated with increased oxidative stress, lower bioavailability of NO, and increased expression of the AngII/AGTR1 receptor axis (14, 15, 51). A similar remodeling was observed in coronary arteries (52) (Figure 3).

ZD during prenatal and postnatal life can alter the normal trajectory of cardiac development. A moderate ZD (diet with 8 mg/kg zinc) in the developing fetus induced adaptive responses of cardiac myocytes in early postnatal life that would become manifest later in adulthood. In early postnatal life (6-d-old rats), ZD offspring showed an increase in the mean diameter of myocytes and in the number of apoptotic cells of the left ventricle. Meanwhile, 81-d-old male rats exposed to ZD during prenatal and postnatal growth showed a reduction in cardiomyocyte size and left ventricle mass that could be related, at least in part, to lower transforming growth factor β 1 (TGFB1) expression (52, 75). In this regard, zinc can participate in ventricular myocardial development by regulating the activity of zinc-finger transcription factors (CASZ1, castor zinc finger 1; GATA4, GATA binding protein 4), metalloenzyme activity (ADAMTS1, ADAM metallopeptidase with thrombospondin type 1 motif 1), and signal pathways (TGFB1) (76). Moreover, it has been reported that severe maternal zinc dietary restriction (<1 mg/kg zinc) can result in several fetal cardiac anomalies (gestational days 13.5, 15.5, and 18.5) due to excessive embryonic cell death, particularly in structures whose complete maturation is dependent on neural crest cells (77). In addition, a Peruvian clinical trial revealed that prenatal supplementation (25 mg/d) of ZD mothers can be beneficial to cardiac maturation and fetal neurobehavioral development (78).

In our experimental model, cardiac morphological changes induced by ZD (8 mg/kg) in male rats were accompanied by decreased contractility and dilation of the left ventricle that altered the ability of the heart to compensate for higher blood pressure (75). These alterations were associated with an increase in $O_2^{\bullet}$ production, cardiomyocyte apoptosis, and proinflammatory cytokine expression, such as TNF-α and IL6, in the left ventricle of adult rats. AZ intake during postweaning growth reversed cardiac morphological and functional changes in male rats. As observed in the kidney, female ZD rats showed milder cardiac alterations than males. Our results accord with another study, performed in spontaneously hypertensive rats with metabolic syndrome related to a nonsense mutation in the leptin receptor gene. This reported that a zinc-free diet increased myocardial fibrosis and decreased left ventricular fractional shortening, contributing to the development of severe cardiac dysfunction (79).

Functional alterations are due, at least in part, to impaired calcium entry into the cardiomyocytes (80). A clinical study has demonstrated that decreased serum zinc concentration (<62 μg/dL) is associated with higher mortality, inflammation (C-reactive protein), ongoing myocardial damage (troponin I), and the progression of heart failure (81, 82). In addition, it has been described that cardiovascular alterations become more pronounced when the zinc deficit is greater (<23 μg/dL) (82) (Figure 3).

Metabolic consequences in adult life of ZD during prenatal and postnatal life

Zinc and diabetes.

The relation between zinc status during pregnancy and early childhood and the development of diabetes needs further research. It was reported that chronic low zinc intake is associated with a reduction in insulin secretion and tissue resistance, and with an increase in circulating glucose, both in adult animals and humans (55, 83–85). In contrast, a population-based case-control study concluded that zinc status at birth does not seem to influence the risk of diabetes type 1 development nor age at onset (86). In line with this study, a population-based Finnish study showed that zinc intake during pregnancy does not influence the risk of advanced β-cell autoimmunity in children who are genetically susceptible to type 1 diabetes (87). Nevertheless, our findings show that dietary zinc restriction (8 mg/kg) during fetal life and lactation in Wistar rats programs lower glucose tolerance because it induces an increase in glycemia following glucose overload that is not reversed by an AZ diet (30 mg/kg) during postweaning life (55) (**Figure 4**). In accordance, Padmavathi et al. (83) reported a decrease in fasting plasma insulin concentrations and post glucose overload in Wistar/NIN adult rats exposed to ZD (10 mg/kg) during fetal life. Jou et al. (88) reported that Sprague Dawley rat offspring exposed to dietary zinc restriction (7 mg/kg) during fetal life and lactation showed higher blood glucose concentrations at 3 wk of life and were less sensitive to insulin and glucose stimulation than controls at 5 and 10 wk. Another study reported that ZS during pregnancy (100 mg/kg body weight zinc sulfate) can protect the

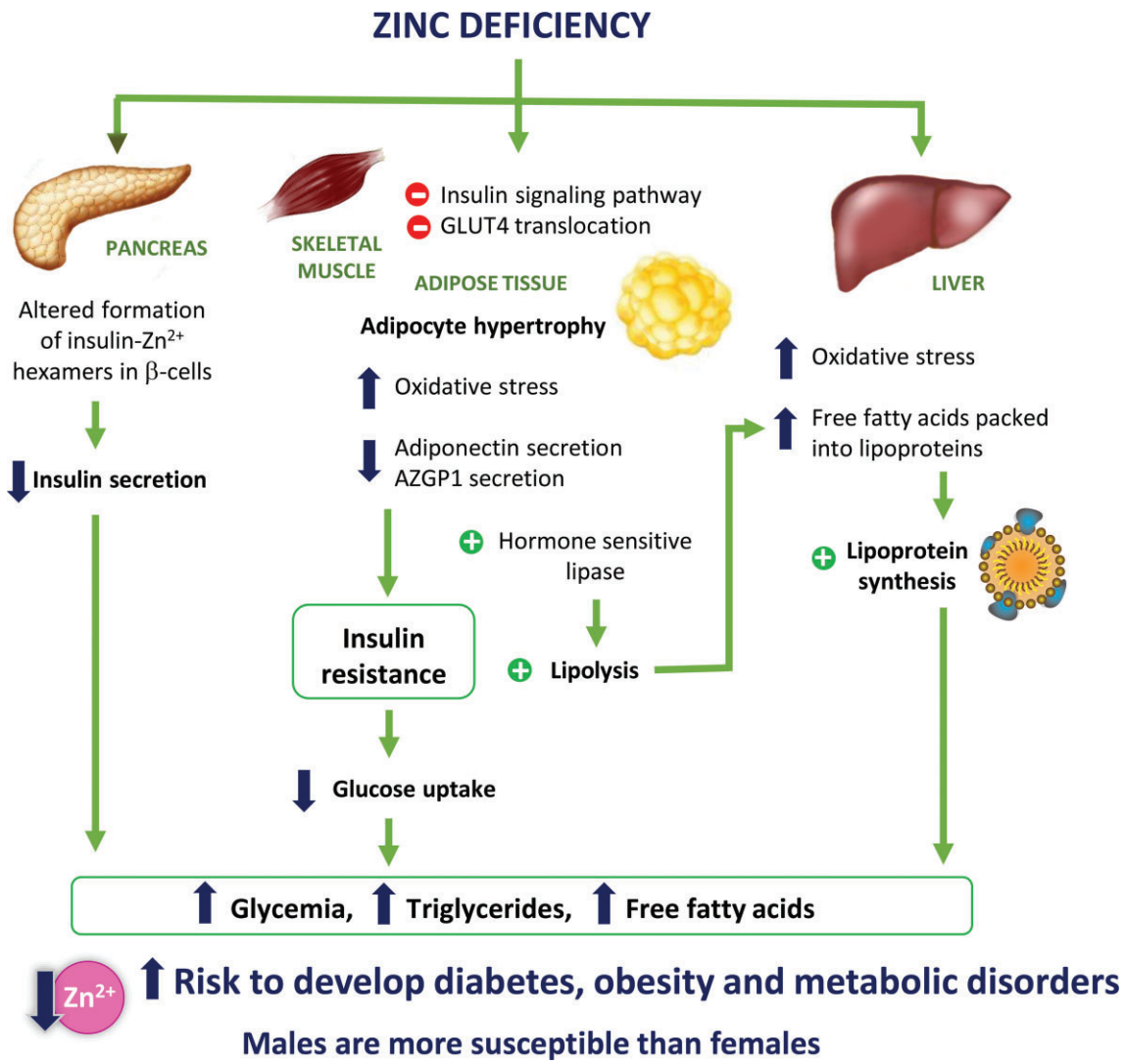

FIGURE 4 Impact of ZD on intermediary metabolism. Low zinc availability in pancreatic β cells affects insulin synthesis and secretion. Moreover, the insulin signaling pathway is affected, and GLUT4 translocation is reduced in tissues that require insulin action for glucose uptake. ZD induces white adipocyte dysfunction related to high oxidative stress and reduced adiponectin secretion. This situation, accompanied by the decrease in AZGP1, contributes to an insulin resistance state. Lipolysis in adipose tissue increases free fatty acid release and their uptake by the liver and results in higher lipoprotein synthesis. Finally, ZD during different stages of life induces alterations in intermediary metabolism, including a rise in blood glucose and triglyceride concentrations, which contribute to the development of diabetes and obesity. AZGP1, adipokine zinc-α2-glycoprotein; GLUT4, glucose transporter type 4; ZD, zinc deficiency.

offspring against alloxan-induced type 1 diabetes, resulting in lower rates of hyperglycemia, polydipsia, and polyuria in Wistar rat offspring (89). In addition, a systematic review and meta-analysis revealed the association between dietary ZS and reduced risk of type 2 diabetes (88). Additionally, a randomized double-blind placebo-controlled trial showed that ZS (20 mg daily for 12 mo) reduced blood glucose, insulin resistance, and disease progression to diabetes (90). Moreover, another double-blind, placebo-controlled trial showed that ZS (50 mg daily for 8 wk) increases antioxidant protection and ameliorates insulin resistance indexes in adult people with overweight and diabetes (91).

The multiple roles that zinc plays in the pancreas, skeletal muscle, and adipose tissue determine the association between ZD and the development of diabetes (92). Zinc has important functions in carbohydrate metabolism because it modulates synthesis, storage, and secretion of insulin (93). Pancreatic β cells express numerous zinc transport proteins in plasma membrane (ZIP1, ZIP4, ZIP6, ZIP10, ZNT1) and in intracellular organelles (ZIP7, ZIP9, ZNT5, ZNT6, ZNT7, ZNT8) (93). After passing through the Golgi apparatus, synthesized insulin is packaged inside granules as hexamers together with zinc ions that significantly reduce its solubility, causing crystallization within the granules and increasing its stability (94). The transporter ZNT8, encoded by the *SLC30A8* gene, has a key role in zinc uptake into the insulin secretory granules in pancreatic β cells (95). People with type 1 diabetes show high prevalence and titer of ZNT8

autoantibodies (96). Moreover, clinical studies performed in different populations have reported that single nucleotide polymorphisms (SNPs) in the *SLC30A8* gene are related to higher risk of impaired glucose tolerance and type 2 diabetes (97, 98). In this regard, Ahmadi et al. (99) have reported a genetic association of SNP rs11558471 in *SLC30A8* with a higher serum concentration of IL17, a proinflammatory cytokine, and increased insulin resistance in Iranian people with type 2 diabetes.

Zinc is an essential trace element that has been considered as a mimetic insulin factor because it acts as a second messenger, activating cellular signaling pathways that generate insulin-like effects on the metabolism of carbohydrates and lipids (96, 97). Zinc enhances the actions of insulin in adipocytes and skeletal muscle cells by increasing phosphorylation of the insulin receptor and proteins involved in the signaling pathway, such as protein kinase B, and by enhancing the translocation of glucose transporter type 4 to plasma membrane (100). The insulin-sensitizing effect of zinc has also been attributed to inhibition of the activity of protein tyrosine phosphatase 1B (92).

The ZIP7 transporter modulates zinc flux and insulin signaling pathways in skeletal muscle cells. In this regard, ZIP7 favors zinc release from the Golgi apparatus, increasing the cytosolic zinc concentration, which could activate cell signaling pathways, including the phosphatidylinositol 3-kinase/protein kinase B pathway, that stimulate glucose mobilization and uptake (101). It has been reported that insulin-resistant mice show reduced ZIP7 expression in skeletal muscle cells, accompanied by a negative modulation of key genes involved in the response to insulin and glucose metabolism (102) (Figure 4).

Zinc and obesity.

Childhood overweight and obesity is becoming an increasingly important contributor to adult obesity, diabetes, and other noncommunicable diseases. A recent meta-analysis suggested that serum zinc concentration was significantly lower in people with obesity compared with controls without overweight (103). Moreover, ZD was associated with high fat mass in children with undernutrition in developing countries (44, 104, 105). Notwithstanding, 1 study found no association between zinc and body composition (106). The addition of zinc (15–30 mg/d) to supplements containing other micronutrients, such as folic acid or vitamin A, improves the beneficial effects of these supplements for offspring when administered to pregnant women (107–109). A systematic review including studies of ZS (3–50 mg/d) in children (aged 0–10 y) showed that this micronutrient has effects on body composition, increasing fat-free mass, although results might not be consistent (110). In addition, only 1 study in children found that ZS (20 mg/d for 8 wk) was associated with reduced serum leptin and insulin (111).

Zinc status can modulate the function of adipose tissue in obesity and other related pathologies, because adipocyte differentiation is regulated by transcription factors that mostly have zinc finger motifs (92, 112). Expression of zinc transporters (ZNT2, ZNT3, ZNT6, ZNT8, ZIP1, ZIP2, ZIP3, ZIP4, ZIP5, ZIP6, ZIP7, and ZIP8) is downregulated in subcutaneous adipose tissue from people with obesity compared with controls without overweight (113). Moreover, zinc transporters are associated with adipose metabolism. The zinc exporter ZNT7 seems to have a crucial role in lipogenesis. The lack of ZNT7 expression in white subcutaneous adipose tissue induces moderate ZD in mice, with low body fat accumulation, and inhibits both basal and insulin-stimulated glucose uptake in adipocytes (114). In addition, a Korean clinical study revealed lower mRNA abundances of ZNT4, ZNT5, ZNT9, ZIP1, ZIP4, and ZIP6 in leukocytes of women with obesity, and expression of some of these genes was inversely correlated with BMI and inflammation biomarkers, such as serum TNF-α and C-reactive protein concentrations (115).

ZD during fetal and postnatal growth can affect adipogenesis, leading to a reduced number of white retroperitoneal adipocytes in adult rats. In our experimental model, adult male rats exposed to prenatal and postnatal dietary zinc restriction (8 mg/kg) showed hypertrophied retroperitoneal adipocytes accompanied by a reduction in adipocyte density and low retroperitoneal adipose mass (55). These changes could be related to alterations in the serum metabolic profile and to higher oxidative stress in retroperitoneal adipose tissue (50, 55) (Figure 4). It was shown that increased adipocyte size results in a shift toward dominance of proinflammatory adipokine production (116).

Zinc also affects lipid metabolism. In our animal model, we found that male Wistar rats exposed to chronic zinc restriction (8 mg/kg) during prenatal and postnatal growth showed an increase in serum triglycerides at 81 d of life. The restitution of AZ dietary concentrations (30 mg/kg) during postnatal life restored this parameter (55). Considering that zinc has insulin-mimetic properties, it is important to note that zinc acts as a negative modulator of the hormone-sensitive lipase (117) and inhibits lipolysis in adipose tissue (118). Consequently, this micronutrient could reduce the release of free fatty acids to the circulation and their flow to the liver, preventing excessive synthesis of hepatic lipoproteins and elevation in blood triglycerides. Moreover, zinc is important for the expression and activity of other enzymes involved in lipid metabolism, such as lipoprotein lipase and fatty acid synthetase (119). In addition, it regulates the catabolism of apolipoproteins such as apoE (120). ZS in prepubertal children with obesity (20 mg/d, double the recommended dietary allowance, for 8 wk) induced a decrease in body weight and in serum total- and LDL-cholesterol and triglyceride concentrations (121).

The association between zinc status and adiposity could also be related to zinc's influence on adipokine production in adipose tissue (Figure 4). Adipokine zinc-α2-glycoprotein (AZGP1) is a zinc-dependent adipokine that induces increased lipolysis and decreased lipogenesis in murine adipose tissue, and stimulates adiponectin secretion in adipocytes,

TABLE 1 Key points for future research

- Adult male and female offspring exhibit different phenotypes in response to zinc deficiency during prenatal and/or postnatal life. More evidence from basic and clinical studies is needed to determine hormonal, genetic, transcriptional, and morphological mechanisms underlying sex differences
- Deeper knowledge about zinc homeostasis, the role of its transporters, and the adequate serum zinc ranges at different stages of life, could be important to develop new therapies for the prevention and treatment of cardiovascular and metabolic disorders
- Further clinical research is needed to elucidate the efficacy and doses of zinc supplementation, in pregnant women, neonates, infants, children, and adults exhibiting adequate or deficient zinc intake, to prevent the development of metabolic syndrome
- Food fortification strategies should be explored and implemented to ensure adequate dietary zinc intake in individuals at different stages of life

which improves sensitivity to insulin in peripheral organs and has anti-inflammatory effects (122). Therefore, alterations in zinc homeostasis in obese individuals could compromise these physiological functions of AZGP1.

The metabolic alterations induced by zinc deprivation during prenatal life are sex specific. Female rats were less sensitive to developing metabolic alterations when subjected to moderate zinc dietary restriction compared with males (55). Moreover, another study showed elevated leptin concentrations only in male offspring born to ZD rat dams (7 mg/kg). Leptin expression and secretion are regulated by sex hormones. In this regard, it has been described that marginally ZD rats have significantly lower serum testosterone concentrations compared with controls, indicating that possible interactions between ZD, serum leptin, and testosterone concentrations might contribute to the gender-specific development of insulin resistance (123).

Conclusions

ZD during critical periods of growth has become an important health concern worldwide, particularly in pregnant women and children having an imbalanced diet. An unhealthy lifestyle and the increased consumption of processed foods based on flours, sugars, and fats in developed countries have been the main drivers of hidden malnutrition.

Experimental and clinical studies suggest that zinc is an essential micronutrient for growth, as well as for the development and function of metabolic and cardiovascular systems. In this regard, moderate ZD during critical periods of prenatal and postnatal development would program cardiovascular, renal, and metabolic diseases in adulthood through different mechanisms such as: *1*) alterations in organogenesis that determine morphological and functional capacities; *2*) activation of oxidative, apoptotic, and inflammatory processes; *3*) dysfunction of the NO system and RAAS; *4*) changes in insulin homeostasis and in cellular signaling pathways that generate insulin-like effects on intermediate metabolism; and *5*) alterations in the cytokine profile secreted by adipose tissue.

Moreover, as in numerous developmental programming experimental models, young adult male and female offspring exhibit different phenotypes in response to this micronutrient deficiency. This underscores differences in genetic, transcriptional, and morphological patterns during development that can be influenced by steroid hormones. However, additional basic and clinical studies are required to obtain more evidence about the sex differences in response to ZD and the involved mechanisms (**Table 1**).

Modulation of zinc status during pregnancy, lactation, and postweaning growth could become a new target in the prevention and treatment of cardiovascular, renal, and metabolic disorders. In this regard, deeper knowledge about zinc homeostasis, the role of its transporters, and the adequate serum zinc ranges at different stages of life, could be important for developing new therapies for these diseases. In addition, further clinical research is needed to elucidate the efficacy and doses of ZS during early stages of growth to prevent the development of metabolic syndrome later in life. Finally, food fortification strategies should also be explored to ensure adequate dietary zinc intake in individuals at different stages of life.

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