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Review Article

Essential Trace Element and Mineral Deficiencies and Cardiovascular Diseases: Facts and Controversies

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Abstract: Deficiencies of minerals and trace elements are common and widespread, and are associated with adverse cardiovascular endpoints. Emerging evidence indicates that, diet rich in these nutrients constitutes a modifiable lifestyle factor that might reduce the risk of cardiovascular disease (CVD). However, the clinical significance of these nutrients in optimizing cardiovascular health and/or ameliorating cardiovascular pathologies is currently debatable. This review aims to explore evidences in favor or against the role of these nutrients in the pathogenesis, progression, management and endpoints of CVDs, and extend the discussion on some discrepant research findings. Literature search was conducted in PubMed, Medline, Scopus and EMBASE databases on studies published in English between 1963 and 2016 using appropriate terms such as minerals, Trace elements, Chromium**,** Copper, Iron, Magnesium, Selenium, Manganese, Zinc deficiencies and CVD. Indeed, trace elements and minerals play significant cardio protective roles when they are present in adequate pharmacologic concentrations due to their antioxidant, anti-inflammatory and immune function modulatory activities. The discrepant results recorded in some studies could be due to the effects of several poorly adjusted covariates such as interactions between paired/complementary micronutrients, absence of uniformly accepted cut off values for normal range, individual susceptibility and environmental factors and several methodology inadequacies. Supplementation of these nutrients in pharmacologic doses in high-risk individuals or those with known deficiency states is cardioprotective.

Keywords: Trace Element, Mineral, Heart Disease

1. Introduction

Micronutrient deficiencies [MNDs] are common and widespread, constituting a major public health and socio-economic problem worldwide [1-3]. Micronutrients are vitamins and minerals that are essential for life. They are dietary components, that although required in very small amounts, are vital to health, disease prevention, and well-being. They are obtained primarily through the food we eat, because most are not made endogenously, or are made in amounts insufficient to meet our needs. Therefore, micronutrients are commonly used as dietary supplements to promote health and prevent disease [4]. There are many micronutrients that perform a variety of specific biological roles in the body's catalytic, structural, and regulatory functions. They include trace elements such as iron, iodine, and zinc, minerals such as calcium and magnesium, and vitamins. They act as antioxidants, anti-inflammatories, and immune modulators [5]. Only a balanced and varied diet can provide enough micronutrients [correct quantity and combination] to meet the body's requirements and to prevent deficiency states. MNDs could result in severe consequences, such as impaired resistance to infection and metabolic disorders, with associated morbidity and mortality. Micronutrients have a century-long record of extensive use in disease prevention and treatment. Hippocrates prescribed copper compounds to treat diseases as early as 400 B. C. [6]. In the 1880s, inclusion of iron and iodine into the diet eradicated beri-beri among Japanese sailors [7]. Fortification of flour with vitamin B caused the disappearance of pellagra in the southern USA in 1920. Likewise, in 1923, addition of iodine to salt prevented

goiter and cretinism in Switzerland [8]. Despite the extraordinary landmarks of 100 years of scientific expertise and innovation in the field of micronutrients, many people still do not have access to adequate vitamins and minerals or do not choose foods rich in micronutrients. At least 2 billion people worldwide do not receive an adequate supply of micronutrients and suffer from chronic MND [1, 2]. This is partly due to poor dietary habits, poor lifestyles, accelerated urbanization, market globalization, increased micronutrient requirements, climate change, altered resources, interference with the natural production of nutritious foods, unstable food prices, and research controversies on the supplementary use of micronutrients [9].

Changes in the world's food economy have contributed to a shifting dietary pattern, from foods rich in micronutrients to the consumption of diets low in micronutrients but high in fat and simple carbohydrates. Even in otherwise "healthy" individuals in industrialized countries, MNDs are surprisingly common due to lifestyle-related factors [10, 11]. Consequently, MNDs are a global problem [12], adversely affecting a third of the world's population [13], potentially with a significant negative impact on health, the economy, and quality of life [2, 9, 14 15]. For instance, in the US, an estimated $11.8 billion is spent annually on micronutrient supplements and about 7% of the annual global disease burden is attributable to deficiencies in key micronutrients [4, 16] with the highest estimated Disability Adjusted Life Years attributed to MNDs in sub-Saharan African countries. Children, women, and the elderly are the most affected by MNDs, but MNDs could also be a significant factor in certain health complications in industrialized societies, more so in countries in transition [2]. In addition, genetics, prescription drugs [17], and even the consumption of less nutritious but more palatable diets over a period of time could create a dearth of micronutrients in the body. Intriguingly, MND has no overt signs but causes many diseases, including cardiometabolic disorders. Hence, MND is collectively known as the "hidden hunger" [9].

The detrimental effects of MNDs on present and future cardiovascular endpoints are extensive and are related to associated vascular endothelial insults, resulting from MND-induced damage to cellular mechanisms such as oxidative stress, insulin resistance, inflammation, and autoimmune vascular dysfunction [17].

Previous reviews on this topic have focused more broadly on the effect of single MND on single or multiple cardiovascular risk factors [18], or on multiple MNDs on a single cardiovascular risk factor [17, 19], or have involved primary prevention studies in adults without known nutritional deficiencies [4]. Given this background, the present review attempts to provide an all-inclusive review of the literature on the seminal role of MNDs on cardiovascular risk factors, including primary, secondary, and tertiary prevention and extending to a discussion on the pathophysiology underlying MND-induced CVDs. Undoubtedly, the evolving understanding of the relationship between MNDs and CVDs may have implications for potential therapies and preventive measures toward minimizing deficiency states, and hence on CVDs among those at risk and in the general population.

2. Methods

A search using Medline, Scopus, and EMBASE databases was conducted to identify published articles within the period 1963–2016 using related terms such as micronutrients, essential nutrients, cardiovascular disease, minerals, antioxidants, and anti-inflammatory and immune-modulatory micronutrients. For the purpose of this review, micronutrients were defined as vitamins, minerals, and trace elements essential for life. For each micronutrient, we considered evidence for or against its cardio-protective effects, its pharmacodynamics and pharmacokinetics, and current research needs.

The inclusion criteria included studies with high methodological quality, investigating the associations between trace element and mineral deficiencies and major cardiovascular events such as hypertension, myocardial infarction, ischemic heart disease, transient ischemic attack and angina. Articles with obvious methodologic flaws (e.g., inappropriate selection criteria, poor analytical methods, inadequately adjusted covariates and inappropriate doses) were excluded. One hundred and ten articles from the initial 210 articles met the inclusion criteria. They were also evaluated for study designs (double blind, randomized, randomized controlled trial or open label), administered doses of the mineral or trace element and duration of treatment. The selection and evaluation were performed only on articles published in English.

3. Pathophysiology of Mineral/Trace Element Deficiency-Induced CVD

Studies of the association between MND and CVD over the past several years have led to a good understanding of the pathophysiologic mechanisms leading to adverse cardiovascular endpoints. Accumulated data indicate that the link between MND and CVD involves three pathophysiologic processes (Table 1 and 2).

Table 1. *Minerals and Trace elements and their cardioprotective mode of actions.*

Antioxidants	Immune modulators	Anti-inflammatory
Vanadium	Iron	Selenium
Chromium	Zinc	-
Magnesium	Selenium	-
Zinc	Magnesium	Magnesium
Selenium	-	-
Copper	-	Copper
Calcium	-	-
Co-enzyme Q10	-	-
Manganese	-	Manganese

Table 2. *Classification of Minerals and Trace elements based on the strength of their cardio-protective mode of actions.*

Minerals and Trace elements	Antioxidants	Immune modulators	Anti-inflammatory
Copper [Cu]	++		++
Chromium [Cr^{3+}]	++	-	++
Magnesium [Mg^{2+}]	++	++	++
Selenium [Se]	++	++	++
Iron [Fe]	-	++	-
Vanadium [V]	++	-	-
Zinc [Zn^{2+}]	++	++	++
Manganese [Mn]	++	-	++

First, MND-induced oxidative stress weakens the antioxidant defense system that helps to subdue the oxidative stress elicited by aerobic metabolism [20] and other external agents. Second, MND-induced inflammatory processes lead to the uncontrolled release of inflammatory cytokines that mediate reactions leading to a compromised hemodynamic state. Third, MND-induced defective innate and adaptive immune responses lead to CVD through three mechanisms: renal damage, cytokine production, and central nervous system stimulation [21]. These three pathophysiologic processes are causally interrelated (Figure 1).

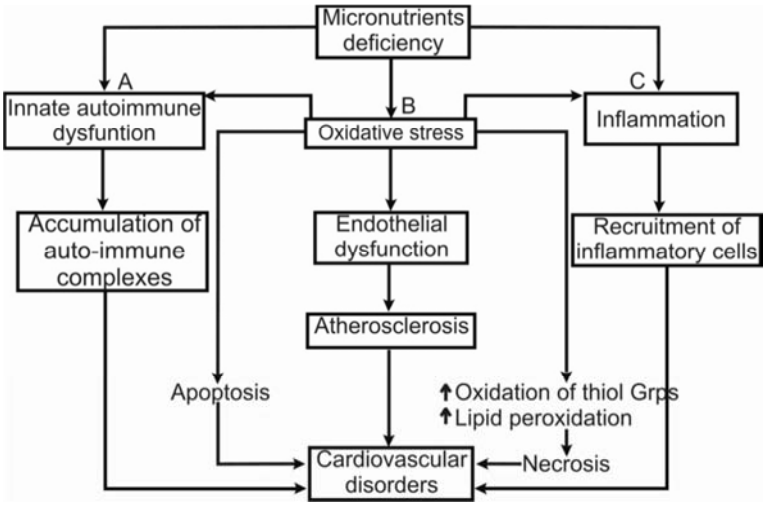

Figure 1. *Mechanisms of micronutrient deficiency-induced cardiovascular diseases.*

Micronutrient deficiency leads to immune function impairment and accumulation of immune complexes, and through series of other interrelated processes leads to CVDs. B-MVD, leads to oxidative stress, endothelial dysfunction, atherosclerosis and via series of other interrelated processes leads to CVD. C-MVD, leads to inflammation, recruitment of inflammatory cells, release of inflammatory cytokines and via series of other interrelated processes leads to CVD.

Oxidative stress leads to imbalance in pro-oxidant–antioxidant homeostasis with resultant generation of toxic reactive oxygen species [ROS]. Numerous established studies have confirmed the association between MND and oxidative stress, and the links between ROS and CVD have been strongly established. Oxidative stress is known to cause damage to endothelial cells, degrade nitric oxide [NO], oxidize low density lipoprotein cholesterol [LDL-C], proteins, and deoxy-ribonucleic acid, and has been implicated in the etiology of several CVDs in numerous interventional, epidemiologic, and observational studies.

Likewise, MND deficiency has been associated with inflammatory CVDs as evidenced by the inverse association between MND and inflammatory cardiovascular risk biomarkers, including high sensitivity C-reactive protein [hs CRP] and other inflammatory cytokines such as interleukin [IL]-IB, IL-6, and tumor necrosis factor alpha [TNF-α]. A higher odds of having a high high-sensitivity C-reactive protein [hs-CRP] level was reported in subjects with MND [22], and a positive correlation between serum ferritin levels and log [hs-CRP] has also been reported [23, 24]. A high level of hs-CRP is not only a risk marker but also a risk factor for CVD. Support for this view comes from the observation that hs-CRP inhibits NO and endothelial NO synthase and other cardio-protective systems, such as down regulation of the angiotensin subtype 2 receptor [25].

4. Minerals and Trace Elements

4.1. Chromium Deficiency and CVD

Chromium is an essential mineral that plays a significant role in lipid and carbohydrate metabolism [26]. It constitutes part of the glucose/insulin-complex system, otherwise known as glucose tolerance factor [27], and acts as a critical cofactor

in the action of insulin [8, 28, 29]. Although limited, epidemiologic data indicate low serum chromium levels are associated with several CVDs. In an incident population-based case-control study in eight European countries and Israel (EURAMIC study), conducted between 1991 and 1997, Guallar et al. [30] found that toenail chromium concentration was inversely correlated with the risk of myocardial infarction [MI] in men (odds ratio 0.56, 95% confidence interval (CI) 0.37–095) [30]. In related studies, Rimm et al. [31] and Rajpthak et al. [32] reported lower toenail chromium concentrations in diabetic men with CVD than in healthy controls. In a study by Kopela and colleagues [33], chromium attenuated vascular abnormalities, impaired NO signaling mechanisms, and increased systolic blood pressure in spontaneously hypertensive rats, induced by a high glycemic [sucrose] index diet [33]. Augmentation of acetyl choline or nitroprusside-dependent vasodilation was also observed. In a cineangiographic study of patients with CAD, Newman et al [34] observed an inverse association between serum chromium level and incident coronary artery disease [CAD] independent of other covariates [34]. Furthermore, autopsies of persons who died of heart disease were shown to have significantly less chromium in their aortas than in the aortas of healthy accident victims [35].

There are several forms of chromium, the most common are the trivalent and hexavalent forms. The hexavalent form of chromium is toxic to humans. Long- and short-term exposures are reported to be associated with bronchitis and asthma, and skin and lung cancer, respectively [36]. In contrast, the trivalent form is safe and is present in most diets.

Dietary sources constitute the main source of chromium for humans. Such sources include green beans, whole grains, nuts, and broccoli. Diet also remains a significant contributor to the deficiency state in humans. Studies by Simonoff et al. [37] and Newman et al. [34] show that a plasma chromium level < 0.06 µg/L is strongly associated with CAD risk. In a similar study, Schroeder showed that chromium deficiency was associated with a higher prevalence of CAD risk factors such as elevated cholesterol level, insulin resistance, low high density lipoprotein-cholesterol [HDL-C], hyperglycemia, and aortic plaques in rats [38]. Likewise, a study by Abraham et al. [39] demonstrated that treatment with potassium-chromate caused improvement of cholesterolemic diet-induced atherosclerotic plaques in rabbits [39]. In a double-blind crossover study of 28 volunteers treated with chromium tripicolinate [3.8 µmol [200 µg]] or placebo daily for 42 days, Press et al [26] found a significant decrease in the level of total cholesterol, LDL-C, and apoprotein β and a corresponding increase in apoprotien A-I and HDL-C [26].

Chromium deficiency occurs when chromium loss is greater than intake, as may be seen in elderly individuals, during pregnancy, and with consumption of a high glucose and highly processed diet. It is also common during periods of stress and infectious conditions. Increased consumption of processed plant foods in modern societies has led the high prevalence of low serum chromium levels in the general population. This has contributed to the increasing incidence of insulin resistance and type 2 diabetes mellitus.

The cardio-protective effect of chromium is explained by its regulatory action on insulin sensitivity and activity, and hence several insulin-mediated metabolic activities including glucose and lipid metabolism. Chromium deficiency is thought to cause insulin resistance, a known risk factor for dyslipidemia and hyperglycemia. These metabolic disorders are associated with atherosclerotic CVD risk in the general population. Good glycemic control is associated with a lower incidence of cardiovascular outcomes, including MI [40]. Insulin resistance also leads to other risk factors for adverse cardiovascular events such as hypertension, obesity, hyperuricemia, and dyslipidemia. A direct relationship between insulin level and CVD has been postulated [41]. Elevated insulin levels have been found in patients with MI and atherosclerosis and peripheral vascular disease [41]. Despite the impressive cardio-protective effects of chromium, other studies found no association between chromium levels and cardiovascular effects [Rajpathak et al 2004], which could partly be ascribed to the presence of adequate dietary intake of chromium [42], and or poor bioavailability [26]. Also, differences in demographic characteristics of the study population may have impacted on the results. For instance, significant results may not be observed in young adult populations, while in aged persons, oral chromium acetate intake failed to alter serum cholesterol levels due to poor bioavailability [38]. Also, high-dose chromium supplementation may be needed to achieve an effect in disease states or conditions associated with increased chromium loss. For instance, while 200 µg/day of chromium had no significant effect on glucose tolerance, use of high-dose chromium [1000 µg/day] reduced insulin requirements in a group of patients with type 2 diabetes mellitus [42].

4.2. Iron Deficiency and CVD

Iron deficiency is known to be associated with several CVDs [43-45] including pulmonary arterial hypertension, CAD, and heart failure. Improvement in these diseases has been recorded following iron supplementation, confirming the hypothesis that iron deficiency is a common problem in patients with cardiovascular conditions. Conversely, iron overload was found to increase the incidence of CAD, including the incidence of MI [46]. However, the cardiotoxic effects of iron overload are not consistent across studies involving patient with CAD [47]. Iron is known to play several physiologic roles in the body, including synthesis and degradation of proteins, lipids, and ribonucleic acids, and myocardial and skeletal muscle metabolism. Iron deficiency may precipitate various biochemical and metabolic disorders leading to adverse cardiovascular endpoints.

4.3. Magnesium Deficiency and CVD

Magnesium is the second most abundant intracellular cation. It is a cofactor of several enzymatic reactions. Dietary sources of magnesium include green leafy vegetables, whole grains, legumes, and nuts [48]. Normal plasma magnesium

concentrations are 1.7–2.1 mg/dL [0.7–0.9 mmol] [49]. Magnesium deficiency could be due to low dietary intake, poor intestinal absorption, or increased excretion. Previous studies have reported an inverse association between serum magnesium level and CVD risk markers, such as hypertension [50], dyslipidemia [51, 52], type 2 diabetes mellitus [50], insulin resistance [53], obesity [general and abdominal] [54, 55], metabolic syndrome [50], CRP [56], IL-6 [57], and low albumin serum level [58]. CVDs associated with low serum magnesium include IHD, irreversible heart failure [59], reduced coronary flow [60], ventricular arrhythmias angina, MI, sudden cardiac death, and stroke.

The detrimental effect of magnesium deficiency-induced CVDs tends to worsen with increasing age and obesity [61]. However, the effect of obesity may surpass the impact of age on magnesium deficiency-induced CVD. Zaakouk et al. [48] reported a strong inverse association between obesity and serum magnesium levels in children despite a high dietary intake of magnesium-rich foods. A significantly higher systolic and diastolic blood pressure, fasting total cholesterol, LDL-C, and triglyceride [TG] levels, and significantly lower HDL level, were also observed in the obese compared with the non-obese participants. Their study findings were consistent with those of several other published studies [62, 63]. Several established studies have confirmed that magnesium deficiency intensifies oxidative stress and inflammatory processes. In one study, the association between blood pressure and the intake of six dietary variables was assessed in 615 Japanese men who had a positive history of CVD or treated hypertension. Magnesium, calcium, phosphorus, vitamin C, and vitamin D intake were significantly and inversely associated with blood pressure in both the univariate and multivariate analysis. Interestingly, magnesium had the strongest inverse association with blood pressure [64]. This association was present with magnesium derived from food as well as with supplemental intake. In the Mexican Health Workers Cohort Study of 1,378 subjects, lack of evidence to support the inverse relationship between magnesium intake and development of hypertension was observed. Likewise, a study of 3,531 middle-aged adult participants in the Framingham Heart Study Offspring Cohort showed no association between serum magnesium level and the risk of developing hypertension or CVD. Similarly, Khan et al. [65] found no relationship between serum magnesium and the development of hypertension.

Mixed clinical findings have also been reported by other investigators [66-68]. Lack of association in many of these studies may be linked to several study limitations, including errors in the measurement of self-reported dietary intake, low response rates at follow-up in a prospective study, small sample size, lack of separation of dietary magnesium from supplementation magnesium, and the effect of residual confounders, environmental factors, poor representativeness of the study population, as well as misclassification of dietary intake which could have led to underestimation of the association. In the Framingham Heart Study Offspring Cohort, the results were confounded by the limited number of study participants with very high or low serum magnesium levels that were far outside the normal range. The age bracket of the study participants [mainly middle-aged and ambulatory individuals], absence of dietary information [hence, the inability to correlate dietary intake with serum magnesium level], the single measurement of serum magnesium [that did not account for natural variation, with poor correlation between dietary intake and serum magnesium], single as opposed to serial or continuous blood pressure measurement, and the use of dietary magnesium [that may have permitted the interaction between magnesium and other constituents micronutrients] could all have impacted the results, thereby producing insufficient efficacy data. Most studies assessed serum magnesium levels, these do not reflect dietary intake and do not correlate well with total body magnesium content [69]. Additionally, most clinical trials often employ micronutrient monotherapy for reasons of scientific purity, whereas some micronutrients require the complementary action of others for full potency and activity [18]. Deficiency of one micronutrient frequently accompanies deficiency of others, supporting the hypothesis of multiple micronutrient supplementation. For instance, high calcium intake strongly confounds serum magnesium concentration. Amiot et al. [70] and Clarkson et al. [71] showed that calcium intakes as high as 2.0–2.5 g/dL reduced the absorption of magnesium. Similarly, several studies have reported interactions between magnesium and manganese at several reaction points.

According to Chiesi and Inesi [72], magnesium can be used in place of manganese in manganese-activated proteins, and manganese can replace magnesium in magnesium-activated proteins [72]. Gaillard et al. [73] reported a direct association between manganese supplementation and urinary magnesium excretion. An inverse association between manganese supplementation and magnesium concentration in both heart and bone was documented by Sanchez-Morito et al. [74]. These findings may suggest that manganese acts as a potential magnesium antagonist in these organs [75], which could partly account for the conflicting research results reported by some investigators.

4.4. Selenium Deficiency and CVD

The role of selenium in CVD is controversial. Proponents assert that adequate intake of selenium protects against CVD, particularly in populations with relatively low selenium status [76]. Several epidemiologic studies, including the German study of 636 patients with suspected CAD [77], the Flemish Study On Environment, Genes, and Health Outcomes [78], and the Finnish study of 722 middle-aged men [79] confirmed the inverse association between serum selenium and cardiovascular endpoints. The cardio-protective activities of adequate serum selenium involves three pathophysiologic processes including antioxidant, anti-inflammatory, and immune modulatory activities.

However, opposite results have been reported in several observational studies and clinical trials particularly in populations with adequate selenium intake. For instance, in

the EVA (Etude du Vieillissement Artériel) study and the US National Health and Nutrition Examination Study 2000–2004 [80], high levels of serum selenium was associated with risk of hypertension. In other studies [81-85], null associations were found between selenium supplementation and CVDs. In one study, high dose selenium supplementation (200 mg/day) failed to show any significant associations with any of the CVD endpoints after 7.6 years of follow-up. A collaborative animal experimental study by Toyran et al. [86] found increased risk of hyperlipidemia in animals treated with high doses of selenium [86]. The authors asserted that moderate to high selenium intake in populations with adequate selenium intake may be associated with adverse cardiovascular outcomes.

These inconsistent results across studies involving different nations can be explained by the fact that optimum activity of serum selenoprotein [gluthathione peroxidase] is reached at a certain serum selenium level [92 μg/L] [87-89], above this concentration, adverse cardio-metabolic outcomes may ensue. This is also true for populations with low or deficient dietary selenium intakes [90, 91]. Thus, a U-shaped relationship exists between serum selenium dietary intake and adverse cardio-metabolic outcomes, with potential detrimental effects at the extremes of serum selenium concentrations.

4.5. Manganese Deficiency and CVD

Manganese is an essential trace element that constitutes a significant component of various enzyme systems. It is important in carbohydrate, fat, and protein metabolism. Its concentration in the body ranges from 10 to 20 mg. Dietary source of manganese includes nuts, whole grains, dried legumes, and pineapple. Various studies indicate that low serum level of manganese is associated with atherosclerosis, a known risk factor for CVD. Likewise, a high serum level of manganese has been reported to be detrimental to cardiovascular endpoints. A recent study by Bagheri et al [92] reported an inverse association between serum manganese level and severity of atherosclerosis. Interestingly, the severity of atherosclerosis increases as the serum manganese level decreases. Higher serum level manganese was found in normal subjects than in patients with CAD. Conversely, serum levels of manganese above physiologic limits have been associated with adverse cardiovascular endpoints, including decreased myocardial contractility [93] and shortened action potential time [94], prolonged P-R and Q-T intervals, and broadened QRS-complexes. Other abnormal electrocardiogram findings (sinus tachycardia, sinus bradycardia, sinus arrhythmia and ST-T changes) have also been reported.

The anti-atherosclerotic effect of manganese is attributable to its antioxidant effect. Manganese is a component of the manganese-superoxide-dismutase (MnSOD) complex, an antioxidant enzyme complex found in the mitochondrial matrix. MnSOD plays a significant role in sequestering ROS generated as a byproduct of metabolic oxidation in the mitochondria, and by extension protects the cardiovascular system from oxidative damage [95]. Deficiency or decreased activity of MnSOD (irrespective of the causative factor) leads to high serum and tissue levels of superoxide [O_2^-] and peroxynitrite [$ONOO^-$]. For instance, a MnSOD knockout experiment resulted in oxidative stress related cardiomyocyte damage and was associated with dilated cardiomyopathy [96]. MnSOD also protects blood vessels from oxidative damage by preventing oxidative stress-associated endothelial dysfunction [97]. At levels above the physiologic limit, manganese has been found to alter autonomic nervous function [98] leading to changes in cardiac rhythm and blood pressure. In addition, a higher serum manganese level has been found to reduce dopamine and serotonin levels. At high serum concentrations it blocks calcium channels and causes damage to myocardial mitochondria [99].

4.6. Zinc Deficiency and CVD

Zinc is the second most abundant intracellular trace element after iron [5]. About 2–4 g of zinc is distributed throughout the human body [100]. Common sources of zinc include oysters, red meat [beef, lamb], liver, beans, nuts, sea foods [crab and lobster], whole grains, cereals, sunflower seeds, almonds, and pumpkin seeds [100]. Zinc is present in all enzyme systems in the body and it acts as a cofactor in various enzymatic activities. Zinc plays a significant role in stabilizing biological membranes, in nucleic acid biosynthesis and protein synthesis, in preservation of vascular endothelial function, and in protecting macromolecules against ROS. It maintains cardiac stem cells essential for cardiac function. Zinc deficiency is more common in patients with CVD [101, 102].

Several studies have documented an inverse relationship between serum zinc levels and CVD [103, 104] and between serum zinc levels and CVD risk markers, including atherosclerosis [102], higher serum hs-CRP [105], hyperuricemia [5], and insulin levels [105]. Direct associations between serum zinc level and albumin, HDL-cholesterol, and red blood cells have also been reported [105]. Evidence indicates that zinc's critical cardio-protective role is due to its ability to inhibit four major pathophysiologic processes leading to CVD: 1) inhibition of acute redox stress in cardio-myocytes, 2) protection against inflammatory process triggered during myocardial damage, 3) enhanced wound healing, and 4) maintenance of cardiac stem cells necessary for cardiac cells regeneration [106, 107] through its antioxidant, anti-inflammatory, and immune function modulatory activities.

As an antioxidant, zinc inhibits NADPH oxidase which plays a significant role in the production of ROS. It is a cofactor of superoxide dismutase, and is involved in generation of metallothionein which contains cysteine and scavenger OH [108]. In a study conducted among healthy adults aged 20–50 years, Prasad et al. [108] found that zinc supplementation decreased serum levels of malondialdehyde, 4-hydroxyalkenals, and 8-hydroxydeoxyguanine.

The inverse associations between serum zinc levels and inflammatory and immune dysfunction biomarkers have also been reported. A low level of zinc is associated with high serum levels of pro-inflammatory cytokines (IL-6, TNF-α,

and IL-β mRNA) in mononuclear cells. Zinc decreased oxidized-LDL-C-induced generation of TNF-α, IL-β, and vascular cell adhesion molecule-1, and vice versa. Zinc deficiency leads to thymic atrophy, lymphopenia, and impaired adaptive and innate immune responses [105, 107, 109]. Collectively, the pro-oxidant/antioxidant imbalance, inflammation, and immune dysfunction are associated with a wide spectrum of cardiovascular dysfunction.

4.7. Copper Deficiency and CVD

Copper is the third most abundant trace metal in the body, present at a concentration of 7.5–10 mg in the body. The recommended dietary allowance of copper is 0.9–10 mg/day for adults aged ≥ 19 years [110, 111]. Dietary copper deficiency is associated with several CVDs [112, 113], including abnormal heart morphology [114] and function [115-117], abnormal blood vessel morphology [118, 119], altered circulatory function [120, 121], and abnormal systemic cardiovascular effects. Adequate intake/supplementation with physiologically relevant levels of copper can reverse pre-existing cardiac defects [121], including hypertrophic cardiomyopathy [122], chronic heart failure with an associated poor left ventricular ejection fraction, increased ventricular volume, and poor quality of life [123] even in the continued presence of the precipitating factors. In several human and animal studies, removal of copper from the diet was found to precipitate defective cardiac tissues, irregular heartbeat, hypertension, clotting disorders, and stroke. CVDs such as MI, congestive cardiac failure, CAD, and arteriosclerosis have also been associated with copper deficiency states.

Several mechanisms underlie copper-deficiency induced CVD, including abnormal functioning of copper-dependent enzymes [lysyl oxidase, cytochrome C oxidase, ceruloplasmin, dopamine β-mono-oxygenase, and peptidylglycine α-amidating mono-oxygenase], peroxidation, glycation, and defective NO activities (Figure 2).

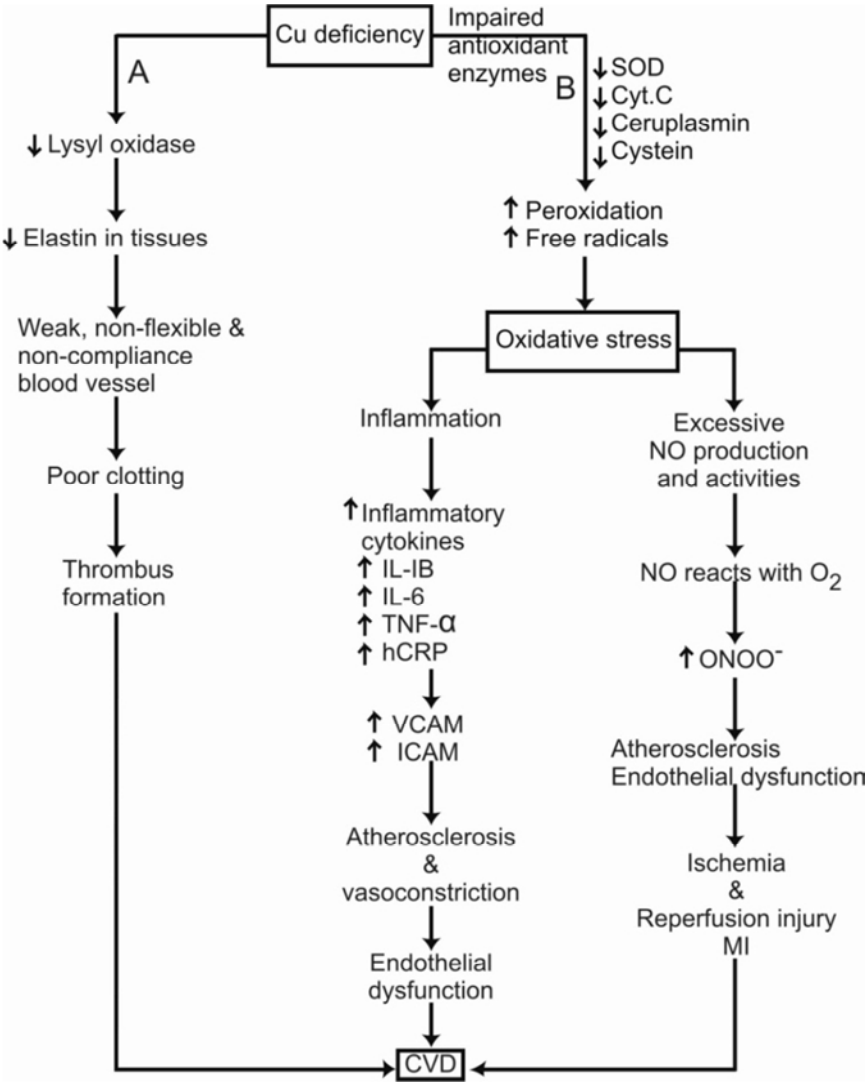

Figure 2. *Schematic diagram showing the pathways of copper-deficiency induced cardiovascular diseases.*

Cyt C=cytochrome C, NO=nitric oxide, ONOO=peroxynitrite, IL-1β=interleukin-1β, IL-6=interleukin-6, TNF-α=Tumor necrosis factor alpha, hCRP=high sensitivity C-reactive protein.

A. Copper deficiency leads to low lysyl oxidase and defective elastin formation, poor cross-links in elastin and collagen, weak and non-flexible, non-compliant blood vessels, poor clotting, thrombus formation, and cardiovascular diseases.

B. Copper deficiency leads to altered antioxidant enzymes, lipid peroxidation, increased free radicals, and oxidative stress. There is an associated increase nitric oxide synthesis and activity, including reaction with superoxide anions [O_2^-] to form potent reactive nitrogen species [peroxynitrite [$ONOO^-$]] and related pathologies, such as atherosclerosis, endothelial dysfunction, ischemia–reperfusion injury, and myocardial infarction. Alternatively, oxidative stress leads to increased plasma levels of pro-inflammatory cytokines such as IL-IB, IL-6 TNF-α, and hs-CRP. These cytokines potentiate the expression of various cell adhesion molecules, such as vascular cell adhesion molecule [VCAM], intercellular adhesion molecules [ICAM], and monocyte attractant protein-I [MAP-I]. This results in transient leukocyte sequestration and migration of leukocytes to the area of injury. There is resultant atherosclerosis and vasoconstriction, leading to cardiovascular disease.

For instance, copper deficiency leads to deficiency of several copper-dependent antioxidant enzymes such as superoxide dismutase, ceruloplasmin, and cytochrome C oxidase, and enhanced lipid oxidation [peroxidation] and damage to cells and tissues in the arterial wall causing inflammation and atherosclerosis. Associated constriction of arteries has also been reported [124]. Adequate dietary copper intake restores the activities of these enzymes and counteracts these processes [125]. Copper supplementation was shown to reverse hypertrophic cardiomyopathy by restoring normal vascular epithelial growth factor production and enhancing angiogenesis [111, 126].

5. Conclusions

Indeed, trace elements and minerals play significant cardio protective roles when they are present in adequate pharmacologic concentrations due to their antioxidant, anti-inflammatory and immune function modulatory activities. The discrepant results recorded in some studies could be due to the effects of several poorly adjusted covariates such as interactions between paired/complementary micronutrients, absence of uniformly accepted cut off values for normal range, individual susceptibility and environmental factors and several methodology inadequacies. Supplementation of these nutrients in pharmacologic doses in high- risk individuals or those with known deficiency states is encouraged.

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