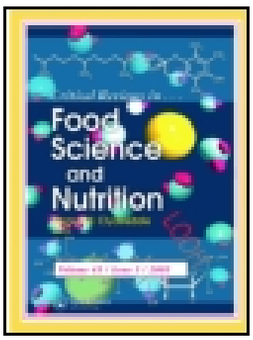

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Noushin Mohammadifard, Karin H. Humphries, Carolyn Gotay, Guillermo Mena-Sánchez, Jordi Salas-Salvadó, Ahmad Esmaillzadeh, Andrew Ignaszewski & Nizal Sarrafzadegan (2017): Trace minerals intake: Risks and benefits for cardiovascular health, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1406332

To link to this article: https://doi.org/10.1080/10408398.2017.1406332

Published online: 13 Dec 2017.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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Trace minerals intake: Risks and benefits for cardiovascular health

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ABSTRACT

Minerals play a major role in regulating cardiovascular function. Imbalances in electrolyte minerals are frequent and potentially hazardous occurrences that may lead to the development of cardiovascular diseases (CVDs). Transition metals, such as iron, zinc, copper and selenium, play a major role in cell metabolism. However, there is controversy over the effects of dietary and supplemental intake of these metals on cardiovascular risk factors and events. Since their pro-oxidant or antioxidant functions can have different effects on cardiovascular health. While deficiency of these trace elements can cause cardiovascular dysfunction, several studies have also shown a positive association between metal serum levels and cardiovascular risk factors and events. Thus, a J- or U-shaped relationship between the transition minerals and cardiovascular events has been proposed. Given the existing controversies, large, well-designed, long-term, randomized clinical trials are required to better examine the effects of trace mineral intake on cardiovascular events and all-cause mortality in the general population. In this review, we discuss the role of dietary and/or supplemental iron, copper, zinc, and selenium on cardiovascular health. We will also clarify their clinical applications, benefits, and harms in CVDs prevention.

KEYWORDS

Trace mineral; iron; copper; zinc; selenium; cardiovascular disease

Introduction

Non-communicable diseases, including cardiovascular diseases (CVDs), cancer, chronic respiratory diseases, and diabetes mellitus, are leading causes of morbidity and mortality in both developed and developing countries (Ralston, et al. 2016). Lifestyle modifications, such as healthy diets, regular physical activity, and smoking cessation, are essential for CVD prevention (Elwood, et al. 2013). According to existing guidelines, a variety of micronutrients have a major role in cardioprotective diets.

Micronutrients, specifically vitamins and minerals, have various functions within the body (Otten, et al. 2006). Despite the known role of micronutrients in maintaining general health, there is controversy over their specific effects on CVD risk (Das De, et al. 2015, Zhang, et al. 2016). Imbalances in electrolytes like sodium (Na), potassium (K), magnesium (Mg) and calcium (Ca) are frequent and potentially hazardous occurrences that may lead to CVDs such as hypertension, coronary heart disease (CHD), cardiomyopathy, heart failure, and arrhythmias (Aburto, et al. 2013, Chrysant and Chrysant 2014, Kolte, et al. 2014, Smyth, et al. 2015).

Transition metals, such as iron (Fe), zinc (Zn), copper (Cu), and selenium (Se), play a major role in cell metabolism (Gudjoncik, et al. 2014). The oxidant or antioxidant function of these metals can also have effects on cardiovascular health. For example, Fe trapped in the macrophages within the arterial wall serves as an oxidative stress mediator and has been identified as a novel risk factor for vascular disease progression (Sullivan 2007). Iron deficiency (ID) is also an important predictor of cardiovascular events and all-cause mortality (Lapice, et al. 2013). On the other hand, the antioxidant properties of Cu, Zn, and Se may prevent the development of CVDs (Sarmento, et al. 2013). Many in-vitro and animal studies have reported the benefits of these supplements in controlling damaging cellular mechanisms. Adequate intake of these elements, through diet and/or supplementation, has thus been recommended for health promotion (Fortmann, et al. 2013).

However, there is no consistent evidence that these supplements can affect CVD, cancer, or all-cause mortality in healthy individuals without known nutritional deficiencies (Fortmann, et al. 2013, Moyer and Force 2014). Although many studies and

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reviews have examined the effects of vitamins and electrolytes such as Na, K, Ca, and Mg (Aburto, et al. 2013, Chrysant and Chrysant 2014, Kolte, et al. 2014, Smyth, et al. 2015) on the risk of CVD events, the effects of transition minerals on cardiovascular health, and their benefits, risks, clinical applications, indications and contraindications have not been comprehensively and critically evaluated (Fortmann, et al. 2013, Moyer and Force 2014). This review seeks to clarify the role of dietary and supplemental intake of these minerals on major cardiovascular events and associated risk factors (Box 1).

Box 1. Review criteria

A search for original articles published between January 1990 and February 2016 was performed in PubMed. The search terms used were "cardiovascular" "coronary heart disease" "coronary artery disease" "sudden cardiac death" "cardiomyopathy" "heart failure" "arrhythmia" "atherosclerosis" "hypertension" "mineral" "iron" "copper" "zinc" "selenium", both alone and in combination. All articles identified were full-text papers published in English. Clinical and population studies were included.

Given that the present article is not a systematic review, we may not have identified all studies, and publication bias should be acknowledged. Our search terms combined the following exposures: iron, copper, zinc and/or selenium, and cardiovascular disease, metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and/or heart failure. We discuss the possible mechanisms involved in these associations, and unanswered research questions for future research.

Iron intake and cardiovascular disease

Physiology and function

Fe is a critical mineral for maintaining homeostasis in the human body. It is essential for several cellular processes, including erythropoietic function, oxygen transfer through hemoglobin, oxidation-reduction reactions, immune responses, cell division and growth, protein metabolism, DNA synthesis, thyroid hormone regulation and production of various neurotransmitters within connective tissue. It is also an important component of various enzymes involved in metabolic processes, such as catalase, peroxidase, and cytochrome (Waldvogel-Abramowski, et al. 2014). While one of Fe's main roles is facilitating oxygen diffusion to mitochondria, it can also be toxic due to its oxidative role in body cells. In oxidative enzymes, Fe is absorbed or stored in the form of ferritin. This element is mostly distributed in hemoglobin and myoglobin, and body levels are regulated by balancing its intake, utilization, and storage (Ganz and Nemeth 2012). Figure 1 shows the metabolism, regulation, maintenance of Fe, and risk of iron deficiency (ID) and overload in the body.

Current dietary recommendations

Generally, the recommended dietary allowance (RDA) for Fe is 8 mg/day in adults (Trumbo, et al. 2001). In women between the ages of 19 and 30, the RDA increases to 18 mg/day. The upper limit (UL) for Fe is 45 mg for all adult populations. Fe supplementation is commonly recommended for the management of ID (Trumbo, et al. 2001).

Role in cardiovascular disease

Fe's role in cardiovascular events was noted in several observational studies. For instance, enhanced Fe uptake following the mutation in HEE-gene haemochromatosis was associated with an increased risk of coronary heart disease (Lian, et al. 2013). Conversely, voluntary blood donation, as well as phlebotomy twice a year, reduced the incidence of non-fatal myocardial infarction (MI) and all-cause mortality (Meyers, et al. 1997, Zacharski, et al. 2011).

Several approaches may explain the association between Fe and cardiovascular events. In 1981, Sullivan proposed that bodily Fe levels contributed to sex differences in heart diseases risk (Sullivan 1981), given that Fe depletion during a woman's menstrual period may decrease the availability of redox-active Fe, which in turn reduces oxidative or inflammatory damage (Sullivan 2007). This observation led to the iron hypothesis replacing the estrogen hypothesis, which previously had been used to explain sex differences in CHD incidence (Mascitelli, et al. 2011). In turn, the iron hypothesis has been criticized since Fe is believed to be an atherogenic factor only in case of hereditary hemochromatosis (Mascitelli, et al. 2011).

Hepcidin, an essential hormone synthesized by the liver, regulates Fe levels in the body by maintaining intracellular availability and reducing intestinal absorption of Fe

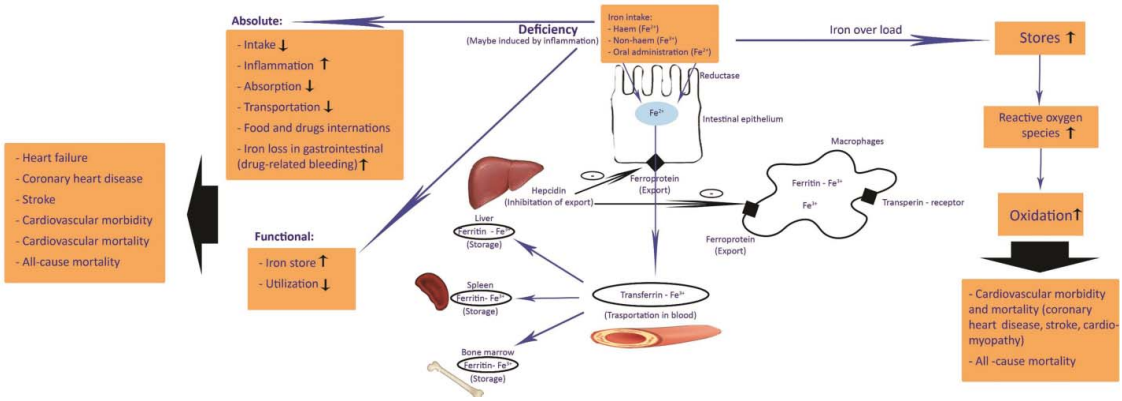

Figure 1. Metabolism of Iron in the body. The metabolism, regulation, maintenance, risk of iron deficiency and overload of iron in the body.

(Waldvogel-Abramowski, et al. 2014). The activity of hepcidin depends on its binding to ferroportin, a trans-membrane protein that transports Fe from the inside to the outside of a cell. This binding decreases Fe flow through the enterocyte, recovers macrophages, increases Fe entrapment in macrophages, and ultimately leads to atherosclerotic vascular disease, even in patients without hemochromatosis (Sullivan 2007, Waldvogel-Abramowski, et al. 2014). Hence, ID may prevent the progression and destabilization of atherosclerotic plaques on vascular walls (Mascitelli, et al. 2011). ID anemia and most cases with hereditary hemochromatosis can significantly reduce hepcidin levels, since both low hepcidin concentrations and hereditary hemochromatosis are distinguished by free or low Fe macrophages (Mascitelli, et al. 2011). Fe can also stimulate the formation of reactive oxygen species (ROC) and thus cause lipid peroxidation and atherosclerosis (Sullivan 2009). Recent reports have identified elevated Fe levels accumulated by macrophages in the arterial wall and the consequent release of oxidative stress and pro-inflammatory agents as a novel risk factor for atherosclerosis (Sullivan 2007). In fact, serum ferritin and hepcidin are independently associated with carotid plaques (Valenti, et al. 2011). However, a cross-sectional study found aortic stiffness was inversely associated with hepcidin level, but not high ferrtin level. This debate on the role of hepcidin in the progression of atherosclerosis may be due to different anatomical structures and cell compositions with the arterial walls (Valenti, et al. 2015).

Additionally, catalytic Fe increases the risk of lipid oxidation, endothelial injury, and resultant atherosclerosis (Rajapurkar, et al. 2012). Free Fe catalyzes the production of homocysteine, an independent CVD risk factor, from methionine (Baggott and Tamura 2015). However, several observational studies and meta-analyses have not supported the adverse effect of Fe status on CHD risk (Danesh and Appleby 1999, Ma and Stampfer 2002). A 2000 study demonstrated the beneficial effects of intravenous (IV) Fe on left ventricular ejection fraction (LVEF) and heart failure (HF). This evidence challenged the hypothetical cardiotoxic effect of Fe and its role in the development of cardiovascular events.

Both absolute and functional ID have been shown to contribute to CVDs. Functional ID is caused by the down-regulation of ferroportin and entrapment of Fe in macrophages, erythrocytes, and hepatocytes. Since hepcidin production due to inflammation may down-regulate ferroportin activity (Ganz and Nemeth 2006), impaired Fe absorption can occur in chronic inflammatory conditions such as HF. Hepcidin has a major function in ID in patients with HF (Arora and Ghali 2013).

Finally, analysis of factors relevant to CHD identified associations between Fe levels and risk factors including inflammation, obesity, proatherogenic as well as antiatherogenic and antioxidant components. Such associations reveal the pathophysiologic mechanisms of the relationship between Fe and CHD (Spasojevic-Kalimanovska, et al. 2014).

Hypertension. The findings on effects of Fe intake are inconsistent. Although total intake of Fe and non-heme iron was inversely associated with blood pressure (BP) and hypertension risk, heme intake was not associated with BP and incidence of hypertension. The positive association between meat intake and systolic blood pressure (SBP) disappeared after adjustment for food intake (Tzoulaki, et al. 2008, Galan, et al. 2010). Thus, a weak association between heme-iron and BP in cross-sectional studies might reflect the unfavorable effect of red meat intake (Rhodes, et al. 2011). Clarification of these results needs more experimental evidence about, possible mechanisms and confirmation in prospective studies and clinical trials (Tzoulaki, et al. 2008). A number of recent studies highlighted the significance of ID, not only in diverse cardiovascular events such as HF and CHD, but also in pulmonary hypertension. Fe has a main effect on vascular homeostasis, though the mechanism is unknown. A potential physiological mechanism may be suppression of Fe absorption (Rhodes, et al. 2011, van Empel, et al. 2014, Cotroneo, et al. 2015); thus, supplemental or IV Fe may be beneficial and reduce hypoxemia in pulmonary hypertensive patients (Smith, et al. 2009, Smith, et al. 2011, van Empel, et al. 2014).

ID is also important in patients undergoing cardiac surgery and may have a synergistic effect with other major CVD risk factors including hypertension (von Haehling, et al. 2015).

Bodily Fe indicators had diverse associations with BP in various studies. Although the level of hemoglobin and ferritin had no association with BP and risk of hypertension in the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study in Korean men, ferritin levels were associated with the incidence of hypertension (Galan, et al. 2010). However, this relation might be mediated through insulin resistance and fatty liver disease (Kim, et al. 2012). Serum ferritin concentration was also inversely related to the use of calcium channel blockers in hypertensive patients (Mainous, et al. 2012).

Cardiovascular events. Previous epidemiological studies have reported inconsistent results regarding the association between Fe and CVDs. Two recent meta-analyses of prospective cohort studies reported inverse relationships between transferrin saturation, serum Fe, and total Fe, and the risk of fatal or non-fatal CHD (Das De, et al. 2015). Meanwhile, heme iron had a positive association with the risk of fatal or non-fatal CHD. None of the above-mentioned factors was associated with all-cause mortality (Hunnicutt, et al. 2014). In another meta-analysis of 55 cross-sectional, case-control, and cohort studies, 27 studies supported the iron hypothesis, eight studies rejected it, and 20 studies were unable to find supporting evidence (Munoz-Bravo, et al. 2013). Finally, a large case-control study in a Taiwanese population demonstrated a positive relationship between ID and ischemic stroke (Chang, et al. 2013).

The main problems in defining the relationship between Fe and CVDs arise from the use of varying indicators of Fe status, including heme, non-heme, and total iron intake assessed by dietary questionnaires, as well as serum Fe, ferritin, transferrin saturation, and total Fe binding capacity assessed by blood samples. The variations in populations and endpoints in different studies may also be responsible for the inconsistency of past findings (Hunnicutt, et al. 2014). A meta-analysis of 32 cohort studies indicated that heme iron had a positive association with CHD events. Moreover, while the incidence of CHD was inversely related with total Fe intake, there was no significant association with non-heme iron. No links were found

between the above-mentioned factors and CHD mortality risk. This inconsistency may be explained by the bioavailability of Fe in different dietary sources, heme iron's ability to promote low density lipoprotein cholesterol (LDL-C) oxidation, and the positive association of heme iron with inflammatory factors (Yang, et al. 2014). The findings may have also been confounded by other nutrients found in dietary sources of heme iron, such as saturated fatty acids. In fact, while heme iron intake was positively associated with the risk of CHD in Western populations, where red meat is a major dietary source of Fe, this relationship was negative in the Japanese, who receive heme iron from fish and shellfish (Sun, et al. 2011). Several studies have reported the incidence of CHD was positively associated with ferritin level and inversely associated with serum Fe and transferrin saturation (Hunnicutt, et al. 2014). As inflammation is correlated with less serum Fe and transferrin saturation, reverse causality and a single measurement at baseline may account for the inverse association between these biomarkers and the incidence of CHD (Friedrich, et al. 2009). Comparing participants in the lowest and the highest category of Fe biomarkers also potentially masks the effects of ID versus Fe overload on CHD (Das De, et al. 2015). Other possible explanations of the inconsistent findings include regression dilution and residual confounding (Das De, et al. 2015). Owing to its less extensive variation and reverse causality of inflammation, ferritin is a more precise Fe biomarker than serum Fe and transferrin saturation (Lapice, et al. 2013). However, since ferritin can be influenced by inflammation, the transferrin saturation to ferritin ratio is the best biomarker of Fe in the context of examining CHD (Lapice, et al. 2013).

Overall, ID and Fe overload are considered risk factors for all-cause mortality and CVDs. They are also critically important in patients who undergo cardiac surgery (Chang, et al. 2013, Lapice, et al. 2013, von Haehling, et al. 2015). In women, U-shaped associations have been observed between Fe biomarkers, including ferritin, transferr in saturation, and total Fe binding capacity, and CVD events (Table 1) (Friedrich, et al. 2009, Lapice, et al. 2013, Munoz-Bravo, et al. 2013).

Heart failure. ID is a frequent condition, with a prevalence of 30 to 50% in patients with chronic HF (Klip et al. 2013). ID, rather than anemia, has been identified as an independent predictor of mortality in HF patients (Jankowska, et al. 2013). Pulmonary hypertension, which has many common symptoms with HF, including subclinical inflammation, increases in patients with ID (von Haehling, et al. 2010). A meta-analysis of more than 150,000 HF patients reported that the risk of mortality was almost doubled in anemic patients compared to their non-anemic counterparts (Groenveld, et al. 2008). The main reasons for anemia and consequent cardiac dysfunction in HF patients are plasma volume expansion and red cell mass reduction, leading to low hemoglobin levels and hyperferritinemia. Moreover, drugs used in the treatment of HF (e.g., aspirin, anticoagulants, and other anti-platelets), along with the activity of pro-inflammatory cytokines, including inerleukin-1 (IL-1), IL-6, interferon gamma, and tumor necrosis factor alpha (TNF-α), decrease erythropoietin formation and inhibit hematopoiesis (Jelani and Katz 2010, Jankowska, et al. 2013). Inflammatory mediators, such as antibodies, also reduce Fe absorption (Nunes, et al. 2015).

In patients with HF, Fe supplementation, especially IV iron therapy, improves short-term outcomes including quality of life, exercise capacity, cardiac structure and function, and reduce re-hospitalization, negative outcomes after cardiac surgery, and death (Lapice, et al. 2013, Jankowska, et al. 2016, Qian, et al. 2016, Drozd, et al. 2017). However, large-scale clinical trials are needed to confirm the effect of IV iron therapy on long-term HF mortality (Saraon and Katz 2016). Oral Fe supplements can be prescribed in HF patients with no acute, unstable, or symptomatic conditions (Drozd, et al. 2017).

Other cardiovascular diseases. Fe overload, caused by either transfusion-dependent anemia or primary hemochromatosis, may lead to cardiomyopathy and left ventricular dysfunction (LV) (Jankowska, et al. 2016). Fe overload cardiomyopathy, due to reverse causality of HF, increases the probability of diastolic dysfunction arrhythmias (Saraon and Katz 2016). While ID may be resistant to Fe supplements in patients with cardiac

Table 1. Intake of Trace mineral and implications with cardiovascular risk factors and cardiovascular disease.

	Increase risk				Decrease risk			
	Iron	Copper	Zinc	Selenium	Iron	Copper	Zinc	Selenium
Cardiovascular risk factors								
High LDL cholesterol	***	**	***	*	***	*	**	***
Low HDL cholesterol	*	*	**	**	*	*	**	*
Hypertension	***	**	***	**	***	**	***	*
Hypetrigliceridiemia	*	*	*	***	*	***	**	*
Obesity	**	*	*	***	*	**	*	*
Type II Diabetes	*	*	*	*	***	**	***	**
Cardiovascular disease								
Myocardial infarction	*	**	***	**	*	***	**	**
Coronary heart disease	*	*	*	***	**	**	*	**
Stroke	**	*	*	***	***	**	*	*
Heart disease	***	*	*	*	*	***	*	*
Cardiovascular mortality	*	**	**	*	*	***	*	*
All-cause mortality	**	*	**	*	*	*	*	**

***High level of evidence from several propsective observational studies and randomized trials.
**Moderate evidence form several prospective observational studies or meta-analysis.
*Reasonable evidence from some prospective observational studies or expert opinions.

transplantation, IV Fe can also be beneficial (von Haehling, et al. 2015): preoperative medication with IV Fe for ID treatment may prevent the need for blood transfusion and other complications of CVDs (Jankowska, et al. 2016).

Copper intake and cardiovascular disease

Physiology and function

Cu, a trace element, is essential for enzyme function and has an important role as both a pro-oxidant and an antioxidant. It acts as a catalytic cofactor of enzymes such as Cu/Zn superoxide dismutase (SOD), ceruloplasmin (CPO), and lysyl oxidase, which has a central role in the strength and integrity of the heart and blood vessels (Al-Bayati, et al. 2015). Cu is also essential to mitochondrial respiration and Fe absorption. Elevated Cu levels may increase the production of reactive oxygen species (ROS) and consequently oxidative stress (Kang 2011, Tsuboi, et al. 2014), resulting in the oxidation of lipids, proteins, DNA, homocysteine and other particles (Galhardi, et al. 2004). Cu deficiency, on the other hand, can cause peroxidative damage (Saari 2000). Both Cu deficiency and overload play key roles in atherogenesis (Aliabadi 2008). Cu concentrations should hence be maintained below toxicity and above deficiency levels (Aliabadi 2008). The level of Cu is regulated through absorption and excretion. Cu absorption is affected by dietary intake, food sources, age, sex, and the use of oral contraceptives (Bost, et al. 2016).

Current dietary recommendations

According to the Institute of Medicine (IOM), the RDA for Cu is 900 μg/day in adults. The UL to prevent liver damage is 10,000 μg/day (10 mg/day) (Trumbo, et al. 2001).

Role in cardiovascular disease

Abnormal Cu levels – either deficiency or overload – are not common. The positive and negative effects of Cu status on the cardiovascular system are under debate. Within normal biological range, the beneficial effects of Cu on the cardiovascular system and overall health have been well described (Kang 2011). On the other hand, long-term intake of Cu less than the RDA may lead to impaired cardiac health (Medeiros 2017). However, increased Cu levels are associated with cardiovascular risk factors (Kang, et al. 1997). The cardiovascular effects of Cu deficiency are classified into four categories: 1) variations in Cu-dependent enzymes resulting in damage to morphology and physiology; 2) peroxidation due to distressing antioxidant functions and accumulation of oxygen-derived free radicals; 3) glycation of proteins due to impaired carbohydrate metabolism and sugar accumulation; and 4) deterioration of protein structure and function, and disturbance of processes which depend on nitric oxide (NO) (Saari 2000).

The effects of Cu deficiency on the risk factors and pathophysiology of CHD were first discussed in several studies dating from the beginning of the 20th century (Klevay 2000). In 1939, Schultze was the first to report the effects of Cu deficiency on cardiac enlargement (Schultze 1939). Cu deficiency was later found to cause hypertrophic cardiomyopathy, apoptosis of cardiomyocytes, and finally, HF (Zhou, et al. 2009, Kang 2011). Cu's antioxidant effect may depend on its involvement in CPO activity. CPO acts as ferroxidase I which oxidizes ferrous to ferric cations. In Cu deficiency, the accumulation of ferrous increases the production of hydroxyl radicals and leads to oxidative damage in proteins, lipids, and DNA. Cu deficiency also reduces SOD activity and thus facilitates the formation of hydroxyl free radicals, a central factor in the pathophysiology of atherosclerosis (Aliabadi 2008). Although Cu may have a role in the production of coagulation enzymes, its antioxidant function is more important. Hypertension, anemia, increased inflammation, and decreased blood clotting may also be caused by Cu deficiency (Aliabadi 2008).

Since Cu deficiency is believed to affect cholesterol metabolism, dietary Cu may improve the lipoprotein profile (Bost, et al. 2016). Moreover, marginal Cu deficiency contributes to cardiac arrhythmia (Bost, et al. 2016) and serves as a risk factor for atherosclerosis, along with other factors such as increased intake of simple sugars in Western diets (Aliabadi 2008). Since both Cu and Fe are released from the ischemic tissue during acute coronary syndrome (ACS), elevated levels of these elements can be used as markers of poor prognosis (Altekin, et al. 2005). Cu is involved in synthesis of dehydroepiandrosterone (DHEA) by oxidizing cholesterol. As such, a decrease in DHEA level due to Cu deficiency results in the development of a variety of adverse conditions, including hypercholesterolemia, hypertension, hyperhomocysteinemia, increased isoprostanes and uric acid, arterial damage, glucose intolerance, paraoxonase impairment, oxidative damage, and thrombosis. These adverse effects may be different according to sex and can be ameliorated by Cu supplementation (DiSilvestro, et al. 2012). Cu supplementation leads to the regression of cardiac hypertrophy, regulates the size and number of heart cardiomyocytes, and subsequently reduces the risk of HF caused by Cu deficiency (Zhou, et al. 2009). Cu supplementation also increases SOD activity and modifies oxidative stress (Duncan and White 2012).

In contrast, while the mechanisms involved are still unclear (Bost, et al. 2016), increased serum Cu levels have been identified as an independent risk factor for CVD. The pro-oxidant property of Cu, especially with the synergistic effect of low Se level as an antioxidant element, can increase atherogenicity (Chen, et al. 2015). Further, in the presence of homocysteine (Hcy), Cu forms a Cu-Hcy complex that can cause vascular dysfunction and damage (Kang 2011). Finally, positive correlations have been found between serum Cu levels and cardiac markers including cardiac troponins T and I, and creatine kinase-MB mass (Altekin, et al. 2005).

Hypertension. The association between serum Cu levels and the risk of hypertension is still a subject of controversy. While some studies have reported a positive relationship between serum Cu and hypertension (Ghayour-Mobarhan, et al. 2009, Afridi, et al. 2013), no such a link has been detected in other studies (Tsuboi, et al. 2014, Lutfi, et al. 2015). Reduced hemoglobin levels and anemia following Cu deficiency may actually increase cardiac output and BP (Saltman 1983).

Cardiovascular events. Both case-control and large prospective cohort studies have shown inconsistent findings regarding the association between Cu and CVDs (Bost, et al. 2016). However,

it has been proposed that effects differ according to ethnicity (Alexanian, et al. 2014). In some studies, patients with ischemic cardiomyopathy, atherosclerosis, or confirmed CHD had significantly higher serum Cu concentrations than controls (Shokrzadeh, et al. 2009, Alexanian, et al. 2014). High serum Cu and CPO levels have been shown to be associated with a 10-year risk of CHD, cardiovascular mortality, and all-cause mortality (Ghayour-Mobarhan, et al. 2009, Kang 2011, Grammer, et al. 2014). In addition, Cu/Zn ratio may be predictor of all-cause mortality in elderly populations (Malavolta, et al. 2010). Serum Cu level was associated with both the incidence and severity of atherosclerosis. It also showed a positive relationship with acute and chronic HF and an inverse association with LV systolic and diastolic function (Alexanian, et al. 2014) (Table 1). Therefore, serum Cu is regarded as an inflammatory marker in the prediction of short-term outcomes, including one-year mortality and hospital readmission (Tang and Francis 2010).

Heart failure. While Cu deficiency has caused cardiac hypertrophy and eventually HF in animal studies (Zhou, et al. 2009), human studies have shown different results. In patients suffering from HF and LV systolic and diastolic dysfunction, several studies found that higher levels of ceruloplasmin predicted all-cause mortality (Alexanian, et al. 2014, Cabassi, et al. 2014, Hammadah, et al. 2014). However, a case-control study found no significant difference in serum Cu levels between patients with and without HF (Ghaemian, et al. 2011).

Cardiovascular risk factors. Observational studies and randomized clinical trials (RCTs) have reported inconsistent findings about the effects of Cu levels on lipid profiles. Prospective cohort studies found significant relationships between serum Cu levels and increased serum total cholesterol, LDL-C, high density lipoprotein cholesterol (HDL-C), body mass index (BMI) and diabetes mellitus type II (Ljungkrantz, et al. 2008, Eshak, et al. 2017). In cross-sectional studies on healthy subjects, serum Cu levels had a negative relationship with LDL-C (Bo, et al. 2008) and a positive relationship with HDL-C (Ghayour-Mobarhan, et al. 2005). However, these findings of the protective effects of Cu levels on lipid profile were not supported by RCTs. In an RCT on healthy adults with moderate hypercholesterolemia, 2 mg/day Cu supplementation for eight weeks did not affect total cholesterol, LDL-C, or HDL-C (DiSilvestro, et al. 2012). Valsala and Kurup (1987) studies the mechanism of Cu^{2+} deficiency on hypercholesterolemia in rats and found Cu deficiency increased 3-hydroxy-3-methyl-glutaryl (HMG) CoA reductase activity and led to elevated serum cholesterol levels (Valsala and Kurup 1987). These studies indicate that while Cu intake has no effect on cardiovascular risk factors and events, abnormal Cu levels (either deficiency or overload) caused by impaired hemostasis can result in cardiovascular dysfunction.

Zinc intake and cardiovascular disease

Physiology and function

Zn is the second most abundant transition metal in the body after Fe. Through its presence in the structure of various enzymes and proteins, Zn plays a major role in normal cell structure and catalytic function, especially in the immune and central nervous systems (Brayer and Segal 2008, Livingstone 2015). It is also critical to growth, cell division and repair, wound healing, energy producing functions, carbohydrate catabolism, hemostasis, and thrombosis, including coagulation, anticoagulation, and fibrinolysis synthesizing NO (Zou, et al. 2002, Vu, et al. 2013). Moreover, intracellular Zn is involved in redox signaling pathways and improves antioxidant, antiapoptotic, and anti-inflammatory activities. Zn deficiency may oxidize and degenerate essential proteins like protein kinase C (PKC) (Suadicani, et al. 1992, Prasad 2008), produce C-reactive protein and inflammatory cytokines, and trap particles in macrophages and monocytes (Bao, et al. 2010). Zn deficiency can influence the development of various organs including the heart, brain, lungs, kidneys, and the skeleton (Marchan, et al. 2012). While the body can preserve its Zn levels within the normal range, low intake, malabsorption, and increased loss in the gastrointestinal system can cause Zn deficiency. The symptoms of Zn deficiency and toxicity are rare (Brayer and Segal 2008).

Current dietary recommendations

The IOM determined an RDA of 8 mg/day for women and 11 mg/day for men with a UL of 40 mg/day for adults (Trumbo, et al. 2001).

Role in cardiovascular disease

Zn is a component of many metalloenzymes including angiotensin-converting enzyme, Cu/Zn-superoxide dismutase, and transcription factors. Thus, Zn deficiency may cause apoptosis, oxidative stress, and inflammation, which are all known factors involved in the development of CVDs (Reiterer, et al. 2005, Jurowski, et al. 2014). Zn plays a major role in arterial pressure regulation and the etiopathogenesis of arterial hypertension via the renin-angiotensin-aldosterone system (Reiterer, et al. 2005). Through its role in reducing oxidative stress and inflammation and its uptake by endothelial cells, Zn may contribute to the prevention of atherosclerosis and endothelial injury (Reiterer, et al. 2005). Several studies have reported that Zn deficiency releases proatherogenic factors (Hosseini, et al. 2017) and is related to subclinical atherosclerosis as evaluated by carotid intima media thickness (Munshi, et al. 2010). This subsequently leads to the occurrence of CVDs including cardiomyopathy, arrhythmia, CHD, stroke, LV hypertrophy, and HF (Little, et al. 2010, Hashemian, et al. 2015, Huang, et al. 2017).

A recent systematic review found an inverse relationship between serum Zn concentration and risk of CVDs, especially in diabetics (Chu, et al. 2016). Zn administration may improve arrhythmias, promote myocardial healing, and prevent PKC degradation (Karagulova, et al. 2007). Moreover, Zn deficiency in fetuses and infants interferes with the growth of vascular, renal, and cardiac tissues and thus increases BP, induces lipid peroxidation, and reduces NO (Tomat, et al. 2011). Due to the interaction between Cu and Zn metabolism, these levels are inversely related in human body (Tsuboi, et al. 2014).

Hypertension. Contradictory findings have been reported on the relationship between Zn levels and hypertension. Some cross-sectional studies found an inverse association between dietary Zn intake and BP (Afridi, et al. 2013, Kim 2013,

Kunutsor and Laukkanen 2016). Other studies, however, showed serum Zn levels were positively associated with BP (Davydenko, et al. 1995, Ghayour-Mobarhan, et al. 2009). Alternatively, Tsuboi et al., (Tsuboi, et al. 2014) and Lutfi et al. (2015), found no association between serum Zn and BP. A recent large prospective cohort study with over 20 years of follow-up could not establish an association between dietary Zn intake and the incidence of hypertension. However, this study found a positive nonlinear relationship between serum Zn levels and risk of hypertension (Kunutsor and Laukkanen 2016). This finding is in contrast with Zn's antioxidant property, but in line with the positive association between serum Zn and other CVD metabolic risk factors, including metabolic syndrome, diabetes, serum lipids, and obesity (Sone, et al. 2013, Ahn, et al. 2014, Yary, et al. 2016).

The potential mechanisms, based on findings from animal models, are 1) inhibition of the adenosine triphosphate (ATP)-dependent calcium pump, which releases Ca from cells and raises Ca levels in smooth muscles and vascular walls, and 2) obstruction of the activity of Zn receptors which increases intracellular Zn. Both mechanisms increase wall tension and lead to hypertension (Vezzoli, et al. 1985, Henrotte, et al. 1992), and it is possible that these mechanisms are also involved in humans. Another known mechanism is the role of Zn in the taste of salt. Zn deficiency leads to decline taste acuity and thus increasing salt intake and raising BP (Mc Daid, et al. 2007). Further research is required to identify the physiological mechanisms of the relationship between Zn and BP and to determine whether these factors have a U- or J-shaped relationship.

Cardiovascular events. The risk of atherosclerosis has been linked to both serum Zn levels and the serum Zn to 24-h urine Zn ratio (Islamoglu, et al. 2011). Serum Zn concentration and Zn intake were positively associated with inflammatory markers, but not with atherosclerosis (De Paula, et al. 2014). Moreover, patients suffering from ACS and CHD had significantly lower serum Zn levels compared to healthy subjects (Bayir, et al. 2013). Another study indicated that patients with acute ischemic stroke had significantly lower serum Zn concentrations than healthy subjects (Munshi, et al. 2010). Researchers have identified low serum Zn levels as an independent risk factor for CHD mortality and fatal or nonfatal MI in patients with type 2 diabetes (Soinio, et al. 2007). A recent systematic review of prospective cohort studies did not find an association between Zn intake and CVD in healthy population, whereas there was an inverse relationship in high risk populations, such as patients with type II diabetes mellitus (Chu, et al. 2016). No link has been established between Zn levels and cardiomyopathy (Shokrzadeh, et al. 2009). According to previous research, the Zn/Cu ratio has a strong inverse association with the 10-year risk of CVD (Table 1) (Ghayour-Mobarhan, et al. 2009). Thus, Zn supplementation may have an atheroprotective effect (Foster and Samman 2012).

Heart failure. Significantly lower serum Zn levels and higher urinary excretion (Shokrzadeh, et al. 2009) have been found in patients with HF (Ghaemian, et al. 2011, Alexanian, et al. 2014). Zn levels also have a negative correlation with LV diastolic function (Alexanian, et al. 2014). These relationships can be explained by decreased uptake due to malabsorption, increased urinary excretion following the use of diuretics, increased lipid peroxidation (Witte, et al. 2001), and the effects of HF medications, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, on Zn metabolism (Ghaemian, et al. 2011, Bayir, et al. 2013).

Cardiovascular risk factors. According to studies using rat models, high dietary Zn and a high Zn/Cu ratio increase serum cholesterol. While the first RCT in humans showed the adverse effects of Zn supplementation on HDL-C in healthy subjects (Foster and Samman 2012), other studies have reported a positive association between serum Zn levels and HDL-C in elderly women (Tsuboi, et al. 2014) and LDL-C in all subjects (Saari 2000). Zn supplementation could decrease HDL-C concentration in healthy subjects (Foster, et al. 2010), as well as total cholesterol, LDL-C, and triglyceride levels (Ranasinghe, et al. 2015). Zn supplementation had no effect on HDL-C in diabetic patients (Foster and Samman 2012). Differences in design and outcomes across studies may be responsible for conflicting findings on the effects of Zn on serum HDL-C. A meta-analysis of 33 RCTs (Foster and Samman 2012) suggested that different health status of the participants explained the dissimilar findings regarding the effects of Zn supplementation on plasma HDL-C levels: HDL-C might be decreased in healthy participants, but increased in patients with conditions known to affect Zn homeostasis (Foster, et al. 2010). According to previous research, serum Zn levels are inversely related to insulin resistance and impaired glucose homeostasis (Giannoglou, et al. 2010), but have no association with metabolic syndrome (Ahn, et al. 2014).

Selenium intake and cardiovascular disease

Physiology and function

Se is an important trace mineral with a pivotal role in the human body. Through proteins known as selenoprotein (Stadtman 1991), Se prevents oxidative stress, facilitates thyroid hormone metabolism, and maintains antioxidant enzyme, redox position of vitamin C, and other antioxidant components (Boosalis 2008). The most important antioxidant enzymes are four types of glutathione peroxidases (GPx), which protect not only red and white blood cells and cell membranes from oxidation, but also the skin from ultraviolet radiation. These enzymes also produce antibodies and therefore protect the body from toxic substances. Se inhibits heavy metal (e.g., mercury, silver, arsenic, cadmium, and thallium) toxicity, which is a risk factor for atherosclerosis, especially stroke and hypertension occurrence (Hu, et al. 2017). For this antioxidant function to occur, Se needs to act in combination with vitamin E. GPx and vitamin E inhibit the peroxidation of endogenous peroxides and membrane lipids, respectively (Patel and Edwards 1988). Se is also involved in liver function, male reproductive ability, and protein synthesis. The most common form of Se is selenoprotein P, which is essential for the growth and health of eyes, hair, and skin. A recent review reported that optimal level of Se reduced lipid peroxidation, protein carbonyle, LDL-C and atherogenic index and also increased antioxidant capacity in liver and kidney as well as in plasma glutathione and NO concentration.

However, the high level of Se decreased glucose and insulin resistance and enhanced in gluconeogenesis and fasting blood sugar as well as SBP and diastolic blood pressure (DBP) and then, induced cardiac dysfunction (Panchal, et al. 2017). Se is also required for the proper functioning of the immune system (Navarro-Alarcon and Cabrera-Vique 2008) and increases the body's resistance to different diseases including infections, cancer, epilepsy, Alzheimer's disease and Parkinson's disease.

Current dietary recommendations

The RDA for both men and women is 55–75 μg (0.7-0.95 μmol)/day based on improving the plasma activity of GPx. A UL of 400 μg (5.1 μmol)/day is set to prevent selenosis (Navarro-Alarcon and Cabrera-Vique 2008).

Role in cardiovascular disease

Se, as a constituent of selenoproteins, plays an important role in the prevention of oxidative stress, inflammation, and consequently, CVDs (Navarro-Alarcon and Cabrera-Vique 2008). Low Se intake was found to be related to a cardiomyopathy identified as Keshan disease (Fryer 2002). The role of Se deficiency in chronic HF has also been documented (de Lorgeril and Salen 2006). The mechanisms responsible for the effects of Se on CVD risk are sporadic, and Se has a constricted therapeutic window. Optimal Se level varies in different populations as determined by polymorphisms in selenoprotein genes (Rayman 2009). One study detected a positive link between regional CVD and low dietary Se intake due to low soil Se content (Joseph and Loscalzo 2013). Although prospective observational studies indicated negative association of Se intake and CVD risk, inconsistent results from RCTs indicate that the potential protective effect of Se supplementation for CVDs is still not established (Zhang, et al. 2016, Liu, et al. 2017). Inorganic Se compounds, such as selenite, induce oxidative stress, which has a major role in not only CVDs but also diabetes and other CVD risk factors (Stranges, et al. 2010). However, the main kind of dietary Se is selenomethionine, which is not prooxidant (Stranges, et al. 2010). Since selenoproteins adjust apolipoprotein E levels and regulate the gene expression of cholesterol synthesis, metabolism, and transport, they are critical to lipoprotein metabolism (Rayman 2009). Using fibrates, a hypolipidemic agent, was found to be associated with higher Se concentration. This may be responsible for the positive association between serum Se levels and dyslipidemia (Arnaud, et al. 2009).

One of the potential mechanisms explaining the associations between Se and CVDs is that supplementation reduces NO production by inhibiting NO synthesis and gene expression (Kang, et al. 1997). High GPx-1 and selenoprotein S activity prevent cardiovascular events, regulate the oxidative stress induced by CVD risk factors, including lipids, smoking, and Hcy concentration, and inhibit platelet aggregation and inflammation (Schnabel, et al. 2008).

Cardiovascular events. Conflicting results have been reported regarding the relationship between plasma Se levels and CVDs across different populations (Stranges, et al. 2010). Se deficiency has been correlated with increased MI, cardiovascular mortality (2.9 fold), and all-cause mortality (Suadicani, et al. 1992, Alehagen, et al. 2016). In a recent meta-analysis of 16 prospective cohort studies and 16 RCTs, Se levels had an inverse and U-shaped association with CVD risk within a limited range of Se. However, Se supplementation had no significant effects on cardiovascular events (Zhang, et al. 2016). A meta-analysis of 25 observational studies, including 14 prospective cohorts, 11 case-control studies, and 6 RCTs of Se supplementation reported that a 50% increase in Se level was related to 24% reduction in the incidence of CHD. In a RCT, there was a non-significant 11% reduction in cardiovascular events following Se supplementation that was complemented with other nutrients (Flores-Mateo, et al. 2006). This meta-analysis concluded that the beneficial effects of Se supplements were not clearly established and that the supplements may increase toxicity, particularly in populations with high Se intake. Moreover, supplements containing only Se may not be useful (Flores-Mateo, et al. 2006). According to another study, Se supplements had no effects on primary prevention of CVDs, particularly among those with adequate or high Se intake (Rees, et al. 2013). Conversely, positive associations between plasma Se levels and both CHD and MI were reported in Finland where Se levels were low (Salonen, et al. 1982).

There remains a concern about the possible adverse cardiometabolic effects of high Se levels, at least in Se-replete populations (Joseph and Loscalzo 2013). The National Health and Nutrition Examination Survey (NHANES) reported a U-shaped relationship between serum Se levels and cardiovascular mortality (Table 1) (Bleys, et al. 2008).

Inconsistent findings about the association between Se levels and cardiovascular events in different studies may be due to differences in Se intake and status among various populations. Data indicate that both low and high Se levels can cause cardiovascular damage. Hence, Se supplementation may be beneficial only in populations with low dietary Se intake. The non-linear association between Se status and CVD risk reported in in observational studies may be due to various limitations, such as reverse causality and single measurements of Se at baseline. Inconsistent findings can also be attributed to multiple methodological variations: Se biomarkers that were examined, sample size, duration of the study, ethnicity of the participants, different Se intakes, Se supplement type, duration and dosage of supplementation, and the interpretations of useful and harmful effects of Se (Zhang, et al. 2016). RCTs are needed that consider all of these factors and include long-term follow-up, measurement of multiple cardio-metabolic outcomes, and a sample size providing adequate statistical power.

Heart failure. The first case of HF induced by Se deficiency was reported in 1937 in China (Keshan disease). The condition was caused by a viral infection of deteriorate cardiomyocytes through Se deficiency (Saliba, et al. 2010). An RCT in patients with HF showed that serum Se levels were lower in patients with reduced LVEF than in those with preserved LVEF (Alexanian, et al. 2014). Greater inflammation and oxidative stress in HF patients increased the need for antioxidant and anti-inflammatory agents.

Hypertension. Observational studies on the relationship between Se and BP have yielded inconsistent results in different populations with different levels of Se intake. While some

cross-sectional studies showed a relationship between higher serum Se levels and lower BP, others failed to establish a link (Stranges, et al. 2010). Serum Se was positively correlated with BP and hypertension prevalence in an American population with high Se intake (Laclaustra, et al. 2009). A prospective cohort study found serum Se levels were inversely associated with the risk of hypertension after 5.2 years (Nawrot, et al. 2007). Only a few RCTs have evaluated the relationship between Se supplementation alone and BP. One study found that the use of supplements containing Se and some antioxidant vitamins had no effects on BP during three years of follow-up. Another RCT, however, reported increased isolated DBP following Se supplementation (Stranges, et al. 2010).

Cardiovascular risk factors. Meta-analysis of Ju et al (2017) and several RCTs found that Se supplementation had no effects on lipid profiles (Ravn-Haren, et al. 2008, Hercberg, et al. 2005). However, a pilot RCT in the United Kingdom, found that Se supplementation with high Se-yeast at 100 and 200 μg/day decreased serum total cholesterol and non-HDL-C. Another study showed that supplementation with 300 μg/day only increased HDL-C (Rayman, et al. 2011). A combination of antioxidants, including 100 mg/day Se as high-Se yeast intake, had an adverse effect on the lipid profile (Hercberg, et al. 2005) and a U-shaped relationship with triglyceride levels (Bleys, et al. 2008). Although the mechanisms underlying the relationship between high Se level and lipid metabolism are not clear, some studies have suggested that Se may play an important role in lipid peroxidation and lipoprotein metabolism. Although higher Se levels may increase oxidative stress (Brown and Arthur 2001), inconsistent results have been reported regarding the association of serum Se levels and BP (Nawrot, et al. 2007, Laclaustra, et al. 2010). While Se supplementation was found to reduce the binding activity of nuclear factor-κ B (NFκB) and therefore lower oxidative stress in diabetic patients, some studies illustrated a non-linear positive association between serum Se levels and the prevalence of diabetes. Supplementation with 200 μg/day Se also increased the risk of diabetes by 2.7 fold after 7.7 years. Se supplementation should hence be avoided in diabetic patients, especially those with adequate Se intake (Boosalis 2008).

Conclusions

There are inconsistent findings regarding the relationships between minerals and cardiovascular events, risk factors, and mortality. Both ID and overload may contribute to increased incidence of CVDs through different mechanisms. Within the normal biological range, Cu has beneficial effects on the cardiovascular system and overall health. However, increased Cu levels are related to cardiovascular risk factors. Several studies have suggested a link between low Se levels and increased risk of CVDs and related mortality. Other studies, however, have presented opposite findings. Cardiovascular events have demonstrated a U-shaped relationship with Fe indicators, Cu and Se levels. Zn plays a role in the maintenance of cardiovascular health and its impaired homeostasis can lead to cardiovascular dysfunction. Finally, large, well-designed RCTs with long-term follow-up are required to rigorously evaluate the effects of the intake of minerals on cardiovascular events, risk factors, and mortality, as well as all-cause mortality in the general population.

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