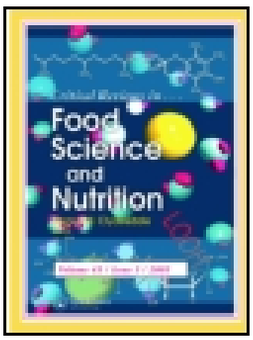

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Electrolyte minerals intake and cardiovascular health

Noushin Mohammadifard[a,b], Carolyn Gotay[c], Karin H. Humphries[d], Andrew Ignaszewski[d], Ahmad Esmaillzadeh[e], and Nizal Sarrafzadegan[f,g]

[a]Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; [b]Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; [c]Centre of Excellence in Cancer Prevention, Faculty of Medicine, School of Population and Public Health, The University of British Columbia, Vancouver, Canada; [d]Division of Cardiology, The University of British Columbia, Vancouver, Canada; [e]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran; [f]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; [g]School of Population and Public Health, Faculty of Medicine, The University of British Columbia, Canada

ABSTRACT

Appropriate intake of micronutrient, such as electrolyte minerals is critical for the well-being of the cardiovascular health system. However, there are some debates regarding the impacts of dietary and/or supplemental intake of these minerals, on the risk of cardiovascular events and associated risk factors. High sodium intake is adversely associated with the risk of hypertension. Although many reports refered to the positive association of Na intake and cardiovascular events and all-cause mortality, however, other studies indicated that low Na intake is related to higher risk of all-cause mortality and HF-related events. By contrast, dietary potassium, magnesium and calcium have an inverse correlation with cardiovascular events and risk factors, especially with blood pressure. There are some controversies about cardiovascular effects and all-cause mortality of high Ca intake, including no effect, preventive or adverse effect with or without vitamin D. Calcium supplementation might be beneficial for prevention of cardiovascular events and all-cause mortality only in individuals with low intake. Moreover, calcium intake showed a J- or U-shaped association with the risk of cardiovascular diseases. Due to the controversies of the effect of electrolyte minerals especially sodium and calcium intake on cardiovascular events, large scale, well-designed long-term randomized clinical trials are required to evaluate the effect of minerals intake on cardiovascular events and all-cause mortality. In this review, we discuss the role of dietary and or supplemental sodium, potassium, magnesium, calcium, in cardiovascular health, as well as their clinical applications, benefits, and risks for the primary prevention of cardiovascular disease, in general population.

KEYWORDS

Mineral; cardiovascular; sodium; potassium; magnesium; calcium; mortality

Introduction

Micronutrients consist of vitamins and minerals that are critical for maintaining health and well-being. As inorganic substances, minerals have various functions in the body including regulation of nerve and muscle function and maintence of acid-base balance and water balance (Otten et al. 2006). Imbalances in electrolytes like sodium (Na), potassium (K), magnesium (Mg) and calcium (Ca) are frequent and potentially hazardous that may lead to many cardiovascular disease (CVD) like hypertension, coronary heart disease, cardiomyopathy, heart failure, and arrhythmias (Aburto et al. 2013, Chrysant and Chrysant 2014, Kolte et al. 2014, Seth et al. 2014).

Ensuring adequate intake of vitamins and minerals, by diet and/or supplementation, is commonly recommended for health promotion (Fortmann et al. 2013). Thus the main reason of micronutrients supplementation is for prevention of CVD and cancer, leading to improvement of associated risk factors, particularly inflammation and oxidative stress (Pham-Huy et al. 2008, Moyer and Force 2014, Mohammadifard et al.). However, recent reviews in humans, have demonstrated that no consistent evidence implies that vitamins and minerals supplements affect CVD, cancer, or all-cause mortality in healthy individuals, without known nutritional deficiencies. In addition,

few trials have investigated the impacts of micronutrient supplementation on the primary prevention of CVD and cancer. (Fortmann et al. 2013, Moyer and Force 2014). Although many studies and reviews have examined the beneficial effect of vitamins, as a micronutrient on CVD, but only a few reports have comprehensively and critically examined the effect of minerals on CVD health, their benefits and risks, clinical applications and indications and contraindications (Fortmann et al. 2013, Moyer and Force 2014). We reported the effect of trace minerals including iron, copper, zinc and selenium on CVD health and risk recently. (Mohammadifard et al.). Among minerals, Na, K, Mg and Ca, as electrolytes, can be effective on CV health (Aburto et al. 2013, Chrysant and Chrysant 2014, Das De et al. 2015, Kolte et al. 2014, Smyth et al. 2015). Thus, the aim of this review is to evaluate the role of dietary and supplemental intake

CONTACT Nizal Sarrafzadegan nsarrafzadegan@gmail.com Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Chamran Hospital, Isfahan, Iran, P. O. Box: 81465-1148.

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of the aforementioned minerals, in all CV events and risk factors.

Review criteria

A search was performed for original articles published in PubMed, between January 1990 and October 2017. The search terms used were cardiovascular, coronary heart disease, coronary artery disease, sudden cardiac death, cardiomyopathy, heart failure, arrhythmia, atherosclerosis, hypertension, mineral, sodium, potassium, magnesium and calcium individually and in combination. All articles identified were full-text manuscripts published in English. Clinical and population studies were included.

Sodium intake and cardiovascular disease

Physiology and function

Na is the major cation of the extracellular fluid and functions, as an osmotic determinant in regulating extracellular fluid and plasma volume, in order to balance water in the body, as well as regulating muscle and nerve function. The different functions of Na are provided by a transmembrane pumping of Na^+ -K^+ -ATPase, accomplishing the active electrogenic translocation of Na^+ and K^+, across the plasma membrane of most of the cells. The balance between Na intake, excretion and extracellular fluid regulate Na maintenance in normal status. A variety of regulators, including renin-angiotensin-aldosterone system (RAAS) via the sympathetic nervous system and carotid baroreceptors and arterial natriuretic peptide, are involved in Na regulation (Coffman 2014). Figure 1 shows the metabolism of Na in the body.

Current dietary recommendations

The global mean Na intake was 3950 mg/day in 2010 (powles et al,2013) inspite of several national and international health organizations recommendations like the World Health Organization (WHO), the American Heart Association (AHA) and the National Institute for Health and Clinical Excellences (NICE) in the UK, to reduce sodium intake to less than 2000, 2400 and 1200 mg/day in the general population, respectively (Eckel et al. 2014, Excellence 2010, World Health Organization 2012)., But the Institute of Medicine (IOM) committee reported lack of enogh evidence to support the beneficial effect of lowering sodium intake to the above recommended levels, on health outcomes other than blood pressure (BP) (Committee on the Consequences of Sodium Reduction. 2013).

Role in cardiovascular disease

If there is no decline in peripheral resistance, high intake of dietary Na increases extracellular volume and cardiac output, leading to an increase in BP (Schmidlin et al. 2007). Na-induced hypertension may occur by different impaired physiological mechanisms, including renal function, fluid hormone, salt sensitivity, smooth muscle in peripheral vasculature and sympathetic nervous system, as the physiological mechanism of Na-

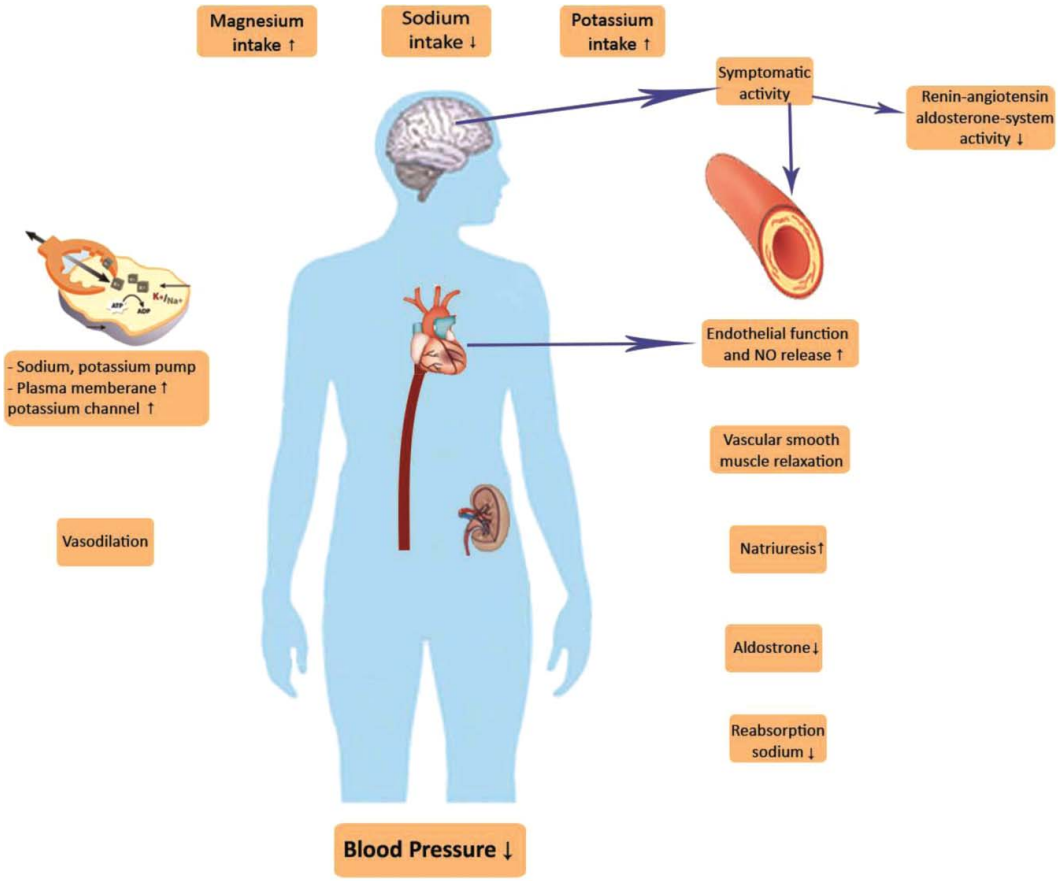

Figure 1. Metabolism of sodium, potassium and magnesium in the body. The metabolism, regulation and maintenance in the body.

induced increase in BP (Farquhar et al. 2015). Na^+ associated with chloride has a different effect compared to when it is binding to other anion such as bicarbonate, therefore, since 1904, it has been considered as a major risk factor for CVD and BP, in the form of NaCl (Ambard and Beaujard 1904). The sodium chloride might have more important role in salt-sensitive hypertension than Na^+. Diverse documents from monogenic syndromes, dietary and *in vivo* studies reported, a main role for Cl^- on BP regulation through renal balance, and Cl^- transporters in vascular tissues (McCallum et al. 2015). A potential hypothesis is inhibition of renin release, due to an increase in Cl^- level, delivering to the renal tube (Lorenz et al. 1991). Thus, further studies are suggested to examine the effect of Na and Cl on the risk of CVD and hypertension, independently (McCallum et al. 2015).

Hypertension

A variety of studies in animals and humans, including ecological, observational, clinical trials and meta-analysis of randomized clinical trials (RCTs), have documented the correlation between high Na intake and BP (Whelton 2015). Large scale observational studies such as INTERSALT in 52 centers worldwide, European Prospective Investigation into Cancer in Norfolk (Khaw et al. 2004) and Prospective Urban, Rural Epidemiological Study (PURE) in18 countries (Mente et al. 2014), as well as some recent meta-analyses of RCTs, demonstrated a positive correlation between Na and BP that was higher in hypertensive than normotensive populations (Graudal et al. 2012, He et al. 2013). Furthermore, the incidence of hypertension declined, after reducing Na intake in the well-designed Trials of Hypertension Prevention (TOPH) II.

Cardiovascular events and risk factors

There are many controversies regarding the correlation between Na and CVD events. Ameta-analysis of 7 RCTs, using at least 6 months sodium restriction, reported no effect of Na intake reduction on CV mortality, morbidity, or all-cause mortality (Taylor et al. 2011). However in other meta-analysis, after excluding the RCT on heart failure (HF) patients, all CV events showed significant decrease of 20% (He and MacGregor 2011). Since no large, long-term RCTs have been performed to examine the effects of Na restriction on CV events (Whelton et al. 2012), most of the evidence has been derived from prospective cohort studies (O'Donnell et al. 2015), which have known methodological limitations (Cobb et al. 2014). Cobb *et al.* reported that diverse studies showed direct, inverse, J-shaped or null associations between Na intake and CV events with 77%, 75%, 100% or 100% systematic error and 31%, 38%, 50% or 0% reverse causality error, respectively (Cobb et al. 2014).

A pooled analysis of four large prospective cohort studies in 49 countries, using diverse methods for Na assessment in various populations, have found a J or U- shaped association between Na intake and CVD mortality and morbidity (O'Donnell et al. 2014b). A meta-analysis of 23 observational studies showed that Na intake less than 3 g/day, increased all-cause mortality and thus argued the recommendation of Na intake reduction, except in hypertensives or subjects with the high Na intake (more than 6 g/day), unless a well done RCT confirm the safety and beneficial effect (Saulnier et al. 2014). It was assumed that although low Na consumption is expected to improve CV events by lowering BP, but an increase also have been found in CV events and mortality, which might be through RAAS activation, catecholamine and lipid disorders (Saulnier et al. 2014).

The PURE study found that an estimation of Na intake of 3–6 g/ day based on single morning spot urine sample was associated with a lower risk of CV events and all-cause mortality compared to lower or higher estimated Na intake (O'Donnell et al. 2014a). However, Cook has criticized the J-shape association of Na intake and CVD mortality in PURE study by indicating that methodological weakness exist, such as the Na assessment method using an overnight Na excretion, reverse causality relevant to recruiting, some patients who reduced their Na intake for therapeutic approaches, using single morning spot urine and non-valid formula, causing under- or over-estimation of Na intake (Cook 2014). The large size of PURE study may not eradicate different biases including selection, confounders or reverse causality (Cook 2014, Cook et al. 2014). Whereas, in TOHP study, Na intake was assessed by an average of three to seven 24-hr urine collections, performed during 1–4 years (Cook et al. 2014) as a most precise method. Recent trial in TOHP study concluded a direct association between Na intake and mortality risk, even at the lowest levels of Na intake, over a 20-year period (Cook 2014). However, it should be notified that the most precise and reliable method for assessment of Na intake, individualy is multiple 24-hr urine collection (Lerchl et al. 2015). Therefore, further studies are required in order to examine the effect of Na on CVD events and risk factors, using multiple 24-hr urine collection.

Endothelial dysfunction

High Na intake may increase the risk of left ventricular (LV) hypertrophy, endothelial dysfunction, vascular dysregulation and remodeling, and renal disease independent of BP (Aaron and Sanders 2013). This aldesterone regulates the activity of epithelial sodium channels in the renal and endothelia, which may damage on these cell to swell, stiffen, and alter its output of nitric oxide (Greaney et al. 2012). The protective barrier of endothelial glycocalyx buffer interferes with high Na intake. It may be due to limiting the sodium pump (i.e. the Na/ K Atpase) and as a mesh of anionic biopolymers covering the endothelium surface, contributes in the progression of stiffness process and thus enhances the permeability of vascular sodium (Oberleithner 2012). Only acute Na loading, can leads to an increase in microvascular Na permeability and induces plasma volume enhancement. It may progress by direct effects of Na+ to the endothelium (Rorije et al. 2015). Na restriction improves endothelial dysfunction and elastic artery stiffness, independent of BP (Jablonski et al. 2009).

Heart failure

Na restriction induces neurohormonal activation and elevates plasma renin activity, which may increase the risk of mortality in HF patients (Verma et al. 2011). Hyponatraemia is considered as a significant determinant of all-cause mortality and HF-related events, such as HF readmissions irrespective of ejection fraction (Rusinaru et al. 2012). Table 1 illustrates

Table 1. Mechanism, clinical application, indications and contraindications in CVD prevention.

Mineral	Regulation	Mechanism	Clinical application in CVD	Type of study	Indications	Contraindications
Sodium	Oral uptake Kidney excretion RAAS Sympathetic nervous system Carotid baroreceptors \arterial natriuretic peptide	Inducing hypertension by impaired: Renal function Fluid hormone Salt sensitivity Smooth muscle in peripheral vasculature Sympathetic nervous system	Extracellular fluid Osmotic determinant Muscle function Nerve function	Animal Ecological Cross-sectional Prospective cohort study RCT Meta-analysis	Dehydration High sweating	Hypertension Allergy
Potassium	Oral uptake Kidney excretion Aldosterone Liver circulation Muscle storage	The BP lowering effect is exerted through: Natriuresis stimulation Endothelial function improvement NO release increasing Sodium-potassium pump and plasma membrane potassium channels activity Reduced sympathetic activity	Intracellular osmolarity Resting potential cell membrane	Cross-sectional Prospective cohort study RCT Meta-analysis	Hypokalemia Prolonged illness with diarrhea or vomiting.	Diarrhea Bloating Nausea Abdominal painVomiting
magnesium	Oral uptake Kidney excretion	Regulating BP by: Improving vascular tone Vascular smooth muscle contraction Endothelial cell function Myocardial excitability Normal BP Bone integrity	Coenzyme in the production and transport Keep normal heart rhythm Vascular smooth muscle tone Glucose and insulin metabolism	Cross-sectional Prospective cohort RCT Meta-analysis	Mg deficiency Preeclampsia BP control Encephalopathy Acute nephritis in children	Heart block Myocardial damage
Calcium	Vitamin D Calcitonin Parathyroid hormone	Increase carotid plaque thickness Calcification BP regulation Insulin secretion and sensitivity Obesity Serum lipids Inflammatory agents Anti-thrombotic agent Vasorelaxation	Muscle contraction Vascular tone Nerve transmission Hormonal system Enzyme-intermediate	Cross-sectional Prospective cohort RCT Meta-analysis	Calcium deficiency Osteoporosis Premenstrual syndrome Preeclampsia Prevention of colon and rectal cancers	Tumor Kidney Stone Kidney Disease Hyperparathyroidism Hypocalcaemia Extreme dehydration

RAAS: Renin-angiotensin-aldosterone system; RCT: Randomised clinical trial; BP: Blood pressure; NO: Nitric oxide; GI: Gasterointestinal; ROS: Reactive oxygen spices.

regulation, mechanism, clinical application in CVD, type of study, indications and contraindications of the minerals.

Potassium intake and cardiovascular disease

Physiology and function

K is the major intracellular cation (98%) in the body (Ekmekcioglu et al. 2016). The main functions of K are resting potential of the cell membrane and regulation of water and Na metabolism in the cell by intracellular osmolarity, acid-base balance, normalization of heartbeat, controlling nerve impulses in muscles and, participation in protein biosynthesis and the conversion of blood sugar into glycogen and the activation of a number of enzymes, especially those involved in energy production (Table 1). The total K concentration is regulated by oral uptake, kidney excretion and circulation in the liver and muscle storage (Eaton and Konner 1985a). The kidney retains Na and excretes K, facilitated by aldosterone function (Eaton and Konner 1985b) (Figure 1).

Current dietary recommendations

Following industrialization, Na intake has been increased, while K intake has been decreased. Thus nowadays dietary guidelines believe that K is a "nutrient of public health concern" (Palmer and Clegg 2016). Different international organizations like the IOM and WHO recommend 90–120 mmol/day (3500–4700 mg/ day) of K for adolescents and adults (Otten et al. 2006, WHO 2012). Global K intake was evaluated as inadequate and less than 70–80 mmol/day (2700–3100 mg/ day) in the INTERSALT study. About 2% of US adult population has adequate consumption of K (Cogswell et al. 2012). K intake among adult population of 10 European countries ranged from 3536 to 4870 mg/ day in men and from 2730 to 3723 mg/ day in women (Welch et al. 2009), respectively. It's intake levels in two Asian populations are 1800 mg/ day in Chinese and 2732 in Iranains respectively (Du et al. 2014, Mohammadifard et al. 2017).

Role in cardiovascular disease

The crucial role of K in CV system and the importance of K maintenance have become an essential issue in cardioprotective treatment. Abnormal serum levels of K may affect CVD, including hypertension, arrhythmia, fatal and non-fatal stroke and myocardial infarction (MI), as well as sudden cardiac death (Table 1) (Sica et al. 2002).

Hypertension

In 1928, Addison proposed an inverse relationship between K and BP (Bulpitt 1981), corroborated by the INTERSALT study, demonstrating an inverse correlation between urinary K excretion and BP in various populations. The BP lowering effect of K is exerted through a variety of mechanisms, including natriuresis stimulation, endothelial function improvement, NO release, increasing Na-K pump function and plasma membrane K channel activity, which causes vasodilatation and reduced sympathetic activity, leading to relaxation of arterial muscle (Ekmekcioglu et al. 2016). Dietary and supplemental K intake had a dose-response effect on BP (Geleijnse et al. 2003, Khaw et al. 2004, Mente et al. 2014), but the beneficial effect plateaus, above 120 mmols/ day of K consumption (Aburto et al. 2013) In addition, increasing K intake was more beneficial in hypertensives, those with high Na intake (Aburto et al. 2013) especially, more than 4 g/ day (Powles et al. 2013). Thus it was concluded that a low Na and high K diet, might be more effective in reducing BP and hypertension risk (Whelton 2014). Whereas some observational studies had inconsistent findings. High intake of Na and low intake of K did not associate with raised BP levels in the normotensive US adult population and serum K level (Sharma et al. 2014). However, among Chinese population, a community-based cohort study,demonstrated a positive correlation between baseline serum K level, but not serum level of Na and incidence of hypertension, after five years (Xi et al. 2015). However, this study had some limitations, including very low sample size and also the serum K level at baseline could not identify K status.

Cardiovascular events and risk factors

Some prospective cohort studies showed that higher dietary K intake was associated with lower risk of CV mortality, after adjustment for potential confounders, including dietary Na intake (Umesawa et al. 2008), as well as all-cause mortality and ischemic stroke, but not hemorrhage type in non-hypertensive women (Seth et al. 2014). However a recent cohort study showed dietary Na to K ratio directly increased the risk of mortality from all strokes, even haemorrhagic one. CVD and all causes mortality. Two meta-analyses were done on prospective cohort studies. A recent review in diverse populations, demonstrated an inverse association between K intake and stroke risk by an overall 24% reduction in stroke incidence and the highest reduction of 30% and 21% in subjects with K intake of 90–120 mmol/ day and 42 mmol/ day, respectively, but there was no significant correlation with total CVD events and coronary heart disease (CHD) (Aburto et al. 2013, D'Elia et al. 2011). However, it should be considered that for assessment of K intake similar to Na intake in individual, multiple rounds of 24-hr urine collection are needed (Birukov et al. 2016).

Heart failure

Mild to moderate hypokalemia in patients with HF, LV hypertrophy and cardiac ischemia, leads to cardiac arrhythmias. Hypokalemia is an independent predictor of mortality and sudden cardiac death in HF patients (Dursun and Sahin 2006). Hypokalemia may be a frequent side effect of treatment with diuretics and digoxin, increased activity of neurohormonal or disease progression (Tomat et al. 2011). A pooled analysis of three prospective cohorts of hospitalized HF patients, illustrated that a reduction of >15% in serum K was an independent predictor of all-cause mortality (Salah et al. 2015).

Magnesium intake and cardiovascular disease

Physiology and function

Mg is an abundant mineral needed for living cells in the human body, playing a critical role as a cofactor in about 300 metabolic reactions (Volpe, 2013). It is involved in several essential physiological, biochemical functions in the body, such as acting as a coenzyme in the production of DNA, RNA, proteins and energy, as well as energy storage (Guasch-Ferre et al. 2014),

mitochondrial membrane stability, maintenance of normal muscle and nerve functions, normal heart rhythm, vascular smooth muscle tone, endothelial cell function, myocardial excitability, normal BP, bone integrity, and glucose and insulin metabolism (Volpe 2013) (Figure 1). Mg regulates BP by improving vascular tone and vascular smooth muscle contraction (Table 1) (Champagne 2008).

Current dietary recommendations

The Recommended Dietary Allowance (RDA) for Mg in adults is 310–420 mg/d, including 410–420 mg/day and 310–320 mg/day for men and women, respectively (Food and Nutrition Board 1997). Mg deficiency is commonly seen, worldwide. Marginal or subclinical Mg deficiency induced by Mg intakes < 250 mg/day, and serum Mg concentrations≤ 0.75 mmol/l is associated with inflammatory indicators including C-reactive protein, cytokines such as tumor necrosis factor-α and interleukin (IL)-1, IL-6, E-selectin, intracellular adhesion molecule-1, vascular cell adhesion molecule-1, and fibrinogen (Nielsen 2014, WHO 2012).

Role in cardiovascular disease

Mg is associated with a number of conditions and chronic diseases. Increasing dietary intake and oral supplement of Mg intake can prevent inflammatory and oxidative stress, endothelial dysfunction, increased vascular reactivity, increased vascular tone, hypertension, CVD, stroke, insulin resistance, type 2 diabetes mellitus and obesity (Champagne 2008, Geiger and Wanner 2012, Qu et al. 2013, Fang et al. 2016). Thus the consumption of Mg-rich foods is the best way to maintain a normal serum Mg level, which consequently prevent the associated health problems (Table 1).

Hypertension

Mg intake and serum concentration levels are correlated with BP and hypertension (Qu et al. 2013, Champagne 2008). A meta-analysis showed that each 10 mmol/day increase in Mg by supplementation, was associated with a 4.3 mm Hg reduction in systolic BP and a 2.3 mm Hg reduction in diastolic BP (Qu et al. 2013). However, there were some controversies on the inverse correlation between dietary Mg intake as well as serum level and the risk of hypertension (Khan et al. 2010, Song et al. 2006, Bain et al. 2015, Grober et al. 2015). One review suggested that the effect of dietary intake of Mg on BP reduction is stronger than supplementation (Champagne 2008). However, no studies have reported adverse effects for Mg supplementation.

Cardiovascular events and risk factors

An inverse association was reported between low serum Mg and C-reactive protein, Coronary Artery Calcium (CAC), as well as Carotid Intima-Media Thickness (CIMT), both as main predictors of atherosclerosis (Simon et al. 2002, Posadas-Sanchez et al. 2016). Recent RCTs in obese subjects pointed out that Mg supplements of 350 mg/day in 24 weeks improved arterial stiffness (Joris et al. 2016).

There are beneficial effects of both dietary and supplemental intake, as well as serum concentrations of Mg on different CV events (Del Gobbo et al. 2013, Champagne 2008). An increase of 150 mg/d to 400 mg/d in Mg intake or an increase of 0.1 mEq/L in serum Mg level, caused 9% reduction in CVD risk (Qu et al. 2013). The benefits of increasing Mg intake on CVD risk factors, such as improvement in lipid profiles, diabetes mellitus, obesity, and metabolic syndrome have been shown in several studies (Del Gobbo et al. 2013, Champagne 2008). In addition, rare reports exist on hypermagnesaemia or Mg toxicity in patients with normal renal function. However, parenteral administration of the Mg supplement is contraindicated in patients with heart block or myocardial damage (Waksman and Ajani 2009)

Calcium intake and cardiovascular disease

Physiology and function

Ca is the fifth most plentiful mineral in the body. Typically 99% of Ca is retained in the skeleton. In addition to its role in bone structural strength, it is a pivotal component in many physiologic pathways like muscle contraction, vascular tone, blood coagulation, nerve transmission (e.g. acetylcholine from presynaptic terminals of nerves), hormonal system involved in digestion, energy and fat metabolism (e.g. insulin from the beta cells in the pancreatic islets) and enzyme-intermediate in α-amylase, phospholipase and protein-kinase (Vaskonen 2003). The potential roles of Ca on BP modification, are due to Ca regulating hormone, sympathetic nervous system, and electrolyte interactions (Figure 2). Ca deficient diet increases intracellular Ca level which enhances production 1,25-dihydroxyvitamin D_3 and parathyroid hormone (PTH). It causes Ca uptake into vascular smooth muscle cells and consequently increases vascular resistance and BP (Hatton et al. 1995). Ca regulates RAAS activity by inhibiting acute renin secretion and expression. In addition, chronic Ca receptor activation associates with increasing the activity of renin. PTH secretion stimulates due to increasing aldestrone or angiotensin II (Vaidya et al. 2015). Bones provide a pool for these vital functions by remodeling. Vitamin D, calcitonin and PTH regulate Ca homeostasis (Table 1) (Mundy and Guise 1999).

Current dietary recommendations

The IOM recommended Dietary Reference Intake (DRI) for Ca, as 1000 mg/day for adults, 1200 mg/ day for women aged over 51 and men over 71 years to prevent osteoporosis and bone fractures. The Tolerable Upper Intake Levels (ULs) of Ca is 2500 and 2000 mg per day for adults and elderly, respectively (Ross et al. 2011). Ca supplementation is a common recommendation in the management and prevention of osteoporosis in individuals at risk, since insufficient intake of Ca was seen in most regions in the world (Shin and Kim 2015).The dietary Ca intake ranges from 175 to 1233 mg/day among 74 countries worldwide (Balk et al. 2017).

Role in cardiovascular disease

Dietary Ca has beneficial effect on CV system through some potential mechanisms including improvement of serum lipids, BP, obesity, insulin secretion and sensitivity, inflammatory and anti-thrombotic agents and vasorelaxation (Chrysant and Chrysant 2014, Tomat et al. 2011).

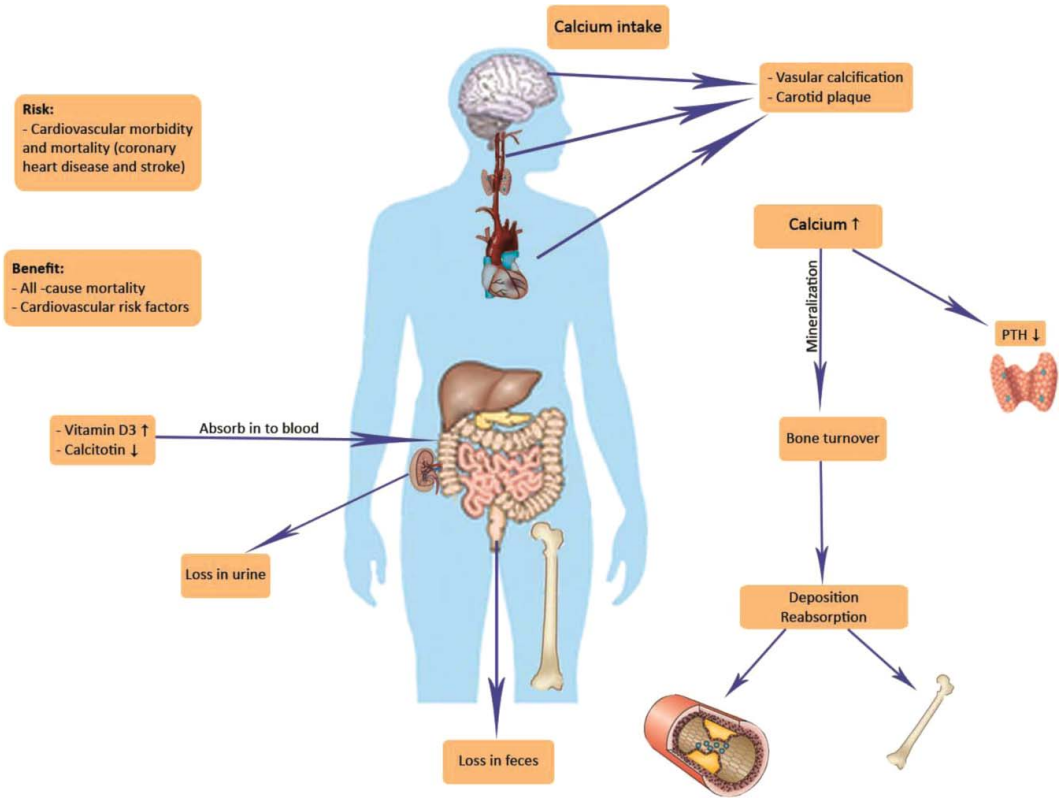

Figure 2. Metabolism of calcium in the body. The metabolism, regulation and maintenance in the body.

However, increase in carotid plaque thickness, aortic calcification, fatal and non fatal CV events similar to hypercalcemic patients may occur subsequently by using Ca supplement. Since it may rapidly increase serum Ca for several hours after consumption, and subsequently pyrophosphate bind to Ca-sensing receptor (Reid et al. 2010). Dietary sources of Ca that are ingested slowly during a day, do not consequently increase the serum Ca concentration, since it is regulated by calciotropic hormones (Wang et al. 2012, Lutsey and Michos 2013). Polymorphisms of the Ca-sensing receptor can also lead to altered serum Ca levels and thus can cause vascular events (Reid et al. 2016).

Cardiovascular events and risk factors

There are some controversies about the effects of high Ca intake on CV events. Two meta-analysis of RCTs have reported that there is no significant association between dietary and supplemental Ca ranged from 500 to 1600 mg/ day (with and without vitamin D) and CHD, MI, stroke, total CVD risks, angina pectoris, acute coronary syndrome and all-cause mortality (Lewis et al. 2015, Wang et al. 2012). Whereas, a meta-analysis of cohort studies (Reid 2013) are popularly known as Women's Health Initiative (WHI), found that 1000 Ca supplemental with and without vitamin D have increased the risk of MI and stroke (Bolland et al. 2011). Other meta-analysis of observational studies demonstrated that total Ca intake is associated with increased risk of CVD mortality in studies with long term follow-up, and decreased risk of all-cause and CVD mortality, in studies with follow-up $\leq$10 years. Ca intake inversely related to all-cause mortality risk (Asemi et al. 2015). In a recent cross-sectional study, Ca intake was associated with atrial fibrillation, which might be one of potential pathways through which, Ca supplementation may cause strokes (Thiele et al. 2015). The adverse effect of Ca supplementation may be due to excess intake, such as 2000–2500 mg/ day (Daly and Ebeling 2010). The Swedish Mammography Cohort found a J-shaped correlation between Ca intake and mortality, since Ca supplementation was positively associated with a mortality rate in women with a dietary Ca intake of >1400 mg/day and it was higher in individuals with Ca intake <600 mg/day (Michaelsson et al. 2013). A meta-analysis by Wang showed U-shaped manner for association CVD mortality and Ca intake and it was not significant with Ca more than 900 mg/ day (Wang et al. 2014). Recently, other meta-analysis by Reid *et al.* found a significant association between serum Ca levels within the normal range and increased risk of CHD, CVD and total mortality as well as plaque, and vascular calcification. The attenuation of this association after adjustment for CVD risk factors including hypertension and dyslipidemia, implies that these risk factors can be the mediators in the correlation of serum Ca and CV events (Reid et al. 2016). The reverse causality is unlikely to be an issue, because serum Ca measurement was performed about 11–30 years before the occurance of CV events (Reid et al. 2016).

While a recent prospective cohort study performed on 41,514 non-hypertensive elderly populations showed that dietary Ca up to 1346 mg/ day, has a beneficial effect on non- fatal CVD events, strokes and all-cause mortality (Khan et al. 2015), a recent cross-sectional study demonstrated that low serum Ca has a positive relationship with left ventricular systolic dysfunction in CHD patients with and without AMI (Wang et al. 2012).

Hypertension

Studies on the correlation between Ca and BP go back to the 1980s (McCarron et al. 1982), and it was confirmed after 20 years (McCarron and Reusser 1999). Clinical and experimental studies demonstrated that Ca has some beneficial lowering effect on BP, which was mediated by suppression of renin activity and an improvement in BP rising effect of Na, particularly in salt-sensitive hypertension. In US population, the risk of hypertension was 11–14% vs. 3–6% in those who took Ca less than 300 mg/ day, compared to subjects with 1200 mg/ day of Ca intake (Singh et al. 1987). However, cross-sectional studies showed that serum Ca levels has direct correlation with BP. Evidence proposed acute rising of BP, following an acute increase in Ca levels might be due to the Ca effect on the contraction of vascular smooth muscle (Reid et al. 2016).

Summary

In summary, there are inconsistent findings regarding the correlation between minerals and CV events, their risk factors and mortality. The incidence of hypertension declined after reducing Na intake in well designed trials. However, there are many controversies, regarding the correlation between Na and CV events. Although, high Na intake is associated with increased risk of CV events and all-cause mortality, several studies indicated that low Na intake and low to normal serum Na level were significantly associated with all-cause mortality and HF-related events, such as HF readmissions. Most evidence support an inverse correlation between dietary K, Mg and Ca with CV events and risk factors, especially BP. Dietary and supplemental K intake have a dose-response effect on BP, but the beneficial effect plateaus above 120 mmols/day of K intake. Higher dietary K intake was associated with lower rates of BP, CV risk and all-cause mortality. A diet that combines low Na and high K might be more effective in reducing BP and hypertension risk. Mg deficiency is associated with a number of conditions and chronic diseases like inflammatory and oxidative stress, endothelial dysfunction, increased vascular reactivity, increased vascular tone, hypertension, CVD, stroke, insulin resistance and type 2 diabetes mellitus. Diverse studies reported the beneficial effects of dietary and supplemental intake of Mg, as well as serum concentrations of Mg on different CV events and risk factors. There is an inverse association between low serum Mg and CAC and CIMT, as main predictors of atherosclerosis. Calcium supplement may rapidly increases serum Ca and subsequently increase carotid plaque thickness, aortic calcification, fatal and non-fatal CV events similar to hypercalcemic patients, but dietary sources of Ca that are ingested slowly during a day, do not increase immediately the serum Ca concentration. There are some controversies about CV effects and all-cause mortality of high Ca intake, including no effect, preventive or adverse with or without vitamin D. A U-shaped correlation between Ca level and CV events has been suggested. The potential adverse effect of Ca intake on CV events has not been supported by most existing evidence. Ca supplementation may be beneficial in individuals with low intake for prevention of fracture and reduction in all-cause mortality. The adverse effect of Ca supplementation may be due to excess intake, such as 2000–2500 mg/ day. As future directions, it is important to conduct a large, well-designed RCT with long term follow-up, in order to rigorously evaluate the effect of the mineral intake on CV events, risk factors, mortality and all-cause mortality in normal population.

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