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HYPERTENSION AND METABOLIC SYNDROME (J SPERATI, SECTION EDITOR)

Selenium, Vanadium, and Chromium as Micronutrients to Improve Metabolic Syndrome

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Abstract Trace metals play an important role in the proper functioning of carbohydrate and lipid metabolism. Some of the trace metals are thus essential for maintaining homeostasis, while deficiency of these trace metals can cause disorders with metabolic and physiological imbalances. This article concentrates on three trace metals (selenium, vanadium, and chromium) that may play crucial roles in controlling blood glucose concentrations possibly through their insulin-mimetic effects. For these trace metals, the level of evidence available for their health effects as supplements is weak. Thus, their potential is not fully exploited for the target of metabolic syndrome, a constellation that increases the risk for cardiovascular disease and type 2 diabetes. Given that the prevalence of metabolic syndrome is increasing throughout the world, a simpler option of interventions with food supplemented with well-studied trace metals could serve as an answer to this problem. The oxidation state and coordination chemistry play crucial roles in defining the responses to these trace metals, so further research is warranted to understand fully their metabolic and cardiovascular effects in human metabolic syndrome.

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Introduction

Metabolic syndrome is a major health concern throughout the world in children [1] and adults [2]. This syndrome is defined as a co-occurrence of symptoms including hypertension, abdominal obesity, dyslipidemia, impaired glucose tolerance, and insulin resistance [3, 4]. Together, these symptoms increase the risk of cardiovascular disease, type 2 diabetes, and fatty liver disease which markedly increase health-care costs. Lifestyle factors such as poor diet and decreased physical activity are important in predisposing individuals to the development of metabolic syndrome [5, 6]. This means that dietary interventions such as prebiotics, Mediterranean diet, polyphenol-rich diet, and regular physical activity alone, or in combination, are suitable strategies for the treatment of metabolic syndrome [7–9].

As part of dietary interventions, different functional foods and nutraceuticals have been considered for treatment of metabolic syndrome, including foods containing anthocyanins, omega-3 fatty acids, olive oil components, prebiotics, and probiotics [9]. These components are nonnutritive phytochemicals from a range of fruits, vegetables, and animal sources. The nutritive components include macronutrients and micronutrients. Macronutrients are carbohydrates, proteins, and lipids that provide carbon sources for energy, building blocks for cells, and many molecular mediators. Micronutrients are the vitamins and minerals that are required at low concentrations for the normal growth and development of living organisms. Micronutrients play central roles in energy metabolism and in maintaining homeostasis [10]. Some of the major functions of the micronutrients include activating cofactors and coenzymes for enzymes that control metabolism, genetic transcription, and oxidative stress

[10]. Micronutrients are also important for the regulation of metabolism in the human body [11] and may be important in the control of hypertension and cardiovascular remodeling [12, 13]. There are many compounds defined as micronutrients, so this review will focus on the metabolic effects of three important but understudied trace metals, selenium, vanadium, and chromium, in metabolic syndrome. Each of these has been proposed as an intervention that improves glucose metabolism, usually by activating or mimicking insulin, and therefore may decrease cardiovascular risk in patients with metabolic syndrome.

Selenium

Selenium is a trace mineral in the human body as it is an important component of enzymes for redox reactions as selenocysteine [14] in glutathione peroxidase and thioredoxin reductase [15]. The dose range for selenium is very narrow between deficiency to sufficiency to toxicity [16]. The National Institutes for Health Recommended Dietary Allowance for selenium is 55 μg/day for adult Americans, 60 μg/day during pregnancy, and 70 μg/day during lactation with an upper limit of 400 μg/day with no adverse effects [17]. Toxicity, bioavailability, and chemoprotective activities of selenium are related to its chemical form and oxidation state [18]. It is now believed that the species of selenium is important for its health benefits with most cereals and Brazil nuts containing predominantly seleno-methionine with seleno-cysteine and selenate to lesser extents as human dietary sources; the very complex range of selenium species in plants and humans including selenium-methylselenocysteine and γ-glutamyl-seleno-methyl-selenocysteine has been reviewed previously [19]. The important dietary sources of selenium include cereals, black tea, milk powder, mushrooms, soybeans, lima beans, bamboo shoots, Brazil nuts, and broccoli [18, 19]. Selenium intake in different countries varies based on the selenium content of the soils so that dietary recommendations are based on these intakes [20]. Selenium exists in its four natural oxidation states as follows: elemental selenium and selenodiglutathione (dipeptide) with 0 oxidation state; sodium selenide (Na_2Se) and hydrogen selenide (H_2Se) with −2 oxidation state; sodium selenite (Na_2SeO_3), selenium dioxide (SeO_2), and selenious acid (H_2SeO_3) with +4 oxidation state; and sodium selenate (Na_2SeO_4) and selenic acid (H_2SeO_4) with +6 oxidation state [21]. The +4 and +6 state compounds are water-soluble and hence more bioavailable than 0 and −2 oxidation state compounds [21]. Structures of some of the important selenium compounds are provided in Fig. 1.

Selenium has a potential role in health as well as in many disease states [22]. Dietary selenium deficiency has been reported in Asia, Africa, New Zealand, and Finland [20, 23]. Selenium deficiency has been linked to Keshan disease (cardiomyopathy) [24], Kashin-Beck disease (chronic endemic osteochondropathy leading to osteoarthrosis) [25], and hypothyroid cretinism [26] since selenium supplementation reverses symptoms in most patients. Further, patients with cardiomyopathy in Friedreich's ataxia show histological similarity to Keshan disease [27]. Keshan disease, first described in 1935 in the Keshan province of China, affects mainly children and women in areas with selenium-deficient soils where it leads to cardiomyopathy and cardiac dysfunction [27]. Selenium deficiency can appear secondary to gastrointestinal disorders because of loss of dietary selenium, after bariatric surgery for weight reduction, and during long-term parenteral nutrition deficient in selenium [28]. Low serum selenium concentrations are a frequent finding in subjects with acute kidney injury or chronic kidney disease [29]. Selenium-free diet in Spontaneously Hypertensive Rats induced ~70% mortality rates due to the progression of hypertension-induced heart failure [30]; selenium deficiency in humans similarly induced heart failure [31]. Further, a broad range of toxic events has been reported following both acute and chronic selenium ingestion [32–35].

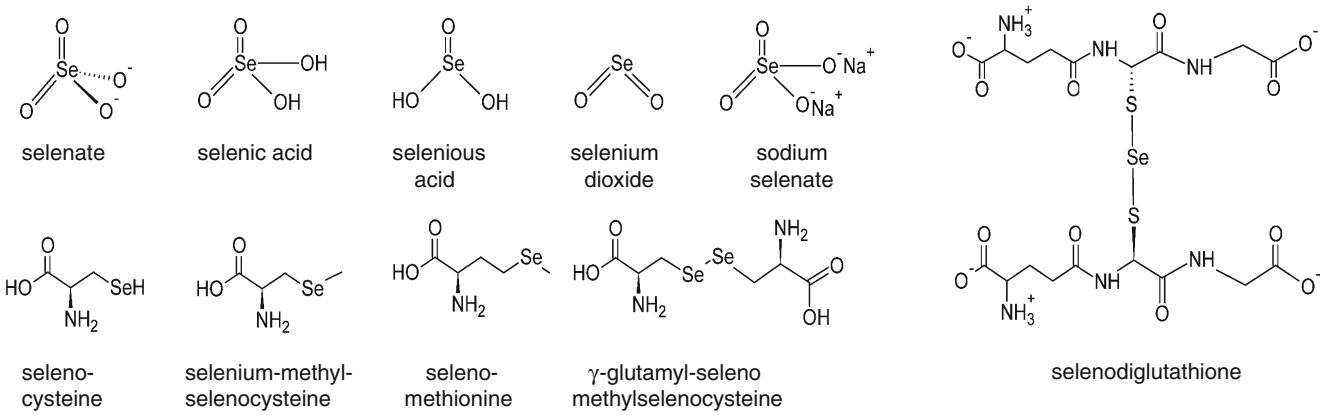

Fig. 1 Selenium species with different oxidation states

Selenium given as either methylselenocysteine, sodium selenite, or selenium-enriched yeast improved antioxidant capacity in the blood, liver, heart, and kidney in D-galactose injected rats as a model of accelerated aging [36]. These improvements were measured as increases in glutathione, total antioxidant capacity, superoxide dismutase activity, glutathione peroxidase activity, and decreases in malondialdehyde and protein carbonyls [36]. These improvements were enhanced when given with vitamin E and anthocyanins from purple carrots [36] thus suggesting that selenium supplementation could prevent or delay aging-related changes.

Selenium in Metabolic Diseases

Selenium acts as an insulin-mimetic to attenuate diabetes [37–39]. Diabetic nephropathy patients receiving 200 μg/day selenium supplements for 12 weeks showed improved serum MMP-2, plasma nitric oxide, plasma total antioxidant capacity, and glutathione, but did not show changes in serum *hs*-CRP, TGF-β, advanced glycation end-products, protein carbonyls, or malondialdehyde [40•].

However, there may be an increased diabetes risk associated with higher intake of selenium [41–43]. An increased selenium intake in rats of 438 μg/kg/day sodium selenite (200 μg/kg/day selenium), compared to the normal equivalent dose of 1–2 μg/kg/day selenium [30], for 6 weeks increased both fasting blood glucose and blood glucose after refeeding along with enhanced gluconeogenesis in liver suggesting high selenium dosage impairs glucose and insulin tolerance, and disturbs insulin signaling, producing the signs of hepatic insulin resistance [44]. One suggested mechanism is by selenium depletion of chromium which resulted in metabolic imbalance leading to increased reactive oxygen species production [44]. On the other hand, selenium also activated selenoproteins such as glutathione peroxidase and selenoprotein P which disturbed insulin-stimulated signaling by reactive oxygen species leading to disturbances of insulin action [44].

In cross-sectional analyses, selenium intake showed positive associations between plasma selenium concentrations and blood lipids [45, 46]. These outcomes were also identified in the UK PRECISE study [47]. However, in an elderly Danish population, administration of 100–300 μg/day selenium for up to 5 years did not cause any positive changes in blood lipids [48•], in fact, showing signs of adverse effects on blood lipids [49].

Selenium in Cardiovascular Control

Selenium deficiency leads to diminished antioxidant defenses which may play an important role in the development of chronic heart failure [50]. Patients with heart failure tend to have lower blood concentrations of selenium when compared with healthy individuals [51]. Selenium deficiency-induced heart failure is reversible after selenium supplementation [52]. Administration of 20–40 μg/kg body weight selenium in Spontaneously Hypertensive Rats for 7 months increased selenium-containing antioxidant enzyme activity and decreased cardiac oxidative injury [30]. In rats, sodium selenite pretreatment at 1 mg/kg for 6 days protected against cardiac damage induced by cyclophosphamide measured as the prevention of changes in histological abnormalities in the heart tissue, reduced plasma concentrations of malondialdehyde, and increased plasma concentrations of glutathione [53]. Other biochemical markers included reduced plasma activity of lactate dehydrogenase and creatine kinase-MB along with reduced plasma concentration of ischemia-modified albumin following selenium pretreatment [53]. Although this study [53] used much higher selenium doses, the duration was only for 6 days compared to 6 weeks where toxicity was observed [44]. In penconazole-treated rats, selenium supplementation reduced lipid peroxidation, protein carbonyls, plasma LDL-cholesterol, and atherogenic index, and increased cardiac concentrations of GSH, vitamin C, and plasma HDL-cholesterol; all these changes suggest cardioprotection [54].

High serum selenium concentrations were related to the occurrence of increased systolic, diastolic, and pulse pressures [55, 56], although no obvious relationship was found between selenium concentrations and hypertension [57]. The potential mechanisms for dose-related cardioprotection and cardiac dysfunction with selenium are given in Fig. 2.

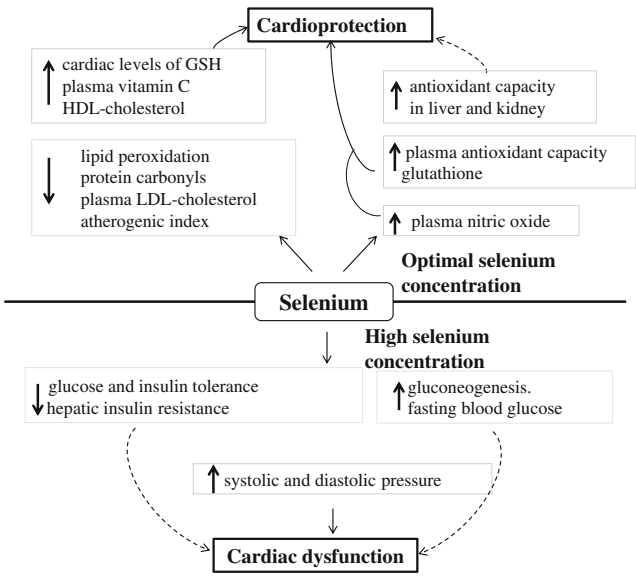

Fig. 2 Mechanisms of changes in cardiovascular structure and function with selenium

Vanadium

Although vanadium is relatively common in nature with an estimated abundance of 0.02% of matter, it occurs in animal tissues at very low concentrations of 0.014–7.2 μmol/L [58]. It is estimated that humans consume up to 60 μg of vanadium daily through foods including mushrooms, parsley, and black pepper [59], but the essentiality of vanadium remains controversial [60]. The upper limit for intake without adverse events is 1.8 mg/day [17].

Vanadium exists in oxidation states from −1 to +5 with +3, +4, and +5 being most common. Elemental vanadium does not occur in nature. Vanadyl (VO^{2+}) with +4 oxidation state is the most stable; vanadium oxide (V_2O_3) has vanadium in +3 oxidation state, while metavanadate (VO_3^-), orthovanadate ($H_2VO_4^-$), and pyrovanadate ($V_2O_7^{4-}$) have vanadium in +5 oxidation state [61]. Metavanadate is the most common state in extracellular body fluids, whereas vanadyl is the most predominant intracellularly [61]. Physiologically, vanadium mainly occurs complexed with proteins including transferrin [62], albumin [63], and hemoglobin [64] by which vanadium is transported to tissues including the liver, heart, kidney, brain, muscle, and adipose tissue [65]. Evidence from electron paramagnetic resonance spectroscopy suggests that VO^{2+} binds to the same sites as Fe^{3+} in holotransferrin [62] and hemoglobin [64] with the majority of VO^{2+} in serum being transported by holotransferrin [63, 66].

Cell-free assays have identified many physiologically active potential ligands of vanadate including free amino acids (lysine, glutamic acid, and glycine), enzyme substrates (citrate, malate, and glycerate), and enzymes (ribonuclease, chymotrypsin, pepsin, aldolase, acetylcholinesterase, and myosin) [67]. Vanadium in its +5 oxidation state acts as a cofactor in haloperoxidases and is responsible for the insulin-mimetic properties of vanadium [68]. Structures of some of the important vanadium compounds are provided in Fig. 3.

Vanadium in Metabolic Diseases

Several insulin-mimicking agents including low molecular weight substances such as zinc [16], lectins, and antibodies [69] have been characterized in vitro. However, translation of these agents into clinical use has proved challenging because they do not satisfy key pharmacological criteria including bioavailability, stability in body fluids, low index of toxicity, and specificity in mimicking the biological responses of insulin [70]. Much of the interest in vanadium as a therapeutic agent is traceable to its insulin-mimetic properties. Both in vitro and in vivo applications of vanadium have reported consistent insulin-mimetic properties [71•, 72].

Glucose intolerance was completely reversed, body weight decreased by 20%, subcutaneous fat width decreased, and hepatic triacylglycerol content decreased when fatty Zucker rats were treated with 44 μmol/kg of $VO(dmpp)_2$, an oxovanadium, over a 4-week period [73]. Similarly, treatment of streptozotocin-diabetic rats with different forms of vanadium normalized blood glucose concentrations [74] and glucose tolerance through β-cell preservation and improved pancreatic insulin stores and secretory function [75]. In L6 myotubes, vanadate and its derivative pervanadate stimulated GLUT translocation to the plasma membrane and glucose transport to the same degree as insulin but by a mechanism independent of phosphatidylinositol 3-kinase and protein kinase C [76].

In humans, there are conflicting reports of the insulin-mimetic properties of vanadium. Oral administration of 1 mg/kg/day of vanadyl sulfate for 2–4 weeks produced 30 mg/dL (15–20%) decreases in fasting plasma glucose in patients with non-insulin-dependent diabetes mellitus [77, 78]. However, a separate study using an oral dose of 125 mg/day sodium metavanadate (+5) over a period of 2 weeks reported no changes in fasting plasma glucose and hepatic glucose production [79]. Since vanadyl has been thought to be the active intracellular form of vanadium [80, 81], this could be the reason for the differences in glucose responses between the two studies. A later study using vanadyl sulfate at a dose of 50 mg twice daily in obese

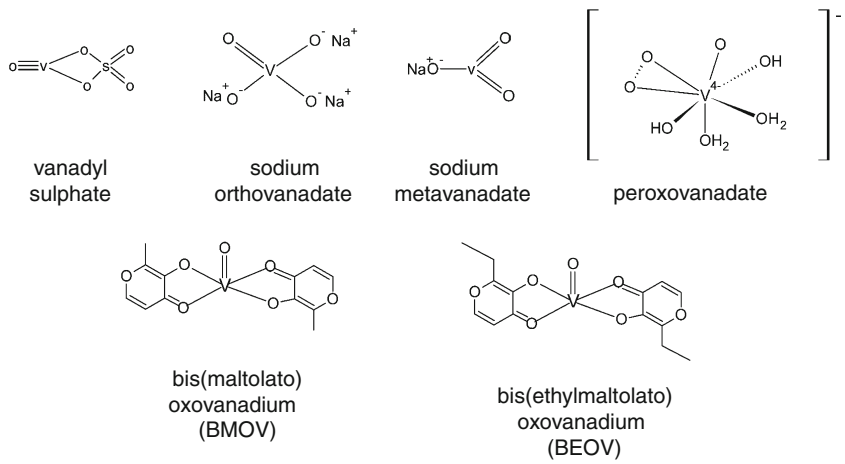

Fig. 3 Vanadium species with different oxidation states

patients with impaired insulin sensitivity also reported no changes in insulin sensitivity but increased plasma triacylglycerols [82]. A new strategy that may greatly enhance the potential of vanadium as an intervention for metabolic disorders is complexing vanadium to existing drugs including rosiglitazone and metformin with vanadyl rosiglitazone showing great potential to attenuate diabetes symptoms [83].

Groundwater containing 7.1–28.09 μg/L vanadium inhibited preadipocyte differentiation and prevented obesity in high-fat diet-fed C57BL/6 mice [84]. However, the limitation of this study was that the water contained other metabolically important ions such as K^+, Ca^{2+}, Mg^{2+}, and Na^+. Vanadium was proposed to inhibit preadipocyte differentiation by decreasing peroxisome proliferator-activated receptor γ (PPAR-γ) and CCAAT-enhancer-binding protein expression [84].

Regulation of Enzymes in Energy Metabolism by Vanadium

Vanadate is a potent inhibitor of many enzymes, probably through its ability to act as a transition state analog and form enzyme complexes that mimic the transition states of enzyme-catalyzed phosphate ester hydrolysis [85]. However, the existence of multiple forms of vanadium complexes including oxovanadium clusters which are able to inhibit enzymes has led to the suggestion that there are other modes of inhibition apart from the transition state mechanism [86]. Vanadium-mediated insulin sensitivity is thought to be caused by the inhibition of phosphotyrosine phosphatases (PTP) thereby stimulating insulin receptor tyrosine kinase (IRTK) activity [81]. However, some studies have suggested that vanadium stimulates glucose uptake independently of any change in IRTK activity [87]. Vanadium in its peroxo oxidation state rapidly oxidized thiol groups in cysteine residues of proteins providing a possible mechanism for regulating enzyme activity [88]. Pervanadate competitively inhibited PTP1B by rapidly oxidizing the active site cysteine [88]. The inhibition of phosphorylases other than phosphatases by vanadate results from the similarity between vanadate and phosphate in the transition state of phosphate ester hydrolysis [89]. Since the vanadyl cation is similar to Mg^{2+} in much the same way as vanadate is to phosphate [90], it is possible that enzymes depending on Mg^{2+} as a cofactor are likely to be competitively regulated by vanadyl. Mg^{2+} catalyzes or activates more than 300 enzymatic reactions as a metallocoenzyme implying that its similarity with vanadyl could have important physiological ramifications [91].

Vanadium in Cardiovascular Health

In various models of hypertension and insulin resistance, treatment with vanadium compounds improved cardiac function and smooth muscle contractility, and lowered blood pressure [92–95]. In the cardiovascular system, vanadium exerted therapeutic effects through mechanisms including increased protein kinase B (Akt) and endothelial nitric oxide synthase activity [96–98], modulation of angiotensin and endothelin expression [99], inhibition of calpastatin and dystrophin breakdown [98], and inhibition of endoplasmic reticulum stress [100]. Vanadium compounds stimulated the expression of Akt in a receptor tyrosine kinase-dependent manner by inhibiting protein tyrosine phosphatases [101, 102] and production of hydrogen peroxide [103]. By activating Akt, vanadium could suppress apoptosis through enhanced phosphorylation of several substrates, including members of the Bcl-2 family such as Bad [104, 105]. In cardiomyocytes, activation of the phosphatidylinositol 3-kinase/Akt pathway by insulin-like growth factor 1 (IGF-1) treatment may be responsible for the anti-apoptotic effects of IGF-1 [106]. Additionally, activation of Akt by vanadium has the potential to attenuate cardiac hypertrophy and angiogenesis [96].

In ovariectomized rats, bis(1-oxy-2-pyridinethiolato) oxovanadium (IV), [VO(OPT)] administered orally at doses of 1.25 or 2.50 mg/kg/day for 2 weeks inhibited myocardial hypertrophy induced by pressure overload [98]. Additionally, VO(OPT) improved nitric oxide synthase activity in the endothelium, restored Akt activity, attenuated hypertrophy-induced left ventricular pressure and contractility, and decreased mortality in pressure-overloaded rats after repeated treatment with isoproterenol [98]. In rats fed fructose for 6 weeks to induce hypertension and insulin resistance, vanadyl sulfate prevented both norepinephrine hyperresponsiveness and supersensitivity and enhanced aortic relaxation after acetylcholine treatment [107].

In Spontaneously Hypertensive Rats fed a high-sucrose diet, treatment with BMOV (*bis*(maltolato)oxovanadium) or vanadyl sulfate decreased systolic blood pressure by 11–16% and decreased the secretion of the vasoconstrictive hormone, angiotensin II, by 25–60% [99]. The decrease in angiotensin II was accompanied by an increase of 61–76% in endothelin-1, a potent vasoconstrictor leading to the suggestion that endothelin-1 is not a key player in sugar-induced high blood pressure [99]. Studies in streptozotocin-induced diabetic rats and type 2 diabetes patients suggested that coordination chemistry rather than oxidation state is important in the inhibition of metabolic syndrome by vanadium [108, 109]. The sum of these observations points to the great potential of vanadium as a therapy for cardiovascular diseases, especially those related to abnormalities in glucose homeostasis.

Prospects of Vanadium in Cardiovascular Disease Therapy

Although treatment with vanadium in different models of diabetic cardiomyopathy has yielded promising results, translation of

these findings into treatment of human cardiovascular diseases is yet to be realized. Several factors may affect the progression of vanadium to clinical use, especially pharmacological factors including bioavailability and toxicity [72]. Since the activity of vanadium is reliant on its pH-sensitive oxidation state [65], the compound may not always reach the target tissue in the desired form, especially if administered orally. After oral administration of 5 μmol radioactive [^{48} V]Na_3VO_4, measurement of the cumulative recovery over 4 days showed 17.52% excreted through urine compared to 69.07% collected in the stool [110], implying less than 20% bioavailability [111]. Additionally, vanadium is toxic to various organ systems [72]. In vitro studies using (50 μg/L) of vanadate demonstrated DNA fragmentation in cultured fibroblasts from healthy donors [112]. Among reported toxic effects of vanadium are gastrointestinal toxicity, diarrhea, dehydration via reduced water intake, appetite suppression, and reduced body weight gain [113–116]. When pregnant diabetic rats were treated with 0.25 mg/mL sodium orthovanadate through drinking water, fatalities occurred in up to 50% of pregnant diabetic animals with elevated serum concentrations of vanadium [117, 118]. Bis(ethylmaltolato)oxovanadium (IV) (BEOV), one of the promising vanadium complexes, advanced to phase II clinical trials but did not progress further due to renal problems observed in some patients [119]. However, the only reported case of fatal vanadium poisoning in humans occurred at a blood concentration of 6.22 mg/L, corresponding to 6000 times higher than normal concentrations in the general population [120]. Obviously, the feasibility of vanadium as a cardiovascular intervention will require formulations which combine insulin-mimetic efficacy with minimal adverse effects. The potential mechanisms for improved cardiovascular function with vanadium are given in Fig. 4.

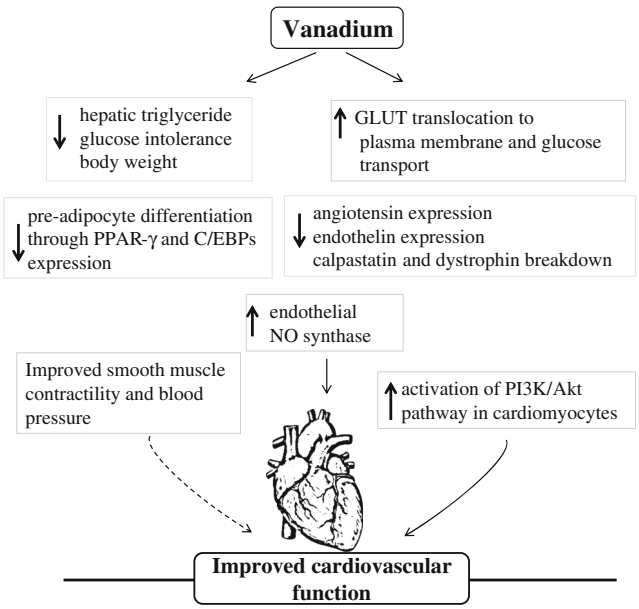

Fig. 4 Mechanisms of improved cardiovascular function with vanadium

Chromium

Chromium is found in water, soil, and biological systems [121]. Out of many forms of chromium, trivalent chromium was considered essential for human nutrition [121]. Questions were raised on the essentiality of chromium as a trace element [122], and chromium has now been removed from the list of essential nutrients [123]. Similar to vanadium, chromium also plays an important role in redox reactions in the cell [124] along with its involvement in maintaining glucose tolerance [121]. Organic chromium (such as chromium picolinate) is absorbed better than inorganic forms such as chromium oxide and is found in all animal tissues below the concentration of 100 μg/kg [121]. The major role for chromium in the body is suggested to be in carbohydrate and lipid metabolism, although the mechanisms of the involvement of chromium are not clear. However, there is sufficient evidence to support the potential benefits of supplemental chromium. The National Institutes of Health suggests a value for adequate intake of chromium of 35 μg/day in males aged 14–50 years, 24–25 μg/day in females aged 14–50 years, 29–30 μg/day during pregnancy, and 44–45 μg/day in lactation [17]. The upper limit for the chromium intake is not able to be defined due to insufficient data [17].

Oxidation states of chromium range from −2 to +6 with the most important states being +3 and +6 [125]. These include chromium acetate, chromium nitrate, chromium chloride, chromium oxide, chromium phosphate, chromium sulfate, and sodium chromite in the +3 oxidation state; chromium dioxide in the +4 oxidation state; and ammonium dichromate, calcium chromate, chromium trioxide, lead chromate, potassium chromate, potassium dichromate, sodium chromate, sodium dichromate, strontium chromate, and zinc chromate in the +6 oxidation state [125].

Chromium in Metabolic Disease

Chromium plays an important role in the maintenance of glucose metabolism [126]. It is proposed to be a second messenger in the cell in response to insulin where it enhances the function of insulin [122]. Once chromium is in the tissue, it binds to chromodulin which then helps in insulin function [127].

Marked dietary chromium restriction may cause an adverse intrauterine environment, causing metabolic symptoms in offspring including obesity, hyperglycemia, and hyperinsulinemia, through the regulation of insulin signaling and Wnt signaling pathways [128]. In contrast, alloxan-induced diabetic rats treated with 3 mg/kg/day bodyweight of chromium as chromium malate for 2 weeks reduced blood glucose, serum triacylglycerol,

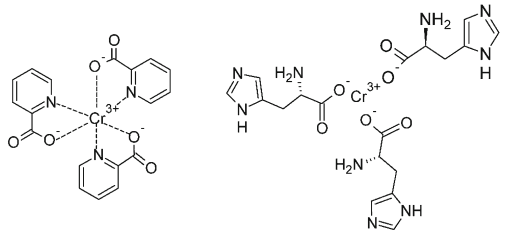

Fig. 5 Organic chromium compounds: chromium picolinate and chromium histidinate

and serum total cholesterol concentrations while increasing liver glycogen concentrations [129]. When high-fat diet-fed rats given streptozotocin were treated with chromium picolinate (80 μg/kg body weight/day for 10 weeks), concentrations of insulin, tryptophan, and serotonin increased in the serum and brain, while serum cortisol and glucose concentrations were decreased [130]. Chromium picolinate (Fig. 5) (80 μg/kg body weight/day for 3 months) in male JCR:LA-cp obese rats reduced plasma concentrations of insulin, total cholesterol, and triacylglycerols along with improved glucose disposal rates in obese rats [131]. These improvements in carbohydrate and lipid metabolism were accompanied by increases in insulin-stimulated phosphorylation of insulin receptor substrate 1 and phosphatidylinositol-3 kinase activity in skeletal muscle along with reduced PTP1B levels [131]. Further improvements in carbohydrate metabolism have been reported with chromium in other studies [132–135]. Chromium picolinate supplementation (600 μg/day) in type 2 diabetic patients reduced fasting blood glucose concentration, postprandial blood glucose concentration, and HbA_{1c} while having no effects on blood lipid concentrations [136•].

Chromium in Obesity

High-fat diet feeding to female rats for 3 months induced central obesity by increasing body weight, adiposity index, and adipocyte size along with increased serum leptin, MCP-1, glucose, and HOMA-IR [124]. These rats showed decreased adipose tissue deposition of chromium and vanadium without any changes in serum concentrations of these trace metals [124] leading to the suggestion that obesity is preceded by an imbalance in these elements. High fat feeding from weaning for 1 month increased adipose tissue weights but reduced adipose tissue content of chromium in male Wistar rats compared to standard diet-fed rats [137]. High-fat diet-fed rats supplemented with 110 μg chromium histidinate (Fig. 5)/kg body weight/day reduced body weight and serum glucose while increasing serum insulin concentrations [138]. Livers from chromium histidinate-supplemented rats showed increased expression of GLUT-2, Nrf2, and HO-1 with decreased NF-κB and 4-hydroxynonenal expression [138]. In contrast, treatment of obese nondiabetic human adults with metabolic syndrome with chromium picolinate (500 μg twice daily) for 16 weeks did not improve insulin sensitivity, body weight, blood lipids, or inflammatory markers [139]. Further, a systematic review of chromium picolinate for its effects on obesity and dyslipidemia suggested that the quality of data available for safety and efficacy was low and conclusions could not be drawn in favor of chromium picolinate [140•].

Chromium in Hypertension

In rats, niacin-bound chromium given at 225 ppm for 130 days reduced systolic blood pressure and blood glucose concentrations along with lower renin-angiotensin system activity, reduced angiotensin converting enzyme activity, and increased nitric oxide system activity [141]. Chromium-enriched yeast supplementation to whole wheat bread in type 2 diabetic humans for 12 weeks reduced body weight, blood glucose, HBA_{1c}, and fasting insulin together with systolic blood pressure [142•]. The potential mechanisms for improved cardiovascular function with chromium are given in Fig. 6.

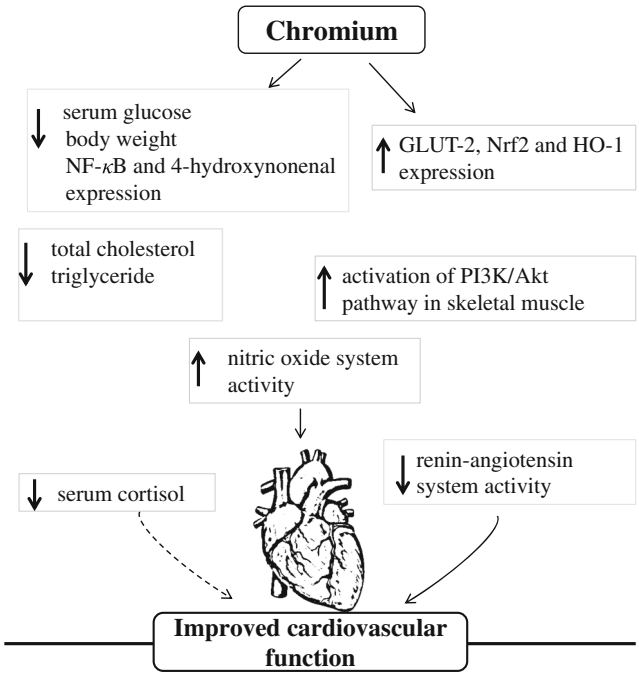

Fig. 6 Mechanisms of improved cardiovascular function with chromium

Conclusions

Considering the level of evidence available for selenium, vanadium, and chromium against symptoms of metabolic syndrome, their health benefits against metabolic complications cannot be proved, although the improvements shown in certain studies with safer doses warrant further research in this area. The importance of these trace metals should be taken into account for the roles they play in metabolic pathways, and developing food products supplemented with safe amounts of these trace metals may provide healthy food products for the future while delivering these micronutrients to avoid deficiency states.

Compliance with Ethical Standards

Conflict of Interest Drs. Panchal, Wanyonyi, and Brown declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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