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Selenium and vascular health*

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Abstract: Selenium (Se) is an important dietary micronutrient required for sustaining optimal health. Se is incorporated into proteins, many of which are antioxidants that protect the body against oxidative damage. As oxidative damage may contribute to the development of chronic diseases including cardiovascular disease (CVD), Se has been proposed to provide a protective role against this disease. Studies in vitro and in animals continue to provide increasing insight into the role of Se in promoting vascular health and ameliorating CVD. Se within vascular cells limits the adhesion together of such cells, an important early step in the development of vascular disease. Organic forms of Se may also afford vascular cells greater protection against oxidative challenge compared to inorganic forms. Nevertheless, current studies in humans investigating the relationship between Se and CVD have so far proved equivocal; larger randomized trials with different Se exposures in populations spanning the broad physiological Se status are needed to determine the criteria whereby Se may influence CVD outcome within different populations. Further studies are also needed to explore the effects of different Se species and the role of different selenoprotein genotypes in modifying Se status and their resultant impact on cardiovascular function.

Keywords: anti-inflammatory; antioxidant; cardiovascular disease; endothelial; selenium; speciation.

INTRODUCTION

Selenium (Se) is an essential dietary micronutrient necessary for maintaining optimal health in animals and humans. The essentiality of this element most likely occurs because of its incorporation as a cofactor (as selenocysteine) into a number of key body proteins or selenoproteins. Many of these selenoproteins are important antioxidant enzymes that help protect the body against oxidative damage induced by free radicals. Free radicals are naturally produced as a result of oxygen metabolism, and they can contribute to the progression of chronic diseases such as diabetes, cancer, and cardiovascular disease (CVD) [1,2]. Other selenoproteins function to regulate thyroid hormone metabolism and play a role within the immune system [3,4].

Se is present to varying degrees within the soil, and it enters the food chain through its uptake by plants, which also accumulate it to varying levels [5]. The amount of Se taken up in the diet therefore largely depends on which food product is consumed in addition to its provenance. The recommended dietary intake (RDI) level of Se averages from 55 to 85 μg/day depending on gender and country of residence (see ref. [6]). However, in many European countries and parts of China, calculated intake amounts of Se are lower than the recommended levels [7,8], results which are substantiated by meas-

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urements of Se status in vivo [see 9]. Evidence indicates that population groups with similar, less than optimal Se intakes (and consequent reduced Se status) have lowered protection against a range of adverse health events.

SELENIUM AND CARDIOVASCULAR DISEASE

There are at least two main mechanisms through which Se could be envisaged to provide protection against CVD — through its antioxidant capacity and through its anti-inflammatory action. CVD occurs due to the narrowing of arteries owing to the formation of fatty deposits or plaques within the arterial wall, a process known as atherosclerosis. Both inflammation and oxidative stress are important etiological factors in atherosclerotic development [10–12]. The recruitment of inflammatory cells from the circulation and their transmigration across the lining of endothelial cells (ECs) covering the artery into the intimal space of the arterial wall is a key early event in atherosclerosis development [13]. This recruitment occurs through the expression of EC-derived adhesion molecules (CAMs) that can be initiated by multiple stimuli including hypertension, pro-inflammatory mediators, and oxidized forms of low-density lipoproteins (oxLDLs) [11,14]. Oxidative stress from free-radical generation promotes the oxidation of LDL particles within the arterial wall leading to plaque build-up within arteries [11]. Free-radical generation additionally leads to damage of the EC layer, which is also a key event in promoting atherosclerotic progression [15].

Selenium as an antioxidant in cardiovascular disease

As oxidative stress has been associated with the development of CVD, Se has been envisaged as providing protection against heart disease owing to its presence as an essential cofactor for a number of important antioxidant enzymes. Glutathione peroxidase-1 and 3 (GPx1, GPx3) catalyze the reduction of hydrogen peroxide and organic hydroperoxides, whereas GPx4 can also directly reduce phospholipid hydroperoxides within membranes and oxLDLs [16]. The thioredoxin reductases (TXNRDs) also have a wide range of substrates including hydrogen peroxide, lipid hydroperoxides, lipoic acid, ubiquinone, and ascorbate, as well as thioredoxin [17]. Furthermore, a number of other selenoproteins including selenoprotein P have been proposed to have antioxidant roles within the body [18,19]. Taken together, the Se-requiring enzymes form a significant part of the body's natural antioxidant defense mechanism. Therefore, when dietary Se intake is lower than optimal (i.e., in most European countries) it may be insufficient to maximize cellular selenoenzyme activities, and this can lead to lowered protection from oxidant damage [20] and increased risk of oxidative damage-associated diseases such as cancer and CVD.

However, reduced Se intakes do not affect expression of all selenoproteins to the same extent, and there are also tissue-specific differences in responses [21]; there is essentially a prioritization of available Se for synthesis of certain selenoproteins (termed the selenoprotein hierarchy [22]). Therefore, varying levels of Se availability within the diet may differentially affect the expression and activity of different selenoproteins, which may have different outcomes on disease progression including CVD.

Although evidence from some observational studies is suggestive of low Se concentrations being associated with increased risk of CVD [23–27] other studies have found no association [28]. Definitive evidence for an ameliorative role of Se in CVD from Se supplementation studies in humans has so far proved elusive [29,30]. This current lack of clear evidence may be due to a number of factors. Relatively few intervention studies have been performed primarily investigating cardiovascular endpoints [29] and some have been relatively small scale, thus potentially lacking sufficient statistical power [31,32]. In addition and perhaps more importantly, populations that have been investigated thus far have tended to be mainly healthy and Se-replete (i.e., carried out in the United States or Australia) [30,33]. Therefore, although, for example, a Se biomarker such as plasma Se level would still demonstrate an increase upon Se supplementation (as its response is observed regardless of the baseline concentration), measurement

of selenoenzyme activity such as plasma GPx3 or platelet GPX1 activity would not as this would likely have reached its dose–response plateau at the start of the intervention within a Se-replete population. This may be relevant to the apparent effectiveness or otherwise of Se intervention as this may depend on whether its potential cardiovascular protective effect(s) are likely to be mainly achieved through optimizing selenoenzyme function or, as in the case of cancer and the immune system, appear more effective at intake levels greater than the recommended daily intake (reviewed in refs. [34,35]). In this regard, a recent cross-sectional analysis on the association of serum Se with peripheral arterial disease prevalence among U.S. men and women suggested that the effects of Se on athlerosclerosis are nonlinear and may follow a U-shaped relationship [36]. In addition, data from both epidemiological and Se supplementation studies have suggested that higher serum/plasma Se levels are associated with increased diabetes, hypertension, and hyperlipidemia, all risk factors for CVD [37–43]. In the United States, analysis of cross-sectional studies found a positive relationship between serum Se and diabetes [39,42] and further analysis of the National Prevention of Cancer trial found supplementation with Se (200 μg/day of high-Se yeast) increased the risk of diabetes compared to placebo [40]. These findings may indicate that increasing Se status in an already Se-replete population may be detrimental to CVD outcomes. Interestingly, in more recent longitudinal studies investigating the relationships between Se status and diabetes and lipid levels, adverse associations were not observed [44–46] and indeed, in studies within European populations with relatively low baseline Se status, Se supplementation had no effect on fasting plasma glucose [47] and a modest beneficial effect on the blood lipid profile [46]. Whilst it is suggestive that Se supplementation does not appear to decrease CVD risk in healthy individuals [30,33], studies in CVD patients may also require careful interpretation due to the apparent interaction of certain cardiovascular medications with Se function [49–52]. For example, statins block production of isopentenyl pyrophosphate (IPP), an essential factor for selenoprotein synthesis [53], and metformin can attenuate selenoprotein P levels and potentially decrease Se availability in peripheral tissues since this protein is the major circulating transport form of Se [54].

Two other factors should also be considered when evaluating the effects of Se supplementation on CVD risk—genotype and species of Se. Genetic variation in key selenoprotein genes and other genes of related pathways may have an impact on the response to Se and CVD risk, which adds complexity to any potential relationship [18,55–60]. The particular species of Se used for supplementation may also be relevant in its apparent effectiveness to treat disease. Most work in this latter regard has been carried out on the effects of different Se species on cancer. The main forms of Se used in supplementation trials investigating CVD endpoints have been selenite [61] and Se-enriched yeast. Selenite is an inorganic form of Se and is not normally present in the diet to any large extent. Se-enriched yeast mainly comprises selenomethionine, an organic form of Se, with other minor forms including *Se*-methyl-selenocysteine and γ-glutamyl-*Se*-methyl-selenocysteine also present. Organic and inorganic forms of Se are metabolized differently [62] and show differences in bioavailability with organic forms more effective at increasing blood Se levels (see ref. [6] for review). Studies investigating the anticancer effect of Se in rodents and in cell models have identified small-molecular-weight methylated forms of Se as being more efficacious than other Se species [63–66]. However, whether these same forms have a similar ameliorative effect on CVD risk is not known as the effect of Se speciation on diseases other than cancer have not yet been fully investigated. On this topic, results from our group have shown that SeMet is able to provide greater protection to EC against a lipid hydroperoxide challenge compared to inorganic forms of Se such as selenite and selenate (Fig. 1). Whether this effect is achieved through altered uptake and differences in seleno-enzyme activities [67] or changes in cell growth arrest/apoptotic regulation [68] is currently being investigated. Protection of the endothelium against oxidative damage may be expected to reduce the incidence of vascular diseases including atherosclerosis. Current work within our group is investigating the effects of Se speciation (including methylated forms of Se) on atherosclerotic plaque development within the ApoE-/- mouse model to determine the role of Se speciation and dose on atherosclerosis in vivo.

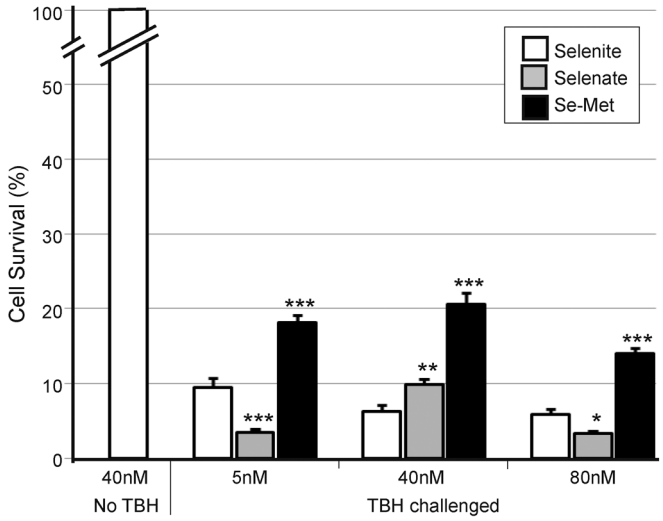

Fig. 1 Effect of different Se species on endothelial cell survival after an oxidative challenge. Human coronary aortic endothelial cells (HCAECs) were grown for 4 days in the presence of 3 different Se species (selenite, selenate, and SeMet) then challenged with *tert*-butyl-hydroperoxide (300 μM for 3 h) before cell viability was assayed (CellTitre-Blue; Promega). Survival is expressed as a percentage of unchallenged cells grown in 40 nM sodium selenite. Significant differences compared to the selenite group at the same concentration were determined by paired student's *t*-tests (*$p < 0.05$, **$p > 0.01$, ***$p < 0.001$).

In conclusion, evidence is lacking that Se may curb CVD risk but larger, longer-term randomized trials within population groups extending over a more complete range of international Se intakes and assessing a broad spectrum of Se status biomarkers are needed in order to demonstrate whether CVD can be improved by Se and under which circumstances.

Selenium as an anti-inflammatory in cardiovascular disease

An additional, although perhaps not unrelated process through which Se could provide protection against development of CVD is through its anti-inflammatory properties. As discussed above, CVD, along with other diseases associated with metabolic syndrome such as type-2 diabetes, stroke, and hypertension, is considered a pro-inflammatory disease involving chronic low-grade inflammation. The central regulator of inflammation is a transcription factor termed nuclear factor κB (NF-κB). NF-κB controls the expression of a multitude of target genes involved in inflammation, thereby mediating cell proliferation and the release of antimicrobial molecules and cytokines which activate the immune response [69]. Within the EC, NF-κB activation induced by pro-inflammatory cytokines or oxLDL upregulates the expression of CAM, which allows subsequent binding of circulatory monocytes, a key early step in the atherosclerotic process. Work within our group has investigated the effect of Se on monocyte binding to ECs in vitro. This has shown that the presence of Se at levels that are optimal for maximizing selenoprotein activity can reduce pro-inflammatory cytokine-induced adhesion between these two cell types by greater than 50 % (Fig. 2). Furthermore, this reduction occurs through effects within both the EC and the monocyte as Se supplementation of either cell type reduces adhesion and these effects are additive (Fig. 2). Subsequent analysis using EC supplemented with Se at levels at 50 % of those required to maximize GPx1 and GPx4 activities show that increases in monocyte-EC adhesion occur at physiologically relevant Se levels (Sneddon et al., unpublished). This data implies that at Se intakes of around half those required to optimize seleno-enzyme activities (as present, e.g., in many East European countries [70]) increased adhesion of monocytes to the endothelium occurs, which may

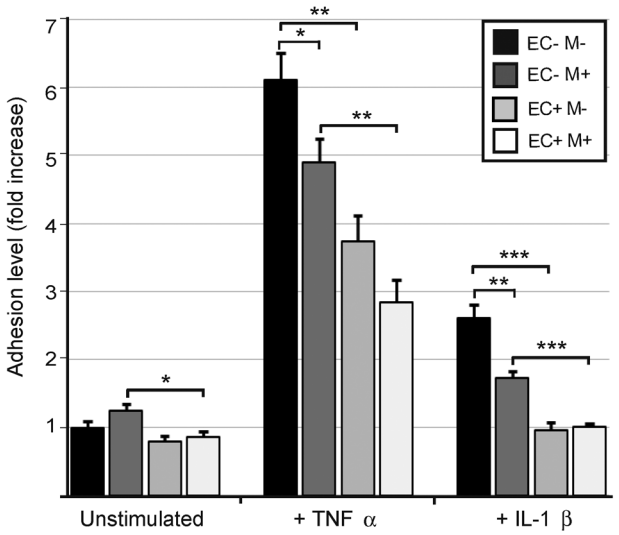

Fig. 2 Effect of Se deficiency and sufficiency (0 or 40 nM sodium selenite) within either the HUVECs (**EC– or +**) and the U937 monocyte cells (**M– or +**) on the level of adhesion of monocyte cells to the EC. Monocytes or EC were treated with or without Se for 4 days and then monocytes were fluorescently labeled with 2',7'-*bis*-(carboxyethyl)-5(6')-carboxyfluorescein acetoxymethyl ester (BCECF-AM) and binding to EC was assayed either without cytokine treatment (**Unstimulated**) or the EC was first pretreated with pro-inflammatory cytokine (5 ng/ml **TNFα** or 10 U/ml **IL-1β**) for 6 h and then assayed for adhesion. The relative fold increase in adhesion compared to the "EC- M-" group is shown along with significant differences between pairs of groups determined using paired student's *t*-tests *t* (*$p < 0.05$, **$p > 0.01$, ***$p < 0.001$).

increase atherosclerotic risk. These effects on monocyte-EC binding were observed using the selenite form of Se and experiments to determine the role of individual seleno-enzymes, and the effects of Se speciation on this response are being investigated.

Se is known to regulate inflammation through inhibition of the NF-κB signalling pathway [71]. Over-expression of either of the seleno-enzymes GPx1 or GPx4 inhibits NF-κB activation in breast cancer and aortic smooth muscle cells [71,72] and in type-2 diabetic patients Se supplementation [albeit with high-dose Se (960 μg/d)] reduces NF-κB activation within peripheral blood mononuclear cells [73]. Within the EC, Se deficiency resulted in increased neutrophil adherence and upregulation of VCAM-1 and ICAM-1 adhesion molecules in bovine mammary aortic EC [74]. In human umbilical vein endothelial cells (HUVECs), the GPx mimic BXT-51072, inhibited expression of VCAM-1, ICAM-1, and P- and E-selectin [75]. Additionally, sodium selenite inhibited TNFα-induced expression of ICAM-1, VCAM-1, and E-selectin in a dose-dependent manner (albeit at supra-physiological levels of Se (500 nM to 2 μM) [76]. The precise mechanism of how Se leads to NF-κB inactivation is unclear at present but may involve its antioxidant action. Reactive oxygen species (ROS) are known to be involved in activation of NF-κB but this is dependent on both the cell type and the nature of the challenge (see [76] for review). Therefore, the process by which Se attenuates CAM expression may differ depending on the type of cell and challenge that is being considered. For example, both TNFα and IL-1β induce CAM expression in HUVEC, but whereas ROS are generally considered an intermediate in NF-κB activation by IL-1β signalling, it may not be required for NF-κB activation by TNFα [77].

Se can also regulate vascular function and inflammation through modulation of eicosanoid levels. Eicosanoids are signalling molecules that are principal mediators of immune function and inflammation, which are synthesized by the oxidation of 20-carbon fatty acids. Numerous studies have shown that Se modulates eicosanoid (prostaglandins and leukotrienes) levels [78–80]. Selenoenzymes, again acting through its antioxidant action, modulate the cellular peroxide tone; it is the peroxide tone that

can modify the activities of the enzymes responsible for eicosanoid biosynthesis and regulate eicosanoid production. [81]. Within the EC, the prostaglandin, prostacyclin (PGI_2), promotes vascular health through its dual role as a potent vasodilator and a platelet activation inhibitor; Se deficiency reduces PGI_2 levels [79] promoting vascular dysfunction. PGI_2 can also inhibit the production of the pro-inflammatory mediator, platelet-activating factor (PAF) [82]. PAF plays an essential role in promoting TNFα- and IL-1β-induced monocyte adhesion to HUVEC [83], and therefore changes in PAF levels within the EC may underlie increases in monocyte adhesion to EC observed under Se deficiency (Fig. 2). Within other vascular cells, Se can inhibit NF-κB activation through promoting production of anti-inflammatory cyclopentenone prostaglandins (e.g., 15-deoxy-Δ-12,14-PGJ_2) [80,84].

Within the context of the diet, the apparent effect of Se on CVD outcomes may, in addition, be influenced both positively and negatively by the presence of other dietary components. In this regard, Se and dietary fatty acids can potentially influence the action of each other. As mentioned above, Se levels can modulate eicosanoid production, but dietary fatty acid intakes also have a major role in influencing eicosanoid output since fatty acids are substrates for eicosanoid production. Arachidonic acid (AA), the most abundant polyunsaturated fatty acid (PUFA) in membrane phospholipids, is the primary precursor of eicosanoids. Consumption of omega-3 PUFAs (EPA and DHA) can lower tissue levels of AA by inhibiting its synthesis and by replacing it within membrane phospholipids [85]. This can cause beneficial effects in relation to inflammation and CVD through reducing eicosanoid levels and/or by replacement with less inflammatory species (e.g., the EPA-derived 3-series eicosanoids are typically less vasoconstrictive and produce less platelet aggregation than those synthesized from AA [85]). Omega-3 fatty acids can also act to reduce EC CAM expression and subsequent monocyte binding/transmigration in vitro [86,87] and in vivo [88,89]. However, when Se is limiting, the reduction in monocyte adhesion to EC by both omega-3 fatty acids (*n*-3s) and other PUFAs such as conjugated linoleic acids (CLAs), observed in the presence of Se, is lost (Fig. 3). These results suggest that Se is

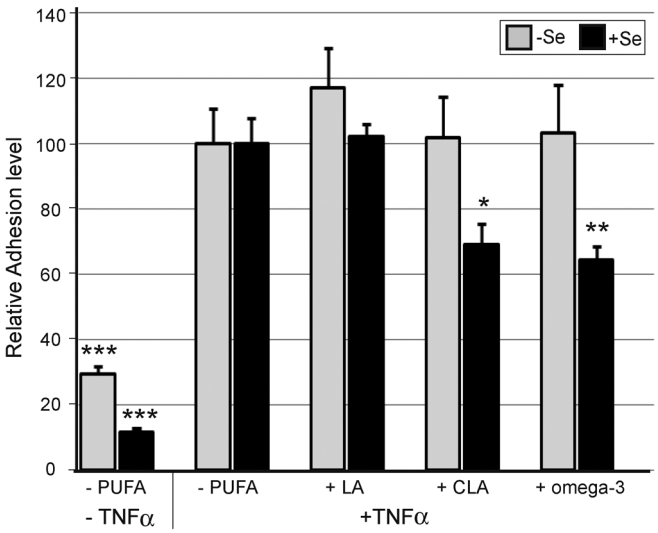

Fig. 3 Effect of Se on modulating adhesion of monocytes to ECs after PUFA treatment. HUVECs were grown for 4 days in the absence or presence of 40 nM sodium selenite (–Se or +Se) and then treated with either linoleic acid (**LA**), conjugated linoleic acid (**CLA**, *cis*-9, *trans*-11 isomer) or docosahexaenoic acid (**omega-3**) at 10 μM for 24 h. Cells were then either unchallenged (–TNFα) or treated with tumour necrosis factor-alpha (+TNFα) at 5 ng/ml for 6 h before the adhesion of U937 monocytes to the EC was assessed. Significant differences compared to the relevant untreated, challenged control (–PUFA, +TNFα) were determined by paired student's *t*-tests (*$p < 0.05$, **$p > 0.01$, ***$p < 0.001$).

required for the beneficial effects of PUFA in attenuating adhesion of monocytes to EC. Se status is known to affect the incorporation of PUFAs into tissues from animal studies [90,91] and, conversely, PUFAs themselves can modify selenoenzyme expression and activity [92,93]. These findings highlight the fact that other components of the diet interact with Se and that such interactions may also need consideration when assessing the effects of Se on vascular health and disease.

Selenium, lipid and lipoprotein metabolism

Another potential mechanism whereby Se may influence CVD risk is through the regulation of lipid and lipoprotein metabolism. Studies in animal models provide support for a clear connection between Se and lipoprotein metabolism. For instance, the apolipoprotein E receptor-2 mediates uptake of selenoprotein P in the testes and brain [94] whereas megalin, another apolipoprotein receptor, mediates uptake in the kidney [95]. Earlier studies have also shown that lipoprotein, in particular, LDL, also contains Se [96]. Furthermore, cholesterol and selenoprotein synthesis are connected through the mutual use of IPP which is required both for isoprenoid synthesis in the mevalonate pathway and for the synthesis of Sec-*t*RNA, for selenoprotein incorporation [97]. It is possible that when IPP is not utilized for selenoprotein synthesis one consequence is to make more IPP available for cholesterol synthesis. This would be consistent with the observations of elevated plasma cholesterol levels upon both Se deficiency [98] and deletion of the liver Sec-*t*RNA gene [99]. In the latter case, alterations in ApoE and cholesterol biosynthesis and metabolism genes were additional consequences, again emphasizing the link between selenoprotein and lipoprotein synthesis [99]. Further work, however, is needed to in order to determine the mechanism(s) that account for the apparent positive association of higher plasma Se levels with hyperlipidemia [41].

SUMMARY

In conclusion, evidence from human trials currently lacks support for a role of Se in preventing CVD. Indeed, Se intakes above the RDI may be associated with increased risk of hypercholesterolemia and diabetes, and therefore current approaches to increase Se intakes in these groups should be dissuaded. Additional, more extensive human studies investigating the effect of Se dosage, speciation, and initial Se status on CVD risk within different populations are needed in order to provide more definitive conclusions regarding this micronutrient and its effect on vascular health and disease risk.

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