Selenium supplementation does not improve vascular responsiveness in healthy North American men

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Hawkes WC, Laslett LJ. Selenium supplementation does not improve vascular responsiveness in healthy North American men. Am J Physiol Heart Circ Physiol 296: H256–H262, 2009. First published November 26, 2008; doi:10.1152/ajpheart.00935.2008.—Selenium is an essential trace nutrient required for the synthesis of selenoproteins such as glutathione peroxidase and thioredoxin reductase, the major forms of selenium in the endothelium that have important functions relevant to inflammation and cardiovascular disease. Selenium deficiency is associated with cardiomyopathy and sudden cardiac death in animals, and a low selenium status is associated with cardiovascular disease in humans. Endothelial dysfunction, measured as the impaired flow-mediated vasorelaxation of the brachial artery, is a reliable indicator of future cardiovascular disease risk in healthy individuals. To test whether selenium supplementation affects endothelial function, we conducted a randomized, placebo-controlled trial in healthy men who were administered 300 µg of selenium a day as high-selenium yeast for 48 wk. Brachial artery responsiveness to transient occlusion was assessed at baseline and after 24 and 48 wk of supplementation. The supplementation increased the selenium concentration by more than half in blood plasma and erythrocytes. However, there was no effect of selenium on arterial diameter or blood flow rate before or after transient occlusion or on the maximum dilated diameter after the administration of nitroglycerin. This study indicates that selenium supplementation is not likely to improve endothelial function or peripheral arterial responsiveness in healthy North American men receiving adequate selenium from their diets.

brachial artery; nutrition; endothelium

Selenium (Se) is an essential trace nutrient required in microgram amounts by humans and by all animals in which it has been tested (recommended dietary allowance = 55 µg/day) (42). Signs of Se deficiency include liver necrosis in rats, pancreatic atrophy in chickens, nutritional muscular dystrophy (“white muscle disease”) in sheep, and skeletal myopathy in patients on total parenteral nutrition without supplemental Se (15). Growing pigs fed rations deficient in Se and vitamin E develop a severe cardiomyopathy known as “mulberry heart disease” (60), and Se deficiency, along with infection by coxsackievirus B3, is a causative factor in the fatal human cardiomyopathy known as Keshan disease (13, 48).

The essential functions of Se in humans are mediated by a group of 25 selenoproteins that contain Se in the form of selenocysteine (Sec), the Se-containing homolog of cysteine. The known human selenoenzymes include glutathione peroxidase (GPX), iodothyronine deiodinase, thioredoxin reductase, and methionine sulfoxide reductase B. Sec is synthesized from serine-aminoacyl transfer RNA and incorporated at internal UGA codons. Recoding UGA from a stop codon to Sec requires several unique factors, including specific secondary structure in the mRNA, a unique tRNA, an RNA binding protein, and a specialized elongation factor (56). Sec is the only element specified in the genetic code (“TGA”), and Sec has become recognized as the 21st protein amino acid (16).

A link between Se intake and cardiovascular disease was first suggested by the negative correlation between regional cardiovascular disease mortality and the Se content of drinking water and crops in a cross-sectional study (53). Subsequent prospective human studies have reported that serum Se is inversely related to risk of progression of carotid artery atherosclerosis (49), ischemic heart disease (59), coronary artery disease (65), cardiovascular disease mortality (22), and hypertension (43). Endothelial dysfunction is an early event in the development of atherosclerosis, hypertension, coronary artery disease, and chronic heart failure.

The available human data support a causative role for oxidative damage in the development of endothelial dysfunction. Hydrogen peroxide and other reactive oxygen species are significant in endothelial dysfunction because of their ability to react with and eliminate nitric oxide (NO), the main small molecule mediator of endothelium-dependent vasodilation. Endothelial dysfunction of the coronary arteries is an independent predictor for the progression of atherosclerosis and subsequent cardiovascular events (51). Patients with impaired endothelium-dependent flow-mediated dilation (FMD) of the brachial artery or with a greater endothelial response to infused vitamin C are at significantly greater risk of subsequent cardiovascular events (35). Plasma lipid peroxides were higher in patients with ischemic heart disease or peripheral arterial disease (58), and double-strand breaks in lymphocyte DNA were significantly negatively correlated with brachial artery FMD in a mixed population of patients with coronary artery disease and matched controls (68).

A meta-analysis of 16 case-control studies found a relative risk for coronary heart disease of 0.43 (95% confidence interval: 0.29, 0.66) in subjects with the highest Se concentrations compared with the lowest but found a nonsignificant risk reduction of 0.89 (95% confidence interval: 0.68, 1.17) from Se supplementation in six randomized trials (25). However, the lack of significance in the meta-analysis of Se supplementation trials should be viewed with caution. First, the pooled relative risk was consistent with a protective effect of Se supplementa-
which baseline measurements were obtained and compliance was assessed. Noncompliant subjects were dismissed before randomization and are not reported further. Two subjects at a time were randomized to treatment from July 2000 to November 2002, with one subject from each pair randomly assigned to each treatment group by coin flip. Fifty-four men satisfactorily completed the run-in period and were randomized to receive placebo yeast tablets or high-Se yeast tablets for 48 wk. Neither the subjects nor the study staff was aware of subjects’ treatment assignments. Subjects took their first tablet the same day that all baseline measurements were completed. The subjects visited the Center every 6 wk during the 48-wk supplementation period. The visits were scheduled relative to each subject’s first day of supplementation. When a visit was missed, the next visit was scheduled based on the first day of supplementation to restore the original schedule. Unused tablets were counted at each visit and were collected at the end of the treatment period to measure compliance. Subjects consumed 93 ± 5.3% of the pills assigned. Forty-two subjects completed the 48-wk supplementation period.

Se supplements. Supplements were provided as high-Se Baker’s yeast (Saccharomyces cerevisiae, SelenoPrecise, 300 μg Se per tablet, 3.81 μmol Se, Pharma Nord, Denmark). Placebo tablets were compounded identically except using the same yeast grown without added Se (≤1.3 μg Se per tablet, ≤16.5 μmol Se). Placebo tablets contained 0.5 g of spray-dried yeast in an inert binder and were coated with titanium dioxide for an identical appearance, smell, and taste. Tablets were provided in 28-tablet bubble packs.

Dietary intake assessment. The intake of nutrients from food was estimated from 3-day diet records. Twice during the run-in period and then at 24 and 48 wk, the subjects kept a written record of all foods eaten for a 3-day period, always including at least one weekday (Monday–Friday) and at least one weekend day (Saturday and Sunday). Records were analyzed for nutrient contents with the Minnesota Nutrition Data System 5.0 (Nutrition Coordinating Center, Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN), using food composition data derived primarily from the United States Department of Agriculture (USDA) National Nutrient Database for Standard Reference (63) to calculate dietary intakes of Se and other nutrients.

Physical activity measurements. During the same 3-day periods that food records were kept, subjects wore a heart-rate monitor (Polar Vantage NV, Polar Electro, Port Washington, NY), except when asleep, and carried a handheld computer that automatically prompted them every 60 min to record all physical activities in 10-min increments (37), based on a simplified version of the Bouchard 3-day physical activity record (9). At the end of each 3-day monitoring period, the digital activity logs were reviewed for completeness and accuracy by a physiologist. The estimated energy expended in each activity was summed to obtain a daily value (2), and the three daily values were averaged to estimate the energy expended per day in voluntary activities at each point in the study.

Laboratory measurements. Blood samples were collected in the mornings, after an overnight fast, and serum was separated by centrifugation and refrigerated until analyzed at a reference laboratory (University of California at Davis School of Medicine Pathology Laboratory, Sacramento, CA). Aliquots of serum, plasma, and washed erythrocytes were stored at −70°C until analyzed. Se concentrations were measured by HPLC of the fluorescent derivative formed from a reaction with diaminomphthalene after digestion in a nitric-perchloric acid mixture (33). GPX activity was measured using the glutathione reductase-coupled assay (46) with 1.36 mM glutathione and 0.5 mM cumene hydroperoxide as substrates, and one unit of activity was defined as oxidation of 1 μmol of NADPH/min. Hemoglobin was determined spectrophotometrically with Drabkin’s reagent (21). Protein was measured by the Lowry method (40). Homocysteine was determined by competitive immunoassay on an Immulite analyzer (“LKHO16”, Diagnostics Products, Los Angeles, CA).

Flow-mediated arterial dilation. Brachial artery vasoreactivity was measured once during the run-in period and then again at 24 and 48
The study measured %FMD represented nitroglycerin were given and the measurements repeated. Percent calculations. After 5 min of recuperation, 0.4 mg of sublingual image depth of 4 cm. Images were recorded on videotape for off-line placed at a position 3–5 cm above the antecubital fossa and set at an radia the brachial artery starting at 1 min postdeflation. Brachial artery diameter was considered significant. When the Se main effect or the Se × time interaction was significant, the Student-Newman-Keuls multiple comparison test was used to identify significant differences between the groups at individual time points.

RESULTS

The baseline characteristics of the 42 subjects that completed the 48-wk intervention are shown in Table 1. Pulse, blood pressure, and serum metabolites were within normal ranges. None of the parameters in Table 1 was significantly different between groups, nor did any change during the study. Se status was increased significantly, as reflected in erythrocyte and plasma Se concentrations (Table 2). However, GPX enzyme activity was not changed in either blood compartment. Se concentration in plasma reached a plateau by 24 wk, when the first posttreatment FMD measurements were made. Because blood Se did not increase significantly after 24 wk, the posttreatment FMD measurements at 24 and 48 wk were averaged together into a single value for each subject for statistical testing.

FMD of the brachial artery in the study subjects averaged 5.7 ± 4.6% (range 0.7% to 15.7%) (Table 3), similar to values reported by others for healthy men (20, 45, 62). Nitroglycerin-induced vasodilation was also similar to previous reports (45, 62). FMD was not affected by Se supplementation, did not change in either group, and was not correlated with plasma Se. The only hemodynamic parameter that appeared to be affected by Se was the postocclusion peak velocity, which increased slightly in the high-Se group and tended toward statistical significance (Fig. 1, \( P = 0.066 \), Table 3). Subjects with smaller-diameter brachial arteries tended to have larger %FMD changes (Fig. 1, \( R = 0.334, P < 0.001 \)). Serum homocysteine was not changed by Se supplementation, and %FMD change was not significantly related to serum homocysteine or fasting serum triglycerides. %FMD was negatively correlated with alcohol intake (Fig. 2, \( R = 0.354, P = 0.020 \)) but was not significantly associated with the intake of Se or total fat, omega-3 fatty acids, cholesterol, arginine, folic acid, vitamin B12, vitamin A, vitamin C, vitamin D, vitamin E, iron, copper, zinc, or the soy isoflavones daidzein, glycitein, or genistein.

Table 1. Baseline characteristics of 42 subjects completing the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo Group</th>
<th>High-Se Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>31 ± 8.7</td>
<td>31 ± 9.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177 ± 7.6</td>
<td>180 ± 7.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.5 ± 12.4</td>
<td>76.9 ± 9.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6 ± 3.0</td>
<td>23.5 ± 2.2</td>
</tr>
<tr>
<td>Pulse, beats/min</td>
<td>65 ± 11</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120 ± 11</td>
<td>121 ± 11</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>70 ± 6.1</td>
<td>70 ± 9.2</td>
</tr>
<tr>
<td>Se intake, μg/day</td>
<td>138 ± 39</td>
<td>137 ± 42</td>
</tr>
<tr>
<td>Total energy intake, MJ/day</td>
<td>10.8 ± 2.0</td>
<td>11.3 ± 3.0</td>
</tr>
<tr>
<td>Polysaturated fat intake, g/day</td>
<td>15 ± 5.3</td>
<td>19 ± 9.6</td>
</tr>
<tr>
<td>Monounsaturated fat intake, g/day</td>
<td>29 ± 10</td>
<td>34 ± 14</td>
</tr>
<tr>
<td>Omega-3 fatty acid intake, g/day</td>
<td>1.56 ± 0.57</td>
<td>1.85 ± 0.96</td>
</tr>
<tr>
<td>Vitamin C intake, mg/day</td>
<td>245 ± 403</td>
<td>169 ± 121</td>
</tr>
<tr>
<td>Vitamin E intake (α-tocopherol equivalents), mg/day</td>
<td>43 ± 90</td>
<td>16 ± 6.7</td>
</tr>
<tr>
<td>Folic acid intake, μg/day</td>
<td>356 ± 292</td>
<td>358 ± 156</td>
</tr>
<tr>
<td>l-Arginine intake, g/day</td>
<td>5 ± 1.6</td>
<td>4.7 ± 1.4</td>
</tr>
<tr>
<td>Serum homocysteine, μmol/l</td>
<td>7.2 ± 2.2</td>
<td>7.1 ± 2.0</td>
</tr>
<tr>
<td>Serum glucose, mmol/l</td>
<td>4.83 ± 0.59</td>
<td>4.97 ± 0.54</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/l</td>
<td>4.60 ± 0.98</td>
<td>4.53 ± 0.91</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/l</td>
<td>1.24 ± 0.44</td>
<td>1.14 ± 0.23</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/l</td>
<td>2.85 ± 0.78</td>
<td>2.87 ± 0.75</td>
</tr>
<tr>
<td>Serum triacylglycerols, mmol/l</td>
<td>1.21 ± 0.56</td>
<td>1.12 ± 0.56</td>
</tr>
<tr>
<td>3,5-Tridithio2nitrobenzoic acid (μmol/l)</td>
<td>1.90 ± 0.38</td>
<td>1.17 ± 0.43</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, mU/l</td>
<td>2.3 ± 1.31</td>
<td>2.10 ± 0.85</td>
</tr>
</tbody>
</table>

Values are means ± SD. Se, selenium.
crease the risk of cardiovascular disease but that a supranutri-
Se and antioxidants can impair endothelial function and in-
status (25). These findings suggest that a suboptimal intake of
risk of cardiovascular disease associated with low Se status
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vascular disease is still uncertain after more than 20 years of
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pathophysiological mechanisms, some of which are influenced
by diet. Although reactive oxygen species and antioxidants
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plasma Se was positively correlated with the HDL cholesterol-
A study of hyperlipidemic Portuguese women reported that
between blood Se and blood lipids in free-living adults (17, 62).
Values are means ± SD; n, number of men. Baseline, values at the end of the baseline period before starting supplementation. *t-test of within-subject changes (average of 24- and 48-wk values minus baseline).

There were no changes in the 24-h heart rate or voluntary
physical activity within or between groups (32).

DISCUSSION

Human vascular function is regulated by a plethora of
pathophysiological mechanisms, some of which are influenced
by diet. Although reactive oxygen species and antioxidants
clearly have roles in endothelial NO metabolism, the potential
health benefits of antioxidant supplementation are far from
clear. The significance of dietary Se in the etiology of cardio-
vascular disease is still uncertain after more than 20 years of
research. Recent meta-analyses of randomized supplementation
trials failed to find a significant protective effect of antioxid-
ants against the progression of atherosclerosis (8) or of
low-dose Se against coronary heart disease (25). On the other
hand, observational studies have consistently found an elevated
risk of cardiovascular disease associated with low Se status
(22, 43, 49, 59, 65), and a meta-analysis found a significantly
higher risk of coronary heart disease associated with low Se
status (25). These findings suggest that a suboptimal intake of
Se and antioxidants can impair endothelial function and in-
crease the risk of cardiovascular disease but that a supranutri-
tional intake confers no additional benefit. This is consistent
with the essential function of Se in oxidation-reduction en-
zymes, the requirements of which for Se appear to be fully
satisfied at low nutritional doses. Additional Se intake beyond
the nutritional requirement may not increase the activities of
these selenoenzymes and thus may confer no additional bene-
fit. The epidemiological evidence is consistent with a satura-
tion effect of Se on cardiovascular health (19), in which Se
status predicts cardiovascular disease risk in populations with
lower Se status but is not associated with risk in populations
with higher Se status (3).

Previous studies have observed significant associations be-
between blood Se and blood lipids in free-living adults (17, 62).
A study of hyperlipidemic Portuguese women reported that
plasma Se was positively correlated with the HDL choles-
toto-total cholesterol ratio (64). Serum Se was positively corre-
lated with serum total cholesterol in a study of healthy men and
women in the United Kingdom (29) and in Korean women
under the age of 40 yr (38). Two studies in Europe reported
significant positive associations of serum Se with serum poly-
unsaturated fat (10, 44). However, we observed no effect of Se

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Fig. 1. Relationship between flow-mediated dilation (FMD) and resting di-
diameter of the brachial artery. Percent change in diameter is plotted against
pretreatment diameter. All measurements are shown. Dashed line shows result
of linear regression: n = 117 measurements, R = 0.334, P = 0.0002.

Fig. 2. Relationship between FMD of the brachial artery and alcohol intake. Percent change in diameter is plotted against the logarithm of alcohol intake [in 
g/day (g/d)] estimated from self-reported food records. Estimates of “zero”
 alcohol intake are not shown. Dashed line shows result of linear regression:
n = 85 measurements, R = 0.201, P = 0.022.

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Table 3. Brachial artery ultrasound measurements before and after occlusion and nitroglycerin treatment in healthy men consuming Se supplements or placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo Yeast</th>
<th></th>
<th>High-Se Yeast</th>
<th></th>
<th>Se Effect (P)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n)</td>
<td>24 wk (n)</td>
<td>48 wk (n)</td>
<td>Baseline (n)</td>
<td>24 wk (n)</td>
</tr>
<tr>
<td>Preocclusion diameter, mm</td>
<td>4.14±0.47</td>
<td>4.18±0.49</td>
<td>4.21±0.42</td>
<td>4.19±0.48</td>
<td>4.22±0.50</td>
</tr>
<tr>
<td>Postocclusion diameter, mm</td>
<td>4.34±0.44</td>
<td>4.41±0.47</td>
<td>4.45±0.41</td>
<td>4.44±0.49</td>
<td>4.41±0.49</td>
</tr>
<tr>
<td>Occlusion diameter change, mm</td>
<td>0.21±0.24</td>
<td>0.24±0.22</td>
<td>0.24±0.17</td>
<td>0.25±0.14</td>
<td>0.19±0.19</td>
</tr>
<tr>
<td>Occlusion diameter change, %</td>
<td>5.2±5.8</td>
<td>5.8±5.4</td>
<td>5.8±4.3</td>
<td>6.1±3.3</td>
<td>4.8±4.8</td>
</tr>
<tr>
<td>Nitroglycerin diameter change, mm</td>
<td>0.63±0.20</td>
<td>0.60±0.28</td>
<td>0.60±0.24</td>
<td>0.65±0.18</td>
<td>0.58±0.17</td>
</tr>
<tr>
<td>Nitroglycerin diameter change, %</td>
<td>15.5±5.5</td>
<td>14.9±7.8</td>
<td>14.5±6.0</td>
<td>15.6±4.3</td>
<td>14.2±5.2</td>
</tr>
<tr>
<td>Preocclusion velocity, cm/s</td>
<td>108±30</td>
<td>104±27</td>
<td>104±21</td>
<td>105±24</td>
<td>107±26</td>
</tr>
<tr>
<td>Postocclusion velocity, cm/s</td>
<td>174±38</td>
<td>165±43</td>
<td>174±30</td>
<td>165±38</td>
<td>181±41</td>
</tr>
<tr>
<td>Occlusion velocity change, cm/s</td>
<td>66±22</td>
<td>61±24</td>
<td>71±23</td>
<td>60±28</td>
<td>74±24</td>
</tr>
<tr>
<td>Nitroglycerin velocity change, cm/s</td>
<td>-11±11</td>
<td>-7.0±14</td>
<td>-9.4±11</td>
<td>-9.6±13</td>
<td>-10±8.8</td>
</tr>
</tbody>
</table>
supplementation on serum lipids, nor any significant correlation of plasma Se with serum lipids in the present study.

In vitro studies have shown that Se supplementation protects human endothelial cells from oxidized LDL, due to an increased expression of GPX1 and thioredoxin reductase (TR) (39). TR, which regenerates active thioredoxin at the expense of NADPH and is the most abundant selenoprotein in human endothelial cells (5), may be even more important than GPX1 for protecting human endothelial cells from oxidative damage (11). NO exposure decreases thioredoxin and TR expression, and an overexpression of thioredoxin prevents NO-induced decreases in NO synthase in cultured porcine pulmonary endothelial cells, providing a mechanism for the Se regulation of endothelial NO metabolism (70). TR is upregulated in human atherosclerotic plaques (28), and an endothelial cell-specific overexpression of thioredoxin improves vasodilation and decreases atherosclerotic lesions in transgenic mice (69). The enhanced relaxation of aortic rings in Se-supplemented rabbits (41) might therefore be due to an increased expression of TR, which responds to supranutritional Se (6).

GPX1 is ubiquitously expressed in the cytosol of all human tissues and is the main catalyst for the removal of physiological levels of hydrogen peroxide. GPX1 has consistently been associated with a lower risk of cardiovascular disease. The relative risk of cardiac complications was 0.29 in patients with the highest quintile of blood GPX1 activity compared with the lowest quintile (7), and blood GPX activity was the strongest univariate predictor of subsequent cardiovascular events during 7.1 years of follow-up (52). The importance of GPX1 in maintaining endothelial function has been clarified in studies with transgenic mice deficient in or overexpressing GPX1. Mesenteric arterioles from mice heterozygous (26) or homozygous (27) for deletion of the GPX1 gene exhibited paradoxical vasoconstriction in response to acetylcholine or β-methacholine, respectively, instead of the normal vasodilation observed in wild-type mice. Relaxation to acetylcholine was markedly impaired in angiotensin II-treated carotid arteries from GPX1−/− transgenic mice (14) and in untreated carotid arteries from homocysteine-treated GPX1−/− transgenic mice (18). Moreover, the overexpression of GPX1 restored the normal endothelium-dependent vasodilator response in hyperhomocysteinemic mice (66). Significantly, the beneficial effect of physical training on vascular endothelial function in patients with chronic heart failure is associated with an increased expression of GPX1 (23). Endothelium-dependent vasorelaxation in high-fat-fed rats is protected by a mixture of dietary antioxidants (50). GPX1 activity in aortic arterial walls was increased by a Se supplementation of rats (67), suggesting that supplemental Se above the dietary requirement may be able to improve endothelial function.

To our knowledge, the present study is the first test of Se supplementation on vasoreactivity in humans. There was no evidence of altered endothelial function in the Se-supplemented subjects. Our failure to detect an effect of Se in the present study is unlikely to be due to our methodology because we were able to detect previously reported associations between FMD and arterial diameter and alcohol intake. It is generally considered that FMD of the brachial artery induced by nitroglycerin, an index of endothelium-independent vascular responsiveness (4). Thus we conclude that Se supplementation did not improve endothelium-dependent or -independent vasoreactivity. The prestudy Se intakes of our subjects was well above the recommended daily allowance, and their average plasma Se was greater than the mean value for men in the Third National Health and Nutrition Examination Survey (24, 36), indicating that our subjects were already receiving adequate amounts of Se from their diets. Our results indicate that Se supplementation does not affect endothelium-dependent vasoreactivity in healthy, well-nourished men. The 60% increase we observed in plasma Se corresponds to an approximate doubling of whole body Se stores (31). The combined Se intake of our Se-supplemented subjects (ca. 437 μg/day) exceeded the “tolerable upper intake level” of 400 μg/day defined by the National Academy of Sciences (47), suggesting that Se intakes within the current recommended range do not impair vasoreactivity.

Overall, the experimental manipulation of Se and antioxidant status in animals have shown significant effects on endothelial function and/or cardiovascular health, whereas the experimental variation of Se and antioxidant intake in humans have not. These disparate trends may be reconciled by the following considerations. First, animal experiments typically compare low or deficient intakes of Se and antioxidant nutrients to superadequate intakes, whereas human experiments are constrained logistically and ethically to compare existing (usually adequate) intakes to those same intakes plus supplements. Thus animal experiments frequently examine the effects of nutrient deficiency and human studies (at least those in developed countries where cardiovascular diseases are of greatest concern) usually examine effects of additional nutrient intake in excess of dietary requirements. Second, experiments in mice, rats, and rabbits typically use young animals whose nutritional status is varied over a considerable portion of their life span, thus including the potential effects of nutrition at every stage of the disease process, whereas human experiments usually involve relatively short-term studies of high-risk individuals with late-stage or occult disease. Since much of an individual’s lifetime risk for cardiovascular disease may be accrued decades before biomarkers or clinical signs of disease are detectable, the opportunity for dietary intervention in most human studies may be long since past. The present study was designed to address some of these issues by studying young men free of any signs of disease and increasing Se intake as much as allowable and long enough to ensure significantly increased tissue Se levels. Our failure to observe any effects on endothelial function in the present study suggests that the role of Se in human endothelial function is either critical only in younger subjects, is expressed only when intake is deficient, or is significant only in individuals with preexisting disease.

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expressed herein represent those of the authors and do not necessarily represent those of the USDA or the University of California.

GRANTS

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