Serum Selenium Concentrations and Hypertension in the US Population

Martin Laclaustra, MD, PhD; Ana Navas-Acien, MD, PhD; Saverio Stranges, MD, PhD; Jose M. Ordovas, PhD; Eliseo Guallar, MD, DrPH

Background—Selenium is an antioxidant micronutrient with potential interest for cardiovascular disease prevention. Few studies have evaluated the association between selenium and hypertension, with inconsistent findings. We explored the relationship of serum selenium concentrations with blood pressure and hypertension in a representative sample of the US population.

Methods and Results—We undertook a cross-sectional analysis of 2638 adults ≥40 years old who participated in the 2003 to 2004 National Health and Nutrition Examination Survey. Serum selenium was measured by inductively coupled plasma-dynamic reaction cell-mass spectrometry. Hypertension was defined as blood pressure ≥140/90 mm Hg or current use of antihypertensive medication. Mean serum selenium was 137.1 μg/L. The multivariable adjusted differences (95% CIs) in blood pressure levels comparing the highest (≥150 μg/L) to the lowest (<122 μg/L) quintile of serum selenium were 4.3 (1.3 to 7.4), 1.6 (−0.5 to 3.7), and 2.8 (0.8 to 4.7) mm Hg for systolic, diastolic, and pulse pressure, respectively. The corresponding odds ratio for hypertension was 1.73 (1.18 to 2.53). In spline regression models, blood pressure levels and the prevalence of hypertension increased with increasing selenium concentrations up to 160 μg/L.

Conclusions—High serum selenium concentrations were associated with higher prevalence of hypertension. These findings call for a thorough evaluation of the risks and benefits associated with high selenium status in the United States. (Circ Cardiovasc Qual Outcomes. 2009;2:369-376.)

Key Words: selenium ■ blood pressure ■ hypertension ■ nutrition surveys

Selenium is an essential element with antioxidant properties mediated through glutathione peroxidases and other selenoenzymes. Because oxidative stress is involved in hypertension development,1 it has been suggested that selenium may be involved in blood pressure control and hypertension prevention.2–4 The few studies that have evaluated the association between selenium and blood pressure have been inconsistent, reporting inverse,3,5 null,6,7 or positive8 associations. These studies were relatively small and were conducted in European countries with moderately low selenium intake. As a consequence, the association of selenium with blood pressure levels is still uncertain, particularly in selenium replete populations such as the United States.

In the United States, selenium intake ranges from 60 to 220 μg/d,4,9,10 well above the recommended dietary allowance of 55 μg/d.11,12 High selenium intake in the United States is a consequence of the high selenium content of US soil, particularly in the Northern Plains. Organ meats, seafoods, muscle meats, and cereals and grains are the main sources of selenium in the diet, although the widespread use of vitamin/mineral supplements also contributes to US selenium intake.13 At these intake levels, additional selenium intake does not increase glutathione peroxidase synthesis or activity, but rather increases plasma selenium concentration by nonspecific incorporation of selenomethionine into plasma proteins.9 Furthermore, selenium has a narrow safety range,14 and high selenium concentrations in US studies have been associated with increased lipid levels14 and diabetes.15,17 The objective of this study was thus to assess the association of serum selenium concentrations with blood pressure levels and with the prevalence of hypertension in the 2003 to 2004 US National Health and Nutrition Examination Survey (NHANES).

Methods

NHANES is conducted by the National Center for Health Statistics using a complex multistage sampling design to obtain a probability sample of the civilian noninstitutionalized US population. We used data from NHANES 2003 to 2004,18 as this was the most recent...
release with selenium data available in adults. Serum selenium measurements were restricted to participants aged ≥40 years (n = 3,299). Among these, 2,903 participants had serum selenium measurements, and 2,699 participants had also blood pressure measurements available. We excluded 2 pregnant women and 59 participants with missing data on relevant covariates (ie, body mass index, education, cotinine concentration, and tobacco consumption). The final sample size was 2,638.

**Serum Selenium**

Collection materials were screened for potential selenium contamination. After blood collection, serum aliquots were frozen at −20°C and shipped to the laboratory. Serum selenium was measured at the Trace Elements Laboratory at the Wadsworth Center of the New York State Department of Health using inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS). The laboratory procedures and quality control methods for serum selenium measurement have been described in detail elsewhere. The between-assay coefficients of variation for quality control pooled samples analyzed throughout the duration of the survey ranged from 2.5% to 2.9%.

**Hypertension**

Blood pressure readings were obtained by trained and certified physicians following procedures developed by the American Heart Association. Study participants rested sitting quietly for 5 minutes before 3 consecutive blood pressure readings were obtained using a mercury sphygmomanometer with an appropriate size cuff (5 sizes available) placed on the bare right arm. If one reading failed, a fourth attempt could be made. Systolic and diastolic blood pressure were registered at the appearance (phase I) and disappearance (phase V) of Korotkoff sounds, respectively. Repeated measurements of systolic

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Population by Hypertension Status</th>
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<tbody>
<tr>
<td><strong>Overall</strong></td>
</tr>
<tr>
<td>n (%)</td>
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<td>Age, y</td>
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**Table 2. Characteristics of the Study Population by Serum Selenium Quintile**

<table>
<thead>
<tr>
<th>Quintile of Serum Selenium, µg/L</th>
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<tr>
<td>n</td>
<td>504</td>
<td>570</td>
<td>524</td>
<td>481</td>
<td>559</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.6</td>
<td>56.3</td>
<td>57.2</td>
<td>55.4</td>
<td>57.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>64.3</td>
<td>57.9</td>
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respectively. We used 3 models with progressive degrees of adjustment. We were calculated using multivariable linear and logistic regression, for blood pressure differences and odds ratios for hypertension status. Participants were divided in quintiles of serum selenium concentration.

### Statistical Methods

Statistical analyses were performed using the survey package in R to account for the complex survey design and weights in NHANES 2003 to 2004. Censored regression models were estimated using the creg command in Stata (version 9.2) weighted for NHANES survey weights.

### Other Variables

Information on sex, age, race/ethnicity, education, menopausal status, smoking, and use of vitamin/mineral supplements was based on self-report. Body mass index was calculated by dividing measured weight in kilograms by measured height in meters squared. Nutrient intake data were obtained from 24-hour dietary recall interviews, the first conducted in-person and a second phone follow-up interview 3 to 10 days later. Average intakes were used when information was available from both interviews. Serum cotinine was measured by isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry.

### Table 3. Adjusted Differences (95% CIs) in Blood Pressure Levels Comparing the 4 Highest Quintiles to the First Quintile of Serum Selenium

<table>
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<tr>
<th>Quintile of Serum Selenium, μg/L</th>
<th>1st (122)</th>
<th>2nd (122 to 131)</th>
<th>3rd (132 to 139)</th>
<th>4th (140 to 149)</th>
<th>5th (150)</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>125.4</td>
<td>127.4</td>
<td>127.5</td>
<td>129.4</td>
<td>129.7</td>
<td></td>
</tr>
<tr>
<td>Model 1*</td>
<td>0.0 (reference)</td>
<td>2.3 (0.6, 5.2)</td>
<td>2.0 (0.0, 4.1)</td>
<td>5.4 (3.0, 7.8)</td>
<td>4.4 (1.5, 7.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Model 2†</td>
<td>0.0 (reference)</td>
<td>2.4 (0.5, 5.4)</td>
<td>2.1 (0.1, 4.2)</td>
<td>5.3 (2.7, 7.9)</td>
<td>4.6 (1.5, 7.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>0.0 (reference)</td>
<td>2.4 (0.7, 5.5)</td>
<td>2.2 (0.1, 4.4)</td>
<td>5.1 (2.3, 7.8)</td>
<td>4.3 (1.3, 7.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Model 4§</td>
<td>0.0 (reference)</td>
<td>3.3 (0.5, 6.1)</td>
<td>2.3 (0.6, 5.2)</td>
<td>6.9 (4.0, 9.8)</td>
<td>6.3 (3.4, 9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70.7</td>
<td>72.9</td>
<td>71.6</td>
<td>74.0</td>
<td>72.4</td>
<td></td>
</tr>
<tr>
<td>Model 1*</td>
<td>0.0 (reference)</td>
<td>2.0 (0.2, 3.8)</td>
<td>0.8 (0.9, 2.6)</td>
<td>2.5 (0.8, 4.2)</td>
<td>1.8 (0.3, 3.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Model 2†</td>
<td>0.0 (reference)</td>
<td>1.9 (0.0, 3.7)</td>
<td>0.6 (1.1, 2.4)</td>
<td>2.2 (0.5, 4.0)</td>
<td>1.5 (0.6, 3.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>0.0 (reference)</td>
<td>1.9 (0.0, 3.7)</td>
<td>0.6 (1.1, 2.4)</td>
<td>2.3 (0.5, 4.0)</td>
<td>1.6 (0.5, 3.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Model 4§</td>
<td>0.0 (reference)</td>
<td>2.1 (0.4, 3.8)</td>
<td>0.5 (1.2, 2.3)</td>
<td>3.2 (1.4, 5.0)</td>
<td>2.8 (1.1, 4.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>54.7</td>
<td>54.4</td>
<td>55.9</td>
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<td>57.3</td>
<td></td>
</tr>
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<td>2.8 (1.1, 4.5)</td>
<td>2.6 (0.7, 4.6)</td>
<td>0.03</td>
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<td>0.0 (reference)</td>
<td>0.6 (1.1, 2.3)</td>
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<td>0.0 (reference)</td>
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<td>1.5 (0.9, 3.9)</td>
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Unadjusted (survey-weighted) averages are shown above the model-specific values. Models 1 to 3 used multiple linear regression models with survey weights, strata, and clusters to account for complex survey design. Model 4 used censored regression with survey weights only. Continuous covariables were included as linear terms in the models. BP indicates blood pressure.

*Model 1 was adjusted for sex, age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), and education (high school or higher vs less than high school).
†Model 2 was further adjusted for body mass index (continuous), smoking (never, former, current), cotinine (continuous), and menopausal status (yes, no).
‡Model 3 was further adjusted for use of vitamin/mineral supplements (yes, no) and use of antihypertensive medications (yes, no).
§Model 4 used censored linear regression to correct for the effect of medication for hypertension, adjusted for the same variables as model 3.

and diastolic blood pressure were averaged discarding the first one. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Quality control and assurance procedures included extensive initial training, quarterly recertification, procedural checklists, and continuous review of data for systematic errors. Hypertension was defined as having an average systolic blood pressure >140 mm Hg, an average diastolic blood pressure >90 mm Hg, or current use of antihypertensive medications.

Participants were divided in quintiles of serum selenium concentration based on the weighted population distribution. Adjusted means for blood pressure differences and odds ratios for hypertension status comparing each quintile of serum selenium to the lowest quintile were calculated using multivariable linear and logistic regression, respectively. We used 3 models with progressive degrees of adjustment. Model 1 was adjusted for sex, age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), and education (high school or higher vs less than high school). Model 2 was further adjusted for body mass index (continuous), smoking (never, former, current), cotinine (continuous), and menopausal status (yes, no). Model 3 was further adjusted for use of vitamin/mineral supplements (yes, no) and, in linear regression models, for use of antihypertensive medications (yes, no). Continuous covariables were included as linear terms in the models. Because adjusting for hypertension treatment may result in biased estimates of the association between selenium and continuous blood pressure outcomes, we conducted an additional analysis using censored linear regression (Model 4) to correct for antihypertensive treatment using NHANES survey weights. Tests for linear trend were calculated by including serum selenium as a continuous variable in the models. To further explore the shape of the relationship between serum selenium and blood pressure measurements and hypertension, we used restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the serum selenium distribution in models adjusted as previously described for Model 3. We also evaluated the interactions between selenium (modeled as quadratic restricted splines) and sex, age, race/ethnicity, education, body mass index, smoking status, or use of vitamin/mineral supplements by fitting separate models for every interaction, including all the adjustment variables described for Model 3 but each with interaction terms for the selenium splines and the variable of interest.
Results

The mean (SD) serum selenium concentration in the study population was 137.1 (19.3) μg/L. The overall prevalence of hypertension was 45.2%. Participants with hypertension were more likely to be older, non-Hispanic black, and have a higher body mass index, and less likely to have a high school education and to be current smokers compared to participants without hypertension (Table 1). Serum selenium concentrations were positively associated with age and with the use of vitamin/mineral supplements and inversely associated with current smoking (Table 2). Men had higher mean serum selenium than women (139.7 versus 134.7 μg/L). Non-Hispanic blacks had lower mean serum selenium compared to non-Hispanic whites and to Mexican-Americans (130.7, 137.7, and 140.4 μg/L, respectively).

Figure 1. Adjusted differences (95% CIs) for blood pressure levels by serum selenium concentrations. Serum selenium was modeled as restricted quadratic splines with nodes at the 5th, 50th, and 95th percentiles. Multivariable linear regression models were adjusted for sex, age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other), education (high school or higher versus less than high school), body mass index (continuous), smoking (never, former, current), cotinine (continuous), menopausal status (yes, no), use of vitamin/mineral supplements (yes, no), and use of antihypertensive medications (yes, no). Blood pressure levels at the 10th percentile (115 μg/L) of the serum selenium distribution were used as reference. The histogram shows the distribution of selenium concentrations in the study population.

Mean serum selenium concentrations were higher in participants with hypertension compared to those without it (138.3 versus 136.1 μg/L, P=0.02). In multivariable adjusted models (Table 3), the average differences (95% CIs) comparing the highest (≥150 μg/L) to the lowest (<122 μg/L) selenium quintiles were 4.3 (1.3 to 7.4), 1.6 (−0.5 to 3.7), and 2.8 (0.8 to 4.7) mm Hg for systolic, diastolic, and pulse pressure, respectively. After correcting for use of medication for hypertension in censored regression models, these differences were 6.3 (3.4 to 9.2), 2.8 (1.1 to 4.6), and 4.6 (1.8 to 7.4) mm Hg for systolic, diastolic, and pulse pressure, respectively. In spline regression models, blood pressure levels increased with increasing selenium concentrations up to 160 μg/L (Figure 1).
The multivariable adjusted odds ratio (95% CI) for hypertension comparing the highest to the lowest selenium quintiles was 1.73 (1.18 to 2.53; Table 4). In spline regression models, the prevalence of hypertension increased with increasing selenium concentrations up to 160 μg/L (Figure 2). The adjusted odds ratio for hypertension comparing the 90th (160 μg/L) to the 10th (115 μg/L) percentiles of the selenium distribution was 1.77 (1.27 to 2.47), with consistent findings across clinically relevant subgroups (Figure 3).

Sensitivity analyses showed similar results after excluding participants with self-reported cancer or cardiovascular disease, and after excluding participants taking any antihypertensive medications. Similarly, results from Model 3 did not substantially change after additional adjustment for dietary variables from the 24-hour dietary recalls (total caloric intake, polyunsaturated to saturated fat intake ratio, sodium, calcium, magnesium, fiber, β-carotene, vitamin E, vitamin C, and alcohol intake), after separate additional adjustment for serum levels of β-carotene, vitamin E, and vitamin C, or after separate additional adjustment for the presence of diabetes and the presence of hypercholesterolemia. Adjustment for the NHANES pseudoprimary sampling units had negligible effects on the results (not shown).

Discussion

In this representative cross-sectional study of the US population, high serum selenium concentrations were associated with higher blood pressure levels and with higher prevalence of hypertension. Compared to the lowest quintile, participants in the highest selenium quintile had increased systolic, diastolic, and pulse pressure by 4.3, 1.6, and 2.8 mm Hg, respectively (6.3, 2.8, and 4.6 mm Hg after correcting for use of medication for hypertension in censored regression models, respectively). These differences are epidemiologically and clinically important, and they add to the concerns raised by the observation of elevated lipid levels and increased risk of diabetes with high selenium concentrations in studies conducted in the United States, a country with high selenium intake.

Few observational studies have evaluated the association of selenium with blood pressure levels. A study in elderly Finnish men from areas with very low mean serum selenium found no relationship between selenium and blood pressure. Conversely, the Kuopio Ischemic Heart Disease Risk Factor Study, a Finnish cohort of middle-aged men, found an inverse association between serum selenium and systolic blood pressure. The Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO) also found an inverse cross-sectional association between blood selenium concentrations and systolic and diastolic blood pressure in men, but this association was largely attributable to markedly higher blood pressure levels in the lowest selenium quintile (<78 μg/L) with little variation across the remaining quintiles. Baseline blood selenium concentrations were also inversely associated with the risk of hypertension after 5.2 years of follow-up in men. No association was observed.
among women, either cross-sectionally or prospectively. A cross-sectional analysis of the French Etude du Viellissement Arteriel (EVA), reported that hypertensive men, but not women, had higher selenium concentrations compared to those without major chronic diseases or risk factors. Plasma selenium concentrations were not correlated with systolic blood pressure in either men or women. Finally, serum selenium concentrations were not associated with blood pressure levels in the Olivetti Heart Study. All these studies were conducted in European countries and had mean selenium concentrations below 100 μg/L.

Compared with previous observational studies, our study was conducted in the United States, a country with high mean serum selenium concentrations (137 μg/L). The increased blood pressure levels and prevalence of hypertension at high selenium levels in NHANES 2003 to 2004 is consistent with previous studies reporting a positive association of selenium concentration with adverse lipid profile and diabetes risk. Indeed, it is possible that high risk factor levels at high selenium concentrations may explain the U-shaped relation-ship between selenium concentration and cardiovascular end points observed in several US studies. Given the high selenium intake in the US population and the popularity of selenium supplements, it is important to elucidate the mechanisms underlying the association of high selenium exposure and cardiovascular risk factors in selenium-replete populations.

Unfortunately, no data are available on the effect of selenium supplementation on blood pressure end points in randomized controlled trials using single selenium supplements. In the HDL-Atherosclerosis Treatment Study (HATS) trial, selenium (100 μg/d) was administered along with vitamin E (800 IU/d), vitamin C (1000 mg/d), and β-carotene (25 mg/d), with no effect on blood pressure levels. In China (Linxian), antioxidant supplementation (selenium 50 μg/d, β-carotene 15 mg/d, and vitamin E 60 mg/d) in a nutritionally deficient population was linked only to increased isolated diastolic hypertension, but other blood pressure end points were not significantly different. The concerns with potential metabolic side effects of elevated selenium levels add to the lack of efficacy of
selenium supplements recently shown in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a mega-trial aimed to evaluate the efficacy of selenium in preventing prostate cancer. SELECT was prematurely stopped by the Data and Safety Monitoring Committee for lack of benefit on the prostate cancer prevention and for safety concerns.35

The strengths of our study come from the rigorous sampling design, the strict adherence to study protocols in measurements and laboratory assays, and the representativeness of the NHANES sample. Several limitations, however, need to be considered in the interpretation of these findings. The cross-sectional design limits our ability to determine the direction and the causality of the observed association. It is possible that pathophysiological changes of hypertension modify serum selenium concentration or that participants with hypertension change their health behaviors, including selenium intake through diet and dietary supplements. Although the observed association persisted among participants who did not use multivitamin/mineral supplements and after adjusting for several intake variables, our findings must be confirmed in prospective studies with incident cases of hypertension. Also, dietary information in NHANES was based on 24-hour recalls, which may not be sufficiently reliable to estimate the nutrient intakes of individuals resulting in potential residual confounding. Another limitation is the use of a single measurement of serum selenium, which may be subject to relatively high within person variability and may bias our findings toward the null.36

In addition, because only total serum Se was measured in NHANES, we do not have information of selenoprotein levels or activity or about nonspecific incorporation of selenium as selenomethionine in other plasma proteins. More detailed analysis of different selenoproteins and related activities will be needed to better understand the association of selenium with hypertension.

Our findings apply to high-selenium intake countries such as the United States, and may not be generalized to other populations with marginal selenium intake. Furthermore, there is not yet a clear mechanism that could explain the effects of high selenium concentrations on cardiovascular risk factors. Although substantial attention has been paid to explain the mechanisms for a potential benefit of increasing serum selenium in low-selenium intake populations, the mechanistic explanation for the effects of selenium above the levels required to maximize glutathione peroxidase activity are unknown.

In summary, high serum selenium concentrations were associated with higher prevalence of hypertension in a representative sample of US adults. The differences between the extreme quintiles, more than 4 mm Hg for systolic blood pressure, may be associated with a substantial number of cardiovascular events and with complications in blood pressure control. Recently, high selenium concentrations have been linked to increased prevalence of hyperlipidemia and diabetes14 and to a U-shaped relationship with cardiovascular events.31 From a clinical perspective, selenium supplements cannot currently be recommended for cardiovascular protection. Furthermore, for individuals living in regions with high selenium intake, selenium supplementation could potentially increase risk of hypertension, diabetes, or hypercholesterolemia. Our findings call for a thorough evaluation of the risks and benefits associated high selenium status in the United States.

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Disclosures

None.

References


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