Dietary selenium intake is negatively associated with serum sialic acid and metabolic syndrome features in healthy young adults

M. Ángeles Zulet, Blanca Puchau, Helen Hermana M. Hermsdorff, Cristina Navarro, J. Alfredo Martínez *

Department of Nutrition and Food Sciences, Physiology and Toxicology, University of Navarra, 31008 Pamplona, Spain

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Abstract

Low-grade and chronic inflammation related to excessive body weight can increase the risk for type 2 diabetes and cardiovascular disease, whereas the intake of antioxidant nutrients appears to produce anti-inflammatory effects. The purpose of this observational study was to assess the potential relationships between serum SA levels, metabolic syndrome features, and dietary selenium intake to test the hypothesis that this antioxidant micronutrient may also have anti-inflammatory properties in healthy young adults. Forty-three healthy participants with a mean age of 18.0 ± 0.93 years and a mean body mass index of 22.2 ± 2.7 kg/m² were enrolled. Anthropometric, body composition, and blood pressure determinations were measured as well as serum lipid profile, glucose, insulin, and SA concentrations. Nutritional intake was estimated by a computerized, validated semiquantitative food frequency questionnaire. The findings included a positive correlation between SA and triacylglycerol levels (\( r = 0.317, P = .038 \)) and a trend to significance with the homeostatic model assessment of insulin resistance index (\( r = 0.297, P = .053 \)). Moreover, subjects with higher dietary selenium intake showed statistically lower SA levels compared with subjects with lower dietary selenium intake (1.8 ± 0.4 vs 2.1 ± 0.4 mmol/L, \( P = .037 \)), while dietary selenium negatively correlated with SA (\( r = -0.331, P = .030 \)) and triacylglycerol levels (\( r = -0.312, P = .041 \)). It can be concluded that a relationship of SA, an inflammatory marker, with metabolic syndrome features such as lipid profile impairment and insulin resistance has been envisaged. In addition, we report (apparently for the first time) a negative association between SA and selenium intake, a recognized antioxidant trace element, in healthy young subjects, reinforcing the view of selenium as a potential anti-inflammatory nutrient.

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Abbreviations: BP, blood pressure; CVD, cardiovascular disease; HOMA-IR, homeostatic model assessment of insulin resistance; SA, sialic acid.

1. Introduction

Inflammation and oxidative stress impairments are contributing factors in the pathogenesis of major public health problems, including type 2 diabetes, dyslipidemias, hypertension, and CVDs, which are related to those who are overweight and obese [1-4]. Furthermore, recent findings indicate that elevated levels of adipokines and acute-phase inflammatory markers are associated with some manifestations accompanying metabolic syndrome features (adiposity, insulin resistance, dyslipidemia, etc) and an increased risk for CVDs [5-8].
Among the acute-phase markers, the SA, belonging to a family of 43 naturally occurring derivatives of the 9-carbon sugar neuraminic acid [9], has been suggested as an inflammatory marker in obesity-related diseases [10]. Sialic acid levels have appeared as a strong predictor of cardiovascular events [11-13]. Furthermore, this molecule seems to be associated with features of metabolic syndrome and type 2 diabetes because increased concentrations were found in individuals with both disorders when compared with control subjects [14-17].

Selenium is an essential trace element that could play an important role in cell defense against oxidative stress by the action of antioxidant selenium-dependent enzymes such as cytolysis and extracellular glutathione peroxidase [18]. Thus, dietary selenium intake or supplementation has been related to higher antioxidant enzymatic activity and lower lipid peroxidation, which some have claimed as potential antiancer and antiatherogenic effects of this essential micronutrient [19,20]. In fact, selenium and vitamin C supplementation protected serum cholesterol oxidation in high-fat–fed rats [21]. In addition, selenium has been shown to inhibit adhesion molecule expression by a modulation of nuclear transcriptional factors in vitro [22,23], whereas the dietary intake of selenium has been inversely associated with retinol-binding protein–4 concentrations [24], and selenium concentration in nails has been inversely related to C3 complement concentrations in healthy people [7], indicating the potential anti-inflammatory functions of selenium. However, the available scientific information regarding the relationship of selenium intake with other inflammatory markers and risk factors for chronic diseases is unclear; and further studies could lead to better understanding of the role of some antioxidant micronutrients in optimal nutrition and health promotion.

In this context, we hypothesized that SA levels could be related to metabolic syndrome features and that daily selenium intake could be negatively associated with an inflammatory marker such as SA. Therefore, the aim of this translational study was to assess the potential relationships of serum SA levels with metabolic syndrome features and dietary selenium intake, a recognized antioxidant nutrient in young adults, to further understand the involvement of intake of this antioxidant trace element in healthy nutrition and inflammation processes.

2. Methods and materials

2.1. Subjects

Forty-three participants (female, 31; male, 12) with a mean age of 18.0 ± 0.93 years were recruited for this translational study through local advertisements. All participants were apparently in a healthy condition after a careful clinical history evaluation carried out by a specifically trained physician. None of the participants were taking vitamin or antioxidant supplements or had any inflammatory-related diseases. Each participant signed a written informed consent of acceptance, which was previously approved by the Investigation Ethics Committee of the University Clinic of Navarra (ref 79/2005), in agreement with the principles of the Helsinki Declaration.

2.2. Clinical features assessment

Anthropometric measurements and body composition were assessed in all subjects after a 12-hour fast at the Metabolic Unit of the Department of Nutrition and Food Sciences, Physiology, and Toxicology as described elsewhere [25]. Three measurements were taken, and their mean was considered to be the final result. Height was assessed with a stadiometer (Seca 713 model; Postfach, Germany) to the nearest 1 mm. Body weight was measured with an electronic microdigital scale (Tanita Body Composition Analyzer, TBF 300 model; Tanita Corp., Arlington Heights, IL, USA) with a 150-kg capacity to the nearest 0.05 kg. Body mass index was calculated by the quotient between weight (kilograms) and squared height (meters squared). Waist circumference was measured in the midway between the lowest rib and the iliac crest, and hip circumference was estimated at the maximal hip circumference, without gluteus contraction, both with elastic and flexible tape to the nearest 1 mm [26]. The waist-to-hip ratio was also calculated. Body composition was determined by bioimpedance on a leg-to-leg analyzer (Tanita Body Composition Analyzer, TBF 300 model). Systolic and diastolic BPs were measured by a calibrated armband equipment (Minimus II; Riester, Jeningen, Germany) in the right arm and with volunteers in resting position as described elsewhere [27].

Venous blood samples were drawn after a 12-hour overnight fast by vein puncture. The serum samples were separated from whole blood by centrifugation at 3500 rpm in 5°C for 15 minutes (Model 5804R; Eppendorf, Hamburg, Germany) and were frozen immediately at −20°C until assay. Total serum SA was assessed by an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) as previously described [14]. Serum total cholesterol, high-density lipoprotein cholesterol, triacylglycerols, and glucose concentrations were measured by specific commercial colorimetric assays (Horiba ABX Diagnostics, Basel, Switzerland) in an automated analyzer system (COBAS MiraS, Roche, Basel, Switzerland). The reported plasma low-density lipoprotein cholesterol data were estimated by the Friedewald equation [28]. Serum fasting insulin was measured by a radioimmunnoassay method (DPC, Los Angeles, CA). Insulin resistance was estimated by the HOMA-IR as follows: HOMA-IR = [(fasting glucose (millimoles per liter) × fasting insulin (micro–international units per liter))]/22.5, as published elsewhere [29].

2.3. Dietary intake assessment

Dietary intake was assessed by the questionnaire of the Seguimiento Universidad de Navarra Study [30]. This semiquantitative food frequency questionnaire, validated for Spanish people [31], includes 136 items and open-
labeled questions for information about the use of dietary supplements and other foods not specified. Nutrient intake was computed using an ad hoc computer program specifically developed for this aim [30]. A diettian updated the nutrient data bank using the latest available information included in the food composition tables for Spain. Specifically, the selenium content in meats, poultry, fish and other seafood, nuts, legumes, cereals, dairy products, and fruits was considered for the assessment of selenium intake [32,33]. This questionnaire has been successfully applied to estimate dietary intake of specific nutrients in relation to several chronic diseases such as obesity or diabetes [34,35] and inflammatory outcomes [7,24,36].

2.4. Statistical analysis

Results are shown as means ± SD. The Kolmogorov-Smirnov test was used to determine variable distribution. To analyze anthropometric, clinical, and dietary data related to selenium intake, this trace element was taken as a suitable variable considering its median cutoff value (82.4 μg/d) and categorizing the current population into “lower” and “higher” selenium consumers according to this value. Median cutoff criteria have been previously applied [37-39] and are based on valid and reliable method of assigning 2 groups of risk in epidemiologic studies [40]. Accordingly, comparisons between these 2 groups were performed by the Mann-Whitney U test. Bivariate correlation coefficients were used to describe associations between variables. Statistical analysis was performed by SPSS 13.0 software (SPSS Inc, Chicago, IL) for Windows XP (Microsoft, Redmond, WA). A P value lower than .05 was set up as statistically significant, and a P value lower than .10 was considered marginally significant.

3. Results

The anthropometric measurements, body composition indicators, and BP data are presented in Table 1. These data indicate that the participants of this study are normal in weight and normotensive subjects. In addition, there was no statistically significant difference between individuals with lower and higher selenium intake, according to the median (82.4 μg/d) criteria for these variables (Table 1).

The biochemical data, shown in Table 2, indicate that the participants of this study also presented lipid and glycemic parameters within the reference range. Interestingly, subjects with higher selenium intake presented statistically significant lower serum SA levels (1.8 vs 2.1 mmol/L, \( P < .05 \)) and lower triacylglycerol levels with a marginal statistical significance (\( P < .10 \)) compared with individuals with lower selenium intake (Table 2).

Regarding daily dietary intake values, there were no statistically significant differences in macronutrient intake (carbohydrate, protein, and total fat intakes) between subjects with higher and lower selenium intake (Table 3), as well as in monounsaturated and polyunsaturated fatty acids intakes (\( P > .05 \), data not shown). Interestingly, higher selenium consumers reported a significantly higher energy intake (\( P < .001 \)) and higher vitamin C (\( P = .005 \)), vitamin E (\( P = .001 \)), and zinc intakes (\( P = .003 \)) (Table 3). Because

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and anthropometric characteristics of the subjects categorized according to the median (82.4 μg/d) of selenium intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 43)</td>
</tr>
<tr>
<td>Sex (%) male</td>
<td>27.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.9 ± 13.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.5 ± 9.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.1 ± 2.9</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>20.2 ± 6.9</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>78.1 ± 9.8</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>102 ± 12</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>65 ± 9</td>
</tr>
</tbody>
</table>

Data are mean ± SD for continuous variables. None of the variables presented statistically significant different values according to the selenium intake (Mann-Whitney U test).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Serum total SA as well as lipid and glycemic profiles of the participating subjects categorized according to the median (82.4 μg/d) of selenium intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower selenium (n = 21)</td>
</tr>
<tr>
<td>SA (mmol/L)</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.3 ± 0.9</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>HDL-c (mmol/L)</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>LDL-c (mmol/L)</td>
<td>2.3 ± 0.7</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>Insulin (μIU/mL)</td>
<td>8.9 ± 4.7</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.0 ± 1.1</td>
</tr>
</tbody>
</table>

Values are mean ± SD. HDL-c indicates high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Total energy, macronutrient, and antioxidant nutrient intakes of the subjects categorized according to the median (82.4 μg/d) of selenium intake</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Lower selenium (n = 21)</td>
</tr>
<tr>
<td>Selenium (μg/d)</td>
<td>60.4 ± 13.5</td>
</tr>
<tr>
<td>Energy intake (kcal/d)</td>
<td>8851 ± 2618</td>
</tr>
<tr>
<td>Carbohydrate (% EI)</td>
<td>44.5 ± 5.0</td>
</tr>
<tr>
<td>Protein (% EI)</td>
<td>17.4 ± 2.4</td>
</tr>
<tr>
<td>Fat (% EI)</td>
<td>37.5 ± 4.3</td>
</tr>
<tr>
<td>Vitamin A (μg/d)</td>
<td>1.8 ± 1139.5</td>
</tr>
<tr>
<td>Vitamin C (mg/d)</td>
<td>205.3 ± 111.9</td>
</tr>
<tr>
<td>Vitamin E (mg/d)</td>
<td>4.9 ± 1.7</td>
</tr>
<tr>
<td>Zinc (mg/d)</td>
<td>13.9 ± 5.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD. EI indicates energy intake.

Statistical difference was maintained after adjusting by energy intake for selenium intake.

\* \( P \leq .01 \), \( \dagger \) \( P \leq .001 \) from Mann-Whitney U test.
subjects with high selenium intake also reported higher energy intake, intake data of this trace element were adjusted by daily energy intake as the daily nutrient intake to daily total energy intake ratio. Thus, values (data not shown) remained significantly different only for dietary selenium intake ($P = .001$).

When bivariate correlation analyses between serum SA levels and biochemical data were performed, serum SA
levels showed a significant positive correlation with triacylglycerol levels ($r = 0.317$, $P = .038$) and a positive marginal significance with HOMA-IR ($r = 0.297$, $P = .053$), as shown in Fig. 1. In addition, when the associations of serum SA and related clinical features with the dietary consumption of this micronutrient were evaluated, selenium intake showed a statistically significant negative association with serum SA ($r = −0.331$, $P = .030$) and with

Fig. 2. Correlation analyses between selenium intake with serum SA (A) and serum triacylglycerols (B) in the assayed subjects (N = 43).
triacylglycerol levels \((r = -0.312, \ P = .041)\), as shown in Fig. 2.

Overall, these results point to the fact that selenium intake is negatively associated with plasma SA concentrations and metabolic syndrome features such as triacylglycerol levels and insulin resistance.

4. Discussion

Inadequate nutrient intake and insulin resistance have important roles in the pathogenesis of metabolic syndrome and are suggested to increase the risk of developing CVD [41]. In addition, several investigations have suggested serum SA as a strong predictor of cardiovascular events [11-13]. Indeed, the significant positive correlation found between serum SA and triacylglycerol levels and the marginal correlation between serum SA levels and insulin resistance, as assessed by the HOMA-IR (both presented in this work), may partially explain the relevance of serum SA as a cardiovascular risk factor. The mechanism by which serum SA can enhance CVD risk is unclear, but it has been attributed to lipoprotein sialylation [12]. Thus, changes in the sialylation process could increase serum SA content in the very low-density lipoprotein cholesterol particles, contributing to hypertriacylglycerolemia [10]. Our results suggest that a single measurement of serum SA might be an early estimate of inflammatory status, before the incidence of metabolic syndrome.

Regarding the relationship of dietary intake with metabolic syndrome features, selenium intake was inversely correlated with triacylglycerol levels, as we found in an earlier cross-sectional study [24]. In fact, other authors have reported that hyperlipidemia could affect the oxidative stress status when assessing antioxidant markers in blood, such as glutathione peroxidase and selenium concentrations [42,43]. Thus, our results indirectly suggest that the consumption of this micronutrient may be useful in the prevention or treatment of oxidative stress and atherosclerosis related to dyslipidemia, as we had suggested in a previous study [21].

Furthermore, dietary selenium was significantly negatively correlated with SA levels, which could give light to a mechanistic involvement between antioxidant intake and inflammatory response, which has been suggested in different investigations [7,23,24,44,45]. Thus, a high intake of selenium through a modulation of oxidative stress status and nuclear transcriptional factors (which are related to inflammation) could be a key issue to understanding the putative interaction of redox balance, inflammation, and some of the complications commonly found in subjects with the metabolic syndrome [20,23].

In addition, the high intake of selenium by some participants of this study, according to the median as cutoff, was greater than the estimated values of consumption in Spanish people (35 μg/d) [19] and greater than the American and Spanish recommendations of 55 μg/d [33,46]. This is possibly because of a higher consumption of fish and seafood, whole bread, nuts, and meats, which are the main sources of selenium in Spanish foods [33]. This information should be taken into consideration because a selenium intake greater than these recommendations could produce anticancer, antioxidant, antiatherogenic, as well as anti-inflammatory effects of selenium, as suggested by other authors [18,23,47,48], despite some contradictory studies that have been published in the literature [49,50].

Moreover, in individuals with high selenium intake, vitamin C, vitamin E, and zinc intakes were also higher than in subjects with low selenium intake. In this context, some observational studies have indicated that total antioxidant, vitamin C, vitamin E, and selenium intakes are associated with lower levels of C-reactive protein [45,51], an inflammatory marker involved in the development of metabolic syndrome. Thus, these findings suggest that the simultaneous consumption of different antioxidant nutrients could be mutually beneficial in the inflammatory and oxidative processes.

One limitation of this study is the variability of selenium content in food sources and consumption tables, depending on geographic areas, soil, climate factors, or the elaboration of dishes, among others [19]. However, we used a semiquantitative food frequency questionnaire validated for Spanish people [31]. Moreover, the software used for the assessment of daily nutrient intake takes into consideration the consumed portion of each food by Spanish people; the foodstuff portion and the nutrient content of each food are based on Spanish food composition tables [32,33]. Indeed, the assessment of foods and nutrients, including selenium intake [7,24], by this questionnaire and methodology has been previously associated with inflammation status and chronic diseases [34-36]. Our data are confirmed by the reports of others addressing the relationship between antioxidant intake and inflammation, which gives plausibility and coherence to our findings.

In summary, this study revealed (apparently for the first time) a negative association between serum SA, an inflammation marker, and dietary selenium intake in healthy young subjects. These findings suggest that an adequate antioxidant intake could beneficially affect inflammation and metabolic stress features related to chronic diseases and may contribute to their prevention. Moreover, considering the characteristics of the sample and the relevance of the results obtained by this translational study, further investigations are needed to explain the potentially involved mechanisms; but a role of the interaction between antioxidant intake and inflammatory process is envisaged.

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