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Factors associated with longitudinal plasma selenium decline in the elderly: The EVA Study☆

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Abstract

Selenium status decreases in elderly populations. Cardiovascular diseases are the primary cause of death in the French elderly, and selenium may protect against cardiovascular diseases. The present work aims to evaluate the relationships between cardiovascular-related risk factors and plasma selenium variability in an elderly population during a 9-year period. Seven hundred fifty-one subjects from the EVA ("Etude du Vieillissement Artériel") study, aged 59 to 71 at baseline, were followed for 9 years. Clinical examinations and lifestyle questionnaires were repeated every 2 years. Plasma selenium determinations were performed at baseline and at the end of the study. The association between the 9-year plasma selenium variability and studied risk factors at baseline or occurring during the follow-up was evaluated by using multivariate linear regression models. After controlling all potential associated factors, age of subjects ($P<.01$), obesity ($P=.02$) and occurrence of cardiovascular disease during follow-up ($P=.03$) increased the longitudinal decline in plasma selenium, whereas gender, education, smoking, alcohol intakes, dyslipidemia, diabetes, hypertension had no effect ($P>.05$). It may be postulated that obesity and occurrence of cardiovascular events are the main factors associated with plasma selenium fall during ageing. The respective roles played by nutritional and metabolism changes in the mechanism of these associations still need to be explored.

Keywords: Selenium decline; Elderly; Cardiovascular diseases; Cardiovascular disease risk factors

1. Introduction

Selenium is an essential trace element mainly involved in redox balance as part of glutathione peroxidases, thioredoxine reductase and selenoprotein P, but also, more specifically, in cerebral function as part of selenoprotein P [1], thyroid function as part of iodine deiodinases, as well as in immune functions [2]. In the elderly, selenium status decreases slightly compared to younger adults as long as subjects are healthy but dramatically drops when subjects are institutionalised or ill [3,4]. Recent epidemiological studies have suggested that an adequate selenium status in the elderly is associated with a lower mortality rate [5,6] and a lower incidence of age-related pathology [2,6–10], possibly due to oxidative stress deleterious effect in ageing [11,12]. Therefore, maintaining an adequate selenium status in the elderly may be of importance, particularly in Europe, where selenium intakes are low compared to recommended dietary daily intake, optimal glutathione peroxidase activity or immune functions [2,3,13,14].

Cardiovascular diseases are the primary cause of death in France [15,16] and low serum selenium concentrations have been reported to increase cardiovascular mortality and morbidity, although the protective role of selenium against cardiovascular diseases remains debated [2]. Repeated measurements of plasma selenium concentration, a good biological indicator to evaluate selenium status [17], were performed on participants of the EVA study ("Etude du Vieillissement Artériel"); a 9-year longitudinal study whose

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aim was to examine determinants of cognitive and cardiovascular functions in a French elderly population [18].

In contrast to previous publications, the present work deals with the relationships between longitudinal plasma selenium variability during this study and main cardiovascular risk factors, cardiovascular disease occurrence or lifestyle at baseline, as well as changes in health status or life style occurring during the 9-year follow-up.

2. Methods and materials

2.1. Study population

From 1991 to 1993 (EVA0), 1389 volunteers (574 men and 815 women; mean age: 65; range: 59–71 years) residing in the town of Nantes (Western France) were recruited from electoral rolls and, to a lesser extent, via information campaigns. During the last follow-up of the EVA study (EVA6), between June 2000 and December 2001, blood sampling was obtained for 773 subjects. The present analysis is restricted to the 751 subjects (455 women and 296 men) who had a plasma selenium determination, both at baseline and at the end of the study, and focuses on the relationships between cardiovascular risk factors or cardiovascular disease occurrence and longitudinal plasma selenium variability. The study protocol was approved by the Ethical Committee of the University Center Hospital of Kremlin-Bicêtre (Paris). Signed informed consent was obtained from all participants at enrolment.

2.2. Questionnaire and medical examination

At baseline (EVA0) and at the end of the study (EVA6), a general questionnaire allowed us to obtain information on socio-demographic factors such as sex, age, educational achievement, marital status and tobacco and alcohol consumption habits. Alcohol consumption was determined from the subject's estimated average amount of alcoholic beverages ingested weekly and expressed in grams of alcohol per day. In addition, height and weight were measured and body mass index (BMI) was calculated. Two independent measures of systolic and diastolic blood pressure were made with a digital electronic tensiometer after a 10-min rest.

2.3. Biological variables

At baseline and at the end of the study, blood samples were drawn between 8:30 am and 9:30 am after a 12-h fast. Biological procedures for the determination of cholesterol and glucose levels have been described elsewhere [19]. Plasma selenium was determined by electrothermal atomic absorption spectrometry (Perkin Elmer 5100) according to a previously described method [20]. The spectrometer was fitted with a Zeeman background correction, a platform pyrolytical furnace and an electrodeless discharge lamp (EDL). Plasma was fivefold diluted in a solution containing 0.2% Triton X100 and 0.1 mol nitric acid, and 15 μg platinum was used as a matrix modifier. Selenium concentration was obtained using standard addition calibration. Precision, expressed as within and between run coefficient of variations, stood at 1.4% and 1.8% respectively. Accuracy was checked by using Seronorm trace element serum as an internal quality control (Sero, Billingstad, Norway) and the tolerance limits were ±10% of the batch target value in use. In addition, the laboratory took part in two external quality assessment schemes and its annual scores were acceptable (values higher than 60%).

2.4. Statistical analysis

The characteristics of subjects at baseline were compared between two groups: those who had the two measurements of selenium at baseline and at the end of the study (complete assessment, $n=751$) and those who did not ($n=658$). Results were expressed by percentage and means with their standard deviation. To test the differences between these two groups, χ^2 test and Student's t-test were used. The characteristics at baseline and at the end of the follow-up of the 751 subjects who had the two plasma selenium measurements were also compared.

Plasma selenium concentrations at baseline and at the end of the study and corresponding plasma selenium differences were normally distributed and were analysed as continuous variables. Multivariate linear regression models were used to analyse factors associated with longitudinal plasma selenium variability. The first model studied the association between the studied factors at baseline and plasma selenium variability. In this model, the following parameters were included: sex, age, education (no school or primary school vs. high school or university) as a socio-economic level index [21], plasma selenium concentrations [22], marital status (single or not) as a loneliness index, tobacco status (current/former/non-smokers), alcohol consumption (≥16 vs. <16 g/day [23]), obesity (BMI ≥30 kg/m^2 [24]), hypertension (systolic or diastolic blood pressure ≥140 or ≥90 mm Hg, respectively, or use of hypertensive drugs or report of hypertension medical history), diabetes (plasma glucose level ≥7.80 mmol/L or use of antidiabetic drugs or report of diabetes medical history), dyslipidemia (total cholesterol ≥6.2 mmol/L or use of lipid-lowering drugs or report dyslipidemia medical history) and history of cardiovascular diseases (myocardial infarction, angina pectoris, stroke or use of vascular drugs). In the second model, the association between changes in studied factors and plasma selenium variability was analyzed. The following variables were included in the model: smoking (nonsmoker vs. smoker or former smoker or stopped smoking during study), marital status (always vs. never or becoming married during follow-up or becoming single), obesity (not obese vs. obese or becoming obese or becoming nonobese), diabetic (none vs. previous history or onset), hypertensive (none vs. previous history or onset), dyslipidemic (none vs. previous history or onset) and cardiovascular diseases (none vs. previous

history or new occurrence). In addition, sex, age and education as main morbidity predictors and plasma selenium concentration at baseline [22] were included. All these potential explaining variables were included simultaneously. Statistical significance was set at $P<.05$. Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

At baseline, 1389 subjects were included in the EVA study. Their main characteristics have been previously described as well as the influence of the studied factors on plasma selenium concentration at baseline [10,18]. Among them, 54.1% ($n=751$) completed the study. Dropout subjects lived alone less frequently (17.2% vs. 24.2%, $P=.001$), were more frequently men (44.8% vs. 37.9%, $P=.009$) and exhibited significantly more frequently hypertension (52.8% vs. 46.5%, $P=.02$) and obesity (12.3% vs. 9.1%, $P=.05$) than the subjects who completed the study, but they did not differ for baseline plasma selenium concentration ($P=.54$), age ($P=.64$), education ($P=.15$), smoking ($P=.06$), alcohol consumption ($P=.60$), dyslipidemia ($P=.51$), diabetes ($P=.36$) and history of cardiovascular disease ($P=.08$).

Reported characteristics of the population at the beginning and after 9 years are shown in Table 1. At baseline, mean plasma selenium concentration was equal to 1.10 μmol/L and median was 1.09 μmol/L. The maximum, 75th and 25th percentiles, and minimum plasma selenium values were 1.94, 1.23, 0.95 and 0.58 μmol/L, respectively. At the end of the follow-up, mean (minimum–maximum) plasma selenium concentrations decreased to 1.00 (0.48–1.80) μmol/L, whereas median (25th–75th percentiles) were 0.99 (0.88–1.11) μmol/L. During the follow-up, 4.9% ($n=24$) of the subjects stopped smoking; 12.7% ($n=95$) became single, whereas 1.7% ($n=13$) got married. Onset of diabetes, hypertension and dyslipemia, and occurrence of cardiovascular events were observed in 27 (3.7%), 248 (33.1%), 142 (19.3%) and 134 (17.8%) subjects, respectively. In addition, 3.0% ($n=17$) of the participants became obese, whereas BMI decreased to a value lower than 30 in 3.7% ($n=21$) of them. During the follow-up, a mean plasma selenium decline of 0.10±0.21 μmol/L was observed and the selenium decrease was estimated at 0.006 (±0.002) μmol/L per year ($P<.0001$). The maximum decrease was 0.97 μmol/L, and the 75th percentile of the plasma selenium variation distribution was equal to 0.22 μmol/L. A decrease in plasma selenium concentration was noted in 71.8% of subjects.

Table 1
Characteristics of the 751 subjects at baseline and at the end of the study

		[a]	Baseline	End
Plasma selenium	μmol/L	Mean±S.D.	1.10±0.20	1.00±0.18
Age	Years	Mean±S.D.	65±3	74±3
Marital status	Married	*n*	580	498
	Single	*n*	170	252
Smoking	Never smokers	*n*	298	298
	Former smokers	*n*	151	172
	Smokers	*n*	45	24
Alcohol intake	g/day	Median (CI)	0.6 (0–20.8)	ND[b]
	≤16 g/day	*n*	525	ND[b]
	>16 g/day	*n*	213	ND[b]
BMI	kg/m^2	Mean±S.D.	25.1±3.6	24.7±3.7
Obesity	No	*n*	682	523
	Yes	*n*	68	47
Dyslipidemia	No	*n*	399	257
	Yes	*n*	338	485
Diabetes	No	*n*	692	665
	Yes	*n*	33	60
Hypertension	No	*n*	397	149
	Yes	*n*	353	601
Personal history of cardiovascular diseases	No	*n*	688	589
	Yes	*n*	63	162

[a] Results are expressed either as mean±S.D., median (CI) or *n* (number of subjects).
[b] ND indicates not evaluated at the end of the study.

Table 2
Association between longitudinal plasma selenium decrease during the 9-year follow-up and risk factors measured at baseline

		Plasma selenium decrease		
		β	S.D.	*P*
Plasma selenium at baseline	μmol/L	0.662	0.032	<.0001
Age at baseline	Years	0.006	0.002	.003
Sex	Women vs. men	0.014	0.018	.41
Education	≥High school vs. ≤primary school	−0.018	0.013	.16
Marital status	Married vs. single	−0.016	0.016	.33
Smoking	Former smokers vs. nonsmokers	0.004	0.017	.80
	Smokers vs. nonsmokers	−0.0003	0.025	.98
Alcohol consumption	>16 vs. ≤16 g/day	0.021	0.016	.18
Obesity	Yes vs. no	0.037	0.023	.10
Dyslipidemia	Yes vs. no	−0.018	0.013	.16
Diabetes	Yes vs. no	0.026	0.032	.41
Hypertension	Yes vs. no	0.023	0.013	.07
Personal history of cardiovascular disease	Yes vs. no	0.023	0.023	.30

Results of linear regression models adjusted on all factors listed in the table. Results of linear regression were expressed by linear regression coefficient (β) adjusted on all factors in the table.

Results of multivariate linear regression models are presented in Tables 2 and 3. Longitudinal plasma selenium decline was significantly associated with age ($P<.01$). Selenium fall was also significantly associated with plasma selenium level at baseline ($P<.0001$) due to the well-known regression to the mean phenomena [22]. No significant association was observed between plasma selenium decline and other studied factors at baseline (Table 2). Association between plasma selenium decline and studied factor modification during the study is indicated in Table 3. The occurrence of cardiovascular events ($P=.03$) as well as

Table 3
Association between longitudinal plasma selenium decrease and changes in risk factor during the 9-year follow-up

		Plasma selenium decrease		
		β[a]	S.D.	P
Plasma selenium at baseline	μmol/L	0.664	0.041	<.0001
Age	Years	0.007	0.003	.007
Sex	Women vs. men	0.022	0.022	.31
Education	≥High school vs. ≤primary school	−0.013	0.016	.44
Marital Status	Becoming married[b] vs. married	−0.128	0.076	.09
	Single vs. married	−0.007	0.021	.73
	Becoming single[b] vs. married	0.032	0.024	.18
Smoking	Stopped smoking[b] vs. nonsmokers	0.035	0.041	.38
	Former smoker vs. nonsmokers	0.037	0.022	.09
	Smoker vs. nonsmokers	0.034	0.044	.43
Obesity	Becoming obese[b] vs. nonobese	0.011	0.054	.85
	Obese vs. nonobese	0.088	0.038	.02
	Becoming nonobese[b] vs. nonobese	0.061	0.041	.14
Dyslipidemia	Becoming dyslipemic[b] vs. normolipidemic	−0.013	0.023	.57
	Dyslipemic vs. normolipidemic	−0.017	0.019	.35
Diabetes	Becoming diabetic[b] vs. nondiabetic	0.072	0.047	.13
	Diabetic vs. nondiabetic	0.010	0.043	.81
Hypertension	Becoming hypertensive[b] vs. normotensive	−0.005	0.022	.81
	Hypertensive vs. normotensive	0.011	0.021	.59
Cardiovascular diseases (CVD)	Past history of CVD vs. no history	0.001	0.045	.98
	CVD event[b] vs. no history	0.01	0.023	.03

Results of linear regression models adjusted on all factors listed in the table.
[a] Results of linear regression were expressed by linear regression coefficient (β) adjusted on all factors in the table.
[b] During the follow-up.

lasting obesity (P=.02) significantly increased the fall in plasma selenium. No association was found between plasma selenium decrease and the other factors taken into account.

4. Discussion

Plasma selenium concentration largely depends on selenium intake and varies widely geographically [2,9,17]. Differences in plasma selenium concentrations between French regions have been reported in the SU.VI.M.AX study [25], and selenium status in the Nantes area is higher than in the east or the center of France [25,26]. The baseline plasma selenium concentrations observed in this study were similar to those reported in France in younger adults [26–28] and higher than the plasma selenium concentrations reported in French institutionalized elderly populations [29,30] in agreement with previous studies conducted in free-living elderly [3,4]. It confirms that low plasma selenium concentrations in the elderly is especially found in those who are institutionalized [3,4,31], due to low intake [3,29], reduced physical functioning [32] or severe pathologies [9], and can reflect undernutrition, lower bioavailability, increased requirements or metabolic changes. However, these values appear to be marginally lower than those necessary to achieve optimal activity of glutathione peroxidase, which occurs at plasma concentrations around 1.25 μmol/L [2,13,17]. Suboptimal selenium status may increase the susceptibility to various pathologies in the elderly [2,8–10,13].

Numerous case-control or nested-control studies report plasma selenium concentrations in cardiovascular diseases [2,33], and its main associated risk factors such as hypertension [34,35], dyslipidemia [36–38], diabetes [39], smoking [40,41], alcohol abuse [40,41] and obesity [42], and the results are conflicting. To our knowledge, this is the first report which focuses on longitudinal plasma selenium variability in a random free-living elderly population. We observe a significant decline in plasma selenium concentrations in free-living subjects during the 9-year follow-up. This decrease is more pronounced in older subjects in agreement with previous cross-sectional studies conducted in Europe [43–46], but it contrasts with the third National Health and Nutrition Examination Survey results [47,48], which show similar serum selenium concentrations in adults and older people. These discrepancies may be related to difference in population characteristics. Among the studied risk factors, age, occurrence of cardiovascular diseases and obesity were pointed out as determinants of longitudinal plasma selenium decline. Smoking, alcohol consumption as well as previous history or onset of diabetes, dyslipidemia and hypertension had no significant effect on longitudinal plasma selenium decline in agreement with some previous case-control studies, which did not report any difference between cases and controls [34,36–42,49]. The positive relationship between age and longitudinal plasma selenium decrease observed in this study confirms the results of previous cross-sectional European surveys [3,4,31,43–46]. In addition, the cross-sectional relationship between plasma selenium concentration and age in EVA was observed at the end (data not shown) of this study but not at baseline [18], confirming that the decline in plasma selenium with age may be delayed in free-living elderly [43–45]. Cardiovascular disease occurrence during the follow-up significantly increased the longitudinal decline in plasma selenium. This observation, together with the lack of effect of previous history of cardiovascular events, may contribute to the explanation of discrepancies reported in the literature [2,33] concerning plasma selenium status and cardiovascular disease relationship and the effect of preventive selenium supplementation. Indeed, the longitudinal decline in plasma selenium concentration may be transient and linked to the significant decrease in plasma selenium reported during acute-phase response [50] and therefore reflects more a

consequence than a cause of the disease in people with plasma selenium concentration higher than the threshold value reported in different studies [2,33]. Finally, our results show the adverse effect of obesity on longitudinal plasma selenium decline. Nevertheless, the association between longitudinal plasma selenium decrease and obesity became significant only in subjects with persistent obesity. This observation may contribute to explaining the discrepancies reported in the literature [25,34,37]. Obesity is associated with increased oxidative stress due to insulin resistance, accumulation of intracellular triglycerides or increase in adipokine release [51,52], and is a well-known key factor for cardiovascular diseases [53]. Taken together, our result suggests that obese elderly may need higher antioxidant, especially selenium, intake to counteract the higher oxidative stress, which leads to vascular oxidative dysfunction.

To the best of our knowledge, this epidemiological survey is the first which studies the association between cardiovascular risk factors or cardiovascular disease occurrence and selenium longitudinal variation in an elderly population. The results highlight the role of obesity and cardiovascular events in decreasing selenium status. Nonetheless, these preliminary data must be interpreted cautiously and need to be confirmed on other elderly populations. Moreover, the respective importance of nutritional and metabolism changes in the mechanism of these associations still needs to be explored.

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