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Selenium status in elderly: Relation to cognitive decline

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ABSTRACT

Studies show that decreased antioxidant system is related to cognitive decline. Thus we aimed to measure selenium (Se) status in Alzheimer's disease (AD) and mild cognitive impairment (MCI) elderly and compared them with a control group (CG). 27 AD, 17 MCI and 28 control elderly were evaluated. Se concentration was determined in plasma and erythrocyte by using hydride generation atomic absorption spectroscopy. Erythrocyte Se concentration in AD group was lower than CG (43.73 ± 23.02 μg/L and 79.15 ± 46.37 μg/L; $p = 0.001$), but not statistically different from MCI group (63.97 ± 18.26 μg/L; $p = 0.156$). AD group exhibited the lowest plasma Se level (34.49 ± 19.94 μg/L) when compared to MCI (61.36 ± 16.08 μg/L; $p = 0.000$) and to CG (50.99 ± 21.06 μg/L; $p = 0.010$). It is observed that erythrocyte Se decreases as cognition function does. Since erythrocyte reflects longer-term nutritional status, the data point to the importance of the relation between Se exposure and cognitive function. Our findings suggest that the deficiency of Se may contribute to cognitive decline among aging people.

Introduction

Life expectancy is continuing to increase and population aging is a worldwide phenomenon that is related to the prevalence of chronic diseases and also to higher risk of dementia since cognitive impairment results from the physiological process of brain aging. Cognitive impairment is an important cause of disability which results in loss of autonomy and thus it is one of the major causes of institutionalization. Because the costs of dementia care include physician services, hospitalization, medications, as well as indirect costs associated with patient and caregiver productivity, it results in a great impact on public health policy [1–3].

Cognitive decline beyond that expected for corresponding age and education marks mild cognitive impairment (MCI) which represents an intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia [4]. Although MCI does not significantly impact daily functioning, it is associated with higher risk of progressing to dementia as Alzheimer's disease (AD) [5,6], which is the main cause of dementia in the elderly. This was showed by Mitchell and Shiri-Feshki [7] who observed in a meta-analysis of 13 clinical studies that the annual conversion rate from MCI to dementia was 9.6% and, over the natural observation period, 39.2% converted to dementia. AD is clinically characterized by progressive and irreversible cognitive deficits and behavioral alterations that affect memory and learning ability, activities of daily living and quality of life [8]. Although the greatest known risk factor for AD is advancing age, diabetes, hypertension, smoking, obesity, elevated lipid levels and cerebrovascular disease are also associated with dementia. On the other hand, higher education, mentally stimulating activities and engagement in mental, social, and productive activities are associated with lower rates of dementia [9,10].

It is known that oxidative stress plays central role in cognitive decline and dementia as Alzheimer's disease. First, it is associated with increasing of protein oxidation, lipid peroxidation, DNA and mRNA oxidation, which leads to believe that the damage resulted from oxidative stress is the first event that precedes dementia. On the other hand, senile plaques and neurofibrillary tangles, which are structures observed in AD patients' brains, generate reactive oxygen species (ROS), thus creating a vicious cycle of ROS generation that far exceeds the antioxidant defense system [11–13].

The brain is particularly vulnerable to oxidative damage because it presents (1) elevated oxygen utilization rate; (2) high content of polyunsaturated lipids that are very susceptible to lipid peroxidation; (3) accumulation of transition metals such as iron, copper and zinc, which are capable of catalyzing the formation of ROS; (4) relatively poor concentrations of antioxidants [12,14,15].

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Selenium plays antioxidant role because it is the main constituent of antioxidant enzymes that are expressed in different tissues, including the brain. Thus, this mineral has an important role to the antioxidant system. This trace element is known for providing protection from ROS-induced cell damage and the proposed mechanisms mainly invoke the functions of glutathione peroxidase family and selenoprotein P [16].

Although some authors found increased levels of selenium in AD patients' blood, others related blood levels of this mineral to cognition and thus the deficiency of selenium, even subclinical, would be a risk factor for disease [17–20]. In this context, the present study aimed to evaluate nutritional status of selenium in AD and MCI elderly and compare them with healthy older adults.

Materials and methods

Subjects

We enrolled twenty-seven patients diagnosed with probable AD according to the NINCDS-ADRDA criteria [21]. MCI group was composed by thirty-one MCI participants who fulfilled the criteria proposed by the International Working Group on Mild Cognitive Impairment [22], which includes the following: (1) the person is neither normal nor demented; (2) there is evidence of cognitive deterioration shown by subjective report in conjunction with objective cognitive deficits; and (3) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. Twenty-eight healthy volunteer elderly with normal cognitive function (normal scores on the Mini-Mental State Examination) were included in the control group.

Eligible subjects were aged 60 years or older, fluent in Portuguese, and free of any other significant neurologic or psychiatric diseases. They did not present major depression or psychosis, nor had a regular intake of Brazil nuts or used supplements with selenium. All participants were attended at the Geriatrics Division, University of São Paulo Medical School (Brazil).

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by Ethics Committee of the Faculty of Pharmaceutical Sciences at the University of São Paulo. Written informed consent was obtained from participants of C and MCI groups and caregivers of AD patients.

Dietary assessment

Diet evaluation was accomplished by using a 3-day (2 weekdays and 1 weekend day) nonconsecutive dietary food record, up to 7 days before blood sample was drawn. In case of the AD patients, their caregivers were requested to register what they had eaten.

The AD patients' caregivers and the participants of MCI and control groups received instructions on how to fill out the records. Upon receiving, all records were checked by trained nutritionists in order to exclude any possible doubt, error or omission in the completion of the forms.

Data were measured by using NutWin software (version 2.5) (EPM-UNIFESP). Software database was supplied with selenium data from the study of Ferreira et al. [23], which determinate selenium levels in foods consumed in Brazil.

Blood sampling

Fasting morning blood samples were drawn by venepuncture in trace element free tubes containing EDTA. Plasma was separated by centrifugation at 3000 × g for 15 min at 4 °C. The erythrocyte pellet that was obtained from whole blood by centrifugation was washed three times with 5 mL of sterile 9 g/L NaCl solution, slowly homogenized by inversion, centrifuged at 10000 × g for 10 min (Sorwall® RC5C) at 4 °C and the supernatant was discarded. Plasma and erythrocyte were stored in demineralized and sterile microtubes at −80 °C until the analyses of the samples.

Selenium status assessment

Selenium concentration was determined in plasma and erythrocyte samples by using hydride generation atomic absorption spectroscopy [24].

Samples of plasma and erythrocyte were prepared for analysis by digestion with 68% nitric acid (Merck, Darmstadt, Germany) and heating at 150 °C for volatilization of the organic material. After that, solutions were reduced from SeVI to SeIV by the addition of 1.2 N hydrochloric acid and heating at 100 °C for 2 h. The samples were diluted to 25 mL in ultrapure water. A calibration curve was prepared using Titrisol® – *selenium standard solution* 1000 mg/L – (Merck, Darmstadt, Germany), diluted in HNO_3 1%, with concentrations of 0, 0.1, 0.3, 0.5 1.0, 3.0, and 5.0 mg/L.

Analysis of external quality controls, Seronorm Trace Elements Serum and Whole Blood (Sero AS, Billingstad, Norway), were performed in order to obtain the method validity. The samples were analyzed in duplicate (technical replicates in order to average out the technical variation) with reading also in triplicate (a total of 6 reading per person). The accepted recovery rate of the reference patterns was never lower than 85% in each analysis.

Trace-element-free techniques were used during the handling and analysis of all the blood samples collected.

Statistical analysis

A descriptive analysis was performed by showing the results as mean and standard deviation (SD).

Kolmogorov–Smirnov test was performed in order to evaluate variables distribution. As all variables showed normal distribution, differences among groups were analyzed with ANOVA test. A p value of 0.05 was considered statistically significant.

In order to describe the relationship between aspects of food consumption and biochemical characteristics independent of energy intake, selenium intake values of all groups were adjusted to energy, according to the residual method [25]. This procedure uses linear regression (linear regression of nutrient intake on total energy intake) and addition of a constant (mean energetic intake of the group).

All statistical analyses were carried out using the Statistical Package for the Social Sciences software, version 20.0, for Windows (SPSS, Chicago, IL, USA).

Results and discussion

In the present study, 28 elderly (39.3% men and 60.7% women) in AD group, 31 MCI patients (30% men and 70% women) and 29 healthy elderly (34.5% men and 65.5% women) in C group were evaluated. There was no gender difference among groups; however, the AD group was older than MCI and C groups (80.6 ± 5.7, 77.7 ± 5.3 and 71.2 ± 6.2 years, AD, MCI and C groups, respectively). In order to verify if in our study age influenced selenium levels, we performed correlation analysis between selenium parameters and age, but correlations were not observed ($p > 0.05$) (data not shown).

Table 1 shows that average daily intake of energy was not significantly different among groups. However, the proportion of carbohydrate intake in the diet was higher in AD group while the proportion of protein and lipid was lower in the same group. AD is generally associated with a progressive change in nutritional behavior. The mesial temporal cortex, which is involved in feeding behavior and memory, as some others brain regions and

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Table 1
Intake of energy, macronutrients and Se by participants according to group.

	Groups		
	Control (mean ± SD)	MCI (mean ± SD)	AD (mean ± SD)
Energy (kcal/d)	1781.43 ± 441.71	1474.42 ± 490.28	1466.02 ± 422.43
Protein (%)	18.29 ± 3.98	20.67 ± 6.43[a]	14.88 ± 2.82[b]
Carbohydrates (%)	54.49 ± 7.69	55.07 ± 12.95	61.72 ± 6.30[b]
Lipids (%)	27.22 ± 7.79	26.83 ± 7.62	23.41 ± 5.23[b]
Se (mcg/d)	48.91 ± 15.5	34.43 ± 9.87[a,b]	40.99 ± 11.23[b]

[a] Different from AD group ($p < 0.005$).
[b] Different from control group.

processes important for the neural regulation of food intake and energy metabolism, are affected in dementia. These disturbances are related with neurotransmitter systems that include serotonin, adrenaline and dopamine, that are involved in the regulation of feeding behavior [26,27]. These physiological changes can result in poor appetite and problems as food refusal, which leads to decrease in energetic intake. These alterations can also justify the changes in food preference with a preference for carbohydrates observed in our data. Wang et al. [28] also observed that although there was no difference in energy intake between AD patients and non-demented subjects, a higher carbohydrate intake was found in AD group.

MCI presented the lowest selenium intake, although all groups presented inadequate intake according to Dietary Reference Intake [29]. Globally, soil selenium levels are highly variable and influence selenium concentration in food [30,31]. This variation is observable in Brazil: while in the north of the country, where Brazil nuts come from, soils are seleniferous, the southern part presents selenium deficient soil. Thus, São Paulo population in general presents low selenium intake and marginal selenium status, as observed in some studies [32,33]. It is important to mention that there is a lack of studies describing selenium intake in AD and MCI patients. We suppose that this is due to the difficulties associated with assessment of selenium intake, as the absence of specific food composition tables for this trace element and selenium variation in different regions.

In Fig. 1 it is possible to see that AD group presented the lowest level of selenium in plasma and in erythrocyte. According to the most accepted serum/plasma selenium cutoff (>84–100 μg/L) [34], almost 100% of three groups showed inadequate selenium level (93.1% of control group; 96.8% of MCI group; 100% of AD group). These data showed that although control group also showed deficient status of selenium, we can observe that selenium status tends to decrease as cognitive function does. This is more easily noted when we observe that erythrocyte selenium was lower in MCI group when compared to control group, and AD group presented the lowest level among groups.

The correlation between selenium status and cognitive performance was also observed in other studies [18,19]. As selenium plays important antioxidant role, it may be particularly important for the maintenance of brain functions. Thus the deficiency of this mineral may increase oxidative stress, which contributes to neuronal loss because free radicals are associated with disturbances in mitochondrial function, synaptic transmission, axonal transport and neuroinflammation [35,36]. Selenoprotein P and glutathione peroxidase are the major selenoproteins in brain. Because selenoprotein P presents up to ten selenocysteine residues, it is the main transporter of selenium. Besides, it was identified in senile plaques and in neurofibrillary tangles, structures observed in brain of AD patients, suggesting that it has an important role in protecting neurons from oxidative damage [37,38]. Glutathione peroxidase enzymes are expressed by neurons and glia cells [39,40]. They have important antioxidant role because they catalyze the reduction of hydrogen peroxide, organic hydroperoxide and lipid peroxides by reducing glutathione thus protecting cells against oxidative damage [41].

It is important to observe that plasma is a marker of current exposure, while erythrocyte is reported to be marker of long-term status [42]. Thus, the deficient intake of selenium is resulting not only in acute, but also chronic deficiency. These data point the association between selenium exposure and cognitive function, and thus nutritional strategies to improve selenium status should be investigated. Food sources are considered better than supplementation, because they are sustainable, less expensive, and have lower risk [43].

In this context, Brazil nuts (*Bertholletia excelsa*, L.) are the richest food source of selenium and besides being high content in magnesium and sulfur amino acids it also is balanced in its essential fatty acids [44]. Selenium in Brazil nuts is found in selenocysteine and selenomethionine species. Selenomethionine is the most

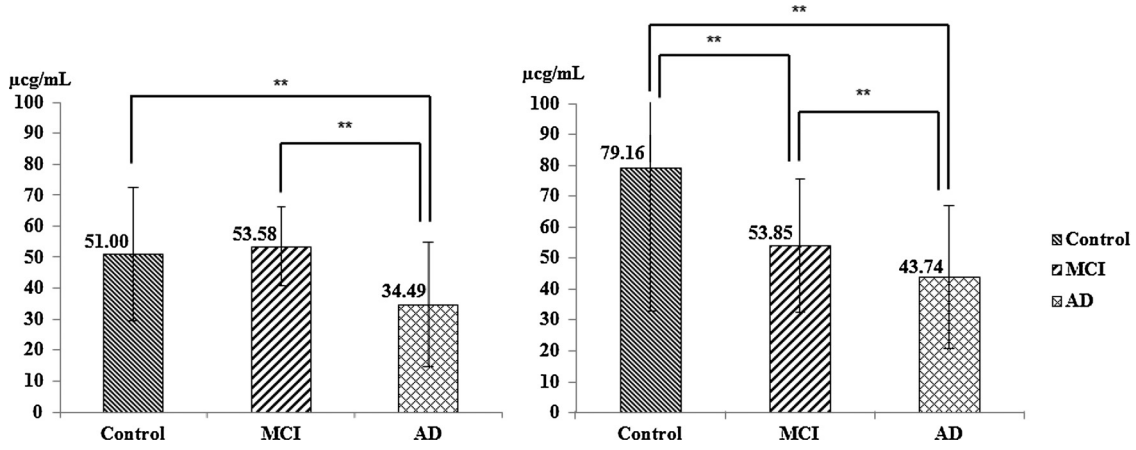

Fig. 1. Se levels in control, MCI and AD groups. (A) Plasma; (B) erythrocyte. $^{**}p < 0.001$.

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bioavailable species of selenium and studies show that it represents 75–90% of selenium in Brazil nuts [45,46]. Besides, we also highlight the data showed by Pires et al. [47] who observed that Brazil nuts demonstrated high antioxidant activity, inhibited lipid peroxidation and scavenged DPPH radicals in vitro, suggesting that these nuts present high antioxidant capacity.

The *Bertholletia excelsa* trees are harvested from the Amazon region in South America and represent the only selenium-accumulator plant regularly used as a food source. Because selenium content in Brazil nut is incomparable to other foods, the inclusion of this nut on the diet has been investigated in our lab in order to know how effective this nut is in increase selenium levels.

Behr [44] showed that one Brazil nut daily during 12 weeks resulted in increase of 49% and 229% in plasma and erythrocyte, respectively, in noninstitutionalized elderly. In the study of Cominetti et al. [48], 37 morbidly obese women consumed one nut daily during 8 weeks, and after treatment, no participants presented deficient selenium status. Besides, high-density lipoprotein cholesterol levels and glutathione peroxidase activity were increased. In other study, the consumption of only one Brazil nut per day during 3 months was effective to increase the selenium concentration and glutathione peroxidase activity in patients on hemodialysis [49]. Moreover, the intake of this nut also reduced inflammation, oxidative stress markers, and the atherogenic risk in these patients [50].

In conclusion, our data suggest that the deficiency of selenium may contribute to cognitive decline among aging people, and thus, the consumption of Brazil nuts should be encouraged in order to restore selenium status and improve antioxidant system.

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