Journal of Trace Elements in Medicine and Biology 27 (2013) 40–44

Contents lists available at SciVerse ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.de/jtemb

Nutrition

Serum selenium and selenoprotein P in patients with silicosis

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ARTICLE INFO

Article history:
Received 8 September 2011
Accepted 7 May 2012

Keywords:
Silicosis
Serum selenium
Serum selenoprotein P
Case–control study

ABSTRACT

Objectives: Selenoprotein P (SeP) is a selenium (Se) supply protein, which is an antioxidant micronutrient considered to be vital for human health. The aim of this study was to assess the serum selenium status in patients with silicosis.
Methods: We conducted a retrospective case–control study where serum samples from a total of 78 patients (males with a median age of 73.5 years old) with silicosis and 20 healthy controls (males with a median age of 72.5 years old) were assayed for Se and SeP. They underwent medical and job history taking, lung function testing, and chest radiography examinations. Levels of serum Se were measured using electrothermal atomic absorption spectrophotomerty, while levels of SeP were assessed with sandwich Enzyme Immunoassay. Spearman's rank correlation test was carried out to evaluate the relationship between Se and SeP. The Mann–Whitney test was used to evaluate differences in serum Se and SeP between study groups.
Results: The median serum Se and SeP concentrations were significantly lower in cases (74.0 μg/l and 4.2 mg/l, respectively) compared with controls (116.0 μg/l and 5.8 mg/l, respectively). In both cases and controls, serum Se was positively correlated with serum SeP (rho = 0.781, $p < 0.001$ and rho = 0.768, $p < 0.001$, respectively). Serum Se and SeP levels were significantly lower in patients classified in category four compared with those who were classified in category two or three.
Conclusions: Serum Se and SeP concentrations were found to be at inadequate levels in patients with silicosis, and decreased significantly with the severity of the disease.

Introduction

Recently, new silicosis cases have become rare in Japan but silicosis remains a public health issue due to past exposure to silica dust. Silicosis is an oxidative stress related disease [1] and remains a common cause of occupational lung diseases despite the evidence that it can be prevented by dust control [2]. The disease develops progressively and irreversibly over decades and currently there is no known cure [3]. Genotoxic and fibrogenic effects of silica and its potential to produce oxidative stress can lead to the development of lung cancer [4,5].

Oxidative stress is defined as an imbalance between oxidants released and antioxidant defenses which can affect proteins, lipids, carbohydrates and DNA in the human body; this imbalance has been implicated in the initiation or progression of cancers [6]. The role of selenium in lung cancer has been a subject of controversy. While no effects of selenium supplementation on cancer in humans have been reported [7], diets rich in anti-oxidants such as selenium, vitamin E, and carotenoids had been shown to protect against lung cancer [8]. Likewise, the Nutritional Prevention of Cancer Trial showed that a selenium supplement decreased the incidence of lung cancer [9]. Selenium is considered to be a chemopreventive agent for lung cancer in subjects with low selenium status, though it increases the lung cancer risk in subjects with higher selenium status [10].

Selenium was discovered in 1817 by the Swede, Jöns Jakob Berzelius. Its beneficial aspects were first noted in 1957 by Schwartz and Foltz, who reported that selenium salts protect against liver degeneration in mice, and later, in 1973 with the discovery of selenium as a component of glutathione peroxidase [11]. Selenium is a key component in enzymes that serve as redox catalysts and participate in the repair of proteins damaged by oxidative stress

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http://dx.doi.org/10.1016/j.jtemb.2012.05.003

[12]. These functions implicate the possible use of selenium in cancer prevention. The other mechanism by which Se is involved as a chemopreventive agent is through the inhibition of NF-κB and activator protein-1 [13]. Selenium has been found to protect cells against oxidative stress through selenoproteins, which are a family of proteins (SeP, glutathione peroxidases, iodothyronine deiododinases, thioredoxin reductases, etc.) containing selenium as the 21st amino acid, selenocystein. The most abundant selenoprotein found in plasma is SeP, which was discovered in the plasma of rats and named "selenoprotein P" in reference to the location where the protein was discovered for the first time [14]. SeP has two domains: the longer N-terminal domain that plays enzymatic roles and the smaller C-terminal domain that transports Se throughout the body [15]. Plasma selenoprotein P (SeP) contains approximately 40–60% of the total plasma Se [16,17], and mediates Se transport from the liver to other organs [18]. Compared with the selenoprotein glutathione peroxidase, plasma SeP is saturated at around 100 μg selenium/l, while the former becomes saturated at levels of 70–80 μg selenium/l and carries less than 20% of Se; therefore, SeP can be used in assessing human selenium status [19]. Lack of Se diminishes selenoprotein biosynthesis and is a risk factor for Keshan disease [20], and for anemia among people with human immunodeficiency virus infection [21].

Plasma selenium has been found to be reduced in asbestos-exposed workers and coal miners [22,23]. Data on selenium and silicosis are scarce; therefore, we aimed to describe the profiles of serum Se and SeP in patients with silicosis.

Materials and methods

Participants

This study was a retrospective case–control study using data from a total of 78 patients with silicosis (median age, 73.5 years old; range, 59–87 years old) engaged in regular check-ups in one of the clinics in Kochi prefecture, Japan. All patients were male, consisting of 69 former smokers and nine who were non-smokers.

Twenty healthy subjects, all males (median age, 72.5 years old; range, 60–81 years old), were selected as the control group. Data on selenium-rich food intake was not available; however, all the participants were from Japan, a country where the median of dietary selenium intake in men has been reported as 177.5 μg/day [24].

The diagnosis of silicosis was done on a clinical and radiological basis. Chest X-ray examinations were performed using digital chest radiographies (CXDI, Canon Inc.) and the chest radiographies for 78 patients with silicosis were reviewed by occupational physicians and classified in the following four categories using the Japanese Classification of Radiographs of Pneumoconioses [25]. Category one: profusion zero of small opacities (0/−, 0/0, 0/1); category two: profusion one of the small opacities (1/0, 1/1, 1/2); category three, and category four. Category three was divided into two subcategories: subcategory A, profusion two of small opacities (2/1, 2/2, 2/3) and subcategory B, profusion three of small opacities (3/2, 3/3, 3/+) and large opacities "A and B types". Category four was also divided into two subcategories, profusion one of the small opacities to profusion four of large opacities with severe pulmonary dysfunction, and large "C type" opacities with or without severe pulmonary dysfunction. Severe pulmonary dysfunction was defined by impaired pulmonary function tests, and abnormal arterial gas analysis. We also measured height and body weight. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Pulmonary function tests were performed using a spirometer (AutoSpiro AS-307/AS-407, Minato Medical Science Co., Japan).

All participants were made aware of the study's objectives and gave their informed consent. The study protocol was approved by the ethical committee of Kochi Medical School and was carried out in accordance with the Helsinki Declaration.

Laboratory assays

Laboratory measurements included serum Se and SeP, and blood samples were collected during the follow-up period at Kinro clinic. Samples were drawn into tubes and left to clot spontaneously, and they were then centrifuged at 2000 × *g* for 10 min. Obtained serum samples were stored in aliquots at −80 °C until measurement. Total serum Se concentrations were measured by electrothermal atomic absorption spectrophotometry using chemical modifiers (Ni^{2+}, Pd and NH_4NO_3) as described by Wang [26].

Serum SeP concentrations were determined by sandwich enzyme immunoassay using purified SeP as the standard, kindly provided by Dr. Saito et al. [27]. Serum selenium ranging from 70–118 μg/l was considered as normal [28].

Statistical analysis

Data processing was performed with the Stata software package version 10 (STATACORP LP, College Station, TX, USA), and a significance criterion of probability value of $p < 0.05$ was used. Spearman's rank correlation test (rho) was carried out to evaluate the relationship between Se and SeP. As serum Se and SeP data were not normally distributed, the non parametric Mann–Whitney test was used to evaluate differences in serum Se and SeP between silicotic participants and control groups. The serum selenium and SeP data were converted to logarithms before using the Student's *t*-test. Results are presented as mean ± SD, geometric means, or as medians (ranges).

Results

Background characteristics of participants

As shown in Table 1, data analysis was conducted for 78 participants with a diagnosis of silicosis, and all of them were removed from silica exposure. Their median age was 73.5 years old (range 59–87 years old), and their mean BMI ± SD was 24 ± 3 kg/m^2. Most of the participants with silicosis were former smokers (88.5%) with a mean of twenty-seven pack-years of smoking. The average number of years since they stopped smoking was 18 years. A majority of the participants with silicosis were tunnel drillers (87.2%) with an average of 16 years (range 1–44 years) occupational exposure to dust. The control groups included 20 healthy subjects, who were former smokers (80%) with a median age of 72.5 years (range 62–81 years old) and a mean BMI ± SD of 24.5 ± 4 kg/m^2.

Serum findings in cases and controls

As shown in Table 2, both Se and SeP concentrations in serum were significantly lower (Mann–Whitney test, $p < 0.001$) in cases (74 μg/l and 4.2 mg/l, respectively) compared with controls (116 μg/l and 5.8 mg/l, respectively). In the group of cases, serum

Table 1
Background characteristics of participants.

Characteristics	Silicotics ($n = 78$)	Controls ($n = 20$)	p value
Age (year)[a]	73.5 (59–87)	72.5 (62–81)	0.33
No of current smokers (%)	0	0	–
No of former smokers (%)	69	16	0.45
Exposure (year)[b]	16 ± 8	–	–
BMI (kg/m^2)[b]	24 ± 3	24.5 ± 4	0.26

[a] Values are presented as medians (ranges).
[b] Values are means ± standard deviations.