Serum Selenium Concentration is Associated With the Development of Age-Related Cataract

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Abstract

Purpose: To evaluate the correlation between the occurrence of age-related cataract (ARC) and the concentration of serum selenium.

Methods: A study group included 95 cataract patients (36 men, 59 women), aged 56-89 years (72.4 ± 7.25), not suffering from other ocular diseases or systemic diseases with proven impact on the eye function or on blood levels of electrolytes. A control group consisted of 187 healthy subjects (71 men, 116 women); mean age-70.9 years old ± 7.36 (range of age: 53-88 years old). Selection matching criteria for the control group were: sex, age (± 3 years) and smoking. Subjects taking any supplements were excluded from the study. Measurement of serum selenium concentration was carried out by Inductively Coupled Plasma Mass Spectrometry. Statistical analysis was performed by Fisher’s exact test.

Results: 1) Lower levels of selenium were associated with greater occurrence of cataract, 2) The threshold point of selenium level for an increase of ARC was ~70 µg/l for females and ~73 µg/l for males 3) The optimal selenium level in ARC patients was estimated 75-85 µg/l and >80-85 µg/l for women and men respectively.

Conclusions: 1) Concentration of selenium in the blood serum may be a marker of occurrence of age-related cataracts. 2) The low selenium levels may be a risk factor for age-related cataract in the population with low selenium baseline level.

Keywords: Selenium; Age-related cataract; ICPMS

Introduction

The age-related cataract (ARC) is responsible for 51% of world blindness and affects up to 20 million people [1]. Globally ARC causes moderate to severe disability in more than 50 million patients [2]. Presently the only effective treatment is a surgical removal of the opacified lens and replacing it with an artificial implant. However the ARC incidence is so great that the available facilities in many countries are unable to cope up with the problem. The cataract surgery is the most frequently performed surgical procedure in USA with 3 million surgeries performed each year [3]. Although serious surgical complications as endophthalmitis are infrequent, post-operative refractive error or posterior capsular opacification are more common [4]. Thus attempts to find non-surgical procedures that will preserve the lens transparency are being made worldwide. During the last twenty years etiology of ARC was studied extensively. Efforts have been directed to slow down progression and to delay the onset of ARC by various agents unfortunately without much success.

The key role in the pathogenesis of ARC is an excessive oxidative stress [5-9]. Selenium (Se) is an active component of glutathione peroxidases (GPx)-enzymes responsible for removal of free radicals and reducing oxidative stress. Results of animal studies indicate that low Se concentration can reduce expression of GPx, and thereby increase ARC progression [10, 11]. Moreover formation of ARC has been observed in GPx-1 knockout mice [10]. Selenium reduces cisplatin-induced oxidative damage of lens [12] and ebselen, a synthetic organoselenium drug molecule, has a protective effect on cataract formation in rats [13]. Several studies in humans suggested a significant role of Se on the occurrence of ARC [14-16]. This impact seems to be especially important in populations with low baseline Se level such as Polish population. In Poland average Se concentration is 70 µg/L, two times lower than in USA [17]. In our observational study, we analyzed Se serum level in a series of ARC patients to determine possible correlation between Se concentration and ARC. The advantages of this project were strict selection criteria for studied groups, homogeneity of population and precision of measuring equipment.

Material and Methods

We qualified for the study 95 patients (36 men, 59 women), age 72.4 years old ± 7.25 (range of age: 56-89 years old) with ARC who underwent surgery in the Department of Ophthalmology, Pomeranian Medical University. The exclusion criteria were other eye diseases (glaucoma, uveitis, elevated intraocular pressure >21 mmHg, myopia >-6 diopters) or history of medical treatments which are known to be associated with an increased risk of cataract (i.e. pilocarpine). Patients were also excluded if they had congenital, traumatic, secondary (i.e. UV exposition) cataract. Patients with systemic diseases with proven
impact on the organ of vision (i.e. diabetes, rheumatoid arthritis), who took drugs affecting electrolytes levels (i.e. diuretics, steroids) were excluded. Control group consisted of 187 healthy people registered at the Centre for Hereditary Cancer, Pomeranian Medical University (71 men, 116 women); mean age was 70.9 years old ± 7.36 (range of age: 53-88 years old). Matching criteria were: gender, age (± 3 years), smoking "packed-years" (the number of packs of cigarettes per day multiplied by the number of years of smoking, ± 20%). This research was approved by Institutional Review Board (IRB) of Pomeranian Medical University in Szczecin, Poland. Informed consent was obtained from all individual participants included in the study. This research has been conducted according to the principles expressed in Declaration of Helsinki.

Venous fasting blood samples were analyzed within two hours of collection. The serum Se level was determined using Inductively Coupled Plasma Mass Spectrometry (ICP-MS), Perkin Elmer, USA. Selenium serum level in each quartile of study and control groups were compared with statistical analysis. The statistical significance was assessed with Fisher’s exact test. Odds ratios were calculated for 20 sliding windows at constant level of concentration of Se data points to establish the relationship between disease risk and serum Se concentration. The smoothing curves and 95% confidence intervals were based on a polynomial regression. The graphics and the calculations were performed using a free statistical software package of R-version-2.13.1.

**Results**

The cohort of 95 patients and 187 controls was divided into quartiles with various Se levels; I-the lowest, IV-the highest (Table 1). OR were estimated to assess the correlation between occurrence of ARC and serum Se concentration between quartiles groups, i.e. group I vs. group II (Table 2). ARC patients were more likely to be in the lowest Se quartile (I group) in comparison to other groups (quartiles). The threshold point of serum Se level for an increase of ARC risk (OR>1) was ~70 µg/l for females and ~73 µg/l for males. The risk curve of ARC in relation to Se levels seems to be similar for both sexes but somewhat steeper for men than for women (Figure 1). The optimal Se level in ARC patients was estimated to be 75-85 µg/l and >80-85 µg/l for women and men respectively (Figure 1). In male group no. I (the lowest Se level-31,64-69,67 µg/l) ARC risk increased 8 times in comparison to group with the highest Se concentration (Table 2, I vs. IV, OR=8, p=0.0016, CI 95%=2.15-29.75). The gradient response was observed with a slight risk-increasing tendency at the end of the curve ("U" - curve model) - characteristic better expressed in women cohort (Figure 1).

![Figure 1](image-url)

**Figure 1:** Serum Se level and ARC risk by sex. The relationship between serum Se level and the risk of ARC in form of odds ratios at each of the Se level. The odds ratios are calculated for sliding windows of 20 Se values each. The reference baseline odds ratio of 1 has been added as a black line. The smoothing curves and 95% confidence intervals (shadows around the curve) are based on a polynomial regression. F: Female; M: Male.
Table 1: Comparison of the number of ARC patients vs. controls in quartiles with various Se level.

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>4</td>
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</tbody>
</table>

Table 2: The comparison of odds ratios of ARC between quartiles with various Se level.

<table>
<thead>
<tr>
<th>Compared quartiles</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>I vs. II</td>
<td>2.47</td>
<td>0.1728</td>
</tr>
<tr>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>I vs. III</td>
<td>5.09</td>
<td>0.0119</td>
</tr>
<tr>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>I vs. IV</td>
<td>8.00</td>
<td>0.0016</td>
</tr>
<tr>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>II vs. III</td>
<td>2.05</td>
<td>0.0016</td>
</tr>
<tr>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>II vs. IV</td>
<td>3.23</td>
<td>0.0118</td>
</tr>
<tr>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>III vs. IV</td>
<td>1.57</td>
<td>0.7217</td>
</tr>
</tbody>
</table>

It is worth noting, that Knekt et al. [16] did not find correlation between serum Se level and ARC occurrence. In the Knekt’s study however, diabetic patients were not excluded, it was not indicated whether blood testing was fasting or not-fasting and whether patients used diuretics. A smoking factor was also not included in matching criteria for control group. As Se levels could be affected by metabolic changes, drugs including diuretics, diabetic diet and latent nephropathy such a study design, may have influenced the results [16-30]. In our study all patients with diseases other than hypertension and patients using diuretics were excluded to minimize the effects of diseases and drugs on serum Se levels. It is widely known, that smoking decreases Se level directly and indirectly, through its influence on other micronutrients such as cadmium, zinc, etc. [15]. Therefore in our study not only smoking factor was included, but also smoking pack-years were calculated to precisely match control group.

In our study there was a slight, not statistically significant, risk-increasing tendency of ARC at the end of the ARC risk curve, a characteristic better expressed among women (Figure 1). According to Jaques et al. [24] ARC risk grows four times (OR=3.96 for any cataract type, OR=3.79 for cortical cataract, 0.05<p<0.1), when Se level is >100.3 µg/l. In that study statistical significance was defined as p<0.10. The other limitation is that smoking was not included in the final regression models. Li et al. [25] studied the prevalence of ARC in high-Se areas of China. It was found that high Se intake was not a risk factor for the increase of ARC incidence. The disadvantage of that study is lack of assessment of baseline serum Se levels in population. That may have profound effect not only on ARC occurrence, but also on Se supplementation effects, which is discussed below. Moreover genetic variations in the proteins that metabolize Se may affect its biological function. Consequently population specific differences in genetic variations (i.e. GPs 1-6 genes) may contribute to the observed alterations [26]. Therefore further research is warranted on a various populations including the assessment of genetic factors. There is no clear data suggesting that high serum Se concentration increases ARC occurrence in humans. It is worth noting that animal experiments have suggested that not only insufficient Se intake [11, 20, 23], but also excessive [27, 28] Se supplementation resulted in cataract formation (“selenite cataract”). It would support an “U”-curve model of Se biological effect and toxicity. The selenite cataract shows some general similarities to ARC: reduced level of glutathione and water soluble proteins, increased calcium concentration, etc [6, 27]. However selenite cataract seems to be dominated by rapid calpain-induced proteolytic precipitation, while human ARC may be caused by oxidative stress over a long time period. Contrary to human ARC, in selenite cataract there is increased disulfide formation and no high molecular weight covalent aggregation [27]. The important pathophysiological differences between ARC and selenite cataract may explain why “U” curve model is not observed in our presented data (Figure 1).

Our observational study indicates that concentration of Se in the blood may be a marker of occurrence of ARC. However in order to determine whether Se level is an ARC risk factor; intervention study should be carried out. There were three randomized controlled trials addressing supplementation of antioxidants, with Se as one of the ingredients (Table 3) [28-30]. Each of them has some limitations. In the largest study conducted in 2015 (The Selenium and Vitamin E Cancer Prevention Trial-SELECT Eye Endpoints Study), 11000 participants were being observed for 5.6 years [28]. The study found that long-term daily supplementation with Se (200 µg per day from L-selenomethionine) was unlikely to have a beneficial effect on ARC. During the study 389 ARC were documented (185 in Se group, 204 in...
no Se group, hazard ratio 0.91; p=0.37). It is worth noting that in North America the average reported Se concentration ranged from 122.4-151.8 µg/l, while in center Europe (i.e. Poland) 70 µg/l [17]. The difference in baseline Se blood levels can have significant consequences on supplementation impact. Some evidence suggests that Se intake required to optimize all selenoproteins would require plasma Se level of 125 µg/l [31]. In other words additional Se supplementation might not be beneficial in USA, while it can contribute to cataract prevention in low-Se areas such as Poland.

### Table 3: Occurrence of ARC in supplemented patients in comparison to control group.

<table>
<thead>
<tr>
<th>Study name</th>
<th>supplement</th>
<th>Study group</th>
<th>Follow-up period (years)</th>
<th>General lens opacity</th>
<th>No. of nuclear cataract</th>
<th>No. of cortical cataract</th>
<th>No. of posterior capsule opacity</th>
<th>Visual outcome</th>
<th>Surgery rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select [28]</td>
<td>Selenium VII E</td>
<td>11000</td>
<td>5.6</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>CTNS [29]</td>
<td>Centrum</td>
<td>1000</td>
<td>9</td>
<td>lower&lt;sup&gt;2&lt;/sup&gt;</td>
<td>lower&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>higher&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Areds [32,33]</td>
<td>Centrum</td>
<td>4400</td>
<td>8-12</td>
<td>lower&lt;sup&gt;2&lt;/sup&gt;</td>
<td>lower&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Linxian [30]</td>
<td>Centrum β carotene</td>
<td>2100</td>
<td>5-6</td>
<td>-</td>
<td>lower&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Linxian [30]</td>
<td>Selenium α-tocopherol β carotene</td>
<td>3200</td>
<td>5-6</td>
<td>-</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ns&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>1</sup> ns: not significant; <sup>2</sup> lower: lower occurrence in comparison to controls; <sup>3</sup> higher: higher occurrence in comparison to controls

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Acknowledgements

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### Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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### References