



## Clinical studies

## Aqueous humor selenium level and open-angle glaucoma

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## ABSTRACT

**Purpose:** Selenium supplementation was seen to be linked to glaucoma disease in a previous study (Lillico A. JE, Reid M et al. (2002) Selenium Supplementation and Risk of Glaucoma in the NPC trial University of Arizona, Tucson, AZ., Arizona Cancer Center). As aqueous humor levels of selenium seemed to be associated with primary open-angle glaucoma (POAG), the aim of this study was to analyze concentrations of selenium in aqueous humor samples of patients with POAG and pseudoexfoliation glaucoma (PEXG) in comparison to normal samples.

**Patients and Methods:** Thirty-eight aqueous humor samples from patients undergoing cataract surgery were collected: Eleven patients with PEXG (age  $65.8 \pm 10.69$ , female 6, male 5), 12 patients with POAG (age  $65.3 \pm 10.50$ , female 7, male 5) and 15 patients without glaucoma (age  $70.9 \pm 12.83$ , female 10, male 5, controls). Aqueous humor levels of selenium were measured by Flow-Injection-Inductively-Coupled-Plasma-DRC-Mass-Spectrometry (ICP-DRC-MS).

**Results:** Maximum likelihood estimation of the least squares means (LS-means) and the relative 95% confidence limits of selenium aqueous humor levels were  $6.90 \pm 1.03 \mu\text{g/L}$  (control),  $6.74 \pm 1.14 \mu\text{g/L}$  (POAG) and  $8.25 \pm 1.18 \mu\text{g/L}$  (PEXG). The data were modeled using a generalized linear model (GLM) analysis, where selenium was set as dependent variable. The model was corrected for group differences in age and gender. The data show no differences among all the calculated differences between the least square means (LS means), taking in consideration the simultaneous 95% confidence limit and the multiple comparison tests with Tukey-Cramer adjustment. The evaluation of the model disclosed that POAG and PEXG patients had no significantly different aqueous humor selenium concentrations compared to controls and to each other. However, the quantile regression analysis of selenium aqueous humor levels showed differences in quantiles for open-angle glaucoma patients considering age and gender.

**Conclusion:** As no significant difference in aqueous humor concentration of selenium was detected between open-angle glaucoma and controls, however, quantile analysis showed differences in quantiles levels for different age ranges in open-angle glaucoma patients, the trace element selenium seemed to be linked to glaucoma disease, yet not in a major role.

## 1. Introduction

Glaucoma is one of most common causes of blindness worldwide

[1]. The diagnosis of this neurodegenerative disease is based on an altered optic disc, elevated intraocular pressure (IOP) and perimetric field defects. Up to date the origin of glaucoma is unknown. It seems

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that the pathogenesis is multifactorial, whereas IOP is a major key-player. However, although IOP regulation can be achieved, some patients show a disease progression. Thus the pathophysiology is influenced by several factors, of which not all are known up to now. Next to molecular findings (e. g. interrupted retrograde transport of neurotrophins [2]) or ocular ischemia [3], nutrition and dietary supplementation seem to be involved via oxidative stress mediated changes. [4] [5];

An imbalance between oxidants (free radicals) and antioxidants results in oxidative stress. If free radicals dominate, molecular interactions and cellular integrity is disturbed. [6] [7]; Considering specific dietary supplementation in diseases, which are linked to oxidative stress (e. g. cancer), the Nutritional Prevention of Cancer (NPC) trial investigated the influence of selenium (Se) substitution on cancer incidence [8]. Selenium supplementation (200 µg per day) decreased significantly cancer incidence. However, glaucoma incidence rose as a side effect with a hazard ratio of 1.78 [9]. This observation generated the hypothesis of a selenium linked pathogenesis of glaucomatous optic nerve atrophy, potentially because selenium can be toxic in large amount supplementation to both animals and humans [10–13]. Bruhn et al. followed this idea of a potential increased selenium concentration in glaucoma patients and researched plasma and aqueous humor levels in primary open-angle glaucoma patients (POAG) [14]. Selenium concentration of plasma and aqueous humor were found to be increased in POAG, however level of significance was not reached. Up to date this is the only study on selenium analysis in aqueous humor of POAG. No trial was performed on aqueous humor selenium level in pseudoexfoliation glaucoma (PEXG) until now.

Thus it was the aim of this trail to investigate selenium concentrations in aqueous humor of POAG and PEXG with the Flow-Injection-Inductively-Coupled-Plasma-DRC-Mass-Spectrometry (ICP-DRC-MS). All data were compared to a control group.

## 2. Material and methods

### 2.1. Patients

Consecutive series of thirty-eight patients of the Department of Ophthalmology and Eye Hospital, Friedrich-Alexander-University of Erlangen-Nürnberg (FAU) were involved in the study: Eleven patients with PEXG (age 65.8 ± 10.69, female 6, male 5), 12 patients with POAG (age 65.3 ± 10.50, female 7, male 5) and 15 patients without glaucoma (age 70.9 ± 12.83, female 10, male 5, controls). Informed consent was obtained from all patients. The study was approved by the Local Ethics Committee and performed according to the tenets of the Declaration of Helsinki.

Glaucoma was diagnosed as an altered optic disc, which was classified after Jonas [15,16], a confirmed untreated IOP > 21 mm Hg and a perimetric field loss (MD > 2.8; ≥3 adjacent test points on the pattern deviation map with a probability of < 5% or ≥2 adjacent test points on the pattern deviation map with a probability of < 1%; Octopus 500, G1 protocol, Interzeag, Schlieren, Switzerland), which was confirmed twice. PEXG diagnosis was based on a glaucomatous optic disc damage, according to the classification after Jonas [15,16], an IOP > 20 mmHg, perimetric field defects, diagnosed as described above, and PEX material deposits on anterior segment structures with an open chamber angle. Controls had no signs of any ophthalmic diseases except cataract.

All patients underwent ophthalmic examinations, including slit-lamp biomicroscopy, funduscopy and Goldmann applanation tonometry. Detailed anamnestic data were obtained from each patient, including their individual lifestyle and nutrition. Patients, taking nutritional supplements (e. g. selenium supplementation) or other medicals, affecting selenium concentrations, were excluded. Further on, patients with malignant neoplasia, a major systemic disease, hypovitaminoses, psychiatric illness, hypothyroidism, severe psoriasis and

gastrointestinal malabsorption in their history were not included. Similarly, cigarette smoking and chronic alcohol use (during the last 6 months) were excluded.

### 2.2. Methods

Samples of aqueous humor (100 to 150 µl) were collected from all patients undergoing cataract surgery with phacoemulsification. Before performing the corneal tunnel, aqueous humor was obtained through an ab-externo limbal paracentesis via a 27-gauge needle on a tuberculin syringe. No bleeding occurred during performing of the paracentesis. The samples were immediately frozen in liquid nitrogen and stored at –80 °C.

### 2.3. Trace element analysis

Selenium concentration was measured by Flow-Injection-Inductively-Coupled Plasma - Dynamic Reaction Cell -Mass-Spectrometry (ICP-DRC-MS) according to [17]. This method is based on the superior detection capability of ICP-DRC-MS using methane as reaction gas [18] and the most abundant <sup>80</sup>Se isotope combined with flow-injection (FI) methodology for low sample volumes. To minimize sample consumption we combined the FI mode with a semi-automated injection. This kept the total sample volume below 80 µL for triplicate analysis per sample. The FI sample introduction was conducted by coupling a Knauer 1100 Smartline inert Series HPLC system with a 25 µl injection loop coupled to the ICP-DRC-MS. Flow rate was 1 ml/min of Milli-Q water. Instrumental settings for ICP-DRC-MS [17] and are given in Table 1.

Se-working standards were prepared daily from the Se-stock standard solution by appropriate dilution at concentrations between 50–5000 ng/L, providing a 9 point calibration curve. All Se-standard solutions, the aqueous humor samples, and control samples were prepared with a final Rh concentration of 1 µg/L as internal standard. For quality control blanks and control-standards were measured periodically between samples. Methodical figures of merit were given in [17] and are confirmed for this work. In short terms: LOD: 26 ng/L, serial or day-to-day precision both at 2 µg/L: 4.5% or 5.6%, mean recovery (2 µg/L): 101 ± 0.1%. The method was validated by measuring reference materials: Accuracy was determined in reference serum (Recipe, Munich, Germany) at 97% (control value: 62 µg/L) and reference urine (Recipe) at 105% (control value: 23 µg/L).

### 2.4. Statistical analysis

All the elaborations were done using SAS version 9.3 (SAS Institute

**Table 1**

The instrumental settings for ICP-DRC-MS (inductively coupled plasma mass spectrometry).

Instrument	Perkin Elmer Sciex ELAN DRC II, Toronto, Canada
<b>Plasma conditions</b>	
Rf power (W)	1250
Plasma gas flow (L/min)	15
Auxiliary gas flow (L/min)	1.05
Nebulizer gas flow (L/min)	0.83, daily optimized
<b>Mass spectrometer settings</b>	
Dwell time (ms)	300
Sweeps per reading	6
Readings per replicate	1000
Autolens	On
Ions monitored	<sup>80</sup> Se, <sup>103</sup> Rh
Reactions gas	CH <sub>4</sub>
Reaction gas flow rate (ml/min)	0.6
Rejection parameter q	0.6
Rejection parameter a	0.0

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