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Mechanisms of interaction of selected environmental factors on the formation of pathophysiological changes in cataracts

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ABSTRACT

Biotechnology is a relatively young interdisciplinary discipline of science. Thanks to her techniques, we can currently do a lot of research. Biotechnologists in cooperation with other scientists are trying to develop new standards that would become the future of treatment for many diseases, including cataracts. Today, cataracts are increasingly recognized as a civilization disease of the eyes. Unfortunately, if left untreated, it can lead to complete blindness. The etiology of this disease is complex and not fully understood. At present, its foundations are being sought to be able to diagnose her faster and to introduce appropriate treatment early. Literature data currently indicate that it can arise as a result

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of: age- related changes, genetic (congenital) conditions, inflammation, metabolic disorders, the effects of certain drugs, and complications of eye diseases. From the latest reports we learn that antioxidation can have positive effects when dissolving the protein directly affecting the formation of cataracts. Biotechnology has amazing opportunities to conduct research that can help bring closer the etiology of cataracts and start to treat the disease faster by which so many people in the world lose sight.

***Keywords*:** cataract, biotechnology, antioxidant, reactive oxygen species, oxidative stress

1. INTRODUCTION

Eyes are one of the basic organs through which we can admire the world around us. The organ of vision consists of two basic parts, namely the eyeball and optic nerve. The eye is exposed to many dangerous factors, both internal and external, which can lead to the formation of pathophysiological changes and worsen its condition. There are currently many eye diseases. The incidence problem is very large and widespread, which is why the etiology of these diseases is constantly being sought in order to be able to diagnose them faster and to introduce appropriate treatment. These diseases include cataracts, diabetic retinopathy, glaucoma and macular degeneration (1-3).

Cataract is a disease affecting the lens of the eye that is responsible for breaking the light rays that reach it. Another name for this disease entity is the cataract, because inflammation was once thought to "flow" from the brain to the eye like a waterfall. The opacity arising within the lens affects visual acuity (4, 5).

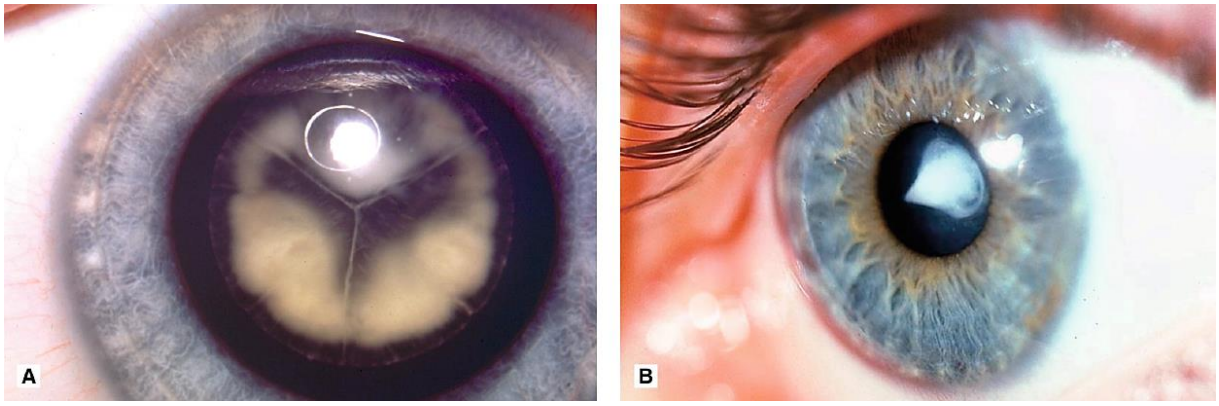

Fig. 1. Developmental cataracts. A. Congenital opacity involves embryonic nucleus of lens, which is delimited by “Y” sutures. B. Anterior pyramidal cataract. Cone of collagenous connective tissue projects from anterior surface of lens. Anterior pyramidal cataract is a development variant of ASC; source: (1)

The lens is located in the front of the eye, between the iris and the vitreous. Its task is to break the sun rays that hit the eye. Participates in the accommodation of the eye, which consists in the correct positioning of the eye depending on the distance from the object. As one of the few parts of the eye, it does not have blood vessels, thanks to which there is no inflammation

of the lens. Unfortunately, her pathophysiology or loss of transparency can lead to blindness (6.5.4.2).

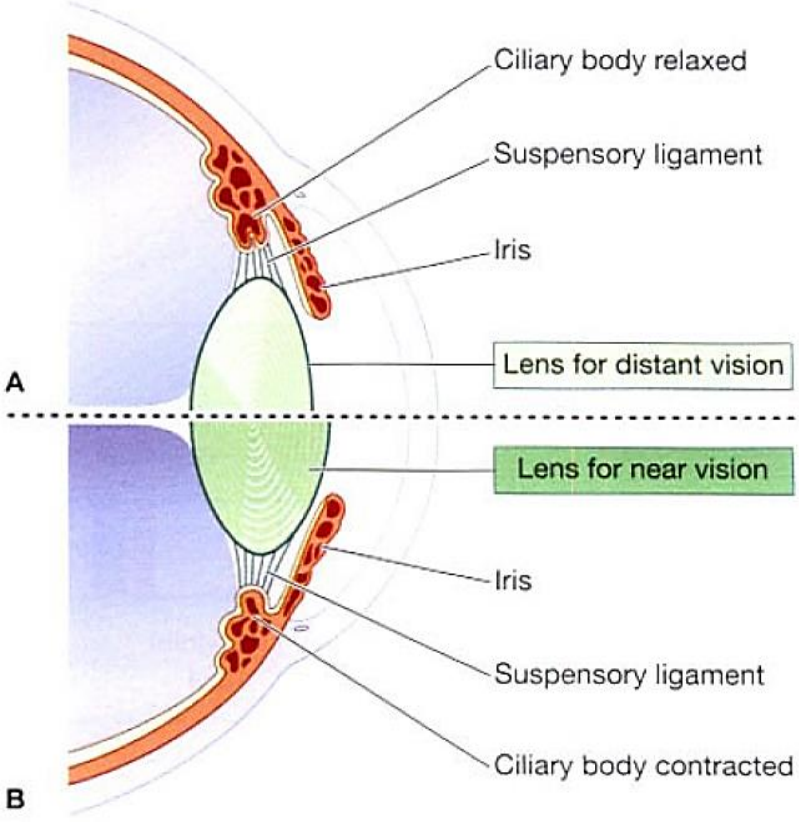

Fig. 2. The shape of the lens changes depending on the distance of the object. A - objects far away, B - objects close; source (8)

The clouding of the lens itself is often due to several (so far confirmed) reasons: age-related changes, congenital changes, complications of eyeball or body diseases, injuries, inflammations, metabolic disorders, nutritional errors, effect of corticosteroids (6, 7).

Nowadays, a lot of attention is paid to the importance of environmental conditions during the formation of lens opacities. There are many indications that environmental pollution, among others heavy metals accelerate the incidence of this disease. Essential oxygen can also be dangerous, because it contributes to the formation of free radicals. Reactive oxygen species (RFT) that directly affect the formation of oxidative stress (7-9).

The first signs that can be seen are blurring of the image and general visual disturbances. The resulting changes depend primarily on the severity of the cataract and its location. The location varies, ranging from subcapsular, cortical or nuclear, to the anterior or posterior. The cataract develops at different rates, the lens may cloud up slowly and very quickly. So far, despite many studies in this direction, scientists have not been able to demonstrate specific and unequivocal causes of these pathophysiological changes. Additional changes that are

determined during cataracts include a change in the color of the lens itself to yellow or amber (6.7).

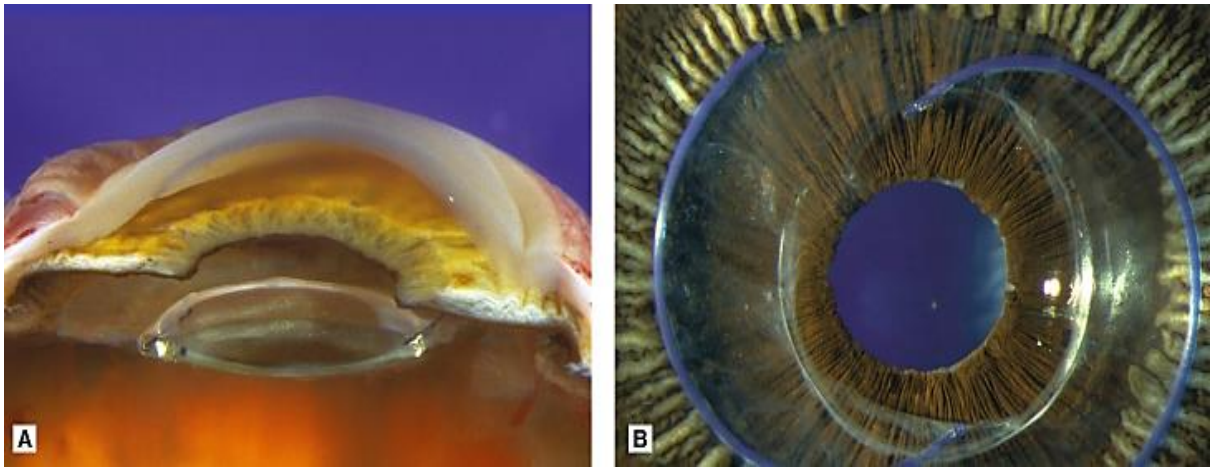

Fig. 3. Pseudophakia. A. Optic of posterior chamber IOL is seen within lens capsular bag in posterior chamber; source (2)

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2. REACTIVE OXYGEN SPECIES

Reactive oxygen species (RFT), which are one of the main causes of oxidative stress, negatively affect eye cells, contributing to their damage. This undesirable effect is eliminated by the use of various antioxidants (8-10). RFTs are alone because they have one or more unpaired electrons in valence orbit. In addition, free radicals are formed as a result of many chemical reactions, and some are even catalyzed by enzymes found in cells. According to WHO, air contains dangerous compounds, among others: carbon monoxide (CO), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2), which, in addition to their own harmfulness, also contribute to the formation of oxidative stress and oxide radicals . It has been proved that there is a relationship that indicates that the appearance of one reactive oxygen species leads to the

appearance of others. One such reaction is the formation of a hydroxyl radical from another ROS, which is hydrogen peroxide. Reactive oxygen species undergo non-specific reactions with selected components of all body cells, including ocular ones, leading to their modification and, ultimately, to their damage (8, 11-14).

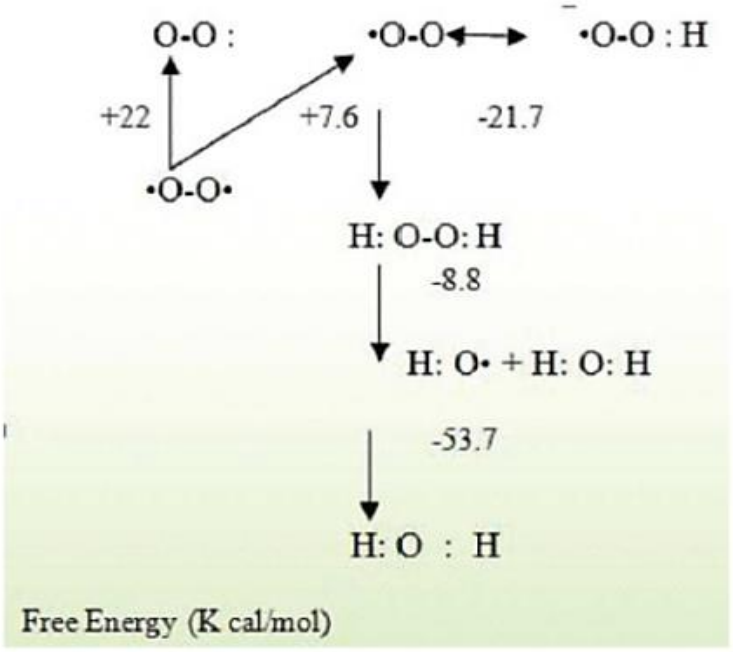

Fig. 4. The activation states of oxygen

The uncontrolled increase in the concentration of reactive oxygen species seriously affects the economy in biological systems and can have serious effects on human health. The action of pro-antioxidant reactions is primarily aimed at inhibiting the effects of ROS and oxidative stress, which directly destroys cells, leading to their degeneration. An imbalance between antioxidants (antioxidants) and oxidants (oxidants) can lead to many diseases, including cataracts. It has been confirmed that antioxidants can reverse some of the changes caused by the effects of ROS and oxidative stress (8, 15-17).

3. IMPACT OF ELEMENTS

It turns out that the chemical elements have an impact on the formation of pathophysiological changes in the human body, also by contributing to the formation of oxidative stress. However, the chemical elements have both oxidative and antioxidant character. It has been proved, among others, that Fe, Cu, Zn or Mn exhibit antioxidant properties, while Cd, Pb have oxidative effects. Scientists confirm that Cd, Fe, Hg and Pb negatively affect the eyes, by increasing the concentration of free oxygen radicals (directly or indirectly). In turn, microelements such as Zn and Se, which are the building blocks of antioxidant enzymes, protect against oxidative stress. (18, 19). It should be noted that there are

significant correlations, synergisms and antagonisms between the elements, which are very often one of the main factors in the formation of diseases such as cataracts (20-22).

Environmental pollution and heavy metal contamination directly affect changes in the body. Interactions to inhibit the formation of dangerous damage are also important (3, 20, 22). Here it is used, among others biotechnology, which thanks to its research methods can contribute to learning about the impact of elements on developing cataracts.

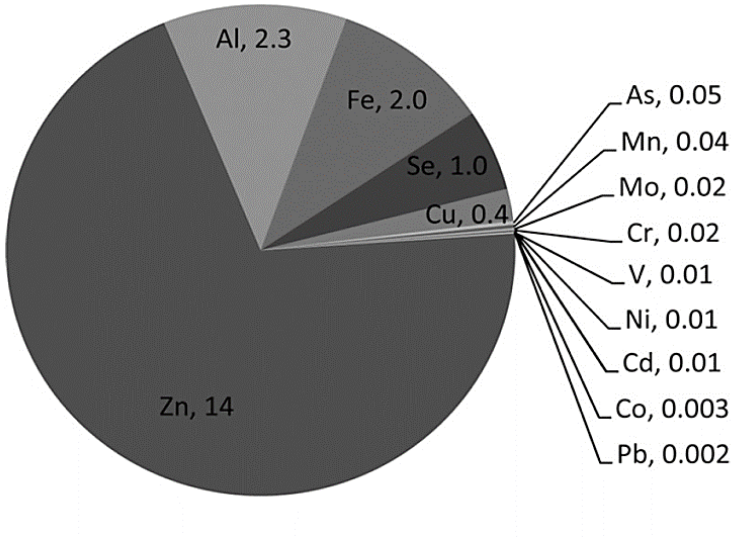

Fig. 5. Comparison of metal ion levels in the human lens. A pie chart showing the relative proportion of 14 metal ions quantified in people without known (obvious) cataract. The average value (μg * g^{-1} dry tissue) is shown next to the symbol of the element concerned; source: (25)

Studies conducted so far indicate concentration, among others heavy metals including lead, which accumulates in the retinal epithelium and in the choroid (16, 23, 24).

One of the methods indicating the concentration of elements in plasma is ICP-MS, i.e. mass spectrometry with inductively coupled plasma excitation. This method allows quantitative analysis of chemical elements contained in plasma. The basic parameters for determining elements by this method is agron as a carrier gas. In addition, ^{45}Sc, ^{89}Y, ^{159}Tb are used as internal standards for the determination of each sample (3, 26, 41).

Many elements affect the lens. Some are positive and have oxidative properties, while others are toxic, damaging and contributing to lens damage. One of the main representatives of this second group are heavy metals, which also include cadmium and lead. They are toxic and have the ability to accumulate in the human body. Their excess in the body contributes to metabolic changes, which at a later stage can cause cataracts (21, 23, 29).

It has been shown that lead can accumulate directly in the lens of the eye, where it acts as a protoplasmic poison. In addition, the presence of lead in the body causes many symptoms that are often confused with other diseases, making it difficult to diagnose its presence sometimes. Lead effectively competes for the binding site of pro-antioxidant ions that could block its harmful effects (24, 25, 30).

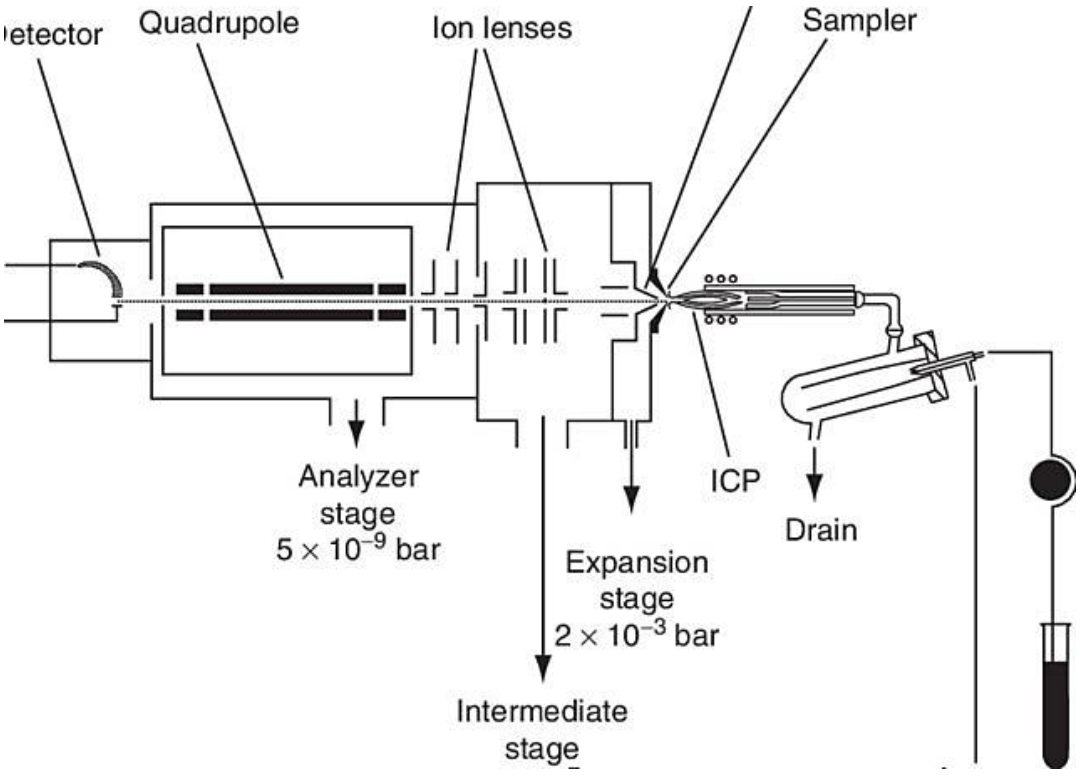

Fig. 6. Schematic diagram of a commercial inductively coupled plasma mass spectrom eter; source: (27)

To date, preliminary studies have been conducted into the effects of cadmium on the eyeball. Cadmium, like lead, has been shown to be toxic and causes oxidative stress, which is an indirect cause of cataract. It is thought that Cd^{2+} divalent cadmium ions can accumulate in mitochondria, which is dangerous by indirectly influencing the formation of reactive oxygen species. These ions additionally contribute to damage in organelles that "produce" lens cells. Unfortunately, they are then more susceptible to damage and not resistant to photo-oxidation. Other studies indicate the possibility of cadmium accumulation in ocular tissues. Excess cadmium is mainly located in the neural retina, retinal epithelial pigments and choroid (18, 24, 31).

4. ABOUT OXIDATIVE STRESS AND CATARACT

The high risk posed by oxidative stress by affecting changes in eye cells causes the body to defend itself against its undesirable effects, using a lot of antioxidants. Eye protection is based on the use of antioxidant reactions (9, 17, 28). It has been confirmed so far that antioxidants inhibit the progression of antioxidant stress, and it may even happen that they reverse the changes caused by its action (17, 29).

In First things first tests are designed to demonstrate what dependencies prevail between oxidants and antioxidants. Biotechnology helps in such research using, among others, spectrophotometric methods (e.g. determination of superoxide dismutase, catalase),

thiobarbituric methods (for malonic aldehyde) or purely enzymatic methods (ceruloplasmin activity). The obtained results can then be thoroughly analyzed using various statistical methods (31-33).

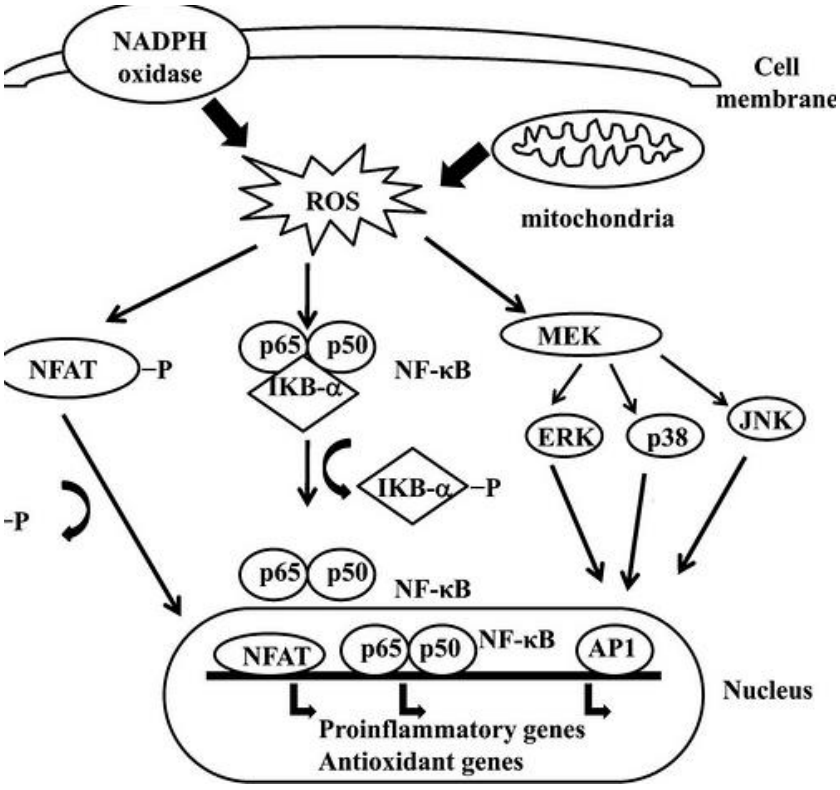

Fig. 7. Effects of oxidative stress on signal transduction inthe cell (30)

Antioxidant activity is divided into further mechanisms that are used. The first field of activity is inactivation of free radicals by destroying them. The second mechanism is a direct reaction with ROS or other oxidants that contribute to the formation of oxidative stress. There are also so-called chelation or "transfer" of a metal with catalysing properties as pro-antioxidants. There is also activation of certain enzymes with antioxidant properties (34). Different enzymes are released in the human body depending on the activation of individual defense mechanisms. The best known antioxidant enzymes that are activated first are catalase, superoxide dismutase and glutathione peroxidase (3, 5, 8, 34).

One of the first and highly active antioxidant enzymes operating on the first line is superoxide dismutase. Its main task is to capture and bind RFT, and the most common reaction is disproportionation of the superoxide anion radical. The reaction results in the formation of hydrogen peroxide H_2O_2 and molecular oxygen O_2 (8, 36-38).

$$SOD - Cu^{+} + O_2^{\cdot -} + 2H^{+} \rightarrow SOD - Cu^{2+} + H_2O_2$$

$$SOD - Cu^{2+} + O_2^{\cdot -} \rightarrow SOD - Cu^{+} + O_2$$

SOD is active because in its structure it has copper on two oxidation levels Cu^{2+} and Cu^{+}. These forms undergo oxidation and reduction reactions, according to the reaction (Bartosz 2013): Currently, a lot of research is conducted to find out the SOD activity in people with cataracts and to determine the effect it has during lens pathophysiology. One such method is the study of the activity of superoxide Pona dtlenkowej that formed, for example. Using a standardized set of Superoxide Dismutase Assay Kit (Cayman Chemical Co.). Analyzes are performed on a 96-well titration plate.

Principle of the method: This method uses the tetrazoline salt, which after binding with superoxide radicals gives a red dye - formazan.

Procedure: The samples and standards with a unit volume of 10 .mu.l is added to 200 µl of the detector of free radicals, that is, the solution of the salt with the tetrazolium. Then 20 ml of xanthine oxidase are added to start the reaction. P by 20 min. incubation on a shaker at room temperature the abs orbance is read at 450 (39).

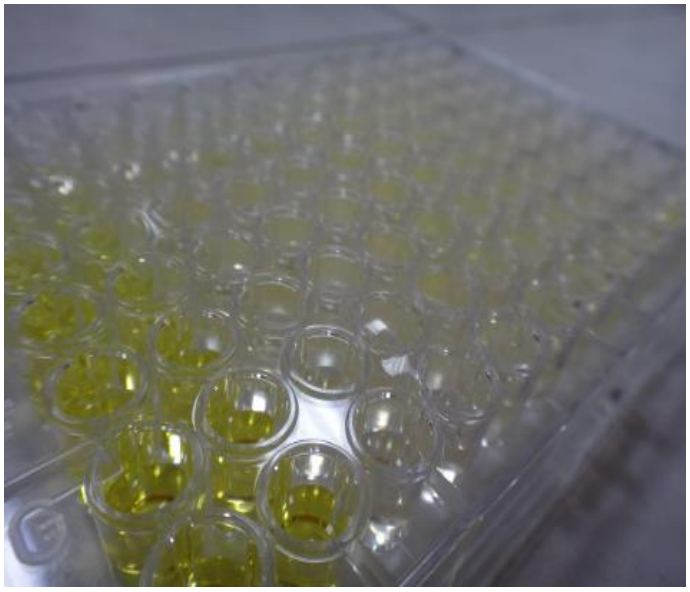

Fig. 8. Titration plate after testing SOD plasma activity; own photo

To date, it has been indicated that superoxide dismutase, found in the cytosol, has high antioxidant activity directly in the lens of the eye. In addition to inhibiting negative RFT activity, SOD has also been shown to stimulate protective cells located in the eyes to act. These cells stabilize proteins and minimize predisposition to oxidation (37-40).

During our research, we obtained the following results regarding the average concentration of superoxide dismutase in a group of 72 patients with cataracts and 59 healthy volunteers. The differences testify to the activation of defense mechanisms (SOD) in patients in the presence of oxidative stress, which is associated with the accumulation of chemical elements and ROS. Oxidative stress arising as a result of various factors, mainly due to the excess of reactive oxygen species, is one of the causes of lens opacification, which is the main pathophysiological change in cataracts.

Scientists confirm, however, that antioxidants inhibit the negative effects of oxidative stress, and in some cases can even undo the effects already caused by its action (17).

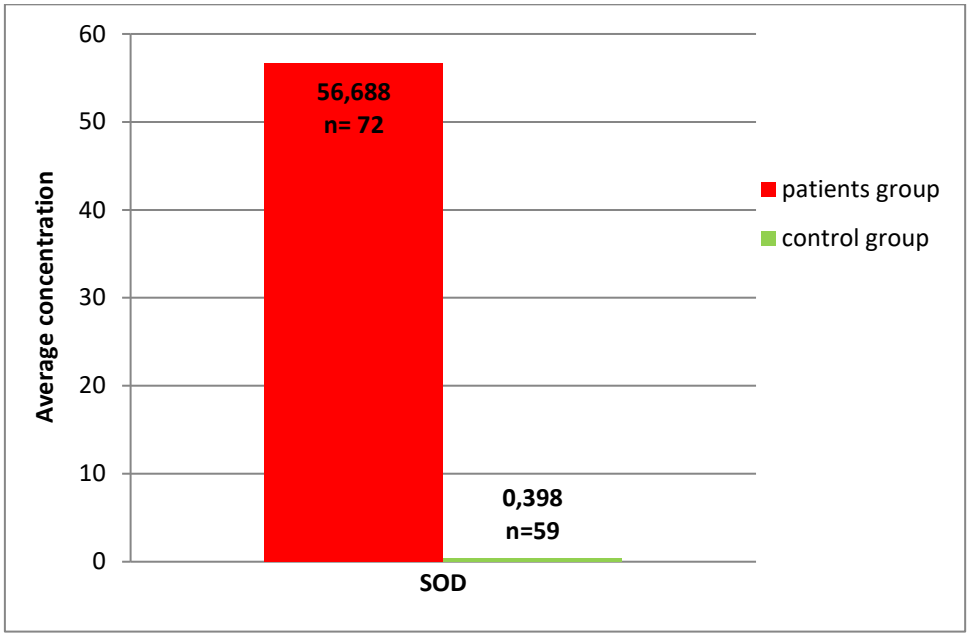

Fig. 9. Average superoxide dismutase concentration in plasma of patients with cataracts and healthy volunteers; own research

5. CONCLUSIONS

Oxidative stress and ROS have a very harmful effect on living organisms, including the eyes. Keeping the balance between oxidants and antioxidants has a major impact on the proper functioning of the body. Various antioxidants reduce the effects of oxidative stress and at the same time may contribute to the reversal of some of the changes already caused. Thanks to various biotechnological methods, it is now possible to determine the concentration of metal ions and chemically active groups, as well as the activity of antioxidant enzymes (SOD, CAT, GPx , GR), which can serve as an appropriate auxiliary diagnostic indicator in environmental diseases, including cataract.

References

[1] Florczak S, Kempka K. The influence of enviromental and genetic factors on developmnt of glaucoma. *World Scientific News* 2016; 57: 474-482

[2] Eagle RC. Eye pathology: An atlas and Text. 3rd Ed. Lippincott Williams & Wilkins (LWW); In 2016.

[3] Kempka K. Environmental conditions of pathophysiological changes in cataracts [master's degree]. [Zielona Gora]: Zielonogórski; 2017.

[4] Korsakova N. Modern Data About Age-related Cataract Pathogenesis in Humans. New York, NY: Nova Science Publishers; 2012. 100 pp. (Eye and Vision Research Developments).

[5] Malhotra R. Cataract. 1st edition London: Butterworth Heinemann Elsevier; 2008. 256 p.

[6] Bradford CA, editor. Cataract. In: Ophthalmology A textbook for students. Urban-Partner; 2006. pp. 58-64.

[7] Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M, Epstein S. Age-related cataract. *The Lancet* 2005; 365 (9459): 599-609

[8] Waught A, Grant A. Anatomy and Physiology in health and illness. Spain: Churchill Livingstone; 2001

[9] Thiagarajan R, Manikandan R. Antioxidants and cataract. *Free Radical Research.* May 2013; 47 (5): 337–45

[10] Lancet T. WHO's global air-quality guidelines. *The Lancet.* October 14, 2006; 368 (9544): 1302.

[11] Bartosz G. The second face of oxygen - free radicals in nature. Warsaw: PWN; 2013.

[12] Bhatia G, Sontakke AN, Abhang S. Role of oxidative stress in cataractogenesis. *International Journal of Research in Medical Sciences.* May 27, 2017; 5 (6): 2390.

[13] Abdal Dayem A, Hossain M, Lee S, Kim K, Saha S, Yang GM, et al. The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles. *IJMS.* January 10, 2017; 18 (1): 120

[14] Çekiç O, Bardak Y, Totan Y, Kavaklı S, Akyol Ö, Özdemir Ö, et al. Nickel, chromium, manganese, iron and aluminum levels in human cataractous and normal lenses. *Ophthalmic Research* 1999; 31 (5): 332-336

[15] Truscott RJW. Age-related nuclear cataract - oxidation is the key. *Experimental Eye Research* May 2005; 80 (5): 709-25

[16] Jung SJ, Mehta JS, Tong L. Effects of environment pollution on the ocular surface. *The Ocular Surface.* April 2018; 16 (2): 198-205

[17] Berthoud VM, Beyer EC. Oxidative Stress, Lens Gap Junctions, and Cataracts. *Antioxidants & Redox Signaling.* February 2009; 11 (2): 339-53

[18] Haddad HH. The Effect of Heavy Metals Cadimium, Chromium and Iron Accumulation in Human Eyes. *American Journal of Analytical Chemistry* 2012; 03 (10): 710-3

[19] Lynn S, Yew FH, Chen KS. Reactive oxygen species are involved in nickel inhibition of DNA repair. *Environ Mol Mutagen* 1997; 29 (2): 208-16

[20] Mehra R, Juneja M. Variation of concentration of heavy metals, calcium and magnesium with sex as determined by atomic absorption spectrophotometry. *Indian J Environ Health.* 2003; 45 (4): 317-24

[21] Kabata-Pendias A., Mukherjee AB Trace Elements from Soil to Human. Springer-Verlag. 2007.

[22] Kabata-Pendias A., Szteke B., editors. Iron and manganese in the environment - ecological and methodological problems. NIH; 2004.

[23] Kabata-Pendias A, Pendias H. Trace elements in soils and plants. 3rd ed. Boca Raton, Fla: CRC Press; 2001.413 pp.

[24] Eichenbaum JW, Zheng W. Distribution of lead and transthyretin in human eyes. *Journal of Toxicology: Clinical Toxicology.* 2000; 38 (4): 377-381

[25] Erie JC, Butz JA, Good JA, Erie EA, Burritt MF, Cameron JD. Heavy Metal Concentrations in Human Eyes. *American Journal of Ophthalmology.* May 2005; 139 (5): 888-93

[26] Langford-Smith A, Tilakaratna V, Lythgoe PR, Clark SJ, Bishop PN, Day AJ. Age and smoking related changes in metal ion levels in human lens: implications for cataract formation. *PloS One.* 2016; 11 (1): e0147576

[27] Liu Y, Hu Z, Gao S, Günther D, Xu J, Gao C, et al. In situ analysis of major and trace elements of anhydrous minerals by LA-ICP-MS without applying an internal standard. *Chemical Geology.* November 2008; 257 (1-2): 34-43

[28] Kellner R, Mermet JM, Otto M, Valcarel M, Widmer HM. Analytical Chemistry: A Modern Approach to Analytical Science. 2nd ed. Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 2004

[29] Forrer R, Wenker C, Gautschi K, Lutz H. Concentration of 17 Trace Elements in Serum and Whole Blood of Plains Viscachas (Lagostomus maximus) by ICP-MS, Their Reference Ranges, and Their Relation to Cataract. *BTER.* 2001; 81 (1): 47-62

[30] Shukla N, Moitra JK, Trivedi RC. Determination of lead, zinc, potassium, calcium, copper and sodium in human cataract lenses. *Science of the Total Environment.* 1996; 181 (2): 161-165

[31] Wills NK, Ramanujam VMS, Chang J, Kalariya N, Lewis JR, Weng TX, et al. Cadmium accumulation in the human retina: Effects of age, gender, and cellular toxicity. *Experimental Eye Research.* January 2008; 86 (1): 41-51

[32] Berthoud VM, Beyer EC. Oxidative Stress, Lens Gap Junctions, and Cataracts. *Antioxidants & Redox Signaling.* February 2009; 11 (2): 339-53

[33] Zeng S, Hernández J, Mullins RF. Effects of Antioxidant Components of AREDS Vitamins and Zinc Ions on Endothelial Cell Activation: Implications for Macular Degeneration. *Invest Ophthalmol Vis Sci.* February 1, 2012; 53 (2): 1041-7

[34] Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative Stress and Antioxidant Defense. *World Allergy Organization Journal.* January 2012; 5 (1): 9-19

[35] Chandrasena LG, Chackrewarthy S, Perera PT, de Silva D. Erythrocyte Antioxidant Enzymes in Patients with Cataract. *Ann Clin Lab Sci.* 2006 Spring; 36 (2): 201-4.

[36] Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. *Experimental Eye Research.* February 2007; 84 (2): 229-45

[37] Anbaraki A, Khoshaman K, Ghasemi Y, Yousefi R. Preventive role of lens antioxidant defense mechanism against riboflavin-mediated sunlight damaging of lens crystallins. *International Journal of Biological Macromolecules.* October 2016; 91: 895-904

[38] Vinson JA. Oxidative stress in cataracts. *Pathophysiology.* August 2006; 13 (3): 151-62

[39] Tokarz P, Kaarniranta K, Blasiak J. Role of antioxidant enzymes and small molecular weight antioxidants in the pathogenesis of age-related macular degeneration (AMD). *Biogerontology.* October 1, 2013; 14 (5): 461-82

[40] Behndig A, Karlsson K, Reaume AG, Sentman ML, Marklund SL. In vitro photochemical cataract in mice lacking copper-zinc superoxide dismutase. *Free Radical Biology and Medicine.* 2001; 31 (6): 738-744

[41] P. A. Fedirko, I. Kadoshnikova. Risks of eye pathology with the victims of the Chernobyl catastrophe. *World News of Natural Sciences* 2016, 3, 12-18