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Initial pro-antioxidant reactions in the patients suffering from cataract in the interactions with cadmium and lead

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ABSTRACT

Cataract is one of the main causes of vision loss. So far, it has been found that one of the causes of cataract formation is the accumulation of heavy metals in ocular tissues and environmental pollution. Research material consisted of blood from healthy volunteers (n = 81; Mogilno Lakeland) and those suffering from cataract (n = 90) from Ophthalmology Clinic, Bydgoszcz (2013, 2016). Samples were prepared in order to obtain plasma, which was used to analyze Fe, Cu, Zn, Mn, Pb, Cd, and Hg concentration (ICP-MS). The purpose of this study is to show the interaction of cataract with cadmium and lead during initial pro-antioxidative reactions and to study element-element interactions. To this end, we analyzed physiological mechanisms that aim to stop the destructive effects of toxic metals. We have shown that the action of zinc, copper and manganese is antioxidant. Concentration of these elements is higher ($\alpha = 0.05$, $p < 0.05$) in the cataract group than in the control. We found interactions Fe-Cu-Zn-Mn-Pb-Cd-Hg. Cd and Pb show a negative effect on the eye tissue and generate

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pathophysiological changes leading to lens opacity and influence the destabilization of pro-antioxidant reactions. Correlations of elements in the control (Cd-Zn: R = 0.240; Cd-Cu: R = 0.316) and in the sick group (Cd-Cu; R = 0.329) were significant. On the basis of our research we found that there are numerous relationships between the concentrations of chemical elements in the patients with cataracts and the controls. Significant role of antagonisms with cadmium and lead has been demonstrated; these elements contribute to the gradual development of cataract. A correlation between elements exhibiting pro-antioxidant activity in the interactions with cadmium and lead (p=0.000) can be a source of cataract changes. The differences in Cd and Pb concentration and their interactions with elements between the control and sick groups can be considered as a factor for the development of cataract.

Keywords: cataract, cadmium, lead, pro-antioxidant, environmental pollution

1. INTRODUCTION

The sight is one of the primary senses of humans. Due to the presence of a complex visual system we can see the world surrounding us. The receiving organ, which processes and receives light waves, is the eyeball and the media that connect it to the visual centre in the cerebral cortex [1], [2]. The eyeball itself is an organ characterized by a complex structure. It is located in the front part of the eye socket in a spherical shape and it has a volume of approximately of 7.2 cm^3, while its weight amounts only to 7.45 g [1]. The structure of the eyeball is directly responsible for the penetration of light rays to the macula. They must maintain transparency, because otherwise serious damage may occur. These organs include: aqueous humour, lens and vitreous body. The changes associated with the second organ, i.e. lens are associated with a common disease – cataract [1]. The lens is a biconvex formation, whose main task is to break the incoming light rays. It is also associated with accommodation of the eye, which enables correct seeing of objects located both close and far. It does not include any blood vessels therefore inflammation of the lens does not occur. The most common pathophysiological change is opacification, i.e. the loss of its transparency leading to cataract [1], [3]. Cataract is one of the diseases that lead to the loss of eyesight in the case of millions of people around the world. WHO (2016) estimates that in 2020 the number of people suffering from cataract may amount to 80-90 million [1], [4]. As a result of changes, the lens becomes non-transparent. This initially causes blurring of the image and leads to total impairment of vision along with the development of this disease. The degree of eyesight impairment also depends on the location of lens opacification and its size [3], [5].

Nowadays, many scientists are trying to find the cause of the formation of cataract. There are many indications that the development of cataract is also caused by environmental pollution, especially in the case of pollution with heavy metals [1], [6]. It's extremely important to maintain a balance between oxidants and antioxidants. Disturbance of this balance may contribute to the formation of cataract [5-7].

2. CATARACT

Cataract, i.e. opacification of the eye lens, is a congenital or degenerative disease. Opacification of the lens impairs its primary feature, i.e. transparency. The first symptoms indicating the occurrence of pathophysiology of the lens include the deterioration of visual acuity and the worsening of existing sight defects. In the advanced stage of this disease, the fundus examination cannot be correctly performed and the so-called white pupil may be observed (*lecocoria)* [7]. Several causes for the formation of cataracts have been identified so far, including among others: traumas, inflammations, complications of eyeball diseases, congenital changes, age-related changes, metabolic disorders, nutrition mistakes [1], [3], [5].

There are several primary types of cataract, which are mainly divided in terms of origin, i.e. congenital and acquired cataract. Congenital cataract is divided into [3,6]:

- ✓ capsular cataract
- ✓ polar cataract
- ✓ nuclear cataract
- ✓ lamellar cataract
- ✓ total cataract
- ✓ membranous cataract

On the other hand, the acquired cataract may be of primary and secondary nature. The first group is divided into: cortical, nuclear and subcapsular. Acquired secondary cataract often results from, among others: metabolic diseases (diabetes, tetany) and toxins, traumas, taking certain medications (miotics, steroids, statins) [1], [8].

3. DEVELOPMENT OF CATARACT AFFECTED BY CHEMICAL ELEMENTS

Significant impact of chemical elements on the formation of pathophysiological changes in the human body has been shown. Environmental pollution and contaminations with heavy metals, such as cadmium and lead have a negative effect on metabolism and may contribute to the occurrence of many damages. There are significant synergies and antagonisms between the elements, which often are also the cause of occurrence of many diseases, including cataract. It turns out that some elements may have pro-antioxidant effects in the interactions with cadmium and lead, including among others: Fe, Cu, Zn and Mn [6], [9], [10].

3. 1. Toxic effect of cadmium and lead on the vision organ

One of the main representatives of heavy metals includes cadmium and lead. They are extremely dangerous and they have the ability to accumulate in the human body. Their presence in the body contributes to metabolic changes, which at a later stage may result in cataract [1], [12], [13].

Due to the strong properties of accumulation in the human body, lead is a highly toxic element that works multi-organically. Most often, the absorption takes place through the digestive system however the absorption through the respiratory system is also possible. It has been proven that in the first place it's deposited in the liver, heart and kidneys. However, the occurrence of trace amounts of lead in the results of laboratory tests is normal, because it's a natural component of body fluids [1], [14]. It has also been shown that it may be deposited in the eye lens, where it acts as a protoplasmic poison. Lead causes many symptoms, which often are not connected with its impact. Lead effectively competes for the binding place of pro-antioxidant ions, which could block its harmful impact [15-17].

Cadmium is also characterized by strong accumulation properties, while long-term exposure to it may lead to the itai-itai disease. In the case of this element, the absorption takes place with equal frequency through the digestive system and through the respiratory system. It's also characterized by very good accumulation in tobacco leaves, therefore smoking tobacco is very dangerous, because it enables the entering of this heavy metal into the body. It has been shown that cadmium directly affects water-electrolyte, as well as catecholamine and lipid balance. Selected harmful impact of cadmium on the human body is presented in the figure 1 [1], [12], [14], [18].

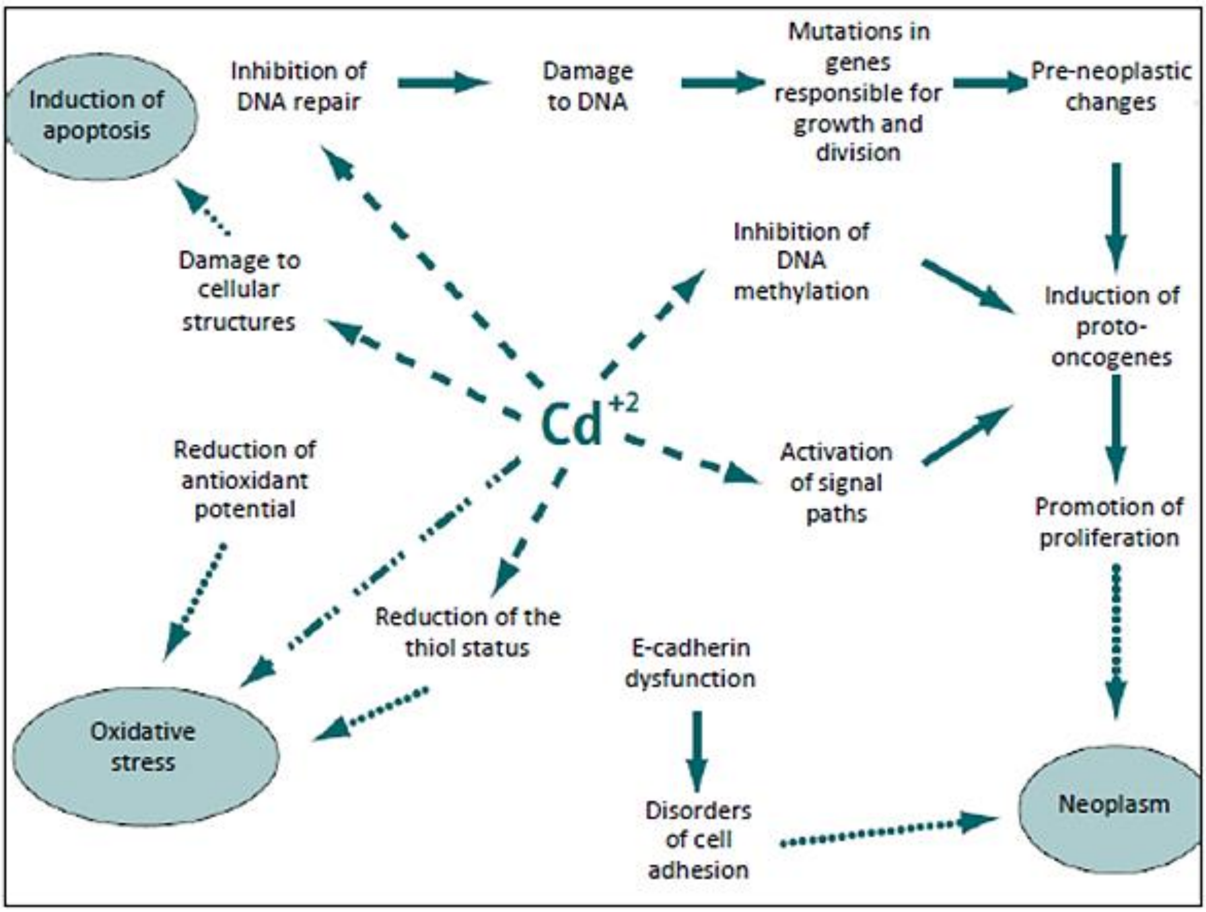

Figure 1. Selected effects of cadmium toxic impact [19].

So far, the preliminary studies have been carried out regarding the impact of cadmium on the eyeball, which showed that similarly like lead, it has toxic effect and causes oxidative stress that is an indirect cause of the formation of cataract. It is believed that divalent cadmium ions Cd^{2+} may accumulate in the mitochondria. This is dangerous, because these organelles are responsible for intracellular respiration and they are also responsible for the formation of dangerous reactive oxygen species (ROS). These ions are also responsible for damages to organelles, which may contribute to the "production" of lenses that are more susceptible to damages and that are not resistant to photo-oxidation. Other studies indicate the possibility of cadmium accumulation in ocular tissues, mainly in the nerve retina, retinal epithelial pigments and choroid. However, its concentration depends on the age and general health of the patient [18], [20], [21].

3. 2. Pro-antioxidant effect in the interaction with lead and cadmium in patients suffering from cataract

Studies conducted so far on the impact of oxidative stress and pathophysiological changes on the cataract confirm that it is one of the factors causing this disease. However, it has been found that antioxidants can inhibit and in some cases even reverse the damages caused by oxidative stress [6]. Antioxidant properties are also exhibited by several chemical elements that counteract the toxic impact of cadmium and lead. Such elements include among others: Zn, Cu and Mn [1], [7], [22].

Zinc is an element that exhibits protective effect against the harmful impact of oxidative stress on the human body. This element is considered to be a kind of bodyguard of the protein sulfhydryl groups against their oxidation by free radicals [7], [14]. It has been proven that Zn plays a very important role during protection of retina against oxidation. This is very important due to the high exposure to light, which used in many metabolic processes leads to the formation of cataract (among others). It was also confirmed that this element is included in the composition of cofactors of the extremely important antioxidant enzyme - superoxide dismutase (SOD) [7], [18], [23], [24]. Copper, similarly to zinc, is part of superoxide dismutase and thus, it is a protective barrier against oxidative stress. It is also responsible for direct neutralization of the superoxide radical, which leads to the formation of oxidative stress. This is due to the copper ions on the 2 and 1 oxidation degree, which reduce this radical [7], [18]. It was also proven that copper ions stimulate protective cells, which naturally occur in the eyes. They occur in the stress route, while their main purpose is to stabilize proteins, which are responsible for the reduction of tendency to oxidation [18], [23].

One of the most important mineral components of living organisms is manganese, which is mainly responsible for effective activity of the vitamin B_1 [1], [12], [14]. It was also found that Mn is a part of the superoxide dismutase, which is located in the mitochondrial matrix. It turned out that manganese superoxide dismutase occurred in organisms much earlier than the two that were described earlier, i.e. CuSOD and ZnSOD, which were formed through evolution much later [7], [22]. It has been proven that the removal of hydrogen peroxide, using among others MnSOD, protects the cells against harmful impact of oxidative stress, while its main occurrence is located in the epithelium of the eye lens [25].

3. 3. Purposes of the study

The reason for engaging this topic is the growing problem of cataract incidence and simultaneous attempt to find the etiology of this disease. The main purpose of this article is to show the trend of pro-antioxidant reactions in patients suffering from cataracts in the interactions with cadmium and lead.

4. MATERIALS AND METHODS

The research material consisted of whole blood samples, collected in heparin-lithium sample tubes, from: healthy volunteers living in the Mogilno Lakeland (ecologically clean areas) collected in 2013 and volunteers suffering from cataract attending the Ophthalmology Clinic at the Jurasz University Hospital in Bydgoszcz collected in 2016. The control group consisted of 81 volunteers and the sick group consisted of 90 patients. The collected whole blood was appropriately prepared in order to obtain plasma, which was used to analyse the concentration of elements using the inductively coupled plasma mass spectrometry (ICP-MS). In order to determine the concentrations of Fe, Cu, Zn, Mn, Pb and Cd, the ICM-MS Agilent 7500CE manufactured by Agilent was used, which was equipped with: micro-mist nebulizer, thermoelectrically cooled double-pass fog chamber (with Peltier effect). The following parameters were used during the analyses:

- ✓ pumping speed - 0.01-0.5 rpm,
- ✓ carrier gas - Argon 5.0 with high purity up to 99.999%

The statistical analysis was carried out with the use of STATISTICA 13 program. The Mann-Whitney U-statistical test was used for non-normal distribution data, while the Student's t-test was used for normal distribution. During the correlation analyses, the Spearman correlation test was used and the interpretation of its indicator may be found in Table 1. During the verification of all analyses, the significance coefficient at the level of $\alpha = 0.05$ was used, which allowed to consider statistically significant variables at $p < 0.05$.

Table 1. Determination of the correlation coefficient in relation to the strength of relationship.

Correlation coefficient (R)	Strength of correlation relationship
0.0-0.3	lack
0.3-0.5	weak
0.5-0.7	average
0.7-0.9	strong
0.9-1.0	very strong

5. RESULTS

The concentration of elements from 81 healthy volunteers (control group) and 90 volunteers suffering from cataract (sick group) was examined. Statistically significant differences were noted for all studied elements, i.e. Cu, Zn, Mn, Cd, and Pb.

In the case of copper, the results are characterized by differences amounting to 450 μg/kg for the mean and 432 μg/kg for the median, while the obtained statistics indicate the occurrence of a significantly higher concentration in the sick group. Zinc has a higher concentration in the control group compared to the sick group, with a difference amounting to 4097 μg/kg for the mean and 3933 μg/kg for the median. In the case of manganese, the average differences in the concentration of elements were noted at the level of 1.764 μg/kg, whilst for the median - 2.880 μg/kg, and in this case the higher mean values appeared to occur in the control group. The cadmium concentration (Cd) is characterized by differences amounting to 0.539 μg/kg for the mean and 0.143 μg/kg for the median. Lead is characterized by average concentration higher by 27.033 µg/kg in the sick group, while the median difference amounts to 10.690 µg/kg (Table 2).

Table 2. Descriptive and statistical analysis of the concentration of elements (Cu, Zn, Mn, Cd, Pb) in the control group (n = 81) and the sick group (n = 90)

Element	Group	x	SD	Min	Q_1	Me	Q_3	Max	U test	P value of U test
Cu [µg/kg]	control	593,4	197,7	209,9	463,1	570,8	738,1	1112,7	-11,737	<0,001
	sick	1044,1	278,9	431,8	847,2	1003,5	1214,0	1778,0		
Zn [µg/kg]	control	4801,7	1522,2	2384,2	3728,5	4666,1	5681,2	12539,8	10,810	<0,001
	sick	704,2	152,8	400,7	581,8	732,7	806,9	1011,0		
Mn [µg/kg]	control	3,122	2,983	0,000	0,630	2,880	4,668	13,113	6,548	<0,001
	sick	1,358	3,641	0,000	0,000	0,000	0,895	24,697		
Cd [µg/kg]	control	0,615	1,518	0,000	0,020	0,181	0,598	12,421	4,298	<0,001
	sick	0,076	0,088	0,000	0,000	0,038	0,125	0,351		
Pb [µg/kg]	control	27,048	135,609	0,000	8,230	10,690	17,135	1231,05	11,103	<0,001
	sick	0,015	0,131	0,000	0,000	0,000	0,000	1,145		

During analyses of the correlation of elements in the case of control, the cadmium exhibited two statistically significant correlations. A weak correlation was found between Zn and Cd (R = 0.240) and the average correlation for Cd and Cu (R = 0.316) (Table 3).

During analysis of the correlation of elements from the sick group, the average correlation was noted for Cd and Cu (R = 0.329) (Table 4). There were significant correlations between cadmium concentration and cataract development. And yes - in the case of control group, cadmium showed statistically significant correlations with some elements: Zn-Cd (R = 0.240, p = 0.031) (Figure 2) and Cd-Cu (R = 0.316, p = 0.004). In the group of patients with cataract, significant correlations were found: Cd-Fe (R = 0.261, p = 0.027) and Cd-Cu (R = 0.329, p = 0.005) and Cd-Zn (R = 0.307, p = 0.009) (Figure 3).

Table 3. Correlation analysis of the concentration of chemical elements in the control group (n = 81).

	Mn [ug/kg]	Cu [ug/kg]	Zn [ug/kg]	Cd [ug/kg]
Cu [ug/kg]	0,532			
Zn [ug/kg]	0,342	0,510		
Cd [ug/kg]	0,065	0,316	0,240	
Pb [ug/kg]	0,254	0,425	0,083	0,212

Table 4. Concentration of chemical elements in the sick group (n = 90).

	Mn [ug/kg]	Cu [ug/kg]	Zn [ug/kg]	Cd [ug/kg]
Cu [ug/kg]	0,127			
Zn [ug/kg]	0,339	0,087		
Cd [ug/kg]	0,151	0,559	0,290	
Pb [ug/kg]	-0,165	0,214	-0,203	-0,020

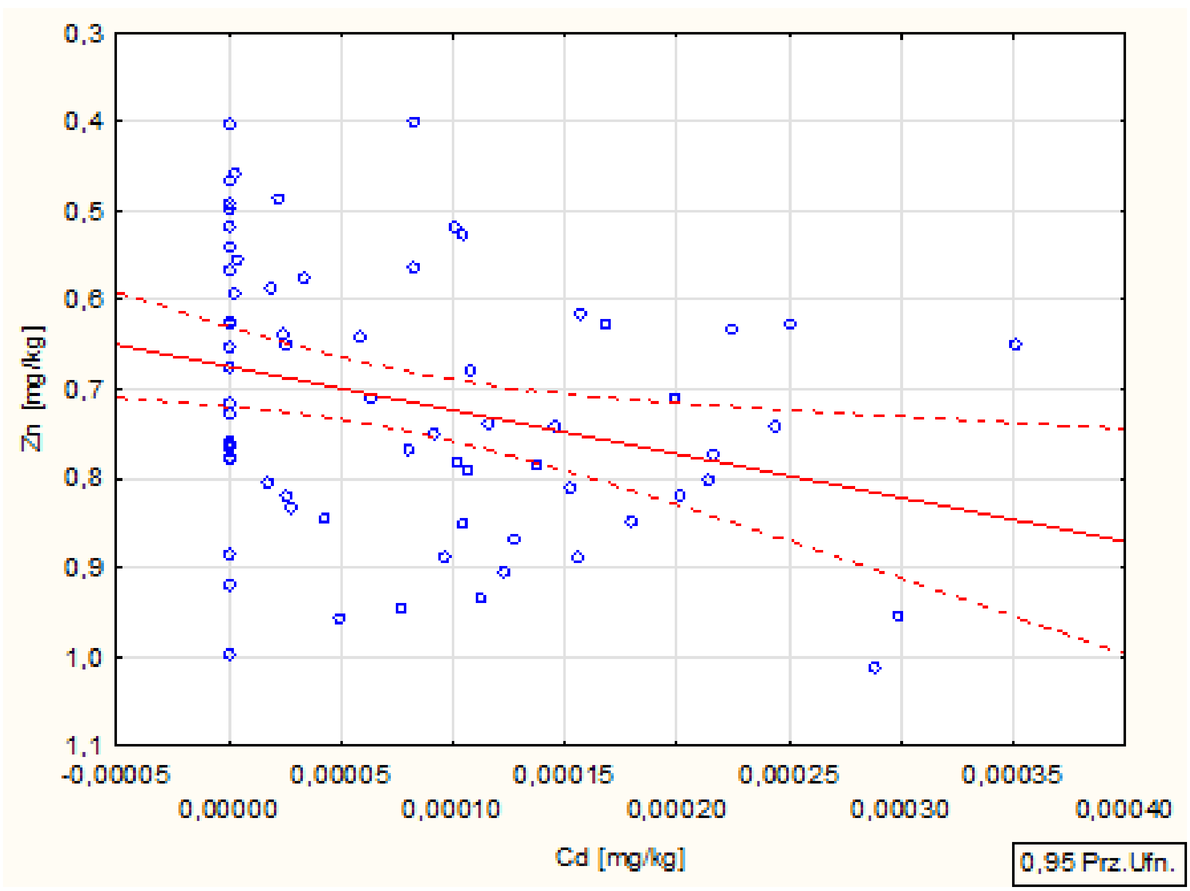

Figure 2. Significant statistical differences for Zn and Cd interactions in the control group (p = 0.031, R = 0.240, n = 81).

In the case of the correlation of lead concentration with pathophysiological changes in the cataract, statistically significant correlations in the control group were shown for the relation: Mn-Pb (R = 0.254, p = 0.022) and Cu-Pb (R = 0.316, p = 0.004). In the group of patients with cataract only one statistically significant correlation was found: Pb-Hg (R = 0.467, p = 0.000).

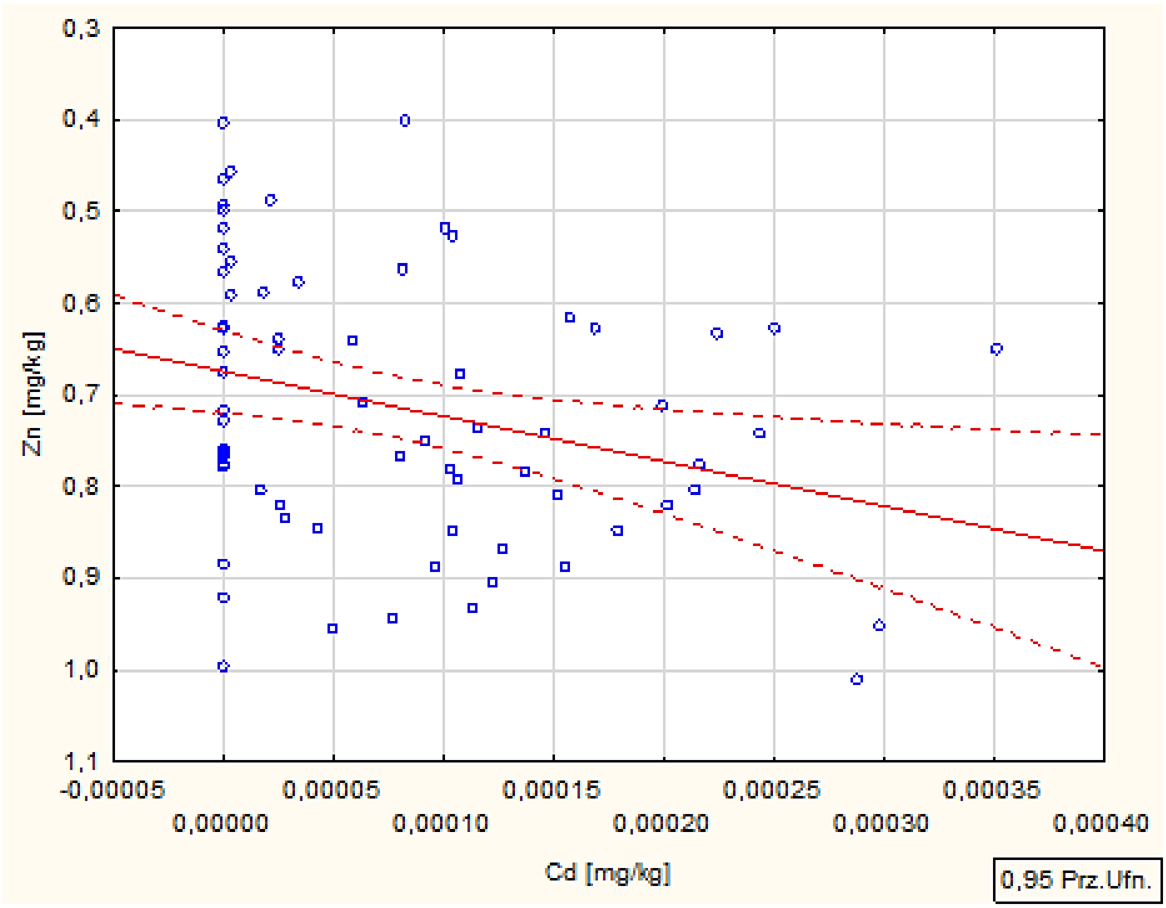

Figure 3. Significant statistical differences for Zn and Cd interactions in the cataract group ($p = 0.009$, $R = 0.307$, $n = 72$).

6. DISCUSSION

The cataract is a disease, which is created as a result of many external environmental factors, both internal and external. It is a frequent subject of many scientific studies aimed at searching for etiology, as well as new diagnostic and treatment methods [6], [26].

It turns out that extremely important role is played by the balance between oxidants and antioxidants, because an excess of one of them may be toxic, especially the excess of oxidants. Among harmful factors contributing to the formation of oxidative stress, i.e. distortion of balance, are cadmium and lead.

It was also showed that heavy metals (particularly cadmium, lead) contribute to damaging the genetic material and indirectly, through the accumulation in human tissues, to the induction of oxidative stress [7], [26], [27]. Some scientists, who study the impact of antioxidant stress and analyse the impact of the concentration of elements, conclude that antioxidants, e.g. copper, zinc or manganese, can inhibit the effects of free radicals, and sometimes even reverse the damage caused by them [8,26].

It has been shown that copper, zinc and manganese are good antioxidants. It has been indicated that the first two play an important role in the functioning of the retina and help in the maintaining of balance in reactions of oxidation-reduction occurring in the organ of vision [18].

Analyses conducted within this study indicate that higher concentrations of these elements occurred in the control group. It has been also shown that significant correlations occur between cadmium, lead and elements exhibiting antioxidant activity. This indicates the possibility that these elements have impact on initial pro-antioxidant reactions in patients suffering from cataract. It's necessary to note the positive effect of these elements in the scope of inhibiting pathophysiological changes leading to cataract.

7. CONCLUSIONS

1) A correlation between elements exhibiting pro-antioxidant activity in the interactions with cadmium and lead ($p = 0.000$) can be a source of cataract changes.
2) The differences in the concentration of cadmium and lead and their interactions with other elements between the control group and the sick group can be considered as factors for the development of cataract.

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