Austin Therapeutics

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Research Article

Selenium Supplementation to Chronic Kidney Disease Patients on Hemodialysis has no Effect on Superoxide Dismutase Activity and Malonyldialdehyde Concentration in Blood

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Received: September 20, 2014; **Accepted:** November 07, 2014; **Published:** November 11, 2014

Abstract

Background: Hemodialysis (HD) is the most common form of treating patients in the End-Stage Renal Disease (ESRD). The most common approach to measuring the effect of oxidative stress has been to measure the activity of Glutathione Peroxidases (GSH-Px), Superoxide Dismutase (SOD) and the product of lipid peroxidation – Malonyldialdehyde (MDA). In Chronic Kidney Disease (CKD) patient's Selenium (Se) level in blood is frequently lower than in healthy subjects and it decreases gradually with the progress of the disease.

Aim: The aim of our study was to examine whether the administration of Se to patients on HD alters the activity of GSH-Px and SOD in red blood cells and the level of MDA in plasma.

Patients and Methods: Our study involved 3 groups of subjects: 1) 52 CKD nondialyzed patients, 2) patients in ESRD supplemented for 3 months with Se-rich yeast, 200 μg/day (n = 30) or placebo (n = 28) and 3) 52 healthy subjects. The GSH-Px and SOD activities in red blood cell hemolysates and lipid peroxidation products [expressed as Thiobarbituric Acid Reactive Substances (TBARS)] in plasma were assayed.

Results: GSH-Px activity in RBCs was significantly lower in nondialyzed CKD patients as compared with control group, but was even more reduced in patients on HD. SOD activity in red blood cells was significantly lower in patients in ESRD than in the healthy subjects and in the nondialyzed patients. Se supplementation to the HD patients has no effect on the change in SOD activity. TBARS level in plasma in patients on HD was significantly higher than in the control group and in nondialyzed patients. Se administration did not reduce this level.

Conclusion: Se supplementation to patients on HD has no effect on the activity of SOD in red blood cells and does not prevent lipid peroxidation.

Keywords: Chronic kidney disease; Hemodialysis; Selenium supplementation; Superoxide dismutase; Malonyldialdehyde

Introduction

Oxidative stress is defined as an imbalance between prooxidants and antioxidants in favor of the oxidants, potentially leading to damaging biological systems [1,2]. Oxidative stress is present and its markers can be measured in both healthy people and those with various clinical disorders [3]. Oxidative stress has been linked with damaged proteins, DNA, lipids in cell membranes (mainly unsaturated fatty acids; PUFA) and carbohydrates [3], and thus leads to the progression of several diseases including cardiovascular diseases, cancer, Chronic Kidney Disease (CKD) and others [4]. Most importantly, oxidative stress is believed to promote the endothelial dysfunction and atherosclerosis and, therefore, cardiovascular complications [5]. Free radicals formed during oxidative stress are also responsible for DNA damage and, as a consequence, for cancer development [6-8]. Long periods of Hemodialysis (HD) treatment are linked to DNA damage due to oxidative stress [9]. The relationship between DNA damage and cancer development has been widely documented [10].

Hemodialysis is the most common form of treatment for End-Stage Renal Disease (ESRD) patients, and is associated with considerable mortality due to cardiovascular disease and cancer [11,12]. The most common approach to the measurement of oxidative stress and free radicals has been to measure the products of lipid peroxidation and PUFA oxidation – the level of Malonyldialdehyde (MDA) [13], as well as the activity of antioxidant enzymes. The body's defenses against lipid peroxidation include the enzymes: superoxide dismutases (SOD; EC 1.15.1.1), glutathione peroxidases (GSH-Px; EC 1.11.1.9) and catalase (CAT; EC 1.11.1.6) [3]. These enzymes destroy dangerous products of oxygen metabolism.

Citation: Zachara BA, Gromadzinska J, Wasowicz W, Swiech R and Zbrog Z. Selenium Supplementation to Chronic Kidney Disease Patients on Hemodialysis has no Effect on Superoxide Dismutase Activity and Malonyldialdehyde Concentration in Blood. Austin Therapeutics. 2014;1(2): 7.

Superoxide dismutases play a central role in catalyzing the spontaneous dismutation of superoxide ($O_2^{\bullet-}$) into oxygen and hydrogen peroxide [14]. Thus, they are an important antioxidant defense in nearly all cells exposed to oxygen. Hydrogen peroxide is then destroyed by GSH-Px and CAT [15].

Selenium (Se) is an essential trace element required in microgram amounts by all mammals. It is incorporated in the form of Selenocysteine (Sec) into 25 selenoproteins [16]. Enzymatic activity has been assigned to 12 of these selenoproteins, and some of them have antioxidant activities [17]. GSH-Px is the most extensively characterized selenoprotein, being found in Red Blood Cells (RBC) and cytosol of nearly all tissues of mammals, birds and several other organisms. It is called classical GSH-Px (cGSH-Px or GSH-Px1) [18-20]. Five isoforms of GSH-Px have been identified [21], two are present in the blood: GSH-Px 1 present in red blood cells and GSH-Px 3 present in plasma. Both have a tetrameric form and contain one selenium per subunit (or four gram atoms of Se per mole of enzyme) in the form of Sec [22-24].

Zinc (Zn) is incorporated in the catalytic site of several hundred metaloproteins [25]. Copper (Cu) is an essential element for all living organisms, serving as a cofactor for many important metaloproteins and enzymes [26]. Cu and Zn form the active site of one of the forms of SOD – Cu^{2+}/Zn^{2+} SOD (called SOD 1), present in cytosol and red blood cells [27]. Concentrations of Se and Zn in blood plasma of CKD patients are decreased [28,29] but the status of copper does not seem to be influenced by CKD [30].

The aim of this study was to determine the activity of SOD and GSH-Px in RBCs, the levels of Zn, Cu and MDA concentrations in plasma of HD patients supplemented for 3 months with 200 μg of Se per day.

Materials and Methods

Patients and controls

A 3-month, randomized double-blind, placebo-controlled trial was carried out. The study involved 3 groups of subjects. Group 1 comprised of 52 of CKD nondialyzed patients in different stages of the disease (creatinine level: 1. 00 – 10.99 mg/dL; mean: 5.16 mg/dL); group 2: 58 CKD patients in ESRD (creatinine level: 4.20 – 16.60 mg/dL; mean: 9.43 mg/dL) on regular HD, divided into 2 subgroups: 30 patients supplemented with 200 μg Se/day in the form as high-Se yeast tablets (produced by Pharma Nord, Bioselenium, Denmark) for 3 months, and 28 patients supplemented with placebo tablets containing identical yeast with no added Se (Pharma Nord). The patients were dialyzed 3 times a week for 4 hours. Group 3 consisted of 52 healthy subjects. The study was approved by the Institute Ethics Committee for Medical Research (No. 18/2003) and all the participants gave their written consent.

Methods

Blood samples were drawn from all the participants into vacutainer tubes containing lithium heparin as an anticoagulant. From the healthy controls and the patients with CKD not on dialysis, blood was taken once, and from the patients undergoing dialysis, three times: before starting the study and after 1 and 3 months of tablets supplementation. Blood was centrifuged (+4° C, 5 000 r.p.m., 10 min), the plasma was harvested and stored at –20°C until analysis. The red blood cells were washed three times with an excess of chilled 0.9% saline solution and were then hemolyzed by freezing and thawing and centrifuged again. Hemoglobin was measured by the routine cyanmethemoglobin method. Creatinine concentration was determined by routine laboratory method using Jaffy reaction (a kit produced by Cormay, Lublin, Poland). SOD activity in RBC hemolysates was determined according to the method of Beauchamp and Fridovich [31] and was expressed in U/g Hb. The GSH-Px activity in red cell hemolysates was assayed by the coupled method of Paglia and Valentine [32] using *tert*-butyl hydroperoxide as a substrate. One unit of the enzyme activity was expressed as 1 mol NADPH oxidized/min/g Hb of hemolysate (U/g Hb). Lipid peroxidation in the plasma was monitored by determining the end product of lipid peroxidation – malonyldialdehyde – described by Wasowicz et al [33]. The values were expressed as Thiobarbituric Acid Reactive Substances (TBARS) in nmol/mL. The concentrations of Zn and Cu were measured by flame atomic absorption spectrometry [34] using Pye Unicam SP9 800 apparatus. The accuracy of the method was checked with serum reference material (Seronorm, Nycomed, lot 704121).

Statistical analysis

Comparisons of the levels under study were made by multivariate analysis of variance [35] at three time points (before the study, one month and three months after study). When significant differences were found between the groups, the differences were tested at all time points. The tests were based on Shapiro-Wilks' statistics, significance being set at 0.05. All statistics were conducted using the STATA 9 package.

Results

GSH-Px activity in RBCs was significantly lower in the patients with CKD not on dialysis ($P < 0.02$) as compared with the controls, but was even more reduced in the patients on HD ($P < 0.0001$) (Figure 1). Dialysis treatment led to an increase in GSH-Px activity in both subgroups, however the increase in activity was much higher ($P < 0.0001$) in the subgroup supplemented with Se in comparison with the placebo group ($P < 0.005$).

SOD activity in RBCs of the nondialyzed patients with CKD did not differ from the activity in the healthy controls. In the dialyzed

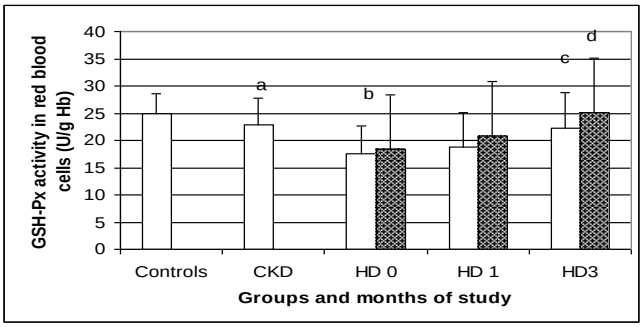

Figure 1: GSH-Px activity in RBCs of the healthy controls, the CKD nondialyzed patients and the patients on hemodialysis supplemented with placebo (white columns) and selenium (dark columns). Statistics: a, the CKD patients vs. controls, $P < 0.02$; b, the HD 0 (both subgroups taken together) vs. the controls and the nondialyzed CKD patients, $P < 0.0001$; c, HD 3 vs. HD 0 (supplemented with placebo), $P < 0.005$; d, HD 3 vs. HD 0 (supplemented with Se), $P < 0.0001$.

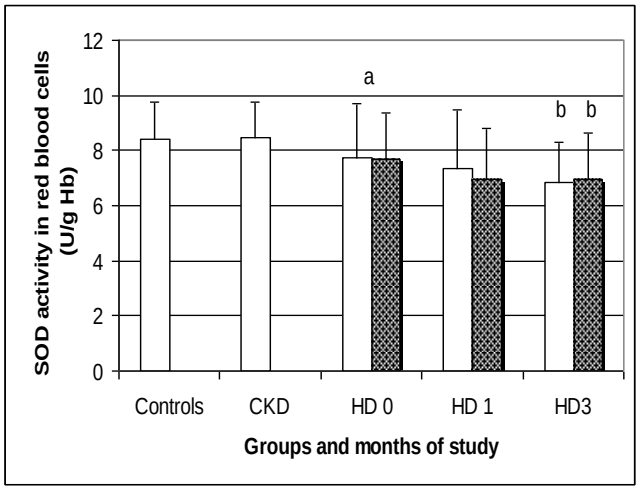

Figure 2: SOD activity in RBCs of the healthy controls, the nondialyzed CKD patients and the patients on hemodialysis supplemented with placebo (white columns) and selenium (dark columns). Statistics: a, the HD 0 (both subgroups) vs. the controls and the nondialyzed CKD patients, P < 0.02; b, HD 3 vs. HD 0, P = 0.1 (NS).

patients, at the baseline (both subgroups taken together), SOD activity was lower only by 8.5% compared with controls (P < 0.02) (Figure 2). Hemodialysis leads to a small reduction in enzyme activity in both subgroups, but after 3 months, these values were not significantly different from the activity found at HD 0. It should be emphasized that selenium supplementation to the patients on HD had no effect on the change in the activity of this enzyme.

Zinc concentration in plasma of the nondialyzed CKD patients and the patients on HD was significantly lower compared with the healthy controls (P < 0.0001) (Figure 3). In the dialyzed patients the concentration was lower than in the nondialyzed (P < 0.05). In the placebo group it did not change during the 3 months study. In the dialyzed patients Se supplementation led to a gradual increase in the concentration of Zn, which after 3 months had reached a value significantly higher compared with the HD 0 (P < 0.01).

Copper concentration in plasma in all groups was nearly the same and ranged from 1.27 to 1.37 mg/L (Figure 4). The values in both subgroups remained constant during the course of the dialysis.

Plasma MDA concentration in the nondialyzed CKD patients did not differ from the values found in the control group, but was significantly higher in the patients on HD (Figure 5). The administration of Se for a period of three months to the dialyzed patients had no effect on the change in the concentration of MDA.

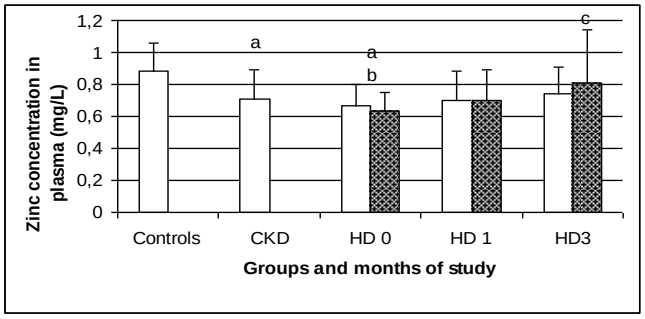

Figure 3: Zinc concentration in plasma of the healthy controls, the nondialyzed CKD patients and the patients on hemodialysis supplemented with placebo (white columns) and selenium (dark columns). Statistics: a, the CKD nondialyzed patients and the HD 0 (both subgroups taken together) vs. the controls, P < 0.0001; b, HD 0 (both subgroups) vs. CKD, P < 0.05; c, HD 3 (+Se) vs. HD 0 (+Se), P < 0.01.

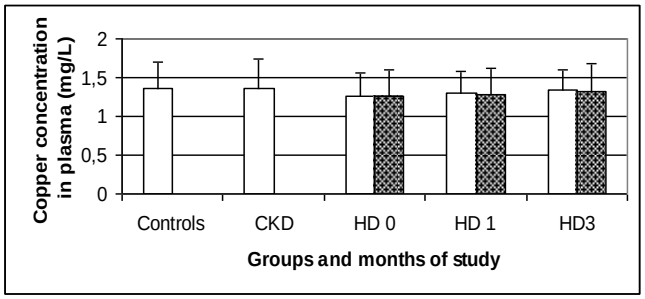

Figure 4: Copper concentration in plasma of the healthy controls, the nondialyzed CKD patients and the patients on hemodialysis supplemented with placebo (white columns) and selenium (dark columns). Statistics: There were no statistical differences between the groups.

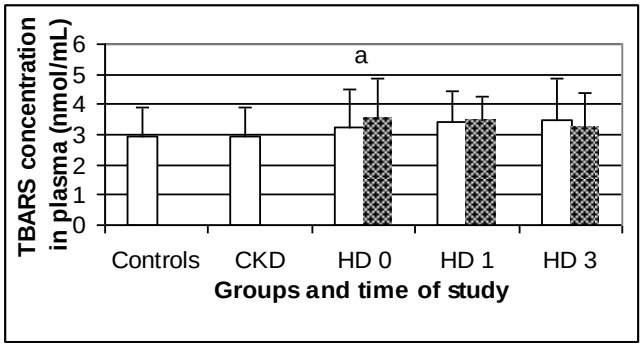

Figure 5: TBARS concentration in plasma of the healthy controls, the nondialyzed CKD patients and the patients on hemodialysis supplemented with placebo and selenium. Statistics: a, HD 0 (both subgroups taken together) vs. the healthy controls and the nondialyzed CKD patients, P < 0.05.

Discussion

Reactive oxygen species have been implicated in the pathogenesis of a broad variety of tissue injuries in various disease states. This is mainly mediated by peroxidation of lipids, injury of nucleic acids (mainly DNA) and proteins [36,37]. The first line of defense against ROS is SOD. There are some studies which have shown decreased activity of red blood cell SOD and GSH-Px in CKD patients and suggest that hemodialysis can produce oxidative stress which leads to lipid peroxidation [3,38]. The decreased activity of red blood cell SOD and GSH-Px in the dialyzed patients found in our study is in accordance with the above observations. Our and other studies have shown that the patients with CKD and especially those on HD have significantly lower Se concentration in blood components and lower GSH-Px activity in plasma [28,29,39-42].

GSH-Px reduces hydrogen peroxide and all organic hydroperoxides [43]. In this study we demonstrated that RBC GSH-Px activity in nondialyzed patients with CKD is significantly lower compared with healthy subjects. Results of this study correspond to our previous study [44] and to the observations of many other authors

[3,36,45-48]. However, studies of several other authors presented conflicting results on the red cell GSH-Px activity in the CKD patients [29,49-51].

Red blood cell GSH-Px is synthesized during erythropoiesis, and is not dependent on kidney function [52] therefore it is not clear why in these patients its activity is reduced. It seems very likely that the main reason for this is selenium deficiency [29,39,42,53].

Montazerifar et al [3] have shown that in the dialyzed patients RBC GSH-Px and SOD activity was more than two times lower compared with the controls and decreased markedly (by about 50% and 33%, respectively) after HD ($P < 0.0001$). The authors believe that dialysis reduces the antioxidant defense of the organism.

There is a dearth of publications on the effect of Se supplementation to CKD patients.

In the literature there is no clear opinion concerning the administration of selenium to patients on HD. Some authors suggest that Se should be administered to these patients [54-56], although it has little or no effect on the GSH-Px activity in plasma [42,57]. Due to the antioxidant properties of Se incorporated in some other selenoenzymes, it has been suggested that supplementation of this element might be of benefit and efficacious in reducing cardiovascular complications in uremic patients [58]. Koenig et al [36] believe that Se supplementation improves the oxygen radical scavenger system and increases selenium concentration in blood and the activity of selenium dependent GSH-Pxs in other tissues. Thus, Se should be considered for micronutrient supplementation in patients on chronic HD therapy.

Our group studied the effect of Se supply on plasma GSH-Px protein level in plasma [39] and on protection of DNA against ROS in lymphocytes in the patients on HD [9]. In a few studies conducted by other authors, the patients on HD were administered with different preparations and doses of Se and for different periods of time. For this reason, the results presented differ widely from each other.

In our study, RBC GSH-Px activity, in the patients on HD receiving Se for three months rose from 18.4 to 25.1 U/g Hb ($P < 0.0001$). Koenig et al [36] supplemented intravenously to the dialyzed patients with 400 μg sodium selenite three times a week for eight weeks and have shown that RBC GSH-Px activity rose significantly (from 16.5 to 24.2 U/g Hb; $P < 0.001$). The authors believe that based on the conclusions presented above, Se should be administered to the CKD patients.

Superoxide dismutase plays a major role in protecting the cells against oxidative stress

This occurs in the patients on HD and is linked to the acceleration of tissue damage in ESRD [59]. SODs work in conjunction with CAT and GSH-Pxs to diminish the harmful effects of ROS [60]. The activity of SOD varies among tissues. The highest levels are seen in the liver, kidney and spleen [37]. Vaziri et al [61] have shown that in rat kidney tissue with surgically induced CKD, Cu/Zn SOD activity was significantly lower (by 55%) compared to sham operated rats.

Studies on the activity of SOD in RBCs in the patients on HD have provided different results. Our results have shown that in the nondialyzed CKD patients RBC Cu^{2+}/Zn^{2+} SOD activity was the same as in the control group but was significantly lower in the patients on HD. Results of our study are fully consistent with the observations of Ceballos-Picot et al [40] who have also shown that the activity of this enzyme was the same as in the controls and was not affected by the progression of renal failure, but in the patients on HD the activity was significantly lower ($P < 0.001$). Similar to our results Atamer et al [62] did not find significant difference in RBC SOD activity between the CKD patients and the control group. Koca et al [63] showed that, similarly to our results, SOD activity in red blood cells in the dialyzed patients is significantly lower than in the healthy controls. Prolonged exposure to HD (up to 11 years) had no effect on the SOD activity.

Our study has shown that dialysis had little effect on the RBC SOD activity: After three-month treatment the activity decreased insignificantly in both subgroups [by 11% (controls) and 9% (+Se)]. Se supplementation to the HD patients had no effect on the activity of this enzyme. Quite different results were obtained by Koenig et al [36] and Mimic-Oka et al [49]. Koenig's group has shown that in the CKD patients on HD, SOD activity in RBCs was significantly higher ($P < 0.001$) than in the control group. With regard to the administration of Se to the dialyzed patients, the results obtained by these authors are consistent with the data of our study: during Se administration RBC SOD activity decreased slightly and rose 4 weeks after the end of supplementation. On the contrary, Mimic-Oka et al [49] found that in all stages of CKD SOD activity in red blood cells increased from 43% (early stages) to 81% (ESRD) compared with the healthy controls. The authors argue that augmentation of erythrocyte SOD activity, which serves a key function in the elimination of ROS, in the CKD patients probably, provides significant protection for red blood cells against exogenous and endogenous oxidant metabolites accumulating in the blood in chronic renal insufficiency. In another experiment Mimic-Oka et al [64] studied the SOD activity in plasma of nondialyzed CKD patients and those on HD and have shown that in the early stages of the disease enzyme activity did not differ from the control group, but in the ESRD and in the patients on HD it was significantly ($P < 0.001$) higher that in the control group. The authors believe that the gradual increase in the activity of SOD in plasma of the HD patients together with the fall in plasma GSH-Px activity may result in an accumulation of H_2O_2 and other hydro peroxides.

Several studies on the erythrocyte SOD activity presented by other authors [47,48,65,66] have reported lower values in patients on HD. Low values of the activity was accompanied by significantly reduced concentrations of Cu and Zn. Richard et al [47] showed also a high, statistically significant ($P < 0.02$) correlation between RBC SOD and Zn ($r = 0.58$) and SOD and Cu ($r = 0.60$). Mimic-Oka et al [67] demonstrated that in the patients on HD red blood cell SOD was significantly lower ($P < 0.001$) compared to the control group and nondialyzed patients. The dialysis did not affect the activity of this enzyme.

According to most studies, the patients with CKD have reduced plasma concentration of Zn and during dialysis this concentration does not change significantly [cf 68]. The results of our study confirm these observations. In Se supplemented subgroup Zn concentration increased significantly in comparison to the baseline. The results of our observation are consistent with the data of other authors [41,69-

72], who have also shown statistically lower levels of this element compared with the healthy subject.

Our study has shown that the concentration of Cu in the plasma of patients with CKD and on dialysis did not differ from the values of the control group. Se supply to the dialyzed patients had no effect on plasma concentration of Cu. Our results are consistent with the data of Agenet et al [73] who did not show differences in the concentration of Cu in plasma and RBC among the dialyzed patients and the control group; the process of dialysis did not affect the change of these levels. Several authors [28,63,71,72] have shown higher levels of plasma/serum Cu in the patients on HD.

Oxidative stress increased lipid peroxidation [74]. Thiobarbituric acid reactive substances are naturally present in biological specimens and include lipid hydroperoxides and aldehydes (mainly MDA) concentration which increases as a response to oxidative stress [75].

Studying the concentration of MDA in blood components in patients on HD most authors found significantly higher values of this compound compared with the healthy subjects. Martin-Mateo et al [46] have shown that in HD patients the baseline concentration of MDA in RBCs before dialysis was higher by 31% compared with the controls and after HD the concentration increased significantly ($P < 0.001$) by about 40%. Ozden et al [43] have shown that MDA concentration in plasma increased significantly after HD ($P < 0.0001$) by 67% compared to pre-HD values. Koca et al [63] showed that the concentration of MDA in plasma of patients on dialysis was nearly two times higher than in the control group, and during dialysis (up to 11 years) it further increased significantly.

However, Samouilidou and Grapsa [76] showed that in the patients treated with HD and Peritoneal Dialysis (PD) plasma MDA levels were significantly higher than in the control group, but after HD – contrary to the above mentioned authors – the concentration was significantly reduced. Paul et al [48] did not find any differences in plasma MDA levels between the HD patients and the control group, while the RBCs MDA concentrations were significantly higher in those patients.

Several studies have shown that administration of certain antioxidant compounds to the dialyzed patients prevented the oxidation of PUFAs. The most often used antioxidants in the dialyzed patients are vitamins E and C, sometimes selenium.

The results of our study showed that selenium supplementation to the dialyzed patients has no effect on lipid per oxidation – TBARS concentration in plasma after 3-month supplementation of the element did not differ from the baseline values and was the same as in the placebo group.

Our results are in some way similar to the data published by Koenig et al [36] who supplemented the patients on chronic HD with sodium selenite and observed that MDA level was only temporarily decreased during Se supplementation, but returned to the restudy level after 8 weeks. In their study [36] MDA concentration in the patients before dialysis was profoundly elevated compared with the normal controls (1.68 vs. 0.36 mmol/L plasma; $P < 0.001$). Also Ardalan et al [77], who supplemented the patients on HD (two times a week) with capsules containing 600 μg Se (sodium selenide) and 400 IU vitamin E found no difference in the concentration of MDA in the serum before and after the completion of the study.

Recently, Salehi et al [78] has shown that administration of 200 μg Se per day (selenium yeast) to the HD patients for a period of 12 weeks resulted in the concentration of MDA in the serum being significantly ($P < 0.001$) lower compared to the placebo group. The baseline concentration of MDA in both groups was the same. Also El-Demerdash and Nasr [79] have recently shown that Se supplementation (200 μg/kg BW/day for 30 days) to rats caused a significant decrease in the level of TBARS and an increase in SOD and GSH-Px activity in serum. The question about supplementation of antioxidants to the HD patients is open although there are some positive data regarding the use of moderate and safe selenium supplementation to those patients. In our experimental studies we have shown that administration of Se to the patients on HD stimulates the activity of GSH-Px in erythrocytes [42]. It has also been shown that Se administration to mammals induces the synthesis of GSH-Px 1 in other tissues [20,80]. Se has a negligible effect on the activity of GSH-Px in plasma, does not induce the synthesis of this enzyme in the kidneys [39] but prevents DNA damage in lymphocytes [9]. Some authors recommend that the impaired kidney function can be improved by Se administration in the CKD patients, particularly in the patients on HD [36,78,81,82]. Zima et al [83] suggest that in the dialyzed patients Se supply may be beneficial (increasing glutathione peroxidase activity, immunostimulatory properties, cardioprotective effect, for the chronic renal failure patients. Supplementation with a trace element may be indicated when its depletion was unequivocally documented and when there is evidence of the positive effects of this element on the quality of life of the dialyzed patients.

In conclusion, **o**ur results suggest that Se supplementation to patients on HD increases the activity of GSH-Px in red blood cells but has no effect on the activity of SOD in these cells. Se administration has no effect on the reduction of MDA concentration in plasma.

Acknowledgement

This study was partly financed by the State Committee for Scientific Research Committee (KBN), Warsaw, Poland (Grant No. 2 P05D 097 27). Thanks are due to Mr. Sven Moesgaard, Pharma Nord, Denmark, for supplying us with selenium rich-yeast and placebo used in this study.

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Austin Therapeutics - Volume 1 Issue 2 - 2014
ISSN: 2472-3673 | www.austinpublishinggroup.com

Citation: Zachara BA, Gromadzinska J, Wasowicz W, Swiech R and Zbrog Z. Selenium Supplementation to Chronic Kidney Disease Patients on Hemodialysis has no Effect on Superoxide Dismutase Activity and Malonyldialdehyde Concentration in Blood. Austin Therapeutics. 2014;1(2): 7.