Send Orders for Reprints to reprints@benthamscience.net

Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2020, *19*, 42-49

RESEARCH ARTICLE

The Impact of Inflammatory Profile on Selenium Levels in Hemodialysis Patients

Marcelo R. Bacci[1], Lívia S.S. Cabral[1], Glaucia L. da Veiga[1,*], Beatriz da C.A. Alves[1], Neif Murad[1] and Fernando L.A. Fonseca[1,2]

[1]*Clinical Analysis Department, Faculdade de Medicina ABC, FMABC Santo André, Brazil;* [2]*Instituto de Ciências Químicas, Ambientais e Farmacêuticas, Universidade Federal de São Paulo, UNIFESP, Diadema, Brazil*

ARTICLEHISTORY

Received: October 31, 2018
Revised: January 06, 2019
Accepted: January 14, 2019

DOI:
10.2174/1871523018666190121165902

Abstract: ***Introduction*:** Hemodialysis stands out as an eligible treatment for patients with chronic kidney disease. The subsequent inflammatory process resulting from this disease and hemodialysis *per se* is exacerbated in this therapy. Selenium (Se) is an essential trace element that can participate in the inhibition of pro-oxidant and pro-inflammatory processes and could be considered a measurement that indicates the progression of chronic kidney disease and inflammation.

***Objectives*:** The present study investigated selenemia in hemodialysis patients of the ABC region of São Paulo and aimed to establish the correlation between an inflammatory marker and selenemia in this conditions disease.

***Methods*:** This is an observational cross-sectional study of the Faculdade de Medicina do ABC in patients submitted to hemodialysis three times a week for at least six months. The eligible group composed of 21 patients, who filled out forms and underwent biochemical tests (colorimetric enzyme methods, flow cytometer, turbidimetric method and mass spectrometry).

***Results*:** The study population showed, women (70%), men (30%) with a mean age of 47 ± 17 years, Caucasians (36%) and non-Caucasian (64%), hypertensive (68%), smokers (53%) and non-smokers (64%). There was a hegemonic prevalence of systolic arterial hypertension (SAH) 68.1% in relation to diabetes *mellitus* (DM) (50%). Pre and post hemodialysis (HD) selenemia showed statistical significance, which did not occur with C-reactive protein. There was a predominance of females in our sample; the pre- and post-HD selenemia were within the normal range of the reference values; there was a statistically significant correlation between pre and post-HD selenemia; there was no correlation with statistical significance between values of pre and post-HD C-reactive protein.

***Conclusion*:** Our data showed that there was no direct relationship between pre- and post-HD inflammation and pre- and post-HD selenemia.

Keywords: Chronic kidney disease, hemodialysis, selenium, pro-oxidant, inflammation, systemic arterial hypertension.

1. INTRODUCTION

Current evidence suggests that systemic arterial hypertension (SAH) and type II diabetes mellitus (DM) are the main causes of chronic kidney disease (CKD) worldwide [1-3]. CKD has a direct relationship with cardiovascular diseases and is considered a high risk factor for death and comorbidities [4-6]. Therefore, renal dysfunction is an additional target for intervention and prevention of cardiopathies [5].

*Address correspondence to this author at the Clinical Analysis Department, Faculdade de Medicina ABC, FMABC Santo André, Brazil; Tel: +55 11 49935488; E-mail: grlveiga@gmail.com

1875-614X/20 $65.00+.00

Both SAH and DM are progressive, and in relation to renal function, are the main causes that contribute to the high risk of progression to end-stage renal disease. This condition requires long-term maintenance of survival therapies such as hemodialysis or renal transplantation [6].

Studies that evaluated the prevalence and incidence of CKD in the world are based on patients who started renal replacement therapy (RRT) [6-8]. In America, a 1.1% increase in incidence was detected, representing 116.395 new cases in the terminal stage [9]. In Japan, the European Union, India and sub-Saharan Africa, the number of TS patients reaches 2000, 800 and 100 per million of the population, respectively [1]. In Brazil, prevalence and incidence increase each year, concurrent with the increase in the number of patients in RRT [8, 9]. In the last Brazilian census of dialysis of 2011-2014, dialytics accounted for 112,004 [10].

Patients with inflammatory CKD constitute an independent risk factor for morbidity and mortality. Studies have shown that inflammation increases cardiovascular risk and mortality in patients with terminal CKD [11, 12]. Inflammation is characterized by elevated levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), albumin and pre-albumin that constitute common findings in dialysis patients. It is also postulated that the traditional risk factors for cardiovascular disease such as hypertension, DM, dyslipidemia and obesity would not be sufficient to explain the high incidence of cardiovascular complications in terminal CKD [12, 13].

Recent findings in the literature attribute to inflammation, oxidative stress, malnutrition, accelerated atherosclerosis as well as renin angiotensin aldosterone system imbalance the responsibility for worse prognosis in kidney diseases. These findings have established an association between inflammation, malnutrition and atherosclerosis in terminal CKD [14, 15]. Beneficial effects are attributed to selenium (Se) in areas such as immunocompetence, cardio-protection and cancer prevention. And low selenium status has been associated with increased risk of mortality, and cognitive decline [16, 17].

The tissue levels depend on daily intake and the form in which Se is consumed, as well as on the chemical form found and metabolism [18, 19]. Associated with this is also the case that selenemia in people from seleniferous regions surpasses those of non-seleniferous areas, especially when observed with antitumor actions [20-22].

The biological effect of Se is due to the amino acid selenocysteine, an active component of glutathione peroxidase (GPX), whose main function is to neutralize hydrogen peroxide and oxidative damage [23-25].

The chronic renal patient has deficient intestinal absorption of Se, on the other hand, there is increased urinary and dialytic loss, in addition to abnormal binding to the proteins involved in its transport. In addition to that, there is a reduction in the intake of Se associated with restricted consumption of protein foods and the urinary loss of albumin. The kidneys are responsible for the synthesis of the enzyme glutathione peroxidase (GSH-Px), a factor that contributes to the low plasma levels of this enzyme in the more advanced stages of CKF [26-28].

Zachara and collaborators have shown that reduced blood levels of Se in association with the decrease of plasma GSH-Px enzyme are correlated with the progression of the kidney disease to the terminal stage [24]. Oxidative stress, a classical risk factor for cardiovascular events and deficiency of selenium antioxidant mechanisms, compose reports from the literature on dialysis. Reduced levels of Se can contribute to endothelial dysfunction, affect coronary flow, and promote accelerated atherosclerosis. In addition to these findings, serum levels of Se are known to be inversely associated with the risk of mortality in patients in HD [17, 24, 25, 27].

2. OBJECTIVES

Our aim was to investigate serum levels of selenium in hemodialysis patients and to establish the correlation between the inflammatory marker and selenemia in hemodialysis patients.

3. MATERIALS AND METHODS

This is an observational cross-sectional study of patients at the Reference Center for Nephrology at the Mário Covas State Hospital of the Faculdade

de Medicina do ABC submitted to hemodialysis 3 times a week for at least 6 months to investigate the correlation between serum Se levels and inflammatory markers.

The eligible group was comprised of 22 patients who filled out forms and submitted to laboratory tests. Individual blood samples were collected for the analysis of inflammatory markers of the serum concentration of Se.

3.1. Inclusion Criteria

Patients over 21 years of age who underwent hemodialysis 3 times a week for at least 6 months and who signed the informed consent form were included.

3.2. Exclusion Criteria

Patients undergoing antibiotic therapy, with chronic and acute inflammatory disorders, zinc supplementation, who were discharged from the hospital 30 days prior to collection, patients with human immunodeficiency virus or acquired immunodeficiency syndrome, and those with viral hepatitis B and C, who had rheumatoid arthritis, scleroderma, systemic lupus erythematosus and who were undergoing continuous corticosteroid therapy were excluded.

The sample size was calculated for convenience because it did not have the expected value for the difference between patients with dialytic renal disease.

Duplicate, individualized blood samples were collected from eligible patients for the analysis of routine parameters: urea, creatinine, serum albumin, complete blood count, in addition to serum Se concentration and C-reactive protein (CRP).

The samples were kept in a freezer at -20°C and later processed in automatic analyzers from the Laboratory of Clinical Analysis of the School of Medicine.

Urea, creatinine and albumin were evaluated by using colorimetric enzyme methods in Cobas 6000® apparatus (Roche®). The total blood counting cells were performed using flow cytometer in ABX Penta 120® apparatus (HORIBA®). CRP ultrasensitive was measured by a turbidimetric method in Immulite 1000® (Siemens®). Finally, selenium concentration was determined by ICP-MS plasma inductively coupled to mass spectrometer.

All parameters were performed following a practical clinical laboratory analysis.

Results are shown as mean ± standard deviation of the mean. The data were analyzed by unpaired T test by STATA 15 software. The level of statistical significance was defined as $p<0.05$.

4. RESULTS

In this study, the following variables were evaluated: blood urea, CRP and plasma Se before and after hemodialysis. The magnitude of inflammatory impairment was assessed through CRP levels and of the renal impairment through the levels of urea, besides the variation in the levels of Se.

Table **1** shows the baseline characteristics of the individuals evaluated in this study, the percentage values were: women (70%), hypertensive (68%), non-Caucasian (64%) and non-smokers (64%), with a mean age of 47 ± 17 years, contrasting with men (30%), non-caucasian, smokers. There was a hegemonic prevalence of SAH 68.1% in relation to DM (50%).

Table 1. Demographic data of hemodialysis patients.

Variables	Values
Sex (M/F)	
Male	7
Female	15
Age (years)*	47 ± 17
Ethnicity	
Non-Caucasians	14
Caucasians	8
Time on Hemodialysis (months) *mean*	2
Other evaluated Parameters	
Smokers	14
Non-smokers *%*	8

Values expressed as absolute and *mean ± standard deviation of the mean (SD).

Table 2. Data from biochemical evaluation pre and post hemodialysis in Female.

Variables (Female) n=15	Pre HD	Post HD
Hemoglobin (12-15 g/dL)	-	10.6 ± 2
Blood Urea (mg/dL)	156 ± 41	74 ± 6*
Blood Creatinine (mg/dL)	12 ± 3	-
Blood Albumin (g/dL)	3.8 ± 0.3	-
CRP (mg/L)	11.8 ± 13	11.2 ± 12
Serum Se (μg/L)	56 ± 23	43 ± 25*

Values of pre and post hemodialysis of Hemoglobin (g/dL), Blood Urea (mg/dL), Blood Creatinine (mg/dL), Blood Albumin (g/dL), C-reactive protein (CRP) (mg/L) and Serum Se (μg/L) in Female. Values expressed as mean ± standard deviation of the mean (SD). * $p < 0.05$ *vs*. Pre-HD.

We observed a statistical reduction in plasma hemoglobin and selenium levels after the hemodialysis session post HD compared to pre HD as shown in Table **2**. We did not observe an alteration in the other biochemical parameters studied.

5. DISCUSSION

The demographic characteristics of the study differed from those of other studies conducted in other countries [28-34].

A prevalence of 68% of SAH was found in this study, a result that was lower than several published studies such as Portolés *et al*. [34], which showed a percentage of 75.8% in Spain within a decade, the study by Ohsawa *et al.* [33] in Japan (87%), and the study by Agarwal *et al.* [35] in the USA, in which 86% of the patients were hypertensive.

Two meta-analyses emphasize the importance of treating hypertension in hemodialysis patients, with the reduction of all-cause mortality and morbidity in those treated with antihypertensive drugs [36, 37].

A prevalence of 50% of DM in this study was higher than the USRDS report, which showed that 38.5% of patients undergoing hemodialysis in the USA are diabetic [38]. Other study [39], this prevalence ranged from 26% to 43%, with the exception of the CHOICE study [40] with a prevalence of 54% of diabetics. Among the individual cardiovascular risk factors, smoking has a significant association with the incidence of cardiac events.

In our study, the prevalence of smoking was 36%, differing from others in the literature which ranged from 40% to 61% in CHOICE [40] and 65% in ANSWER [39]. It is possible that this difference between the data found in this study and others already described present different population, in diet and period studied. We did not identify differences in selenium or CRP levels when we separated gender.

In the population sample of ABC, pre-HD selenemia was at the lower limit, wherein the selenemia reduced before hemodialysis. The variability of these values stems from innumerable factors, which can be due to the selenium content in the soil of each region, which determines the concentration of this element in foods of plant origin and subsequently those of animal origin, both terrestrial and aquatic [21].

The values in the northeastern region has consubstantiated to the consumption of Brazil nuts, which contain high amounts of selenium due to the high concentration of this micronutrient in the soil. Stockler-Pinto *et al.* [20-22], determined the selenium content in foods consumed in Brazil from samples taken from the retail trade in several states and showed higher levels of selenium in plasma of hemodialysis patients. Selenium contents in foods of plant origin were observed to be generally below 5.0μg/100g. In Brazil, the presence of fish, mainly, and other products of animal origin in the diet is important to guarantee the recommended levels of selenium. This variability evidences the lack of homogeneity of the results due to the fac-

Table 3. Data from biochemical evaluation pre and post hemodialysis in Male.

Variables (Male) n=7	Pre HD	Post HD
Hemoglobin (12-15 g/dL)	-	11 ± 2
Blood Urea (mg/dL)	196 ± 19	67 ± 6*
Blood Creatinine (mg/dL)	12 ± 5	-
Blood Albumin (g/dL)	4 ± 0.4	-
CRP (mg/L)	7.4 ± 6	6.5 ± 4
Serum Se (μg/L)	58 ± 7	34 ± 15*

Values of pre and post hemodialysis of Hemoglobin (g/dL), Blood Urea (mg/dL), Blood Creatinine (mg/dL), Blood Albumin (g/dL), C-reactive protein (CRP) (mg/L) and Serum Se (μg/L) in Male. Values expressed as mean ± standard deviation of the mean (SD). * $p < 0.05$ *vs*. Pre-HD.

tors, already reported, that influence the concentration of Se, especially food habits.

The normal values of Se are needed to saturate GPX, resulting in maximum activity of the enzyme [41-43]. What remains unknown in this sample is lack of information about the eating habits that are not contextualized in the applied questionnaire. There was a statistically significant reduction of selenium between pre- and post-HD, which is consistent with the literature showing that HD promotes a decrease in this micronutrient. Selenium deficiency is a constant in dialysis patients (Table **3**).

Serum selenium levels are markedly low in hemodialytics [44] compared to non-dialytics; in view of the essential role of selenium in GPX activity, selenium deficiency is associated with increased cancer [45] and coronary artery disease [46] in the general population. Selenium is an essential micronutrient with known antioxidant properties [42, 43]. Prabhu *et al*. (2002) suggested that Se supplementation dietary can be used to prevent and/or treat inflammatory diseases mediated by oxidative stress, considering that HD patients present an oxidative imbalance and an increase of inflammation. It is possible that selenium supplementation is a viable treatment in this case [42]. Furthermore, strongly positive correlations between selenium levels and nutritional markers such as serum albumin have been reported [44, 47].

Therefore, selenium deficiency may also contribute to malnutrition in patients with HD [48]. The decrease in post-HD levels of selenium did not promote any clinically detectable infectious alterations during the observational period, since pre- and post-HD values of C-reactive protein did not show statistical significance. Thus, our data paradoxically showed no correlation between selenemia and inflammation.

CONCLUSION

Summing up the data of this study, we verified that there was a predominance of females in our sample. Pre- and post-HD selenemia values were within the normal range of the literature reference values. There is a correlation between pre- and post-HD selenemia, but not between selenemia pre-HD and post-HD with CRP values. Therefore, this suggest that the concentration of selenium does not affect CRP levels in pre- and post-HD patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Research Ethics Committee of Faculdade de Medicina do ABC, Brazil, under Protocol no. 2.302.284.

HUMAN AND ANIMAL RIGHTS

The present study was carried out in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Patients who agreed to participate in the study were given a free and informed consent form

(FICF) with the appropriate explanations of the adopted protocols and the informed consent forms were signed by the participants.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, [G.L. da V.] upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Barsoum, R.S. Chronic kidney disease in the developing world. *N. Engl. J. Med.,* **2006**, *354*(10), 997-999. http://dx.doi.org/10.1056/NEJMp058318 PMID: 16525136

[2] Haroun, M.K.; Jaar, B.G.; Hoffman, S.C.; Comstock, G.W.; Klag, M.J.; Coresh, J. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J. Am. Soc. Nephrol.,* **2003**, *14*(11), 2934-2941. http://dx.doi.org/10.1097/01.ASN.0000095249.99803.85 PMID: 14569104

[3] Kosmas, C.E.; Silverio, D.; Tsomidou, C.; Salcedo, M.D.; Montan, P.D.; Guzman, E. The impact of insulin resistance and chronic kidney disease on inflammation and cardiovascular disease. *Clin. Med. Insights Endocrinol. Diabetes,* **2018**, 11, 1179551418792257. http://dx.doi.org/10.1177/1179551418792257

[4] Vanholder, R.; Van Laecke, S.; Glorieux, G.; Verbeke, F.; Castillo-Rodriguez, E.; Ortiz, A. Deleting death and dialysis: Conservative care of cardiovascular risk and kidney function loss in Chronic Kidney Disease (CKD). *Toxins (Basel),* **2018**, *10*(6), E237. http://dx.doi.org/10.3390/toxins10060237 PMID: 29895722

[5] Mann, J.F.; Gerstein, H.C.; Pogue, J.; Bosch, J.; Yusuf, S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann. Intern. Med.,* **2001**, *134*(8), 629-636. http://dx.doi.org/10.7326/0003-4819-134-8-200104170-00007 PMID: 11304102

[6] Greco, F.; Fornara, P.; Mirone, V. Renal transplantation: technical aspects, diagnosis and management of early and late urological complications. *Panminerva Med.,* **2014**, *56*(1), 17-29. [PMID: 24637470

[7] de Zeeuw, D.; Hillege, H.L.; de Jong, P.E. The kidney, a cardiovascular risk marker, and a new target for therapy. *Kidney Int. Suppl.,* **2005**, *98*(98), S25-S29. http://dx.doi.org/10.1111/j.1523-1755.2005.09805.x PMID: 16108967

[8] Mastroianni-Kirsztajn, G.; Bastos, M.G.; Burdmann, E.A. Strategies of the Brazilian chronic kidney disease prevention campaign (2003-2009). *Nephron Clin. Pract.,* **2011**, *117*(3), c259-c265. http://dx.doi.org/10.1159/000320741 PMID: 20861650

[9] Collins, A.J.; Foley, R.N.; Chavers, B.; Gilbertson, D.; Herzog, Z.; Johansen, K. US renal data system 2011 annual data report. *Am. J. Kidney Dis.,* **2012**, *59*, e1-e420. http://dx.doi.org/10.1053/j.ajkd.2011.11.015

[10] Sesso, R.C.; Lopes, A.A.; Thomé, F.S.; Lugon, J.R.; Martins, C.T. Brazilian chronic dialysis census 2014. *J. Bras. Nefrol.,* **2016**, *38*(1), 54-61. http://dx.doi.org/10.5935/0101-2800.20160009 PMID: 27049365

[11] Keith, D.S.; Nichols, G.A.; Gullion, C.M.; Brown, J.B.; Smith, D.H. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch. Intern. Med.,* **2004**, *164*(6), 659-663. http://dx.doi.org/10.1001/archinte.164.6.659 PMID: 15037495

[12] Suliman, M.E.; Stenvinkel, P. Contribution of inflammation to vascular disease in chronic kidney disease patients. *Saudi J. Kidney Dis. Transpl.,* **2008**, *19*(3), 329-345. [PMID: 18445891

[13] Stenvinkel, P.; Ketteler, M.; Johnson, R.J.; Lindholm, B.; Pecoits-Filho, R.; Riella, M.; Heimbürger, O.; Cederholm, T.; Girndt, M. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia--the good, the bad, and the ugly. *Kidney Int.,* **2005**, *67*(4), 1216-1233. http://dx.doi.org/10.1111/j.1523-1755.2005.00200.x PMID: 15780075

[14] Oberg, B.P.; McMenamin, E.; Lucas, F.L.; McMonagle, E.; Morrow, J.; Ikizler, T.A.; Himmelfarb, J. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney Int.,* **2004**, *65*(3), 1009-1016. http://dx.doi.org/10.1111/j.1523-1755.2004.00465.x PMID: 14871421

[15] Donderski, R.; Stróżecki, P.; Sulikowska, B.; Grajewska, M.; Miśkowiec, I.; Stefańska, A.; Siódmiak, J.; Odrowąż-Sypniewska, G.; Manitius, J. Aldosterone antagonist therapy and its relationship with inflammation, fibrosis, thrombosis, mineral-bone disorder and

cardiovascular complications in peritoneal dialysis (PD) patients. *Int. Urol. Nephrol.,* **2017**, *49*(10), 1867-1873. http://dx.doi.org/10.1007/s11255-017-1655-2 PMID: 28710615

[16] Steinbrenner, H.; Speckmann, B.; Sies, H. Toward understanding success and failures in the use of selenium for cancer prevention. *Antioxid. Redox Signal.,* **2013**, *19*(2), 181-191. http://dx.doi.org/10.1089/ars.2013.5246 PMID: 23421468

[17] Čobanová, K.; Faix, Š.; Plachá, I.; Mihaliková, K.; Váradyová, Z.; Kišidayová, S.; Grešáková, Ľ. Effects of different dietary selenium sources on antioxidant status and blood phagocytic activity in sheep. *Biol. Trace Elem. Res.,* **2017**, *175*(2), 339-346. http://dx.doi.org/10.1007/s12011-016-0794-0 PMID: 27411926

[18] Valea, A.; Georgescu, C.E.; *Selenoproteins in human body: focus on thyroid pathophysiology., Hormones (Athens).,* **2018**, 5. http://dx.doi.org/10.1007/s42000-018-0033-5

[19] Combs, G.F. Biomarkers of selenium status. *Nutrients,* **2015**, *7*(4), 2209-2236. http://dx.doi.org/10.3390/nu7042209 PMID: 25835046

[20] Stockler-Pinto, M.B.; Lobo, J.; Moraes, C.; Leal, V.O.; Farage, N.E.; Rocha, A.V.; Boaventura, G.T.; Cozzolino, S.M.; Malm, O.; Mafra, D. Effect of Brazil nut supplementation on plasma levels of selenium in hemodialysis patients: 12 months of follow-up. *J. Ren. Nutr.,* **2012**, *22*(4), 434-439. http://dx.doi.org/10.1053/j.jrn.2011.08.011 PMID: 22217537

[21] Stockler-Pinto, M.B.; Malm, O.; Azevedo, S.R.; Farage, N.E.; Dorneles, P.R.; Cozzolino, S.M.; Mafra, D. Selenium plasma levels in hemodialysis patients: comparison between North and Southeast of Brazil. *J. Bras. Nefrol.,* **2014**, *36*(4), 490-495. http://dx.doi.org/10.5935/0101-2800.20140070 PMID: 25517278

[22] Sesso, R.C. Diálise crônica no Brasil - relatório do censo bra-sileiro de diálise. **2011**, *J. Bras. Nefrol.,* **2012**, *34*(3), 272-277.

[23] Sanz Alaejos, M.; Díaz Romero, C. Urinary selenium concentrations. *Clin. Chem.,* **1993**, *39*(10), 2040-2052. http://dx.doi.org/10.1093/clinchem/39.10.2040 PMID: 8403389

[24] Zachara, B.A.; Gromadzińska, J.; Wasowicz, W.; Zbróg, Z. Red blood cell and plasma glutathione peroxidase activities and selenium concentration in patients with chronic kidney disease: a review. *Acta Biochim. Pol.,* **2006**, *53*(4), 663-677. http://dx.doi.org/10.18388/abp.2006_3294 PMID: 17160142

[25] Wołonciej, M.; Milewska, E.; Roszkowska-Jakimiec, W. Trace elements as an activator of antioxidant enzymes. *Postepy Hig. Med. Dosw.,* **2016**, *70*, 1483-1498. http://dx.doi.org/10.5604/17322693.1229074 PMID: 28100855

[26] Thomson, C.D. Assessment of requirements for selenium and adequacy of selenium status: a review. *Eur. J. Nutr.,* **2004**, *58*391402.

[27] Fujishima, Y.; Ohsawa, M.; Itai, K.; Kato, K.; Tanno, K.; Turin, T.C.; Onoda, T.; Endo, S.; Okayama, A.; Fujioka, T. Serum selenium levels are inversely associated with death risk among hemodialysis patients. *Nephrol. Dial. Transplant.,* **2011**, *26*(10), 3331-3338. http://dx.doi.org/10.1093/ndt/gfq859 PMID: 21372251

[28] Gómez de Oña, C.; Martínez-Morillo, E.; Gago González, E.; Vidau Argüelles, P.; Fernández Merayo, C.; Álvarez Menéndez, F.V. Variation of trace element concentrations in patients undergoing hemodialysis in the north of Spain. *Scand. J. Clin. Lab. Invest.,* **2016**, *76*(6), 492-499. http://dx.doi.org/10.1080/00365513.2016.1201852 PMID: 27362816

[29] Rayman, M.P. Selenium and human health. *Lancet,* **2012**, *379*(9822), 1256-1268. http://dx.doi.org/10.1016/S0140-6736(11)61452-9 PMID: 22381456

[30] Foley, R.N.; Sexton, D.J.; Drawz, P.; Ishani, A.; Reule, S. Race, ethnicity, and end-of-life care in dialysis patients in the United States. *J. Am. Soc. Nephrol.,* 2018, *29*(9), 2387-2399. http://dx.doi.org/10.1681/ASN.2017121297 PMID: 30093455

[31] Stack, A.G.; Bloembergen, W.E. Prevalence and clinical correlates of coronary artery disease among new dialysis patients in the United States: a cross-sectional study. *J. Am. Soc. Nephrol.,* **2001**, *12*(7), 1516-1523. [PMID: 11423581

[32] Sarnak, M.J.; Coronado, B.E.; Greene, T.; Wang, S.R.; Kusek, J.W.; Beck, G.J.; Levey, A.S. Cardiovascular disease risk factors in chronic renal insufficiency. *Clin. Nephrol.,* **2002**, *57*(5), 327-335. http://dx.doi.org/10.5414/CNP57327 PMID: 12036190

[33] Ohsawa, M.; Kato, K.; Itai, K.; Onoda, T.; Konda, R.; Fujioka, T.; Nakamura, M.; Okayama, A. KAREN Study Group. Cardiovascular risk factors in hemodialysis patients: results from baseline data of kaleidoscopic approaches to patients with end-stage renal disease study. *J. Epidemiol.,* **2005**, *15*(3), 96-105. http://dx.doi.org/10.2188/jea.15.96 PMID: 15930806

[34] Portolés, J.; López-Gómez, J.M.; Aljama, P. Cardiovascular risk in hemodialysis in Spain: prevalence, management and target results (MAR study). *Nefrologia,* **2005**, *25*(3), 297-306. [PMID: 16053011

[35] Agarwal, R.; Nissenson, A.R.; Batlle, D.; Coyne, D.W.; Trout, J.R.; Warnock, D.G. Prevalence, treatment, and control of hypertension in chronic hemodi-

alysis patients in the United States. *Am. J. Med.,* **2003**, *115*(4), 291-297. http://dx.doi.org/10.1016/S0002-9343(03)00366-8 PMID: 12967694

[36] Heerspink, H.J.; Ninomiya, T.; Zoungas, S.; de Zeeuw, D.; Grobbee, D.E.; Jardine, M.J.; Gallagher, M.; Roberts, M.A.; Cass, A.; Neal, B.; Perkovic, V. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet,* **2009**, *373*(9668), 1009-1015. http://dx.doi.org/10.1016/S0140-6736(09)60212-9 PMID: 19249092

[37] Agarwal, R.; Sinha, A.D. Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis. *Hypertension,* **2009**, *53*(5), 860-866. http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.128116 PMID: 19273737

[38] The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. United States Renal Data System. Excerpts from USRDS 2009 Annual Data Report. U.S. Department of Health and Human Services. *Am. J. Kidney Dis.,* **2010**, *55*(Suppl 1), S1NS420.

[39] Pérez-García, R.; Martín-Malo, A.; Fort, J.; Cuevas, X.; Lladós, F.; Lozano, J.; García, F. ANSWER study. Baseline characteristics of an incident haemodialysis population in Spain: results from ANSWER--a multicentre, prospective, observational cohort study. *Nephrol. Dial. Transplant.,* **2009**, *24*(2), 578-588. http://dx.doi.org/10.1093/ndt/gfn464 PMID: 19028750

[40] Longenecker, J.C.; Coresh, J.; Powe, N.R.; Levey, A.S.; Fink, N.E.; Martin, A.; Klag, M.J. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J. Am. Soc. Nephrol.,* **2002**, *13*(7), 1918-1927.

[41] Tonelli, M.; Wiebe, N.; Hemmelgarn, B.; Klarenbach, S.; Field, C.; Manns, B.; Thadhani, R.; Gill, J. Alberta kidney disease network. Trace elements in hemodialysis patients: a systematic review and meta-analysis. *BMC Med.,* **2009**, *7*, 25. http://dx.doi.org/10.1186/1741-7015-7-25 PMID: 19454005

[42] Prabhu, K.S.; Zamamiri-Davis, F.; Stewart, J.B.; Thompson, J.T.; Sordillo, L.M.; Reddy, C.C. Selenium deficiency increases the expression of inducible nitric oxide synthase in RAW 264.7 macrophages: role of nuclear factor-kappaB in up-regulation. *Biochem. J.,* **2002**, *366*(Pt 1), 203-209. http://dx.doi.org/10.1042/bj20020256 PMID: 12006087

[43] Yavuz, O.; Bicik, Z.; Cinar, Y.; Guney, Y.; Guler, S. The effect of different dialysis membranes on oxidative stress and selenium status. *Clin. Chim. Acta,* **2004**, *346*(2), 153-160. http://dx.doi.org/10.1016/j.cccn.2004.03.025 PMID: 15256316

[44] Bonomini, M.; Forster, S.; De Risio, F.; Rychly, J.; Nebe, B.; Manfrini, V.; Klinkmann, H.; Albertazzi, A. Effects of selenium supplementation on immune parameters in chronic uraemic patients on haemodialysis. *Nephrol. Dial. Transplant.,* **1995**, *10*(9), 1654-1661. [PMID: 8559485 http://dx.doi.org/10.1097/01.ASN.0000019641.41496.1E PMID: 12089389

[45] Persson-Moschos, M.E.; Stavenow, L.; Akesson, B.; Lindgärde, F. Selenoprotein P in plasma in relation to cancer morbidity in middle-aged Swedish men. *Nutr. Cancer,* **2000**, *36*(1), 19-26. http://dx.doi.org/10.1207/S15327914NC3601_4 PMID: 10798212

[46] Flores-Mateo, G.; Navas-Acien, A.; Pastor-Barriuso, R.; Guallar, E. Selenium and coronary heart disease: a meta-analysis. *Am. J. Clin. Nutr.,* **2006**, *84*(4), 762-773. http://dx.doi.org/10.1093/ajcn/84.4.762 PMID: 17023702

[47] Dworkin, B.; Weseley, S.; Rosenthal, W.S.; Schwartz, E.M.; Weiss, L. Diminished blood selenium levels in renal failure patients on dialysis: correlations with nutritional status. *Am. J. Med. Sci.,* **1987**, *293*(1), 6-12. http://dx.doi.org/10.1097/00000441-198701000-00003 PMID: 3812549

[48] Liu, M.L.; Xu, G.; Huang, Z.Y.; Zhong, X.C.; Liu, S.H.; Jiang, T.Y. Euthyroid sick syndrome and nutritional status are correlated with hyposelenemia in hemodialysis patients. *Int. J. Artif. Organs,* **2011**, *34*(7), 577-583. http://dx.doi.org/10.5301/IJAO.2011.8474 PMID: 21786251