Journal of Trace Elements in Medicine and Biology ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.de/jtemb

Clinical studies

Chronic treatment with statins increases the availability of selenium in the antioxidant defence systems of hemodialysis patients

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ARTICLE INFO

Article history:
Received 19 November 2008
Accepted 28 June 2009

Keywords:
Hemodialysis
Oxidative stress
Selenium
Statins

ABSTRACT

Project: Oxidative stress (OS) is enhanced in hemodialysis (HD) patients. Lipid peroxidation and oxidative damage to glycids, proteins and nucleic acids are the main consequences of OS and are associated with increased cardiovascular risk. Vitamin E and glutathione peroxidase (GSH-Px) represent the main antioxidant systems in human cells. Selenium (Se), bound to the active sites of GSH-Pxs, plays a critical role in this antioxidant defence system. Statins are widely used and extensively investigated in the prevention of cardiovascular disease, notably in high-risk subjects. Several studies show antioxidant effects of statins not related to their lipid-lowering action. Our study aimed to compare serum Se concentration in ESRD patients on maintenance HD and in homogeneous healthy subjects and to investigate whether chronic treatment with statins may interfere with serum Se concentration in HD patients.

Procedure: A total of 103 HD patients and 69 healthy subjects were enrolled; HD patients were divided into patients who were not treated with statins (group A) and patients who assumed statins since 6 months at least (group B). Serum Se was determined by atomic absorption spectrometry.

Results: Serum Se was significantly lower in HD patients of group A compared with healthy subjects (81.65 ± 19.66 Vs. 96.47 ± 15.62 mcg/L, $p < 0.0040$). However, in HD patients who assumed statins serum, Se was significantly higher than in HD patients who did not (111.83 ± 18.82 vs. 81.65 ± 19.66 mcg/L, $p < 0.0001$).

Conclusions: Our results suggest that in HD patients chronic treatment with statins is related to higher-serum Se concentration.

Introduction

Oxidative metabolism in aerobic organisms leads to the generation of reactive oxygen species (ROS). ROS are able to oxidize almost all classes of macromolecules, including proteins, lipids and nucleic acids [1]. A physiological level of ROS is usually maintained by antioxidant enzymatic systems. In humans, there are at least three groups of antioxidant enzymes: superoxide dismutases (SODs), catalases and notably glutathione peroxidases (GSH-Pxs). Some trace elements, such as copper (Cu), zinc (Zn) and selenium (Se), play an important role in the antioxidant processes when bound to the active sites of these enzymes. Hence, as a component of antioxidant enzymes, Se directly participates in elimination of ROS and in antioxidant defence of the organism. The generation of free radicals is involved in the oxidative stress (OS) and in the inflammatory response. Lipid peroxidation and oxidative damage to glucose, proteins and DNA are main consequences of OS, which is involved in a large number of diseases related to uremia and renal replacement therapies (RRTs). Whole OS and incidence of cardiovascular disease (CVD) are increased in ESRD patients on maintenance RRT, together with systemic amyloidosis associated with protein modifications and changes in both structure and function of many cellular components [2].

Hydroxy-methyl-glutaryl-coenzyme-A-reductase inhibitors (i.e. statins) and other lipid-lowering drugs are widely used and extensively investigated in the prevention and management of CVD, notably in high-risk subjects. Several studies have demonstrated antioxidant effects of statins unrelated to their

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0946-672X/$ - see front matter © 2009 Elsevier GmbH. All rights reserved.
doi:10.1016/j.jtemb.2009.06.005

lipid-lowering action [3,4]. Chronic treatment with statins may thus reduce the need of GSH-Pxs and other antioxidant enzymes activation and eventually increase serum Se concentration in hemodialysis (HD) patients.

The aims of the present study were (a) to compare serum Se concentration in a group of end-stage renal disease (ESRD) patients on maintenance HD and in a homogeneous group of healthy subjects and (b) to investigate whether chronic intake of statins may interfere with serum Se concentration in HD patients.

Materials and methods

Selection of patients and control subjects

Men and women aged 18 years or more were considered suitable for the study. The study protocol complied with the declaration of Helsinki and was appointed by our local ethical committee. A written fully informed consent was provided by all ESRD patients and healthy subjects before enrollment into the study. Exclusion criteria for both ESRD patients and control subjects were a clinical history of major acute cardiac event (MACE), congestive heart failure (CHF), cerebrovascular accident, uncompensated diabetes mellitus (fasting blood glucose >140 mg/dL, hemoglobin AIC $>7\%$), virus hepatitis B and C or serum AST and/or ALT $\geq$ twice the upper limit of normal values, rheumatologic disorders such as systemic lupus erythematosus (SLE), and active malignancy.

Our study population was selected among ESRD patients on outpatient renal replacement therapy at the Dialysis Units of "Umberto I" General Hospital, Frosinone, and of "Policlinico Tor Vergata" University Hospital, Rome.

All patients of the two centers are maintained under stable aggressive pharmacologic control of blood pressure, serum glucose, calcium-phosphate balance and platelet aggregation. Patients are assigned to lipid-lowering therapy if clinically indicated, and are then maintained under treatment regardless serum low-density lipoprotein (LDL)-cholesterol. All patients considered for the study were treated with standard bicarbonate dialysis with 1.5–2.0 m^2 hollow-fiber low-flux polysulphone membranes (Lo-PS Diacap Polysulphone, B. Braun gmbh, Melsungen, Germany), 4 h 3 times weekly, through a well-functioning native A-V fistula or a cuffed internal jugular indwelling venous catheter. The vascular access performance was satisfactory with a blood flow of at least 300 ml/min and a Kt/V ratio >1.2. After obtaining a fully informed consent a total of 103 ESRD patients on maintenance HD since 6 months at least were enrolled into the study. A total of 69 age-matched healthy subjects (control group) were enrolled at the Department of Occupational Medicine of "Tor Vergata" University, Rome, among the University staff and/or outpatients with no history of renal disease, normal renal function (i.e. estimated GFR higher than 70 ml/min according to Cockroft and Gault's [5] formula) and serum lipids within normal ranges (serum LDL-cholesterol below 130 mg/dL, serum triglycerides below 160 mg/dL). ESRD patients and volunteers were on free diet with a normal and constant intake of essential fatty acids, and none of them was treated with any medication or dietary supplement with established or potential antioxidant effect. In particular, healthy subjects were never treated with statins. Healthy subjects treated with statins and hemodialysis patients treated since less than 6 months were considered unsuitable for the study.

To investigate the possible effects of uremia and of lipid-lowering therapy on serum Se concentration, HD patients were divided into two groups: 32 patients who were never treated with statins (group A) and 71 patients who were treated since 6 months at least (group B). Serum Se concentration was first compared between HD patients of group A and healthy controls and then between HD patients of groups A and B. To investigate the possible effects of lipid-lowering therapy on chronic inflammatory status and eventually on whole OS in ESRD patients, serum homocysteine (HCy) and C-reactive protein (CRP) were also compared between HD patients of groups A and B. To rule out the possible influence of age on whole OS and serum Se, results were finally stratified for patients older or younger than the median of age distribution.

Laboratory findings

Blood samples for determination of serum lipid profile components and mindless, plasma hemoglobin, serum HCy and CRP, and Se were drawn from the antecubital vein in healthy subjects and from the arterial site of the vascular access before dialysis in HD patients. For selenium quantitative determination samples were diluted 1:4 with a 0.2% nitric acid solution and then analyzed by graphite furnace atomic absorption spectrometry, which is an established technique commonly used for the determination of trace-element concentrations.

Serum lipid profile components and mindless were determined by enzymatic colorimetric tests using Modular SWA (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). Hemoglobin dosage was performed by XE 2100 (Sysmex corporation, Chuo-ku, Kobe, Hyogo 651-0073, Japan).

Serum CRP was determined by nephelometric assay (BN IITM Nephelometer and PROTIS Program, Siemens Healthcare Diagnostics, Milano). Serum HCy was determined by a fluorescence polarization immunoassay (FPIA, IMX® Homocysteine Assay, Abbott). Serum Se was determined by graphite furnace atomization and atomic absorption spectrometry (atomic absorption spectrometer AAnalyst800, Perkin-Elmer Inc., Waltham, MA 02451, USA) using Zeeman background correction, equipped with selenium single-element hollow cathode lamp, a THGA graphite tube furnace and an AS 800 automatic sampler. All aqueous solutions were prepared with ultra-pure water (MilliQ system, Millipore, San Giovanni Teatino 66020 (CH), Italy). Concentrated nitric acid was purchased from Sigma and was of analytical grade quality. Calibration solutions were prepared by serial dilutions from a commercial selenium standard solution of 1 mg/mL from Perkin-Elmer. Two levels of quality control solutions (Contox®, levels I and II, Kaulson Laboratories Inc., West Caldwell, NJ 07006, USA) were used for prior sample analysis. The collected serum samples were stored at $-20\,^{\circ}C$ until instrumental analysis.

Statistical analysis

Results reported in this paper are the mean $\pm$ SD of at least three independent determinations. Two-tailed independent-sample *T* test and two-sided Fisher's exact test were employed for analysis of results; *p*-values <0.05 were considered statistically significant. Data were elaborated through the MedCalc Statistical Software (MedCalc Software, 9030 Mariakerke, Belgium).

Results

Baseline epidemiological features of HD patients and healthy subjects (control group) are reported in Table 1. Patients and controls were homogeneous for all characteristics examined. Baseline clinical features and laboratory findings of HD patients of group A and group B are reported in Tables 2 and 3. The two groups of patients are homogenous and there are no significant

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Table 1
Baseline epidemiological features of HD patients and healthy subjects (control group).

	Hemodialysis patients	Control group
No. of patients	103	69
M/F	64/39	41/28
Age (years)	67.61 ± 14.77[a]	61.32 ± 7.11[a]
Time on HD (months)	65.80 ± 64.79[a]	
Smokers	15/103	7/69

[a] Data are expressed as mean ± SD.

Table 2
Baseline clinical findings of HD patients of groups A and B.

	HD patients		
	Group A ($n = 32$)	**Group B ($n = 71$)**	***p***
Age (years)	62.8 ± 12.4	63.4 ± 13.8	0.838
Time on HD (months)	60.89 ± 13.4	63.9 ± 13.6	0.299
A) Cause of ESRD			
1. Nephroangiosclerosis	12/32	27/71	1.000
2. Chronic glomerulonephritis	10/32	21/71	1.000
3. Polycystic kidney disease	6/32	11/71	0.776
4. Chronic pyelonephritis	4/32	12/71	0.770
B) Diabetes	8/32	15/71	0.799
C) Hypertension	23/32	56/71	0.458
D) Pharmacological treatment:			
1. Statins	0/32	71/71	
2. Hypotensive medications	23/32	56/71	0.458
3. Anticoagulants	20/32	45/71	1.000

Table 3
Baseline laboratory findings in HD patients.

	Group A ($n = 32$)	**Group B ($n = 71$)**	***p***
Glucose (mg/dl)	103.6 ± 37.12	106.1 ± 38.16	0.757
Urea (mg/dl)	167.1 ± 35.86	165.7 ± 34.40	0.851
Creatinine (mg/dl)	9.45 ± 2.80	9.70 ± 2.79	0.676
Uric acid (mg/dl)	5.80 ± 0.96	5.50 ± 0.93	0.137
Sodium (mEq./l)	139.3 ± 2.86	138.7 ± 2.88	0.329
Potassium (mEq./l)	5.40 ± 0.80	5.34 ± 0.74	0.711
Phosphorus (mg/dl)	4.20 ± 1.33	4.07 ± 1.42	0.662
Calcium (mg/dl)	8.75 ± 0.75	8.51 ± 0.59	0.083
Hemoglobin (g/dl)	12.01 ± 0.64	11.83 ± 0.99	0.348
Total cholesterol (mg/dl)	136.34 ± 39.83	136.53 ± 31.16	0.979
HDL cholesterol (mg/dl)	34.38 ± 11.31	41.18 ± 8.72	**0.0032**
LDL cholesterol (mg/dl)	82.71 ± 30.91	72.60 ± 31.76	0.133
Triglycerides (mg/dl)	129.53 ± 52.52	153.80 ± 73.92	0.097

Data are expressed as mean ± SD.

differences for all examined features except for serum HDL cholesterol, which was significantly higher in patients of group B, possibly as effect of treatment with statins. Daily lipid-lowering therapy was Atorvastatin 10 mg in 21 patients, Atorvastatin 20 mg in 18 patients, Simvastatin 20 mg in 15 patients and Pravastatin 40 mg in 17 patients of group B. Treatment was effective (LDL-cholesterol was always below 100 m/dL) and well tolerated by all patients; no collateral effect possibly related to the administration of lipid-lowering drugs was previously reported in patients treated with statins.

Serum CRP and HCy were significantly higher in HD patients of group A compared with patients of group B (respectively, 10.70 ± 9.56 vs. 3.23 ± 1.26 mg/ml, $p = 0.0002$ and 36.19 ± 17.78 vs. 23.62 ± 12.12 mcMol/L, $p = 0.0024$.

Serum Se was significantly lower in HD patients of group A compared with healthy subjects (81.65 ± 19.66 (mcg/L) vs. 96.47 ± 15.62 mcg/L, $p = 0.0004$). However, in HD patients who assumed statins (group B) serum Se was significantly higher than in HD patients who did not assume statins (111.83 ± 18.82 (mcg/L) vs. 81.65 ± 19.66 mcg/L, $p < 0.0001$).

Among ESRD patients there was no clear-cut relationship between age and chronic inflammatory status.

Discussion

The unbalance between formation of reactive oxygen species and activity of antioxidant defence mechanism is defined as oxidative stress. OS may contribute to tissue damage and the development of atherosclerosis [6]. Lipid peroxidation of cell membrane polyunsaturated fatty acids, together with protein and nucleic acid oxidative damage, is the main consequence of OS [7]. Increased formation of ROS and impaired antioxidant defences, in particular a reduced activity of GSX-Pxs, are common in ESRD patients on maintenance HD [1] and OS is an important risk factor for the development of CVD. Vitamin E and GSH-Pxs are the most effective antioxidants at the cellular level, may prevent free-radical formation and halt the harmful free-radical chain reaction once it starts [8,9]. During HD, contact of mononuclear cells with artificial dialysis membranes may also stimulate the formation of ROS and superoxide anions. These free radicals are scavenged by SODs. The resulting hydrogen peroxide is degraded by peroxidases and catalases [10]. Selenium (Se) is an essential trace element and a component of the catalytic sites of GSH-Pxs, which catalyses the breakdown of toxic hydrogen peroxide and lipid hydroperoxides. In normal healthy subjects, Se is significantly linked with red blood cell (RBCs) GSH-Pxs activity, which may be significantly enhanced by Se supply [11]. A significant correlation between whole-blood GSH-Pxs activity and serum Se concentration has been reported previously by Yanur et al. [12] and Richard et al. [10].

In patients with chronic renal failure (CRF), Se concentration in blood components is usually lower compared with healthy controls. Plasma Se-dependent GSH-Px, one of the five known forms of the enzyme, is synthesized primarily in the kidney and it is reduced in CKD patients, proportional to the progression of the disease. Previous studies demonstrated that patients on maintenance HD show significant modifications in the status of trace elements. A significant decrease in GSH-Px activity resulting in increased OS is accompanied by widespread Se deficiency [10].

Administration of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) is a well-established treatment option in the primary and secondary prevention of atherosclerosis, CVD and vascular complications of diabetes [13,14]. In 4S and MRC/BHF studies lipid-lowering therapy reduced all-cause and cardiovascular mortality in patients with stable coronary artery disease over a period of 5 years. Retrospective and observational studies did also suggest that early treatment with statins may improve short-time event-free survival after acute coronary syndrome [15,16]. Furthermore, statins may reduce mortality in a number of other settings, including percutaneous coronary angioplasty and carotid endoarterectomy, sepsis and finally in ESRD patients on maintenance HD [17–20].

A number of studies did also demonstrate that statins have anti-inflammatory properties: lipid-lowering therapy reduced the number of inflammatory cells and the expression of cytokines within atherosclerotic plaques [21,22]. Furthermore, treatment with statins reduced serum CRP with a dose-dependent effect [23,24]. Several studies reported that statins have antioxidant properties too. Lipid-lowering therapy may protect low-density

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lipoproteins from oxidation and hence prevent the effects of oxidative modified LDL in the initiation and the progression of atherosclerotic lesions [2]. Pizzi et al. [25] reported that treatment with statins was associated with a reduction in SOD activity and improved endothelial responses, possibly due to reduced superoxide anion production. Oranje et al. [26] observed that atorvastatin increases the resistance to LDL-oxidation in type-2 diabetic patients. A significant reduction in mean serum Zinc (Zn), Copper (Cu), Ceruloplasmin and C-Reactive protein was recently reported after a 4-month treatment with statins in 20 dyslipidemic patients, previously never treated with a lipid-lowering drug [27]. No significant effects were then observed in serum Se and gluthatione-peroxidase activity.

In ESRD patients on maintenance HD, OS and chronic inflammation are enhanced compared to non-uremic subjects; together with hyperhomocysteine, malnutrition and Ca–P metabolism derangements, OS and chronic inflammation constitute the "emerging" cardiovascular risk factors in renal population. However, although data on serum Se concentration in uremic patients are not few [1,28–30], reports on serum Se concentration during chronic treatment with antioxidant agents such as statins in ESRD patients are lacking in the literature.

Our results confirm previous observations [1,29,30] that showed a reduced serum Se concentration in maintenance HD patients compared with healthy controls. However, our results show as well that a higher concentration of serum Se can be observed in maintenance HD patients treated with statins (group B) compared with patients not treated (group A), together with a significantly lower concentration of serum CRP and HCy. Our results suggest that the lower concentration of free serum Se observed in MHD patients compared with healthy controls may also be related to its increased consumption as co-factor of GSX-Pxs due to the enhanced OS related to uremia and dialytic procedures. Conversely, the higher concentration of free serum Se in MHD patients on chronic lipid-lowering therapy may be related to its higher availability because of the reduced activation of GSX-Pxs and other antioxidant enzymes, due to the anti-inflammatory and antioxidant properties of statins [31,32].

In conclusion, our results confirm the role of statins as antioxidant/anti-inflammatory medications and suggest their administration for the prevention and possible control of endothelial damage even beyond their traditional indications in lipid-lowering therapy, regardless of serum LDL-cholesterol, at least in high-risk populations such as ESRD patients on maintenance HD.

Acknowledgement

We thank Mrs. Nadia Consalvo, Chief Nurse of the dialysis unit of Policlinico Tor Vergata – "Tor Vergata" University, Rome, for her skilled nursing assistance. This work was presented in abstract form at the ASN Renal Week 2008.

References

[1] Zachara BA, Gromadzińska J, Wąsowicz W, Zbróg Z. Red blood cell and plasma lutathione peroxidase activities and selenium concentration in patients with chronic kidney disease: a review. Acta Biochem Polon 2006;53:663–7.
[2] Wratten ML, Tetta C, Ursini F, Sevanian Al. Oxidative stress in hemodialysis: prevention and treatment strategies. Kidney Int 2000;76:S126–32.
[3] Rikitake Y, Kawashima S, Takeshita S, et al. Anti-oxidative properties of fluvastatin, an HMG-CoA reductase inhibitor, contribute to prevention of atherosclerosis in cholesterol-fed rabbits. Atherosclerosis 2001;154:87–96.
[4] Wassmann S, Laufs U, Muller K, et al. Cellular antioxidant effects of atorvastatin *in vitro* and *in vivo*. Atheroscler Thromb Vasc Biol 2002;22:300–5.
[5] Cockroft D, Gault MK. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[6] Becker B, Himmelefarb J, Henrich W, Hakim RM. Reassessing the cardiac risk profile in chronic haemodialysis patients: a hypothesis on role oxidant stress and other non traditional cardiac risk factors. J Am Soc Nephrol 1997;8:475–86.
[7] Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C. The importance of diabetic nephropathy in current nephrological practice. Nephrol Dial Transplant 2003;18:1716–25.
[8] Holben OH, Smith AM. The diverse role of selenium within selenoproteins: a review. J Am Diet Assoc 1999;99:836–43.
[9] Ardalan MR, Tubbs RS, Shoja MM. Vitamin E and selenium co-supplementation attenuates oxidative stress in hemodialysis patients receiving intradialysis iron infusion. Nephrol Dial Transplant 2007;22:973–5.
[10] Richard MJ, Arnaud J, Jurkovitz C, et al. Trace elements and lipid peroxidation abnormalities patients with chronic renal failure. Nephron 1991;57:10–15.
[11] Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. Selenium: biochemical role as a component of glutathione peroxidase. Science 1973;179:588–90.
[12] Yanur 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;346:153–60.
[13] Scandinavian simvastatin survival study investigators. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study. Lancet 1994;334:1383–9.
[14] Heart protection study collaborative group. MRC/BHF heart protection study of cholesterol lowering with Simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial Lancet 2002;360:7–22.
[15] Aronow HD, Topol EJ, et al. Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. Lancet 2001;357:1063–8.
[16] Ferrieres J, Cambou JP, Cantet C, Guize L. Prognosis at six months for coronary and cerebrovascular patients: impact of antiplatelet agents and statins: results from the prevenir III study. Cardiovasc Drugs 2006;20:55–61.
[17] Chan AW, Bhatt DL, Chew DP, et al. Early and substained survival benefit associated with statin therapy at the time of percutaneous coronary intervention. Circulation 2002;105:691–6.
[18] McGirt MJ, Perler B, Brooke BS, et al. Hydroxy-3-methylglutraryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endartectomy. J Vasc Surg 2005;42:829–36.
[19] Yasuda H, Yuen P, Hu X, Zhou H, Star RA. Simvastatin improves sepsis induced mortality and acute kidney injury via renal vascular effects. Kidney Int 2006;69:1535–42.
[20] Taccone-Gallucci M, Manca di Villahermosa S, Tedesco M, et al. Aggressive medical management in asymptomatic hemodialysis patients: cardiovascular outcome during a three-year follow-up (Abs.). J Am Soc Nephrol 2007;18:991A.
[21] Sukhova GK, Williams JK, Libby P. Statins reduce inflammation in atheroma of nonhuman primates independent of effects on serum cholesterol. Atheroscler Thromb Vasc Biol 2002;22:1452–8.
[22] Nachtigal P, Pospisilova N, Jamborova G, et al. Atorvastatin has hypolipidemic and anti-inflammatory effects in apo-E/LDL receptor double-knockout mice. Life Sci 2008;82:708–17.
[23] Ferms GAA. Differential effects of statins on serum CRP levels: implications of recent clinical trials. Atherosclerosis 2003;169:349–52.
[24] Nahrendorf M, Sosnovik D, Chen JW, et al. Activatable magnetic resonance imaging agents reports myeloperoxidase activity in healing infarcts and noninvasively detects the antiinflammatory effects of atorvastatin on ischemia-reperfusion injury. Circulation 2008;117:1153–60.
[25] Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxi-3-methylglutaryl coenzyme A reductase in cardiac syndrome X. Role of superoxide dismutase activity. Circulation 2004;109:53–8.
[26] Oranje WA, Sels JP, Rondars-Golberg SJ, Lemmens PJ, Wolffenbuttel BH. Effect of atorvastatin on LDL-oxidation and antioxidants in normocholesterolemic type 2 diabetic patients. Clin Chim Acta 2001;311:91–4.
[27] Ghayour-Mobarhan M, Lamb DJ, Taylor A, et al. Effect of statin therapy on serum trace element status in dyslipidemic subjects. J Trace Elem Med Biol 2005;19:61–7.
[28] Zachara BA, Salak A, Koterska D, Manitius I, Wasowicz W. Selenium and glutathione peroxidases in blood of patients with different stage of chronic renal failure. J Trace Elem Med Biol 2004;17:291–9.
[29] Bonomini M, Albertazzi A. Selenium in uremia. Artif Organs 1995;19:443–8.
[30] Bonomini M, Manfrini V, Marini A, et al. Hemodialysis with regenerated cellulosic membranes does not reduce plasma selenium level in chronic uremic patients. Artif Organs 1995;19:81–5.
[31] Maccarrone M, Meloni C, Manca di Villahermosa S, et al. Vitamin E suppresses 5-lipoxigenase mediated oxidative stress in peripheral blood mononuclear cells of haemodialysis patients regardless of administration route. Am J Kidney Dis 2001;37:964–9.
[32] Taccone-Gallucci M, Manca di Villahermosa S, Battistini L, Giacominelli-Stuffler R, Tedesco M, Maccarrone M. N3-PUFAs reduce oxidative stress in ESRD patients on maintenance hemodialysis by inhibiting 5-lipoxigenase activity. Kidney Int 2006;69:1450–4.

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