Clinical studies

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

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**ABSTRACT**

Project: Oxidative stress (OS) is enhanced in hemodialysis (HD) patients. Lipid peroxidation and oxidative damage to glycosids, proteins and nucleic acids are the main consequences of OS and are associated with increased cardiovascular risk. Vitamin E and glutathione peroxidase (GSH-Pxs) 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.

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**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...
lipid-lowering action [3,4]. Chronic treatment with statins may thus reduce the need of GSH-Px 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 > 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 m² hollow-fiber low-flux polysulphone membranes (Lo-PS Diacap Polysulphone, B. Braun gmbh, Melsungen, Germany). 4h 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 Cockcroft 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.

Statistical analysis

Results reported in this paper are the mean ± 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
Table 1
Baseline epidemiological features of HD patients and healthy subjects (control group).

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis patients</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>103</td>
<td>69</td>
</tr>
<tr>
<td>M/F</td>
<td>64/39</td>
<td>41/28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.61 ± 14.77</td>
<td>61.32 ± 7.11</td>
</tr>
<tr>
<td>Time on HD (months)</td>
<td>65.80 ± 64.79</td>
<td>7/69</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 32)</th>
<th>Group B (n = 71)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.8 ± 12.4</td>
<td>63.4 ± 13.8</td>
<td>0.838</td>
</tr>
<tr>
<td>Time on HD (months)</td>
<td>60.89 ± 13.4</td>
<td>63.9 ± 13.6</td>
<td>0.299</td>
</tr>
</tbody>
</table>

A) Cause of ESRD

1. Nephroangiosclerosis

2. Chronic glomerulonephritis

3. Polycystic kidney disease

4. Chronic pyelonephritis

B) Diabetes

C) Hypertension

D) Pharmacological treatment:

1. Statins

2. Hypotensive medications

3. Anticoagulants

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 polysaturated 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 endarterectomy, 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 lipoprotein from oxidative stress. This mechanism may be accentuated by the ability of statins to prevent LDL oxidation and the modification of its structure, thus hindering the uptake of oxidized LDL by macrophages, which is the first step in foam cell formation.

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.

Data are expressed as mean ± SD.

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).

Table 3
Baseline laboratory findings in HD patients.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 32)</th>
<th>Group B (n = 71)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>103.6 ± 37.12</td>
<td>106.1 ± 38.16</td>
<td>0.757</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>167.1 ± 35.86</td>
<td>165.7 ± 34.40</td>
<td>0.851</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>9.45 ± 2.80</td>
<td>9.70 ± 2.79</td>
<td>0.676</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.80 ± 0.96</td>
<td>5.50 ± 0.93</td>
<td>0.137</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>139.3 ± 2.86</td>
<td>138.7 ± 2.88</td>
<td>0.329</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>5.40 ± 0.80</td>
<td>5.34 ± 0.74</td>
<td>0.711</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.20 ± 1.33</td>
<td>4.07 ± 1.42</td>
<td>0.662</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.75 ± 0.75</td>
<td>8.51 ± 0.59</td>
<td>0.083</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.01 ± 0.64</td>
<td>11.83 ± 0.99</td>
<td>0.348</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>136.34 ± 29.83</td>
<td>136.53 ± 31.16</td>
<td>0.979</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>34.38 ± 11.31</td>
<td>41.18 ± 8.72</td>
<td>0.0032</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>82.71 ± 30.91</td>
<td>72.60 ± 31.76</td>
<td>0.133</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>129.53 ± 52.52</td>
<td>153.80 ± 73.92</td>
<td>0.097</td>
</tr>
</tbody>
</table>

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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 glutathione-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 [128–30], 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 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 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

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References


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