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Antioxidants Enzymes Activities and NO Levels in Hemodialysis and Continuous Ambulatory Peritoneal Dialysis—A Comparative Study

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Abstract

It consists of a retrospective study with twenty-two individuals diagnosed with DRC: fourteen HD and eight CAPD, followed up in the dialysis center of Antonio Pedro University Hospital (HUAP) of Fluminense Federal University (UFF), between 2015 and 2017. Fifteen healthy control (HC) subjects were included, without diagnosed CKD. Patients with HIV positive, hepatitis A, B, and C, pregnant, cancer, smokers, alcoholics and those exposed to X-rays in the last 3 months, were excluded. **Objectives**: As oxidative stress and endothelial dysfunction may be linked to the higher prevalence of CVD in CKD patients, we measured the activities of the antioxidants enzymes: SOD and GPx and total NO levels in the plasma and serum of end-stage CKD patients undergoing dialysis therapy, comparing with the HC group. **Methods:** Quantification of NO levels was performed by fluorometric kit, while activities of SOD and GPx were determined using kinetic methods. **Results:** We found higher plasma SOD activity in HD (8.58 U/ml) and CAPD (10.14 U/ml), compared to C (3.73 U/ml) group, while GPx activity was decreased in HD (115.38 nmol/h/ml) and CAPD (122.76 nmol/h/ml) groups compared to HC group (275.83 nmol/h/ml). Total serum NO concentration was decreased in HD (14.09 pmol/μl) and CAPD (10.26 pmol/μl), compared to non-CKD patients (49.65 pmol/μl). **Conclusion:** Decreased total serum NO and GPx activities may lead to endothelial dysfunction and consequently a higher prevalence of CVD in CKD patients.

Keywords

Hemodialysis, CAPD, SOD, GPx, NO

1. Introduction

Chronic kidney disease (CKD) is a worldwide health problem characterized by cardiovascular disease (CVD) and the progressive loss of renal function, evidenced by the decrease in glomerular filtration rate < 60 ml/min, ultimately leading to end-stage renal disease (ESRD [1]. Patients with ESRD replace kidney function through Hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) [2] [3]. The ESRD population is more susceptible to CVD although traditional risk factors (hypertension, diabetes mellitus and hyperlipidemia) are not always detected in these subjects [3]. On the other hand, CVD is associated with persistent microinflammation evidenced by a reduction in serum albumin and/or elevated C-reactive protein (CRP), reduced nitric oxide (NO) availability and oxidative stress (OS) [4] [5]. As CVD and kidney disease are closely related and OS is present in both conditions, unveiling the role of OS markers is of vital importance to improving the clinical outcomes of CKD patients.

The kidney is a highly metabolic organ, rich in oxidation reactions in mitochondria, which makes it vulnerable to damage that can accelerate kidney disease progression [6]. Therefore, OS can be produced by either excessive free radicals produced by the kidneys or by inefficiency of antioxidant defense systems, mainly represented by the enzymes: superoxide dismutase (SOD) and glutathione peroxidase (GPx) that remove ROS, while the non-enzymatic antioxidant defense system is composed of vitamins C, E and glutathione (thiol) [7]. Studies have confirmed a significant reduction in the antioxidant capacity of chronic renal failure patients [8] [9] [10] and the lack of vitamins and trace elements, which decreases the antioxidant defense [11]. The HD therapy itself increases OS [12] and leads to NO inactivation and deficiency [13], which might contribute to a high risk of CVD in HD patients. Moreover, the type of membrane used in HD (artificial) [14] or CAPD (natural filter, the peritoneum) [15] [16] can contribute to the formation of ROS. In this way, HD can lead to the contamination of the dialysis solution and stimulate neutrophils to produce more ROS [15] and may generate more OS when compared to CAPD.

Since OS is associated with accelerated kidney disease progression [6], the present study was undertaken to investigate OS parameters in CKD patients undergoing HD and CAPD procedures. Moreover, as OS induces endothelial dysfunction and progression of atherosclerosis by reducing NO availability [13], we evaluated NO levels, urea, creatinine, SOD and GPX activities in ESRD patients, according to dialysis therapy adopted: HD or CAPD, compared with individuals without CKD.

2. Methods

2.1. Patients

The study included 22 individuals diagnosed with DRC, 14 on HD and 8 on CAPD, followed up in the dialysis center of HUAP of UFF. HC subjects (n = 15) were included, without diagnosed CKD (GFR > 60 ml/min), serum creatinine and urea within the normal range. The control group was appropriately matched to the CKD group in terms of age and gender. Patients with HIV positive, hepatitis A, B, e C, pregnant cancer, smokers, alcoholics and those exposed to X-ray in the last 3 months, were excluded. Laboratory parameters were obtained from patient charts and were measured in patients plasma or serum, using automated methods (Dimension EXL 200, Siemens Healthcare, Erlangen, DE).

2.2. Serum and Plasma

Blood was collected into tubes containing anticoagulant (citrato) to obtain plasma and in tubes without anticoagulant to obtain serum. Tubes were centrifuged at 1000 rpm for 20 minutes to obtain the plasma and 3000 rpm and for 15 minutes to obtain serum. Serum and plasma obtained were aliquoted and stored in a freezer at −80˚C until the tests.

2.3. Measurements of Total Nitric Oxide ($NO^{\bullet}$)

Concentration of total serum $NO^{\bullet}$ was obtained from the reduction of nitrate (NO_3^-) to nitrite (NO_2^-) catalyzed by nitrate reductase (NR), estimated by fluorometric assay kit (Cayman Chemical®, Michigan, USA). The fluorescence was read in a fluorimeter (SPECTRA MAX) at the wavelength of 375 nm excitation and 471 nm emission.

2.4. Antioxidant Enzymatic Activities

SOD and GPx activities were measured in the plasma using colorimetric kit (Cayman Chemical®, Michigan, USA), in a SPECTRAMAX, spectrophotometer M3 Multi-Mode Microplate Reader (Molecular Devices, California, USA). The plasmatic SOD activity was estimated by the U/mL intensity of red formazan by the absorbance measured at a wavelength of 440 nm. The GPx activity was measured in the plasma of patients through the oxidation of NADPH to $NADPH^+$ that was accompanied by the decrease in absorbance obtained, at a wavelength of 340 nm.

2.5. Statistical Analysis

Results were expressed as median (p25 - p75). For comparison between the groups, the test for analysis of variance (one-way ANOVA) and nonparametric Kruskal-Wallis test were used and the post comparison test non-parametric of Dunn was used, with 95% confidence interval. All statistical tests were performed at a significance level of $p < 0.05$. Graph Prism 4 (GraphPAD Software, Inc.) was used for statistical analysis.

3. Results

In this study, the primary causes of CRD patients in ESRD were: hypertension (n = 9), diabetes and hypertension (n = 6), lupus erythematosus (n = 1), chronic glomerulonephritis (n = 1), and unknown (n = 5). Biochemical parameters of HC, HD and CAPD patients are described in Table 1.

We found no significant differences between HC, HD and CAPD groups, based on the age, levels of glucose, TC, LDL-c and TG. HDL-c levels were decreased in HD (33 mg/dl) and CAPD (33 mg/dl) groups, compared to HC (50 mg/dl) ($p < 0.05$). In all groups serum levels of creatinine were significantly higher in HD (4.67 mg/dl) and CAPD (8.79 mg/dl) groups, compared to HC group (0.73 mg/dl) ($p < 0.001$). Serum levels of urea were also significantly higher in HD (101 mg/dl) and CAPD (85 mg/dl) groups, compared to HC group (31 mg/dl) ($p < 0.001$ and $p < 0.01$, respectively). Serum levels of CRP and albumin did not differ significantly between groups (Table 1).

Concerning antioxidative parameters, we evaluated total NO concentration, SOD and GPX activities (Table 2).

Total $NO^{\bullet}$ concentration was significantly higher in HC group (49.65 pmol/μl) in relation to HD (14.09 pmol/μl) ($p < 0.05$) and CAPD (10.26 pmol/μl) ($p < 0.01$). SOD activity was significantly lower in the C (3.73 U/ml) group compared to HD (8.58 U/ml) ($p < 0.01$) and CAPD (7.63 U/ml) ($p < 0.001$). GPX activity was significantly higher in HC (275.83 nmol/h/ml) group compared to HD

Table 1. Demographic data and biochemical parameters of HC, HD and CAPD patients.

	HC	HD	CAPD	
	Median (p25 - p75) (n = 15)	Median (p25 - p75) (n = 14)	Median (p25 - p75) (n = 8)	p value
Sex (♂/♀)	5/10	10/4	5/3	
Age	57 (53 - 64)	58 (48 - 70)	52 (36 - 66)	
Glucose (mg/dl)	90 (86 - 95)	89 (78 - 161)	87 (86 - 107)	
TC (mg/dl)	185 (154 - 206)	169 (111 - 213)	173 (112 - 181)	
HDL-c (mg/dl)	50 (38 - 62)	33 (29 - 47)	33 (21 - 42)	*a* = p < 0.05
LDL-c (mg/dl)	91 (76 - 115)	107 (80 - 135)	83 (51 - 111)	
TG (mg/dl)	153 (77 - 192)	137 (103 - 252)	133 (87 - 216)	
Serum creatinine (mg/dl)	0.73 (0.56 - 0.94)	4,67 (3.41 - 6.12)[b]	8.79 (6.24 - 10.0)[b]	*a* = p < 0.05; *b* = p < 0.001
Urea (mg/dl)	31 (22 - 37)	101 (73 - 132)[c#]	85 (72 - 101)[c]	*c#* = p < 0.001 *c* = p < 0.01
CRP (mg/dl)	—	4.03 (1.59 - 10.73)	1.08 (0.24 - 2.16)	
Albumin (g/dl)	—	2.5 (1.9 - 3.3)	2.8 (2.3 - 3.1)	

HC = Healthy Control, HD = hemodialysis and CAPD = continuous ambulatory peritoneal dialysis; Total cholesterol = TC; LDL-c = LDL cholesterol; HDL-c = HDL cholesterol; TG = Triglycerides; CRP = C-reactive protein. Results are represented as median (p25 - p75), HD and CAPD different from HC, with a = p < 0.05; b, c# = p < 0.001; c = p < 0.01.

Table 2. Total serum NO•, SOD and GPx plasmatic activities of HD, CAPD e controls (C) groups.

Parameters	HD Median (p25 - p75)	CAPD Median (p25 - p75)	HC Median (p25 - p75)
Total NO• (pmol/µl)	14.09 (3.69 - 33.43)[a] (n = 6)	(3.42 - 10.26)[a#] (n = 6)	49.65 (37.9 - 63.29) (n = 15)
SOD (U/ml)	8.58 (6.83 - 15.78)[b] (n = 14)	7.63 (6.87 - 15.78)[b#] (n = 8)	3.73 (3.36 - 4.2) (n = 7)
GPx (nmol/h/ml)	115.38 (88.89 - 141. 61)[c] (n = 14)	122.76 (81.25 - 136.26)[c#] (n = 8)	275.83 (241.44 - 286.78) (n = 7)

ANOVA Kruskal-Wallis test and the post test of Dunn were used in the comparison between groups. Results are represented as median (p25 - p75). Total oxide nitric concentration (NO•) was measured in C, HD and CAPD groups, [a]$p < 0.05$ (HC and HD) and [a#]$p < 0.01$ (HC and CAPD). Plasma SOD activity in HC, HD and CAPD groups, [b]$p < 0.01$ (HC and HD) and [b#]$p < 0.001$ (HC and CAPD). Plasma GPX activity in the HC, HD and CAPD groups, [c]$p < 0.01$ (HC e HD) and e [c#]$p < 0.001$ (C e CAPD).

(115.38 nmol/h/ml) ($p < 0.01$) and CAPD (122.76 nmol/h/ml) groups ($p < 0.001$). There was no significant difference between the HD and CAPD groups in all parameters analyzed.

4. Discussion

In this study we compared biochemical parameters and OS markers in CKD individuals undergoing HD or CAPD treatment. Major limitations of this study is that it is an unicentric, cross-sectional and a small sample size. The lower enzymatic antioxidant defense in dialysis patients versus HC subjects was reported before, as was the lack of differences between HD and CAPD with respect to antioxidant systems [15] [16] [17].

Inflammatory state and OS have been proposed as non-traditional risk factors for CVD in CKD patients [5]. We performed total serum NO measurements, plasma SOD and GPx antioxidant activities. Endothelial dysfunction is one of the first alterations that give rise to the pathogenic process of atherosclerosis which is related to the reduction of synthesis, release and activity of NO•, an endothelium-derived vasodilator. In our study, total NO serum in HD and CAPD groups were significantly lower when compared to the HC group.

We found decreased levels of NO in HD and CAPD patients compared to HC. Some authors also found decreased levels of NO in patients undergoing peritoneal dialysis [15] [18] [19] [20]. One possible explanation is that l-arginine concentration, the main substrate used in NO production, is decreased in uremic patients due to reduction of renal parenchyma. Additionally, it has been reported increased levels of endogen inhibitors of NO synthase (NOS) such as asymmetric dimethylarginine (ADMA) [20], which could suggest alterations in the bioavailability of NO in the vascular endothelium. However, Kovačević *et al*., found increased levels of NO in CAPD [21], probably due to increased production of NO from endothelial cell [22] and also NO generated by macrophages involved in inflammatory processes in peritonitis [23], which is frequently in

CAPD patients. In our study, patients peritonitis were controlled. As NO levels were decreased in HD and CAPD groups compared to HC C group, we can deduce that these individuals may have a higher risk for the development of atherosclerosis and consequently CVD.

In our study, the activity of SOD was found to be significantly increased, while GPx activity was decreased in HD and CAPD patients vs. HC. The increase in SOD activity could be a compensatory effect of the enzyme in the ROS and free radicals accumulation to avoid altering mitochondrial membrane stability and mitochondrial oxidative damage. The novelty of this study is that we found a different response in CKD individuals, concerning OS and antioxidant enzyme activities. While total NO level and GPx activity were low, SOD activity was high in HD and CAPD patients compared with healthy controls.

SOD is an important antioxidant enzyme because it eliminates O^{-2} that can cause tissue damage due to proliferation and apoptosis of endothelial cells. In our study, SOD activity was significantly lower in the HC group, compared to HD and CAPD. It was reported elevated activity of plasma SOD in dialyzed patients [10] [11]. The increase in the production of O^{-2} may have increased SOD activity of CKD patients, as a compensatory mechanism to the increased OS.

Herein, GPx activity was significantly lower in the dialytic groups and CAPD, compared to the C group. Zachara *et al.* also reported that plasma GPx activity is often reduced in renal disease compared to HC [24]. A progressive decline in plasma GPx activity is linked with the fact that this enzyme is primarily synthesized in the kidney and the progressing damage of this organ is reflected in diminished enzyme activity [25]. Besides, Selenium (Se) is an essential component for the enzyme and kidneys play an important role in the homeostasis of this mineral. With the progression of the kidney impairment, Se concentration decreases in whole blood and this was evident in the end-stage of the CKD, where Se concentration was lower by 47% [26]. Therefore, decrease in GPx activity in our study may be due to the current stage of CKD in these patients, leading to a decrease in the production and activity of GPx activity. However, a recent study found SOD and GPX activity increased in peritoneal dialysis patients with and without type 2 diabetes mellitus, possibly in an attempt to compensate for the imbalance between oxidants and antioxidants [27]. Given the findings obtained in the present study, we consider it is important to consider the presence of comorbidades when measuring oxidative state markers.

In addition to OS, dyslipidemic factors contribute to high cardiovascular risk in patients with CKD [28], although, TG/HDL-c consists of a protective factor for CVD [29]. We found decreased HDL-c levels in individuals who underwent dialysis treatment, compared to HC. Indeed, in the advanced stages of CKD or in patients undergoing dialysis, levels of this lipoprotein are frequently decreased [28]. Hypoalbuminemia leads to changes in lipid metabolism due to the decrease in oncotic pressure, stimulating the hepatic synthesis of proteins, including apo-

lipoproteins. This leads to increased levels of TC, TG and lipoprotein and decreased levels of HDL-c [30]. Herein, Individuals of HD and CAPD groups showed decreased levels of albumin which may have contributed to the increase in TC and LDL-c synthesis, in a compensatory way.

In our study, HD, CAPD and HC had elevated (<150 mg/dl) TG levels. One of the main characteristics of changes in lipid metabolism in patients with CKD is hypertriglyceridemia, which represents the imbalance between the removal and the production of triglycerides [29], so this lipid profile is in agreement with the dialytic groups of our study. Moreover, our patients showed decreased HDL-c levels and increased triglycerides, which is strongly associated with the risk of developing CVD, as previously described [29].

Regarding kidney function, it was shown a linear reduction in total protein and albumin concentrations along with progression of renal insufficiency [30] [31]. Herein, HD and CAPD patients had decreased albumin levels and increased creatinine and urea levels, as expected for individuals on advanced CKD. A chronic micro inflammatory state is found in a large part of uremic patients, especially those in HD or CAPD treatment, evidenced by increasing CRP [31]. In our study, we found high levels of CRP in both HD and CAPD, which corroborate with the high risk of cardiovascular mortality and the inflammation status of CKD patients.

It is well known that the incidence of CVD is higher in dialysis patients and the leading cause of death in ESRD patients [3]. The nontraditional risk factors for CVD, such as inflammation and oxidative stress, contribute to cardiovascular risk in CKD patients. From our results, we concluded that the imbalance in the production of vasoactive substances, such as NO and altered antioxidant enzymes, mainly SOD and GPX can lead to disturbance in local blood flow, endothelial response, leading to significant hemodynamic disturbance that may lead to hypertension and atherosclerosis [7]. The use of antioxidant enzymes can be a good strategy for the treatment of chronic kidney disease in patients undergoing CAPD or HD.

5. Conclusions

The study has the limitation of having been carried out in a small population. We found no significant difference between the HD and CAPD groups in all parameters analyzed. NO levels of HD and CAPD groups were decreased in relation to the HC group. From our results, we concluded that an imbalance in the production of vasoactive substances (NO) and altered antioxidant enzymes, mainly SOD and GPX, can contribute to the higher risk for the development of atherosclerosis and consequently CVD. This imbalance can lead to disturbance in local blood flow, and endothelial response, leading to significant hemodynamic disturbance that may lead to hypertension and atherosclerosis. The use of antioxidant enzymes can be a good strategy for the treatment of chronic kidney disease in patients undergoing CAPD or HD. Future studies in larger popula-

tions are required to increase the representation of the CKD population.

This study was funded by FOPESQ 2013/PROPPi-UFF. The authors declare that there is no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The project was approved by the institutional ethics committee: (CAE = 18538413.8.0000.5243) Informed consent was obtained from all individual participants included in the study.

Author Contributions

N.C.A.R.R, A.M.T. and J.H.S wrote the manuscript and researched data. S.K contributed to the discussion. J. P L D and L.C.CW contributed to the discussion and reviewed/edited the manuscript. N.C.A.R.R is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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