Glutathione, Glutathione-Related Enzymes, and Total Antioxidant Capacity in Patients on Maintenance Dialysis

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Introduction. Oxidative stress due to overproduction of reactive oxygen species and impairment in antioxidant defense mechanisms have been suggested as possible factors contributing to the pathogenesis of atherosclerosis in patients with end-stage renal disease. We compared glutathione levels, glutathione peroxidase and glutathione reductase activities, and total antioxidant capacity between patients on hemodialysis and peritoneal dialysis and healthy individuals.

Materials and Methods. Thirty patients receiving regular hemodialysis and 12 on continuous ambulatory peritoneal dialysis were recruited as well as 25 healthy volunteers. Diabetes mellitus, recent febrile or infectious episodes, and hospitalization during the past month were the exclusion criteria. Erythrocyte glutathione level, plasma activities of glutathione peroxidase and glutathione reductase, total antioxidant capacity were determined and compared between the three studied groups.

Results. Glutathione levels and glutathione peroxidase activity were markedly lower in the patient groups than in the controls. Conversely, higher activity of glutathione reductase and total antioxidant capacity were noted in the patients than in the controls. There were no significant differences between antioxidant markers of the patients on hemodialysis and peritoneal dialysis. Strong positive correlation were observed between total antioxidant capacity and uric acid in the patients ($r = 0.59$, $P = .045$ and $r = 0.63$, $P = .03$, respectively).

Conclusions. Although total antioxidant capacity of plasma is increased in patient on dialysis, depletion of glutathione as a key antioxidant component and disturbances in its related enzymes show oxidative stress. This condition may increase the risk of developing cardiovascular disease in patients with end-stage renal disease.

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INTRODUCTION

Patients with end-stage renal disease (ESRD) receiving renal replacement therapy are at increased risk of developing cardiovascular disease.[1,2] The excess risk is only partially explained by the "traditional" risk factors, including hypertension, diabetes mellitus, smoking, and dyslipidemia.[3] Therefore, other factors such as increased oxidative stress are postulated to contribute to increased cardiovascular risks in uremic patients.[4]

Oxidative stress is a consequence of the imbalance between reactive oxygen species (ROS) production and antioxidant capacity. This can occur as a result of either increased ROS generation, impaired antioxidant system, or a combination of both. In the presence of oxidative stress, the ROS attack will modify and denature functional and structural molecules leading to tissue injury and dysfunction.[5] Factors such as exposure of blood to dialysis membranes, high risk of acute and chronic infections, and dietary limitations in the intake of the antioxidant vitamins make patients on dialysis susceptible to more oxidative stress.

The biological oxidative effects of free radicals on macromolecules are controlled by a spectrum of enzymatic and nonenzymatic antioxidants.[6] Glutathione, together with its related enzymes, comprises a system that maintains the intracellular-reducing environment and acts as primary defense against excessive generation of harmful ROS. The oxygen radical scavenging activity of glutathione directly facilitates ROS neutralization and the repair of ROS-induced damage.[7] In addition to its antioxidant activity, glutathione has many physiological functions including detoxification of xenobiotics, modulation of redox-regulated signal transduction, regulation of cell proliferation, and immune responses.[8]

Tepel and colleagues have shown that in patients with ESRD, administration of the N-acetyl-cysteine, a precursor for glutathione synthesis, significantly reduced the incidence of cardiovascular events.[9] Glutathione peroxidase (GP) catalyzes the reduction of organic hydroperoxides and hydrogen peroxide by using glutathione as the reducing agent. Several types of GP have been identified, among which plasma GP shows significant diagnostic value in kidney disease.[10] Glutathione reductase (GR) plays a critical role by regenerating reduced glutathione from the oxidized form (GSSG).

Although evaluation of glutathione was considered in previous studies, the results varied and it needs further studies. Some authors found decreased erythrocyte glutathione levels in patients on dialysis, and some observed unchanged or even increased levels.[9,11,12] The aim of this study was to compare glutathione levels, GP and GR activities, and total antioxidant capacity (TAC) between patients on hemodialysis, patients on peritoneal dialysis (PD), and healthy individuals.

MATERIALS AND METHODS

Participants

We enrolled patients on maintenance dialysis in Urmia hemodialysis center and those on continuous ambulatory PD in 2005. Diabetic patients and those who had any febrile or infectious episode or hospitalization during the past month were excluded. Thirty patients on maintenance hemodialysis and 12 on PD were recruited. As a control group, 25 healthy adults were selected from among the university medical students and staff. They had no evidence of clinical cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus, or kidney disease, confirmed by their medical history, physical examination, and paraclinical studies (if necessary).

All patients on hemodialysis received dialysis 3 times weekly, each for 4 hour, using bicarbonate dialysis solution with polysulphone membrane. Patients on PD were treated with standard PD solutions, and glucose concentrations were adjusted with the excess fluid to be removed from the patients. The diet of the patients was not modified from the already prescribed. All patients were on vitamin E, 400 IU, once daily. Informed consent was obtained from all participants and the study was approved by the local ethics committee.

Blood Sampling and Laboratory Methods

Blood samples of the patients and control individuals were taken after an overnight fast. Three milliliters of blood containing disodium ethylenediamine tetra-acetic acid (1 mg/mL) was centrifuged at 3000 g for 5 minutes at 4°C. The separated plasma was stored at -80°C for measurement of GP, GR, and TAC. After removing the buffy coat, the cells were washed 4 times with 3 volumes of isotonic saline and the packed cells were analyzed for total glutathione concentrations. Three milliliters of blood were centrifuged and serum samples were used for measurement of creatinine, blood urea nitrogen, uric acid, triglyceride, cholesterol, and high-density lipoprotein.

Analytical Procedures

Erythrocyte Total Glutathione. Glutathione was measured as total glutathione in the erythrocyte

as described by Tietze.[13] In this method, the sulfhydryl group of glutathione is oxidized with 5,5′-dithiobis-2-nitrobenzoic acid (Ellman's reagent) and produces a yellow-colored 5-thio-2-nitrobenzoic acid (TNB). The mixed disulfide, GSTNB (between glutathione and TNB) that is concomitantly produced, is reduced by GR to recycle the glutathione and produce more TNB. The rate of TNB production at 412 nm is directly proportional to the concentration of glutathione in the sample.

Glutathione Peroxidase and Glutathione Reductase. Plasma GP was measured indirectly by a coupled reaction with GR as described by Paglia and Valentine,[14] using tert-butyl hydroperoxide as a substrate. The product of GP and tert-butyl hydroperoxide act with glutathione as a substrate for GR and oxidized nicotinamide-adenine dinucleotide phosphate (NADPH) to $NADP^+$. The NADPH oxidation was measured with spectrophotometery by following absorbance at 340 nm. Each NADPH molecule that is oxidized by GR corresponds to 1 molecule of tert-butyl hydroperoxide reduced by GP. The activity was expressed as the amount of NADPH (in micromole) oxidized per minute per liter of plasma. Glutathione reductase activity was measured as described by Calberg and Mannervic.[15] Glutathione reductase catalyzes the reduction of GSSG by oxidizing NADPH to $NADP^+$. The activity was measured at 340 nm and expressed as the amount of NADPH (in micromole) oxidized per minute per liter of plasma.

Total Antioxidant Capacity. Plasma TAC was determined by the ferric-reducing antioxidant power assay.[16] In this method, colorless ferric-tripyridyltriazine complex is reduced to a blue ferrous complex by the antioxidants. The change in absorbance at 593 nm is directly related to the total reducing power of electron-donating antioxidants present in the plasma. The ferric-reducing antioxidant power value of the samples tested is expressed as an equivalent of the concentration of a water-soluble vitamin E analog, Trolox solution (in millimole).

All materials and reagents for determination of the above antioxidant markers were purchased from the Sigma chemical company (St Louis, Missouri, USA). Clinical markers were measured by standard automated clinical chemistry laboratory methods. Commercially available standard kits (Pars Azmoon, Tehran, Iran) were used for this purpose.

Statistical Analyses

The quantitative data were presented as mean ± standard deviation and compared between the three independent groups by the 1-way analysis of the variance. For variables without a normal distribution, the Kruskal-Wallis test was used. Correlations were evaluated with the Pearson correlation coefficient test. A P value less than .05 was considered significant.

RESULTS

The enrolled participants were 30 patients on maintenance hemodialysis (16 men and 14 women, aged 24 to 83 years old), 12 on PD (4 men and 8 women, aged 19 to 80 years old), and 25 healthy adults (21 men and 4 women, aged 22 to 45 years old). The demographic, clinical, and biochemical profiles of the patients and the healthy controls are summarized in Table 1. Blood urea nitrogen, serum creatinine, and triglyceride levels were significantly higher in the patients groups compared to those in the controls. Also, higher levels of cholesterol and lower levels of high-density lipoprotein were observed in patients on PD and hemodialysis, respectively, as compared to the controls (Table 1).

Plasma levels of the antioxidant markers in the study groups are shown in Table 2. Compared to the controls, markedly lower glutathione level and GP activity were seen in both groups of the uremic patients. Plasma TAC and GR activity were significantly elevated in both groups of the patients in comparison to those in the control group. There were no significant differences in the antioxidant parameters between the patients on PD and those on hemodialysis. Strong direct correlations were observe red between the TAC and serum uric acid in the patients on PD and hemodialysis ($r = 0.59$, $P = .045$ and $r = 0.63$, $P = .03$; respectively). In addition, significant correlations of serum triglyceride with high-density lipoprotein ($r = -0.87$, $P < .001$) and LDL with serum cholesterol ($r = 0.92$, $P < .001$) were seen in the patients on PD. Correlations of serum cholesterol with serum triglyceride ($r = 0.64$, $P < .001$) and serum cholesterol with LDL ($r = 0.87$, $P < .001$) were significant in the patients on hemodialysis, too.

Table 1. Clinical and Biochemical Characteristics of Patients on Dialysis and Healthy Controls*

Parameters	Participants			*P*		
	Hemodialysis (n = 30)	PD (n = 12)	Control (n = 25)	PD vs Control	Hemodialysis vs Control	PD vs Hemodialysis
Age, y	50.7 ± 14.8 (24 to 83)	49.5 ± 15.5 (19 to 80)	30.4 ± 4.5 (22 to 45)	.001	.001	.30
Sex						
Male	16	4	21			
Female	14	8	4	…	…	…
Dialysis duration, y	2.49 ± 1.96 (0.1 to 6.0)	1.54 ± 0.62 (0.7 to 2.8)	…	…	…	.11
Serum creatinine, mg/dL	7.65 ± 1.50 (4.9 to 12.3)	9.80 ± 4.20 (4.4 to 19.2)	0.91± 0.81 (0.6 to 1.3)	< .001	< .001	.006
Blood urea nitrogen, mg/dL	48.4 ± 9.6 (32 to 80)	37.5 ± 12.7 (18 to 69)	15.8 ± 4.8 (9.35 to 28.4)	< .001	< .001	.001
Uric acid, mg/dL	7.29 ± 1.40 (4.3 to 10.4)	6.55 ± 0.94 (4.6 to 8.0)	6.03 ± 0.68 (5.0 to 11.0)	.94	.21	.21
Serum lipids						
Triglyceride, mg/dL	201.5 ± 148.6 (52 to 364)	219.9 ± 107.1 (45 to 800)	98.23 ± 23.5 (59 to 160)	.01	.003	.88
Cholesterol, mg/dL	173.5 ± 43.7 (91 to 309)	205.3 ± 45.9 (138 to 291)	160.6 ± 24.7 (122 to 230)	.01	.73	.045
HDL, mg/dL	37.3 ± 9.4 (20 to 70)	42.2 ± 18.0 (16 to 79)	47.2 ± 10.0 (31 to 67)	.43	.004	.38
LDL, mg/dL	118.5 ± 65.9 (48 to 190)	119.1 ± 44.5 (42.2 to 209.8)	97.7 ± 21.6 (64 to 160)	.16	.45	.59

*PD indicates peritoneal dialysis; HDL, high-density lipoprotein; and LDL, low-density lipoprotein. Ellipses indicate not applicable. Continuous variables are shown as mean ± standard deviation (range).

Table 2. Levels of Antioxidant Markers in Patients on Dialysis and Healthy Controls*

Antioxidant Markers	Participants			*P*		
	Hemodialysis (n = 30)	PD (n = 12)	Control (n = 25)	PD vs Control	Hemodialysis vs Control	PD vs Hemodialysis
Glutathione, µmol/mL	1.26 ± 0.34 (0.47 to 1.99)	1.17 ± 0.28 (0.80 to 1.63)	1.42 ± 0.25 (0.65 to 2.60)	.045	.049	.73
GP, U/L	59.90 ± 31.28 (8.05 to 144.90)	57.10 ± 21.82 (28.30 to 95)	142.50 ± 33.77 (75.05 to 203.72)	< .001	< .001	.90
GR, U/L	53.65 ± 13.60 (34.89 to 107.16)	57.50 ± 16.40 (42.36 to 99.68)	32.00 ± 9.40 (24.92 to 57.32)	< .001	< .001	.64
TAC, µmol Trolox/mL	0.65 ± 0.12 (0.64 to 1.16)	0.60 ± 0.09 (0.42 to 0.74)	0.47 ± 0.11 (0.26 to 0.71)	.02	< .001	.50

*PD indicates peritoneal dialysis; GP, glutathione peroxidase; GR, glutathione reductase; and TAC, total antioxidant capacity. Continuous variables are shown as mean ± standard deviation (range).

DISCUSSION

Oxidative stress represents an emerging threat to the cardiovascular outcome in patient's with ESRD. The aim of this study was to evaluate the enzymatic and nonenzymatic antioxidant markers in these patients. Glutathione plays a key role in cellular resistance against oxidative damage.[7] In our study, erythrocyte glutathione levels were significantly lower in the patients on PD and hemodialysis when compared with a group of healthy individuals. Our results are consistent with the previous investigations.[17] A similar study was performed on an Iranian population by Hemmati and colleagues who compared concentration of glutathione and TAC before and after dialysis in 24 patients on hemodialysis with 20 healthy subjects.[18] It was revealed that after dialysis, the level of these molecules significantly decreased compared to the levels before dialysis. In agreement with our results, Hemmati and colleagues observed markedly lower levels of glutathione in the patients group than in the controls. It has been suggested that the decrease in the glutathione level in patients on dialysis may occur as a result of the inhibition of glutathione

production, an increase in glutathione extrusion from erythrocytes as GSSG, or enhancement of consumption for suppressing the oxidant stress.[17,19,20] Decreased activity of γ-glutamylcysteine synthetase, the rate-limiting enzyme in glutathione biosynthesis, has also been reported as a possible factor that negatively affects de novo glutathione synthesis.[21]

Plasma GP is an important antioxidant enzyme that is mainly produced in the kidneys.[10] Our present results showed that the activity of GP in the patient groups was markedly (60%) lower than that in the healthy controls. In agreement with our results, significantly lower (by 49% to 65%) plasma GP activity was found in patients on dialysis.[22,23] Ceballos-Picot and coworkers showed a positive correlation between creatinine clearance and GP levels in patients on both PD and hemodialysis. They suggested that the decline in plasma GP activity resulted from the damage of an active part of the nephron responsible for the biosynthesis of this enzyme.[24] Some authors have indicated a gradual decrease in the GP activity with advancing stage of kidney disease.[25] Additionally, because GP may play an important role in the protection of extracellular fluid component and cell surface against peroxide-mediated damage, any reduction in its activity will therefore result in increased lipid peroxidation, and potentially, an increase risk of atherosclerosis.[26]

Glutathione reductase catalyses regeneration of reduced glutathione from oxidized glutathione. In this study, a significantly increased activity of plasma GR was observed in the patients groups in comparison with the control group. There is conflicting evidence on the fate of GR in patients on dialysis. McGrath and colleagues demonstrated a low level of GR in patients on PD, but not in patients on hemodialysis.(27) In contrast, Ceballos-Picot and colleagues reported increased GR activity in the erythrocyte of patients on hemodialysis too; however, they could not observe any changes in plasma GR activity.[24] Total antioxidant capacity is an indicator of plasma resistance against oxidant agents. Measuring the total radical-trapping capacity of antioxidants in human plasma, it has been found that their contributions were 35% to 65% from urate, up to 24% from ascorbate, 5% to 10% from vitamin E, and 10% to 50% from plasma protein.[28] In our study, we found a higher ferric-reducing ability of plasma (about 32%) as a measurement of TAC, in both uremic patients as compared with the control subjects. Studies on TAC in patients on dialysis show controversial results. It has been shown by some that TAC is increased in chronic kidney failure and this has been attributed to an increase in uric acid level.[29]

A significant positive correlation was obtained between TAC and uric acid in all uremic patients in our study. There are paradoxical studies that have shown the association of hyperuricemia and oxidative stress. It is not well known that oxidative stress is the cause or consequence of hyperuricemia, but overall, uric acid is not a good scavenger of some biologically important radical species.[30] The use of multivitamin preparations including vitamin E (400 U/d) by our patients may be a second possibility for increment of TAC. However, there are no convincing evidence in favor of reduced mortality or improved cardiovascular outcomes by using antioxidant supplements.

It should be mentioned that our control subjects were not age- and sex-matched with the patients group which is our study's limitation. However, some studies have shown that age and sex have no effect on the levels of antioxidant molecules.[31,32] For instance, Samadian and associates measured oxidative stress indicators consisting of glutathione, vitamin E, and TAC in 25 patients on hemodialysis (18 men and 7 women). In their study, the levels of antioxidant markers showed no significant variation between men and women.[32]

CONCLUSIONS

Although the total antioxidant capacity of plasma is increased in patients on long-term dialysis, as its unresolved issues, depletion of glutathione as a key antioxidant molecule and decreased activity of GP may show oxidative stress. This condition may increase the risk of developing cardiovascular disease in patients with ESRD.

CONFLICT OF INTEREST

None declared.

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