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Oxidative Stress in Hemodialysis Pediatric Patients

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Abbreviations: Alb: Albumin; ASA: Arylesterase activity; Ca: Calcium; CAT: Catalase; Creat: Creatinine; Dia. BP: Diastolic blood pressure; Dur: Duration of dialysis; GPx: Glutathione peroxidase; GSH: Glutathione; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; MDA: Malonyldialdehyde; PON: Paraoxanase activity; P: probability; r: Pearson's correlation tests; SOD: Superoxide dismutase; SD: Standard deviation; Sys BP: Systolic blood pressure

Abstract

BACKGROUND: Oxidative stress may play a role in complications of hemodialysis patients as atherosclerosis, thrombosis, and inflammation.

AIM: The aim of the study was to evaluate the oxidative stress in hemodialysis pediatric patients through measurement of oxidative stress enzymes as paraoxanase activity (PON), arylesterase activity (ASA), superoxide dismutase (SOD) and also non-enzymatic antioxidant vitamins as vitamins A, C and E levels.

METHODS: The study included 50 hemodialysis pediatric patients with mean age 11.4 ± 5.4 years and 30 normal children of matched sex and age as a control group. Assessment of oxidative stresses was done using ELIZA technique.

RESULTS: SOD, ASA, and vitamin C were significantly lower among hemodialysis patients in comparison to control group ($p = 0.004$, 0.004, > 0.001 respectively).

CONCLUSION: The study concluded that oxidative stress was common finding in hemodialysis pediatric patients which may play a role in complications encountered among these patients.

Introduction

The global prevalence of chronic renal failure is on the rise in pediatric age group. It constitutes one of the major causes of death. It is associated with oxidative stress which is a significant factor in children suffering from renal failure and it may be partly responsible for complications of the disease as hypertension, anemia, atherosclerosis and related cardiovascular disturbances, neurological disorders, impaired immunity, and hemostatic abnormalities [1], [2], [3], [4], [5].

Oxidative stress is defined as tissue damage resulting from an imbalance between excessive production of free oxygen radical and oxygen scavenger which are responsible for antioxidant activity [6]. The excess generation of reactive oxygen species may be partially due to activation of peripheral polymorphonuclear leucocytes interacting with dialyzer artificial membrane [7]. The ability of cells to scavenge excess reactive species is largely dependent on the efficiency of the overall antioxidant defense system. The antioxidant defense network consists of endogenous and exogenous antioxidants. The endogenous antioxidants comprise the enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and non-enzymatic antioxidants including glutathione (GSH), vitamins A, C and E as well as small molecules. The exogenous antioxidants comprise the

micronutrients and other exogenously administered antioxidants [8], [9].

Malonyldialdehyde (MDA) is one of the end products of polyunsaturated fatty acid peroxidation in cells which was repetitively measured in many studies, while vitamin E is a major antioxidant in biological systems and acts as a powerful chain-breaking agent because of its ability to scavenge peroxyl radicals. An increase in free radicals causes an overproduction of MDA, which is a marker of oxidative stress, and a reduction in plasma vitamin E levels, which may contribute to the development of oxidative stress conditions. Vitamin E is mainly transported by lipoproteins in the bloodstream. The vitamin E/cholesterol ratio indicates how much vitamin E can be delivered to cell membranes via the LDL receptor [10]. SOD catalyzes dismutation of superoxide to hydrogen peroxide. Hydrogen peroxide, in turn, is converted to water and molecular oxygen by catalase or glutathione peroxidase (GPx) which uses glutathione as a substrate [11].

The oxidation of low-density lipoproteins (LDL) due to oxidative stress conditions is one of the first steps in the atherosclerotic process. Oxidized LDL initiates an inflammatory reaction that ultimately leads to the formation of atherosclerotic plaques. High-density lipoproteins (HDL) have long been known to be antiatherogenic, but their exact mechanism of action has yet to be determined. Paraoxonase 1 (PON1), an enzyme associated with HDL, is thought to play a crucial role in the anti-oxidative properties of HDL [12].

Unfortunately, studies of oxidative stress in children had limited sample sizes and not enough convincing evidence to prove the causal relation between oxidative stress and disease conditions.

The aim of the study was to evaluate the oxidative stress in hemodialysis pediatric patients through measurement of oxidative stress enzymes as Paraoxanase activity (PON), Arylesterase activity (ASA), superoxide dismutase (SOD) and also non-enzymatic antioxidant vitamins as vitamins A, C and E levels.

Patients and Methods

The study included 50 pediatric patients who had been treated by conventional regular bicarbonate hemodialysis three times weekly using polysulfone filter and Fresenius 4008 dialysis system (Fresenius Medical Care, Hesse, Germany). Thirty normal children of matched age and sex served as a control group were collected from outpatient's clinic. The hemodialysis patients were recruited from the hemodialysis unit of the Centre of Pediatric Nephrology and Transplantation, in Cairo University Children Hospital. The studied patients consisted of 24 (48%) females and 26 (52%) males. The mean age of the study population was 11.4 ± 5.4 (4 -20) years for hemodialysis patients. Patients with evidence of infections, inflammation or malignancy were excluded.

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of National research Centre and informed written consent was obtained in every case from their legal guardians.

All patients were subjected to full history taking, thorough clinical examination, and laboratory investigations including routine investigations as urine analysis**,** complete blood picture, blood urea nitrogen, creatinine, serum sodium, potassium, calcium, phosphorus, alkaline phosphatase, SGOT, and SGPT.

Special tests for assessment of oxidative stresss were done including: enzymatic antioxidants as Paraoxanase activity (PON), Arylesterase activity (ASA), superoxide dismutase (SOD) and non-enzymatic antioxidant as serum vitamins A, C and E levels for hemodialysis and control groups. All of them were measured using ELIZA double antibody sandwich technique with the commercial available kits from Glory Science Co., Ltd (Add: 2400 Veterans Blvd. Suite 16-101, Del Rio, TX78840, USA). With catalog #: A16846 (ASA), #: 11086 (SOD), #: 90081 (vitamin C), #: 11345 (vitamin A), #: 11344 (vitamin E), #: 95462 (PON1).

Statistical Analysis

Standard computer program SPSS for Windows, release 13.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). Comparison of different variables in various groups was done using Student t test. Pearson's correlation tests (r = correlation coefficient) were used for correlating numerical variables. For all tests, a probability (P) less than 0.05 are considered significant.

Results

At the time of the study, the mean dialytic time was 55.5 ± 42.64 months (6-180). Descriptive data of studied hemodialysis pediatric patients were represented in (Table 1).

The comparison between hemodialysis and control group as regard oxidative enzymes and antioxidant vitamins revealed decreased all oxidative enzymes in hemodialysis group than healthy subjects where SOD and ASA were highly significantly reduced

while PON was not significantly reduced (p = 0.004, 0.004, 0.092) respectively (Table 2).

Table 1: Descriptive data, hematological and biochemical results of patients under study

Parameters	Hemodialysis patients
Age in years	11.4 ± 5.4 (4-20)
Sex	26 males & 24 females
Duration of dialysis (months)	55.5 ± 42.64 (6-180)
Dry weight (kg)	24.2 ± 9.8
Ultrafiltration (ml)	1573.3 ± 871.6
Fractional Shorting (FS)	33.4 ± 7.1
Blood Pressure	
Systolic (mmHg)	128.2 ± 20.4
Diastolic (mmHg)	82.8 ± 14.4
Electrolytes (mEq/l)	
Na predialysis	130.2 ± 5
Na postdialysis	135.8 ± 6.1
K predialysis	7.1 ± 0.6
K postdialysis	3.8 ± 0.5
Minerals	
Ca (mg/dl)	8.8 ± 1.2
P (mg/dl)	4.6 ± 2
Alkaline phosphatase (IU/L)	632.4 ± 488
Albumin (gm/dl)	3.7 ± 0.5
Complete Blood Picture	
Hb (g/dl)	10.1 ±1.5
RBCs (10^6/µL)	3.6 ± 0.5
WBCs (10^3/µL)	5.9 ± 2.4
Platelets (10^3/µL)	197 ± 82.9
Kidney function (mg/dl)	
Creatinine predialysis	8.7 ± 3.5
Creatinine postdialysis	3.2 ± 1.5
Creatinine improvement	63.1 ± 15.5
Urea predialysis	112 ± 45.7
Urea postdialysis	21.7 ± 11.3
Urea improvement	79.3 ± 10.3
Liver function	
SGOT (U/L)	21.7 ± 14
SGPT (U/L)	24.8 ± 22

Data are represented as mean ± sd (range) and as frequency.

As regard antioxidant vitamins, vitamin C was significantly reduced in hemodialysis group while vitamins A and E were not significantly affected (p = > 0.001, 0.163, 0.817) respectively (Table 2).

Table 2: Comparison between hemodialysis and control as regard oxidative stress

	Hemodialysis group (50 patients)	Control group (30 patients)	t-test	
			t- value	p-value
Enzymatic Oxidative Stress				
Arylesterase Activity (ASA) (ng/ml)	12.54 ± 18.98	26.45 ± 22.439	-2.962	0.004
Superoxide Dismutase (SOD) (mU/L)	41.5 ± 42.99	159.8 ± 205.36	-3.114	0.004
Paraoxanase Activity (PON) (nmol/L)	126.83 ± 250.09	232.68 ± 296.52	-1.708	0.092
Non Enzymatic Oxidative Stress				
Vitamin A (nmol/L)	427.52 ± 798.58	205.39 ± 603.27	1.408	0.163
Vitamin C (ng/L)	1342.23 ± 1390.12	2085.83 ± 465.52	-3.905	< 0.001
Vitamin E (nmol/L)	373.79 ± 1017.44	327.91 ± 478.55	0.232	0.817

In hemodialysis group, the correlation between oxidative enzymes, antioxidant vitamins and different parameters revealed positive correlation between vitamin A and age (r = 0.374, P = 0.007).

Table 3: Correlation between studied oxidative stress parameters

		Vit A	Vit C	Vit E	PON	SOD	ASA
Vitamin A	r		- 0.115	- 0.124	- 0.111	- 0.067	0.198
	p		0.428	0.390	0.444	0.644	0.169
Vitamin C	r	- 0.115		0.275	0.554**	0.389**	0.100
	p	0.428		0.053	0.000	0.005	0.491
Vitamin E	r	- 0.124	0.275		0.295*	0.545**	0.154
	p	0.390	0.053		0.037	0.000	0.284
Paraoxanase	r	- 0.111	0.554**	0.295*		0.410**	- 0.028
Activity (PON)	p	0.444	0.000	0.037		0.003	0.849
Superoxide	r	- 0.067	0.389**	0.545**	0.410**		0.397**
Dismutase (SOD)	p	0.644	0.005	0.000	0.003		0.004
Arylesterase	r	0.198	0.100	0.154	- 0.028	0.397**	
Activity (ASA)	p	0.169	0.491	0.284	0.849	0.004	

r = correlation coefficient P = P Value * P < 0.05 Significant, P < 0.005 highly significant.

SOD was positively correlated with vitamin C (r = 0.389 p = 0.005), vitamin E (r = 0.545, P= 0.000), PON (r =0.410 P = 0.003), ASA (r = 0.397, P= 0.004), and Ca (r = 0.361 P = 0.01). PON was also positively correlated vitamin C (r = 0.554, P = 0.000), vitamin E (r = 0.295 P = 0.037), predialysis urea level (r = 0.298, P = 0.036), Ca (r = 0.361, P = 0.01) (Table 3 and Table 4).

Table 4: Correlation between studied oxidative stress parameters and clinical and laboratory findings

		Age	Dur	Sys BP	Dia BP	Urea	Creat	Ca	Alb	Kt/v
Vit A	r	- 0.374**	- 0.059	- 0.022	- 0.159	- 0.166	- 0.055	0.246	0.078	- 0.038
	p	0.007	0.685	0.881	0.272	0.249	0.704	0.085	0.590	0.792
Vit C	r	- 0.105	0.227	- 0.244	- 0.198	0.120	- 0.071	0.168	0.049	- 0.003
	p	0.468	0.113	0.087	0.167	0.408	0.626	0.244	0.734	0.981
Vit E	r	0.076	- 0.135	0.041	0.132	0.072	0.033	0.153	- 0.026	0.000
	p	0.598	0.348	0.775	0.362	0.619	0.820	0.288	0.858	0.999
PON	r	0.009	- 0.022	- 0.026	0.103	0.298*	0.132	0.361**	0.277	- 0.024
	p	0.951	0.880	0.859	0.476	0.036	0.361	0.010	0.052	0.868
SOD	r	0.100	0.104	0.089	0.187	0.066	0.063	0.361*	0.224	0.088
	p	0.492	0.471	0.538	0.194	0.649	0.666	0.010	0.117	0.543
ASA	r	- 0.150	- 0.163	0.067	0.076	- 0.215	- 0.106	0.057	0.050	0.023
	p	0.298	0.258	0.642	0.598	0.134	0.463	0.693	0.730	0.873

Duration of dialysis; Sys BP: Systolic blood pressure; Dia BP: diastolic blood pressure; Creat: Creatinine; Ca: Calcium; Alb: Albumin; Dur: after duration of Dialysis.

Discussion

Hemodialysis in addition to uremia is characterized by excessive oxidative stress which is due to loss of antioxidants as vitamins C and E, accumulation of oxidative product. During hemodialysis, activation of complement factors, platelets, and polymorphonuclear leucocytes are triggered by dialyzer membrane and dialysate and subsequently reactive oxygen species production. Also inflammatory state and lipid peroxidation, which occurred in hemodialysis, promote formation of oxidative products. Oxidative stress is also triggered by iron infusion, anemia, central venous catheter, bioincompatible dialyzers, and endotoxin challenge [13], [14].

In this study, alteration of oxidative stress and antioxidant activity has been demonstrated among hemodialysis pediatric patients in comparison to control. Antioxidant defense mechanisms have been observed including decreased all studied enzymatic antioxidant while vitamin C is the only affected among non-enzymatic antioxidant vitamins in hemodialysis group in comparison to healthy control subjects where only SOD, ASA, and vitamin C were highly reduced in significant manner.

Superoxide dismutase represents a major defense system against oxidative damage by enzymatically converting O_2 to H_2O_2. Zwołińska (2006) study on 21 hemodialysis pediatric patients found that SOD was significantly decreased [15] which is in agreement with our study. Similar to our study, SOD activity was significantly lower in hemodialysis patients whatever children or adults [16], [17], [18],

[19], [20], [21], [22]. In contrast to our study, activity of SOD has been increased in few studies which were explained by invoking adaptation to the increased rate of oxidation [23], [24], [25]. In Lim (1999) study, no significant difference of Erythrocyte-SOD (E-SOD) level was found between hemodialysis and control but the plasma level of SOD was increased in hemodialysis in comparison to control [26].

Paraoxonase (PON) is another marker of antioxidant activity. It is esterase enzyme associated with HDL and functions to protect LDL and HDL from oxidation. PON activities are decreased in subjects with renal failure with increased risk of cardiovascular disease especially the hemodialysis patients which had the lowest activity. In contrast to previous studies that revealed reduced paraoxonase levels than control [27], [28], [29], [30], [31], [32]; our results revealed insignificant reduction of PON which was used as a marker of antioxidant activity in hemodialysis patients in comparison to controls.

Human arylesterase enzyme is a member of the paraoxonase family that has a protective effect against lipoprotein oxidation in CKD through hydrolysis of organophosphate compounds. Also arylesterase displays Hcy-thiolactonase activity and poses antiatherogenic properties. Similar to our study, few studies reported that ASA decreased in CKD patients on hemodialysis when compared to healthy controls [28], [33], [34].

Vitamin E exerts its effect as antioxidant through interruption of the radical cascade to protect cell membranes from lipid peroxidation by forming a low-reactivity vitamin that attack lipid substrate. Vitamin E can protect the cell membrane against free radicals induced oxidative damage by LDL in biological membranes [35]. In this study, the vitamin E levels were insignificantly increased. Similar to our study, Nguyen-Khoa (2001) study showed that plasma vitamin E levels were insignificantly different in hemodialysis patients and control subjects [18], while in Locatelli et al., (2003) study, the intracellular levels of vitamin E were significantly reduced [3]. Also Zwolinska et al., (2006) study revealed significant reduction of plasma vitamin E levels among hemodialysis patients in comparison to control while the erythrocyte vitamin E levels of HD pediatric patients were not different [36]. The reduced level of vitamin E can be explained by reduced dietary intake, malnutrition, and loss during hemodialysis. In contrast to previous studies, Joyce et al., (2018) study revealed that hypervitaminosis E was present in 87% of pediatric patients [37].

Vitamin C is considered as a potent antioxidant in biological fluids and thus prevents oxidative damage to important biological macromolecules. As regard vitamin C levels, Francesco Locatelli and Zwolinska et al., [3], [36] studies showed reduced vitamin C levels which coincide with our results and can be explained by reduced dietary intake of fresh fruits and vegetables to avoid hyperkalemia, malnutrition and loss of the vitamin during hemodialysis with clearance rate 30%-53% and losses from 80 to 280 mg per session [3], [36], [38], [39].

As regard vitamin A level, hypervitaminosis A is present in hemodialysis pediatric patients as in CKD patients and is associated with hypercalcemia among hemodialysis [40]. In Joyce et al., (2018) study, hypervitaminosis A was present in 94% of pediatric patients [37]. Hypervitaminosis A is explained by homeostatic dysregulation of its plasma carrier, the retinol binding protein [41]. Only one study done by Zwolinska (2006) revealed reduced levels of plasma vitamin A [36] but in our study no significant difference was found between hemodialysis patients and control.

The correlation between different parameters of this study revealed positive correlation between different antioxidant which means that oxidative stress may act synergistically to increase cardiovascular morbidity and mortality risk in maintenance hemodialysis patients.

There are few limitations to our study findings: 1. The nutritional data is not collected from our patients to assess the amount of vitamins ingestion; 2. There is wide range of variability in enzymes and vitamins levels.

The study concluded that oxidative stress was common finding in hemodialysis pediatric patients who may play a role in complications as atherosclerosis and adequate vitamin supplementation may be recommended and have therapeutic potential.

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