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Estimation of Oxidant and Antioxidant Levels in Hemodialysis Treated end Stage Renal Disease Patients and Comparison with Normal Population

Sadia Rehman, Santosh Kumar, Om Lal, Suniya Rehman, Hasan Ali, Fatima Rehman

ABSTRACT:

Objectives: To estimate the plasma oxidant and antioxidant levels in hemodialysis treated end stage renal disease patients and to match them with normal population.

Study Design and Setting: It was a comparative prospective study. This study was carried out at Jinnah Post Graduate Medical Center Karachi, from January 2018 till December 2018.

Methodology: The hemodialysis patients (group B) were selected from the Dialysis Center of JPMC Karachi whereas the controls (group A) were recruited from normal healthy population. Consecutive sampling technique was used. The cases taken were receiving maintenance hemodialysis thrice a week. Antioxidant levels were determined by estimating plasma superoxide dismutase (SOD) while oxidant levels were estimated by detection of serum malondialdehyde (MDA) and compared with the levels of control group.

Results: The mean superoxide dismutase level in control group was 108.53±19.44 while mean SOD levels in hemodialysis group was 46.20±19.18. . In control group mean MDA was 10.87±3.04, and in hemodialysis group mean MDA was 31.01±8.48.This results show the increased risk of oxidative stress resulting in complications in hemodialysis patients.

Conclusion: Antioxidant levels are reduced in hemodialysis patients as compared to the normal population while the oxidant levels are much increased in hemodialysis group. This imbalance contributes to the oxidative stress related complications taking place in these patients. This study will help the nephrologist to elaborate the protective role of antioxidant administration in oxidative stress that can improve the cardiovascular mortality rate in hemodialysis treated end stage renal disease.

Keywords: Antioxidants,End Stage Renal Disease, Hemodialysis, Oxidants, Oxidative Stress.

How to cite this Article:
Rehman S, Kumar S, Lal O, Rehman S, Ali H, Rehman F. Estimation of Oxidant and Antioxidant Levels in Hemodialysis Treated end Stage Renal Disease Patients and Comparison with Normal Population. J Bahria Uni Med Dental Coll. 2023;13(2):77-81 DOI: https://doi.org/10.51985/JBUMDC2021056

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Received: 07-09-2021
Accepted: 01-02-2023

INTRODUCTION:

Development of chronic renal failure has become serious problem all over the world. Chronic renal failure (CRF) is characterized by slow and progressive decline in the kidney function. Haemodialysis (HD) is the commonest renal replacement therapy in developing countries and has been reported to induce repetitive bouts of oxidative stress primarily through membrane bio-incompatibility. While CKD is a pro-oxidant state, HD may contribute significantly to oxidative stress in these patients.[1] Oxidative stress in chronic kidney disease (CKD) results from increased production of prooxidant molecules such as reactive oxygen species (ROS) and nitric oxide (NO), insufficient clearance of oxidative products, and deficient antioxidant defense mechanisms.[1]

Total antioxidant capacity is described as the sum total of all endogenous and exogenous antioxidants in a medium.[2] There exists an equilibrium among the free radicals and antioxidants in humans.[2] The imbalance between these systems is called oxidative stress. Oxidative stress occurs due to disturbance in the equilibrium between the pro-oxidant and antioxidants which results in the formation of reactive

oxygen species (ROS) and free radicals which cause damage to the body cells. Reactive oxygen species (ROS) are highly reactive molecules derived from molecular oxygen.[3] These ROS include hydrogen peroxide (H_2O_2) and superoxide anion (O_2^-).[4]

The half-life of free radicals is very short that is only a few seconds so the clinical evaluation of oxidative stress is done by estimating stable oxidized compounds or their derivatives.[5]

Malondialdehyde (MDA) is a low molecular weight, 3-carbon containing aldehyde with the $\hat{E}CH_2(CHO)_2$ and a byproduct of lipid metabolism in the body. MDA is commonly used as a biomarker of lipid peroxidation.[6] Reactive oxygen species causes the degradation of$\hat{E}$, causing lipid peroxidation and formation of MDA. This compound also forms mutagenic DNA adducts when it reacts with and in DNA. Thus the levels of production of MDA can be used as a biomarker to estimate the level of$\hat{E}$.[7]

Oxidative stress leads to over production of free radicals and hence more MDA is formed.[8] Certain theories explain this reduction in antioxidant levels; these include the uremic state itself, the impermeability of the dialyzer membrane to antioxidants and the bacterial contamination of the dialysate.[10] Superoxide dismutase (SOD) is one of the most important enzymatic antioxidants and a major defense system against oxidative damage. A recent study suggests that superoxide dismutase is a major antioxidant enzyme, involved in managing oxidative stress during progressive renal injury.[9] SOD is involved in prevention of atherogenesis by causing inhibition of oxidative damage caused by O_2^-, inhibition of O_2^- mediated removal of NO and therefore enhancing endothelium-dependent vasorelaxation,$\hat{E}$inhibiting the adhesion of leukocytes and altered vascular cellular responses.[10] Hence the deficiency of SOD acts as an important cause in the development of oxidative stress related complications in hemodialysis patients. When SOD levels were measured in patients with chronic inflammation, their enzyme activity was significantly lower when compared to healthy individuals. Researchers suggest new therapeutic possibilities that target SOD antioxidant pathways so that pro-inflammatory responses can be limited.[10]

New pharmacological antioxidant therapies and dialysis strategies can help in reducing the complications of oxidative stress in hemodialysis patients. The presence of oxidative stress even before the initiation of maintenance dialysis therapy suggests that therapeutic antioxidant strategies should preferably be developed very early in the course of renal failure.

Hence the current study is planned to estimate the levels of superoxide dismutase and malondialdehyde in hemodialysis patients in order to access their antioxidant and oxidant levels and to match these levels with the control group.

METHODOLOGY:

This comparative prospective, hospital based study was carried out in Nephrology Department Ward 22 of Jinnah Post Graduate Medical Centre, Karachi from January 2018 till December 2018 in collaboration with the Department of Biochemistry, Basic Medical Science Institute of JPMC Karachi. Ethical permission for the present study was taken by the Institutional Review Committee JPMC, Karachi dairy no: NO.F.2-81-IRB/2018-GENL/5173/JPMC. Informed consent was obtained from all study participants and the data obtained from the study subjects was kept confidential. Open epi website calculator was used for calculation of sample size by using a reference study carried out in Shanghai, China.[13] A sample size of 120 subjects was calculated which was further divided into two groups. Group A (control group) included 60 normal controls from healthy population and Group B (hemodialysis group) included 60 patients receiving maintenance hemodialysis for more than 2 years duration and were not on any supplementary antioxidant therapy.

The subjects' age, gender, duration of hemodialysis and drug history was noted. Height, weight, BMI, blood pressure (BP), pulse, temperature, respiratory rate and previous medical record were also noted. A written informed consent was taken from every subject. A pre formed proforma was used as a data collection tool.

The inclusion criteria included subjects both males and females with age between 18 to 50 years, and receiving hemodialysis therapy for more than 2 years and not taking any supplementary antioxidants.

The exclusion criteria were patients suffering from any other chronic inflammatory state like malignancy or tuberculosis and patients receiving hemodialysis due to acute renal failure and all subjects having history of any previous cardiovascular disease or event and all subjects not willing to participate in the study were excluded from the study.

Non probability consecutive sampling technique was used for the recruitment of study subjects. Biochemical parameters (serum malondialdehyde, plasma superoxide dismutase) were measured in both the study groups.

BMI was calculated by using the formula for BMI i.e weight (kg)/height (m^2)

Levels of SOD were measured by using reagent method (method of Kono, 1978)

The malonldialdehyde (MDA) was estimated in the form of thiobarbituric acid reacting substances (TBARS) by the method of Okhawa et al, 1979.

Data was analysed using SPSS 23. Descriptive statistics of categorical data were presented as frequencies and percentages.

RESULTS:

Results showed that mean age of control group samples (Group A) was 34.67±7.73, mean BMI was 23.47±3.26,

mean systolic blood pressure was 107.33±9.80 mmHg, mean diastolic blood pressure was 66.33±8.09 mm Hg, mean weight was 66.10±7.75 Kg, and mean height was 1.69±0.12 meters whereas hemodialysis group patients (group B) had mean age 43.20±4.66 years, mean BMI was 22.21±4.21, mean systolic blood pressure was 159.0±12.42 mmHg, mean diastolic blood pressure was 93.67±10.66 mmHg, mean weight was 64.67±6.13 Kg and mean height was 1.63±0.12 meters. The mean superoxide dismutase level in control group was 108.53±19.44 while mean SOD levels in hemodialysis group was 46.20±19.18. In control group mean MDA was 10.87±3.04, and in hemodialysis group samples mean MDA was 31.01±8.48. The mean difference in serum MDA concentration was found statistically significant with p-value less than 0.01.

Table 1: Comparison of Anthropometric Measurements among study groups

Characteristics	A (controls) (n=60)		B (hemodialysis group) (n=60)		p value
	Mean	**SD**	**Mean**	**SD**	
Age (years)	34.67	7.73	43.20	4.66	0.20
Body Mass Index (kg/m2)	23.47	3.26	20.21	4.21	<0.01*
Systolic Blood Pressure	107.33	9.80	159.00	12.42	<0.01*
Diastolic Blood Pressure	66.33	8.09	93.67	10.66	<0.01*
Weight (kg)	66.10	7.75	59.19	6.13	<0.01*
Height (m)	1.69	0.12	1.63	0.12	0.20

*p<0.05 was considered statistically significant using t-test

Figure 1: Comparison of mean plasma superoxide dismutase (SOD) levels between studied groups

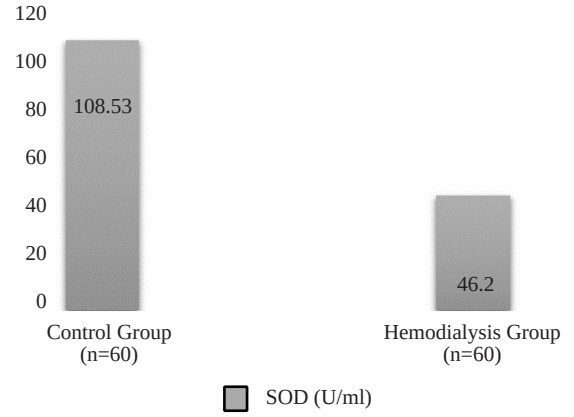
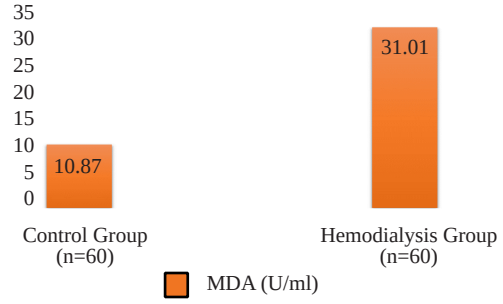


Figure 2: Mean comparison of serum malondialdehyde (MDA) levels among studied groups



DISCUSSION:

Oxidative stress is a major complication in patients treated with hemodialysis. The dialysis procedure itself leads to a decrease in the antioxidants and an increase in oxidative molecules, thus aggravating the already present oxidative stress.[22] Uremic state along with dialysis procedure is a major risk factor for oxidative stress related complications in these patients. The present study was designed to estimate oxidant and antioxidant levels in hemodialysis treated end stage renal disease patients. Significant results were seen during the comparison between the studied groups.

The aim of our study was to estimate the antioxidant and oxidant levels in hemodialysis treated end stage renal disease patients. For this purpose we estimated serum malondialdehyde and plasma superoxide dismutase levels. We found a significant increase in the mean systolic BP (159± 12.42mmHg) and diastolic BP (93.67±10.6mmHg) of the hemodialysis patients as compared to the control group (107.33±9.80mmHg) and (66.33±8.09mmHg) respectively. Our results are similar to the findings of Wang *et al* [14] who reported a mean SBP of 143.2 ± 32.7mmHg and mean DBP of 79.0 ± 15.9 mmHg among hemodialysis patients. This increase in blood pressure can be due to fluid overload, over-activity of renin angiotensin system, erythropoietin administration and enhanced stimulation of the sympathetic nervous system.[15] No significant difference in the mean ages among the two groups was found. A significant decrease in the weight and BMI was seen in the hemodialysis patients. This is similar to the findings of Rysz *et al.*[16] Li *et al* [17] who also reported a decrease in BMI in hemodialysis treated patients. The decreases in BMI may be due to protein energy wasting, chronic inflammation, repeated infections and restricted diet in hemodialysis patients.[18] Moreover the uremic state and chronic illness also contributes to anorexia, nausea and vomiting in these patients.[11,12,19]

We also explored the relationships between oxidants and antioxidants. Our study showed that very low levels of SOD were found in hemodialysis group (46.2U/ml) as compared to the control group (108.53U/ml). The possible mechanism behind this low level depends on several factors, such as age, creatinine clearance, the duration of dialysis, arteriosclerosis, imbalance of hemostasis and coagulation factors. Chronic inflammation and uremic state contributes to the formation if reactive oxygen species which causes an imbalance between oxidants and antioxidants. Moreover the selective permeability of the dialyzer membrane to antioxidants also significantly contributes to the decreased levels of antioxidants in these patients as the antioxidants are decreased after every cycle of dialysis. Our results are similar to the published work of Rysz *et al* [16] and Kundoor *et a.l*[20] Marjani *et al* [21] also reported a decrease in the

antioxidant levels in hemodialysis patients. These findings of our study and international studies show that hemodialysis patients are subjected to a constant reduction in antioxidant levels due to repeated infections, dietary restrictions, removal of antioxidants during dialysis procedure, impermeability of the dialyzer membrane to antioxidants and enhanced inflammatory cascade. Decreased SOD activity may also be due to a direct inactivation of the enzyme by its product hydrogen peroxide, or by superoxide anion itself. This reduction in antioxidants is a major factor that leads to oxidative stress in these patients. The morbidity and mortality can be much reduced if this imbalance is treated prior to development of complications.

Serum malondialdehyde was also significantly increased in hemodialysis group (31.01 U/ml) as compared to control group (10.87U/ml). Kundoor *et al* [20] and Barati *et al* [22] also described a significant increase in serum MDA in hemodialyzed patients as compared to controls. The possible mechanism which leads to an increase in MDA levels is that ROS activate phospholipase A2 causing peroxidation of many mediators by arachidonic acid which is finally metabolized to MDA. As MDA is a biomarker of oxidative stress hence elevated MDA levels indicate excessive reactive oxygen changes and oxidative changes in low density lipoprotein molecule and other lipid and protein molecules. This could be due to the fact that hemodialysis by the application of a modified circulation and forced passage of blood through a number of filters, activates, endogenous inflammatory mechanisms and induces chronic release of molecules resulting in an increased production of reactive oxygen species.[22] The enhanced oxidative stress in hemodialysis patients is caused due to poor intake of exogenous antioxidants in diet, formation of oxidative products and loss of antioxidants during hemodialysis. The levels of MDA rise with repeated cycles of dialysis. This relationship of repeated dialysis cycles and MDA concentration was shown by Hou *et al* [23] in his study.

These factors are linked to the development of atherosclerosis and chronic inflammation and lead to cardiovascular complications in these patients. Yeter *et al* [24] studied the effects of dialysis membranes on inflammation and oxidative stress. He concluded that increased oxidative stress in this patient population is multi-factorial and is affected by other factors other than inflammation which include the dialysis membranes also. Lestaringsih *et al* [25] studied the relationship of oxidative molecules with the development of atherosclerosis in hemodialysis treated patients and showed that increase in oxidative molecule lead to excessive formation of oxidized LDL which leads to development of atherosclerosis.

Our data led us to conclude that oxidative stress is enhanced in hemodialysis patients which may contribute to the development of dialysis-related complications such as cardiovascular disease, anemia etc. The administration of antioxidants plays a protective role against oxidative stress by neutralizing the harmful effects of oxidative molecules, however, it has still not been adopted as a regular treatment protocol in clinical practice. Antioxidant supplementation with vitamins A, C, and E; beta-carotene; or N-acetylcysteine (NAC) seems to be beneficial in decreasing cardiovascular risk in hemodialysis patents. Vitamin E is a powerful antioxidant exerting anti-inflammatory properties; it has been shown to interfere with cell membrane lipid peroxidation. Observational clinical studies have shown that the intake of vitamin E (more than 100 IU/day), which inhibits oxidized LDL formation by hindering lipid peroxidation, reduced the rate of coronary events in hemodialysis. Vitamin C plays a significant antioxidative role as it can reduce ROS levels, thus providing protection against kidney oxidative damage and helping to maintain vascular and endothelial function. Wang et al.[25] demonstrated that vitamin C (ascorbic acid) diminished oxidative damage, inflammation and renal injury in ischemia nephrotoxic acute kidney injury and rhabdomyolysis-induced renal injury. More prospective studies are required to elaborate the protective role of antioxidant administration in oxidative stress that can improve the cardiovascular mortality rate in hemodialysis treated end-stage renal disease. More over the oxidative stress parameters in these patients need to be monitored to avoid the possible outcomes of oxidative stress. Dietary guidelines should also be developed to ensure the intake of adequate vitamins and minerals in these patients. This study will help the nephrologists to elaborate the protective role of antioxidant administration in oxidative stress that can improve the cardiovascular mortality rate in hemodialysis treated end-stage renal disease. We recommend the addition of antioxidants in the treatment regimes of these patients.

The limitations of the study were small sample size and limitation to only one dialysis center. It was a self-funded study so the scope of study could not be extended beyond one study setting. Also, since non-probability sampling technique was used, it was difficult to make inference about the entire population. Other markers of oxidative stress like CRP, glutathione peroxidase and myeloperoxidase enzyme could not be included due to budget limitations. More studies with bigger sample size and multiple centers are required for further investigation of these findings. More markers of oxidative stress should be explored. Interventional studies using supplementary antioxidants should be carried out to further validate the protective role of antioxidants in hemodialysis patients.

CONCLUSION:

Antioxidant levels are reduced in hemodialysis patients resulting in elevated oxidant levels in hemodialysis patients as compared to control group. This decrease contributes to the oxidative stress related complications which are the major factors of mortality in these patients.

Authors Contribution:
Sadia Rehman: Principal researcher
Santosh Kumar: Research supervisor
Om Lal: Data collection and analysis
Suniya Rehman: Literature review and writeup
Hasan Ali: Approval of draft and literature review
Fatima Rehman: Statistical analysis

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