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Original Research Article

PRE- AND POST-DIALYSIS ASSESSMENT OF IMMUNE AND OXIDATIVE PROFILES IN CHRONIC KIDNEY DISEASE. EVIDENCE FROM A HOSPITAL BASED STUDY IN INDIA

Nishu Bala[1], Achileshwar Prasad Pandey[2]

[1]Assistant Professor, Department of Physiology, Prasad Institute of Medical Sciences, Sarai Shahzadi, Banthara, Kanpur Road, Lucknow, Uttar Pradesh, India
[2]Associate Professor, Department of Physiology, Prasad Institute of Medical Sciences, Sarai Shahzadi, Banthara, Kanpur Road, Lucknow, Uttar Pradesh, India

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Corresponding Author:
Dr. Achileshwar Prasad Pandey,
Email: draupandey@gmail.com

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ABSTRACT

Background: Chronic kidney disease (CKD) is a disorder which is characterized by the inflammation and sever oxidative stress, which results in complications like cardiovascular disease, malnutrition, insulin resistance which causes the progression to renal disorder. **Materials and Methods:** This is a cross-sectional study among 40 chronic kidney disorder patients who have underwent with haemodialysis. The samples of blood has been collected during the pre- and post-dialysis for the evaluation of the inflammatory markers TNF-α, IL-6, HMGB1, and other oxidative stress factors like the SOD, MDA or the NO. The data analysis has been done by the paired t test, where $p < 0.05$ was considered. **Result:** Among the 40 CKD patients, there are 24 males and rest 16 were females, having the mean age of 58 ± 12 years, and the haemodialysis have reduced the levels of the inflammatory markers like the TNF-α, IL-6, HMGB1. The function of the renal gland has been reduced due to low level of nitrogenous wastes like the urea and creatinine, but there are certain slight changes regarding the liver enzymes. **Conclusion:** The study concluded the efficient renal function, the reduction in the inflammation and the oxidative stress, which rises the liver enzymes, leads to hepatic stress.

INTRODUCTION

Acute kidney disease is an acute injury in kidney, which is reversible disorder, progressing up to the end-stage renal disease (ESRD), while chronic kidney disease is a chronic state, composed by proteinuria which is characterized by the normal or decreased level of glomerular filtration rate (GFR) and severe damage in the glomerular, tubular and interstitial regions. The prevalency of CKD is enhancing, with an estimated amount of 8 to 16% globally.[1,2] Several complications are related to the CKD condition including the severe hypertension, diabetes, and various immunity related conditions, glomerulonephritis and various tubulo-interstitial disease along with some inherited kidney disease, which can get progression to the ESRD, which requires immediate replacement of the renal tube by dialysis or transplantation of the kidney.[3] The high level of the uremic toxin stimulates the CKD to progress causing various complications.[4] The CKD progression is related to various other inflammatory responses and the oxidative stress.[5] Chronic inflammation is the major complication among patients,[6] and antioxidative cascades can affect the renal failure.[7] These inflammation and the oxidative stress are very significant defence system, but can lead to the high level of cytokine and enhance the mediators of the both, which requires the treatment intervention of the inflammation and oxidative stress in case of uremic condition.[8] The increase of the inflammatory markers like cytokines increases the inflammation, acute phase proteins, involving the innate immune system. The increase of the pro-inflammatory cytokines, the oxidative stress, and the acidosis along with the intestinal dysbiosis and the metabolism of tissue in the adipose cells can cause CKD inflammation.[9] Studies have demonstrated that the inflammatory markers is associated with various complications like the malnutrition, coronary artery calcification, atherosclerosis, atrial fibrillation, left ventricular hypertrophy, and the mortality due to CKD.[10-12] Also inflammation can cause resistance to insulin, the irregular functioning of the endothelial and different mineral and bone diseases, like anaemia.[13,14] C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), several adipokines can impact the CKD progression, the marker is related to the

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malnutrition, atherosclerosis, resistance to erythropoietin and mortality and morbidity rate related to the cardiovascular condition.[15]

Oxidative stress is rarely observed in case of CKD patients, is a crucial prognostic factor for the target specific intervention in case of CKD. High level of oxidative stress is associated in the early state of CKD,[16] enhances the CKD progression to ESRD.[17] ESRD patients enhance the oxidative stress in case of peritoneal dialysis, thus HD and PD both increases the oxidative stress. Oxidative stress is associated with the high reactive oxygen species (ROS) intermediates at the time of inflammatory reaction, which enhances the inflammatory response due to stimulation of the pro-inflammatory mediators like the NF-κB. Reduced level of the pro-oxidative agents for the defensive system, get inactivated due to the glutathione and some antioxidants like the scavengers, due to their neutralizing ability. Various enzymes associated with the mitochondrial respiration like the NADPH oxidase (NOX) produces the ROS in kidneys. Different isoforms of the N OX is there, like the NOX1, NOX2 and NOX4 which enhances the oxidative stress, reducing the functionality of the vascular region, results in fibrosis.[18,19] The enhanced ROS production is not stabilized by the ROS system, which causes damaging property to the proteins, nucleic acids and the lipids, resistance to enzymatic functions, causing imbalances between the oxidising elements and the defense system, results in oxidative stress. This causes the base modification in DNA and breaks in strands, where the guanine is sensitive to oxidative stress and reactions produces the oxidized products like 8-hydroxy-2′-deoxyguanosine (8-OH-dG).[20] This damage is linked to different chronic and degenerative conditions including the CKD. In case of CKD, the high level of oxidative stress have been observed due to abnormality in the functionality of the defense process, results in oxidative damage to the nucleic acid, enhancing the probability of tumours.[21]

MATERIALS AND METHODS

Research design: This is a cross sectional study regarding the assessment of the immune and the oxidative profiles among the CKD patients. This study was conducted for 1 year from February 2024 to January 2025. The study was conducted in the Prasad Institute of Medical Sciences, Lucknow, Uttar Pradesh. The total subjects taken are 40, based on various inclusion and exclusion criteria and the ethical approval from ethical committee board. The CKD patients of above 18 years were selected for the study and proper written and verbal consent is required for the study. Pregnant women or women in their lactation state are opted out of the study. Apart from these, if any patient have been diagnosed with inflammatory disorder other than Diabetes Mellitus, hypertension, autoimmune disorder, malignancy or known haematological disorder are excluded from the study.

Inclusion criteria

- Patients those who are diagnosed with Chronic kidney disease have been selected for the study.
- Patient who are underwent with haemodialysis have been selected for the study.
- Patients of more than 18 years of age have been selected for the study.
- Verbal and written consent of the patients have been taken before inclusion of the participants.

Exclusion criteria

- The pregnant women or patients those who are in their lactation period have been excluded from the study.
- If diagnosed with any chronic inflammatory disease, they are excluded from the study.

Procedure: After the written and verbal consent from the CKD patients who are undergoing with haemodialysis, all patients were advised to fill proforma for the patient profile information regarding their health and the history of illness or family health history or any pre-medication. About 3ml of blood sample has been collected and stored in the 200 µl of sodium citrate tubes during any one of the haemodialysis events maintaining the aseptic process. Both of the samples were centrifuged at 3000 rpm at 40oCfor 10 minutes, for the separation of the serum from the pool of blood cells. The serum was pipetted out and was stored in the -80oC temperature for future use. During both of the pre and the post-dialysis CKD samples, assessment of the tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and high mobility group box 1 (HMGB 1) was performed for the inflammation examination and to assess the oxidative stress by evaluating the levels of the superoxide dismutase (SOD), nitric oxide (NO) and malondialdehyde (MDA) enzymes.

TNF-α, IL-6 AND HMGB 1

ELISA was performed from the plasma samples of blood, in which incubation of 50 µL of plasma was done in an equal volume of buffer solution [0.5M carbonate buffer (pH 9.6)] placed in an assay plate, for the whole night at 4°C. All the nonspecific bindings need to be blocked by the use of 5% BSA added in the buffer solution. Washing of the samples was done by PBS containing 0.05% Tween 20 and 2 hours of incubation with the diluted primary antibody (TNF-α, IL-6 and HMGB 1) added in the buffer used for blockage in the ratio of 1:500. The sample was again washed and further incubation was done with the secondary antibody-HRP in the ratio of 1:2000 added in the same buffer for 2 hours. After washing, the incubation was followed by the p-nitrophenyl phosphate (1 mg/mL) which was added in the carbonate buffer with 10 mM MgCl2. The colour was assessed at the 450 nm and the reaction was paused due to the addition of the 50 µL of 1 M NaOH. Results were expressed in mean and standard deviation values.

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Superoxide Dismutase

This method evaluates the effect of the SODs on the self-oxidization of the pyrogallol. Various reaction mixtures were prepared, for different concentrations of standard, tests and controls. The mixture of the assay in the volume of 3ml, comprises of 100 µL each of 1-mmol/l EDTA and 1-mmol/l Diethylene triamine pentetic acid (DTPA) in air which is equilibrated with the tris HCl buffer (50 mmol/l, pH = 8.2). In this reaction mix 100 µL of standards having varying SOD concentration or the test sera was mixed. In the control tube, the test sample and the standard was not added to not to resist the self-oxidization of the pyrogallol. The 100 µL volumes of 0.2 mmol/l pyrogallol was added to the vials for the initiation of the reaction. After 10 seconds, there occur an alterations in the absorbance at 420nm and the spectrophotometric value is recorded at an interval of 10 seconds for 4 minutes. The average of the change of the absorbance value per minute has been calculated along with the percentage of inhibition. The enzyme requires for the inhibition of the self-oxidization of the pyrogallol by 50% is known as the one unit of the SOD and by that way, the enzymatic activity was measured at different concentrations and a standard curve has been plotted, between the percentage of inhibition and the SOD values. SOD activity was calculated by the test serum by a standard graph.

MDA-Thiobarbituric Acid Reactive Substances (TBARS) estimation

The estimation of the Lipid peroxidation (LPO) was done by the method, where the 0.05 mL serum sample, 0.58 mL phosphate buffer (0.1M, pH 7.4), 0.2 mL ascorbic acid (100mM) and 0.02 mL ferric chloride (100mM) were used in the mixture and were added. The total volume taken is 1mL and the incubation is done at 37℃, in the water bath for duration of 1 hour and the reaction was stopped by the gentle addition of 1 ml 10% trichloroacetic acid, which is followed by the addition of the 1mL 0.67% thiobarbituric acid. All of the tubes were put in the boiling water bath for the duration of about 20 minutes and were crushed in the ice bath for the centrifugation process at 2500 g for 10 minutes. The amount of the malondialdehyde (MDA) in the samples are evaluated by the measurement of the optical density of the supernatant at 535 nm by the use of the spectrophotometer, where the extinction coefficient is1.56 × 105 M-1 cm-1.

Nitric Oxide Assay

The NO synthesis have been evaluated by the rate of conversion of the oxyhemoglobin to methemoglobin, by the NO by using a scanning spectrophotometer (Lambda 35, Perkin-Elmer, Norwalk, CT). The plasma samples were putted in the reaction mix, having the Krebs buffer (pH 7.4) added in the 15mM oxy-haemoglobin, 10mM L-arginine, and 240nM insulin, and the total volume is 2.5 mL and it is continued for 45 minutes at 37 °C temperature and stirred continuously. The quantification of the NO content was recorded by the changes of the spectral in the reaction mixture, for the conversion of the oxy-haemoglobin to met-haemoglobin. The decrease in the absorbance rate have been observed 575 and 630 nm maxima by a standard curve which is constructed by the pure commercial (> 99% pure) NO, which is placed in the 0.9% NaCl. The NO amount was measured by the chemiluminescence process.

Protein estimation

The protein estimation is estimated by the reaction of the protein with Folin' Ciocalteu phenol reagent which gives a coloured complex and the colour is formed by the reaction of the copper with protein in the Biurets test and the reduction reaction of the phosphomolybdate by the use of the tyrosine and tryptophan.

Statistical analysis: Statistical analysis was performed by the GraphPad software, where the continuous variables are expressed by the mean and standard deviation range. The qualitative data was presented as percentages. The paired sample t-test was used for the comparison of the mean values between the pre and post dialysis process. The p-value of <0.05 was considered for the statistical significance.

RESULTS

The [Table 1] highlights the baseline features of the study population for the haemodialysis patients. Total 40 patients were included, where 24 were males and 16 were females and the mean age of all the participants are 58 ± 12 years, indicating commonly are the mid age to elder individuals. The range for the duration of the haemodialysis is 33 ± 3 months, which reveals the long term adherence to the renal replacement therapy. The haemodialysis was continued for 4 hours, 3 times in a week, consistently with all the conventional protocols for dialysis and the balance of fluid.

Table 1: The representation of the values for baseline characteristics of the patients

Variable	Value
Total Patients	40 (24 Male, 16 Female)
Mean Age (years)	58 ± 12
Duration on Haemodialysis (months)	33 ± 3
Maintenance Haemodialysis Regimen	4 hours/session, 3 sessions/week

[Figure 1] shows the comorbidities among the CKD patients. While the major comorbidity is the hypertension, which affect the 55% of the patients, revealing the strongest association. While the Type

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2 diabetes mellitus is observed among 15% of patients and the hypertension and type 2 diabetes is observed among the 25% people. A major portion of patient having the cardiovascular and metabolic disorder, creating the need for the management of pressure and the glycemic control for the disease progression and the enhancement of the associated complication.

In [Table 2], the biomarker levels showed a significant decline following dialysis. Tumor necrosis factor-α (TNF-α) decreased from 5.1 ± 0.4 to 2.5 ± 0.1 with a p-value of 0.042, indicating a statistically significant reduction. Similarly, interleukin-6 (IL-6) dropped from 4.5 ± 0.2 to 2.5 ± 0.1 with a p-value of 0.045, also reaching significance. High mobility group box 1 protein (HMGB1) demonstrated the most marked decline, from 25.3 ± 0.5 to 8.2 ± 0.3, with a significant p-value of 0.041. These results suggest that dialysis effectively reduces pro-inflammatory biomarker levels.

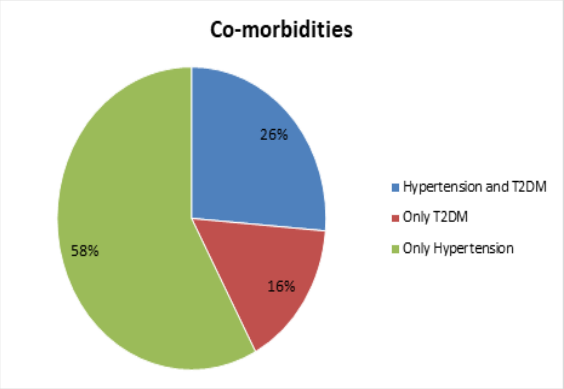

Figure 1: Different percentages of the comorbidities among the CKD patients

Table 2: The value of the biomarkers during the pre and the post dialysis

Biomarker	Pre-Dialysis (Mean ± SD)	Post-Dialysis (Mean ± SD)	p-value
TNF-α	5.1 ± 0.4	2.5 ± 0.1	0.042
IL-6	4.5 ± 0.2	2.5 ± 0.1	0.045
HMGB1	25.3 ± 0.5	8.2 ± 0.3	0.041

[Table 3] highlights the changes in oxidative stress markers before and after dialysis. Malondialdehyde (MDA), a marker of lipid peroxidation, decreased from 2.1 ± 2.5 to 1.5 ± 1.9, with a significant p-value of 0.0412. Superoxide dismutase (SOD) activity, however, showed a notable reduction from 37.5 ± 2.5 to 19.5 ± 0.1, with a highly significant p-value of 0.036, suggesting a decline in antioxidant defense post-dialysis. Nitric oxide (NO) levels also declined significantly from 1.7 ± 0.5 to 1.2 ± 0.3 with a p-value of 0.044. Collectively, these findings point towards a decrease in oxidative markers, though the reduction in SOD implies a complex impact on antioxidant balance.

Table 3: The serum level in the pre and the post dialysis phase

Serum levels	Pre-Dialysis (Mean ± SD)	Post-Dialysis (Mean ± SD)	P-value
MDA(umol/mg protein)	2.1 ±2.5	1.5 ± 1.9	0.0412
SOD(%inhibition per mg protein)	37.5 ± 2.5	19.5 ± 0.1	0.036
NO (µmol/mg protein)	1.7 ± 0.5	1.2 ± 0.3	0.044

In [Table 4], the enzymatic parameters revealed significant elevations following dialysis. Aspartate aminotransferase (AST) rose from 30.1 ± 5.5 to 35.1 ± 5.5 with a p-value of 0.046, while alanine aminotransferase (ALT) increased from 27.5 ± 7.5 to 35.6 ± 5.1 with a p-value of 0.047. Both results were statistically significant, suggesting possible transient hepatic stress or enzyme release induced by the dialysis procedure.

Table 4: The level of the enzymes during the pre and post dialysis process

Enzyme levels	Pre-Dialysis (Mean ± SD)	Post-Dialysis (Mean ± SD)	P-value
AST (IU/L)	30.1 ±5.5	35.1 ± 5.5	0.046
ALT (IU/L)	27.5 ± 7.5	35.6 ± 5.1	0.047

[Table 5] demonstrates the classical biochemical efficacy of dialysis in reducing nitrogenous waste. Urea levels dropped substantially from 115.1 ± 5.5 to 49.5 ± 5.5, with a highly significant p-value of 0.039. Likewise, creatinine levels decreased from 118.5 ± 7.5 to 68.6 ± 5.1, with a p-value of 0.042, confirming the effective clearance of these metabolites by dialysis.

Table 5: The level of the component of urea and the creatinine values during the pre and post dialysis

Component	Pre-Dialysis (Mean ± SD)	Post-Dialysis (Mean ± SD)	P-value
Urea (mg/dl)	115.1 ±5.5	49.5 ± 5.5	0.039
Creatinine (mg/dl)	118.5 ± 7.5	68.6 ± 5.1	0.042

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DISCUSSION

Various studies related to the condition, have been considered, in a study which reveals the CKD condition is linked to the inflammation and oxidative stress to progress the CKD to the ESRD condition to enhance the cardiovascular disorder. The CKD patients have increased the level of the inflammatory markers like CRP, IL-6, and TNF-α, as well as the oxidative stress biomarkers, malondialdehyde (MDA). While, the level of the supoeroxide dismutase (SOD), and the functioning of the catalase have been decreased. The irregular balance is observed in early CKD condition and get worst due to dialysis.[22] Another study have highlighted the CKD patients, those on dialysis have enhanced ixidative stress due to high level of lipid peroxidation markers such as malondialdehyde (MDA) as well the high level of the thiobarbituric acid–reactive substances (TBARS), which is high twice or thrice in comparison to the healthy people. Also SOD, catalase and the glutathione peroxidase (GPx), reduces 20-40% comparing to the control group, revealing the impairment of the antioxidant defence mechanism. Also haemodialysis can enhance the oxidative stress, as the bio-incompatibility and the activated form of the neutrophils can increase the free radicals producing the oxidative stress.[23] The study of single haemodialysis reveals that the post dialysis can enhance the level of ROS and the products results due to the lipid peroxidation and also enhances the increase in the malondialdehyde (MDA) levels nearly to 25 to 30% in comparing to the pre dialysis state. Different antioxidant enzyme like the catalase, the SOD get reduced, reveals the imbalance state of the acute oxidative stress. Also, the study results in low level of the CD4+ T cells and alterations in the functions of the natural killer (NK) cell.[24] The single HD can results in alterations of the inflammatory and the markers associated with the oxidative stress among the CKD patients. There is increase in the CRP level from 20 to 25% after dialysis, also there is rise in the level of interleukin-6 (IL-6). The malondialdehyde (MDA) marker in enhanced by 30%, but the levels of the superoxide dismutase (SOD) and glutathione peroxidase (GPx) get reduced. The HD can increase the inflammation and the oxidative stress, reveals the bio-incompatibility of the membrane of the dialysis along with the immune activation.[25] The ESRD is linked with the ageing process, characterized by the immunosenescence and the chronic inflammation. The study have revealed the decrease in the naïve CD4+ and CD8+ T cells concentration, while increasing the memory cell and the T cell causing the senescence. The increased level of the markers like IL-6 and TNF-α, which is linked with the immune impairment results in systemic inflammation. Some biomarkers which reduced the length of the telomere and decrease the thymic output trigger the ageing process of the immune response among the dialysis patients. ESRD have increased the pro-inflammatory, immunosenescent which causes the patients with severe infections, poor response against vaccines and associated cardiovascular disorders.[26] The haemodialysis among patients have resulted in the erythrocyte change and the enzymes of the plasma antioxidant. The SOD activity has decreased to 25 to 30%, but the level of catalase and glutathione peroxidase (GPx) gets reduced. Low level of zinc and selenium concentrations has been observed in blood plasma around 20-35%, while increasing the level of copper. The single HD has resulted in alterations with reduction in the enzymatic functions after the dialysis. Thus the chronic dialysis causes impairment in the antioxidant defences mechanism and also causes disruption in the level of trace element which increases the oxidative stress among the CKD patients.[27]

CONCLUSION

The study have concluded Pro-inflammatory biomarkers such as TNF-α, IL-6, and HMGB1 showed marked reductions post-dialysis, indicating a decrease in systemic inflammatory burden. Similarly, oxidative stress markers including MDA and NO declined significantly, though the reduction in SOD activity suggests a concurrent compromise in antioxidant defense mechanisms. Enzymatic parameters, particularly AST and ALT, were found to increase after dialysis, pointing to possible transient hepatic stress associated with the procedure. Importantly, dialysis was highly effective in reducing classical biochemical waste products such as urea and creatinine, reaffirming its efficacy in metabolic clearance. Overall, these results highlight that while dialysis substantially improves inflammatory and metabolic parameters, it may simultaneously alter oxidative and enzymatic balance, underscoring the need for integrated monitoring of immune, oxidative, and hepatic profiles in chronic kidney disease management. The Hemodialysis get reduced due to the reduction of the values of the TNF-α, IL-6 and HMGB1. The oxidative stress markers also get reduced, the values of the MDA get reduced, along with the markedly decline have been observed in case of the SOD activity and NO, thus highlighting the management of the oxidative damage. The enzymes present in the liver get increased after the dialysis, the value of the AST and ALT get elevated, which highlights the heaptic stress. The function of the renal region get improved and the values of urea and creatinine get reduced, which reflects the proper clearance of the nitrogenous waste from the body. The study result findings confirm that the haemodialysis not only balances the metabolic component balance but also resulted in effective reduction of the inflammation and the oxidative stress among the CKD patients.

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