

Serum malondialdehyde in different stages of chronic renal disorder



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ABSTRACT

Background: Chronic kidney disease (CKD) is a widespread public health problem, which may have several adverse consequences such as renal failure, cardiovascular disease, and premature death. Kidney-related pathologies have increasing prevalence rates, produce a considerable financial burden, and are characterized by elevated levels of oxidative stress (OS). Several markers emerged as well-suited indicators of OS such as malondialdehyde (MDA) and lipid hydroperoxides. The reduced activities of antioxidant enzymes status and increased production of MDA in the CKD patients confirm the presence of OS. The alteration in antioxidant status and MDA in CKD patients supports the role of OS in CKD patient. **Aims and Objectives:** The aim of the study was to compare serum MDA in different stages of CKD with that of control. It is well known that inflammation has an important role in CKD and MDA is an oxidant biomarker. **Materials and Methods:** This was a cross-sectional study having 400 participants with 300 known cases of CKD and 100 healthy controls. Serum MDA levels were measured by thiobarbituric acid assay. **Results:** There was a significant difference between the groups regarding the MDA values ($P < 0.001$) with that of control. The mean MDA value in Stage III (5.64 ± 1.93 Umol/L), Stage IV (6.14 ± 1.584 Umol/L), and Stage V (10.761 ± 3.347 U mol/L) of CKD patients were high in comparison to healthy control (1.88 ± 0.181 U mol/L). **Conclusion:** We concluded that MDA is a useful biomarker in CKD patients. The correlations of serum MDA among different stages of CKD patients were significant. Larger studies focused on CKD severity and antioxidant/oxidant biomarkers are required.

Key words: Chronic kidney disease; Malondialdehyde; Oxidative stress; Antioxidant

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INTRODUCTION

Chronic kidney disease (CKD) continues to increase in prevalence rate worldwide with high morbidity and mortality.¹ According to data published by the American Society of Nephrology, European renal society, and International Society of Nephrology, the total number of people affected by kidney disease stood at 850 million worldwide in 2018. A report published by the Global Burden of Disease Study states that CKD was 17th most prevalent cause of death in 2015.² Common risk factors associated with CKD are diabetes, chronic pyelonephritis, tuberculosis, polycystic kidney disease, hypertension, renal stone disease, etc. The most common cause of CKD is diabetic nephropathy but due to scarce resources

that only 10% of Indian ESRD patients receive any renal replacement therapy. Early diagnosis and initiation of dialysis can prevent progression and decrease mortality in patients with CKD. In addition, CKD is an independent risk factor for various cardiovascular complications.³

According to KDIGO guidelines, CKD is defined as any structural or functional abnormality of kidney present for 3 months with serious health implications. The best global indicator of a healthy kidney is glomerular filtration rate (GFR) as it is indicative of excretory strength of kidney and exhibits direct correlation with its functioning. It also helps to classify CKD according to the heightened risk of CKD progression and in estimating the correct drug dose for possible treatment. Creatinine is one of the most

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prominent waste product of muscle metabolism. It is a small molecule of 113 daltons and is nearly excreted by the glomerular filtration. Despite of several limitations, creatinine is still the most commonly used marker for evaluating functional status of kidney.¹

The increasing cases of CKD cannot be explained by traditional risk factors. A study conducted by atherosclerosis risk in communities revealed that novel factors play a critical role in CKD progression.⁴ In addition, studies strongly suggest that novel factors are even more important in patients undergoing hemodialysis.⁵ Among others, oxidative stress (OS), which represents over production of reactive oxygen species (ROS) and/or decrease in antioxidants levels, is well documented in Uremic patients. OS is prevalent in CKD patients and it is considered to be an important pathogenic mechanism. Impaired oxidative balance in CKD is an outcome of increased ROS production and reduced clearance as well as an ineffective antioxidant defense mechanism. The oxidative burden in uremic patients is primarily due to diminished activity of glutathione peroxidase, glutathione, and catalase and reduced levels of vitamins C and E and high-density lipoproteins.^{6,7} These pro-oxidants are closely associated risk factors of CKD such as old age, diabetes, increased inflammation, and uremic toxins.⁸ Available literature suggests that OS condition in CKD patients arise mainly because of (i) enhanced concentration of lipid, protein, and nucleic acid biomarkers and (ii) impaired anti-oxidant defense mechanism. Increased OS in patients of CKD include accumulation of lipid peroxidation product such as malondialdehyde (MDA) and hydroperoxides (LPO). This study aims to determine value of MDA in different stages of CKD and also of healthy controls.

Aims and objectives

An experimental study which involved quantification of serum malondialdehyde (MDA) as a biomarker of oxidative stress in different stages of chronic renal disorder patients with that of control.

MATERIALS AND METHODS

The study included 300 patients with CKD, age >18 years attending department of Nephrology, IGIMS Patna, and satisfying all the criteria for inclusion and exclusion were enrolled. One hundred healthy controls were in the study. Patients suffering from disease such as acute kidney disease, rapid progressive glomerulonephritis, and congenital anomalies of the kidney and urinary tract were excluded from the study. In addition, patients on dialysis and those who had recent exposure to any nephrotoxic drug were also excluded from the study. The study was approved by

the Ethics Committee of the IGIMS, Patna. The patient consent was obtained from all participants.

After overnight, fasting 5 mL venous blood was collected in plain vacutainer with aseptic precaution. After proper clotting, serum was separated and estimation of parameter was done and in case of if test is delayed that sample is stored at 0–4°C. All detections were performed within 8 h of sampling and in triplicates.

Creatinine quantification was done on autoanalyzer by Jaffes's method which is a kinetic mode of estimation. Briefly, the principle of behind the procedure is that creatinine reacts with picric acid in alkaline pH to form a yellow orange complex. The rate of change in absorbance at 520/800 nm is proportional to the creatinine concentration in the sample. The e-GFR was calculated from serum creatinine using the CKD epidemiology collaboration CKD formula. Based on the eGFR and the national kidney foundation practice guidelines, kidney function was function that was classified into following stages: Stage 1 with normal or high GFR (GFR≥90 mL/min), Stage 2 Mild CKD (GFR=60–89 mL/min), Stage 3A Moderate CKD (GFR=45–59 mL/min), Stage 3B Moderate CKD (GFR=30–44 mL/min), Stage 4 Severe CKD (GFR=15–29 mL/min), and Stage 5 Severe CKD (GFR<15 mL/min).

A modified thiobarbituric acid (TBA) method was used to determine the concentration of MDA in serum. MDA formed from the breakdown of polyunsaturated fatty acids serves as a convenient index for the determination of the extent of peroxidation reaction. MDA, a product of lipid peroxidation, reacts with TBA to give a pink colored product having an absorption maximum at 535 nm. Briefly, the procedure involved addition of 1 mL of trichloroacetic acid (20%w/v) and 1 mL of TBA (0.67% w/v) were added to 20 µL of fresh serum sample and mixed thoroughly. The mixture was heated in a boiling water bath for 20 min. The tubes were centrifuged at 1000 g for 10 min and the absorbance was read at 535 nm in a spectrophotometer against reagent blank. The MDA equivalent of the samples was calculated using extinction coefficient $1.56 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$. The MDA was expressed as TBA -reactive substances and detected by spectrophotometer.

Statistical analysis

The statistical analysis was performed with the help of GraphPad Prism software version 8.4.686. The data were presented in the form Mean±SD. P<0.05 was considered statistically significant. Ordinary one-way ANOVA using Dunnett's multiple comparison tests was done to ascertain the statistical significance of creatinine, eGFR, and MDA quantification between cases (all three stages) and controls. To establish correlation between eGFR and MDA and creatinine

and MDA, two-way ANOVA was done using Sidak's Multiple test assuming no sphericity of data with $\alpha=0.5$.

RESULTS

There was statistically significant difference in the level of creatinine between control and CKD stages (III, IV, and V) with highest creatinine level being reported for CKD V patients (6.484 ± 2.568 mg/dL) (Table 1). Similarly, in eGFR, highest titer was reported in control group (108.7 ± 17.71 mL/min/ 1.73 m²) followed by CKD III (38.90 ± 6.957 mL/min/ 1.73 m²). The level of TBARS was much higher in CKD patients ($P < 0.001$) as compared to healthy controls. The mean MDA value in Stage III (5.64 ± 1.93 U mol/L), Stage IV (6.14 ± 1.584 U mol/L), and Stage V (10.761 ± 3.347 U mol/L) of CKD patient were high in comparison to healthy control (1.88 ± 0.181 U mol/lit) (Figure 1). The results showed that there was statistically significant difference between the obtained values of parameters under consideration ($P < 0.05$). The correlation of eGFR with MDA illustrates that MDA was negatively correlated to kidney function. Two-way ANOVA with

the help of Sidak's multiple comparison test was done to ascertain the correlation between MDA versus eGFR and MDA versus creatinine, respectively (Figures 2 and 3, Table 2). The results showed that for MDA, apart from CKDIII versus CKDIV ($P=0.3784$), all comparisons were statistically significant ($P < 0.0001$). In case of eGFR and creatinine, all multiple comparisons were significant ($P \leq 0.0001$).

DISCUSSION

A comparative study was conducted in CKD patients to assess lipid peroxidation and anti-oxidant defense during the progression of CKD and to evaluate the role of antioxidant in these patients. Lipid peroxidation involves oxidation of polyunsaturated fatty acids such as arachidonic acid and linoleic acid by free radicals and can result in severe tissue damage.⁹ Lipids constitute a major component of cellular membrane and its peroxidation cause alteration in its properties and subsequently function.¹⁰ MDA is one of the most well-studied biomarkers of lipid peroxidation.¹¹⁻¹³ MDA

Table 1: The data represents values (Mean±SD) of eGFR (mL/min/1.73m²) and creatinine (mg/dL) of cases and controls. One-way ANOVA was done using Dunnett's Multiple test to access the statistical significance of data with $P < 0.5$ considered significant

Group	eGFR (mL/min/1.73m ²)	P-value	Creatinine (mg/dL)	P-value
Control	108.7±17.71	<0.0001	0.790±0.14	<0.0001
CKDIII	38.90±6.957		1.871±0.32	
CKDIV	21.05±4.372		3.191±0.75	
CKDV	9.710±3.033		6.484±2.56	

CKD: Chronic kidney disease

Table 2: Two-way ANOVA was done for multiple comparisons for MDA versus eGFR and MDA versus creatinine with the help of Sidak's multiple test

Sidak's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P value
MDA					
Control versus. CKDIII	-3.764	-4.289--3.239	Yes	****	<0.0001
Control versus. CKDIV	-4.264	-4.688--3.841	Yes	****	<0.0001
Control versus. CKDV	-8.883	-9.794--7.973	Yes	****	<0.0001
CKDIII versus. CKDIV	-0.5004	-1.250--0.2493	No	ns	0.3784
CKDIII versus. CKDV	-5.119	-6.205--4.033	Yes	****	<0.0001
CKDIV versus. CKDV	-4.619	-5.548--3.689	Yes	****	<0.0001
eGFR					
Control versus. CKDIII	69.84	64.73--74.95	Yes	****	<0.0001
Control versus. CKDIV	87.69	82.84--92.54	Yes	****	<0.0001
Control versus. CKDV	99.03	94.16--103.9	Yes	****	<0.0001
CKDIII versus. CKDIV	17.85	15.61--20.09	Yes	****	<0.0001
CKDIII versus. CKDV	29.19	27.13--31.25	Yes	****	<0.0001
CKDIV versus. CKDV	11.34	9.914--12.77	Yes	****	<0.0001
Creatinine					
Control versus. CKDIII	-1.081	-1.724--0.4375	Yes	***	0.0001
Control versus. CKDIV	-2.401	-3.044--1.758	Yes	****	<0.0001
Control versus. CKDV	-5.694	-6.337--5.051	Yes	****	<0.0001
CKDIII versus. CKDIV	-1.321	-1.964--0.6778	Yes	****	<0.0001
CKDIII versus. CKDV	-4.613	-5.256--3.970	Yes	****	<0.0001
CKDIV versus. CKDV	-3.293	-3.936--2.650	Yes	****	<0.0001

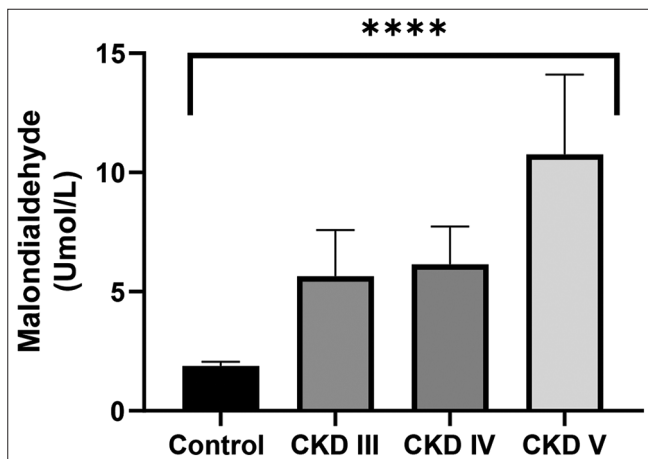


Figure 1: Malondialdehyde (Umol/L) in control and CKD patients. Results are in Mean± SD. ($P < 0.0001$)

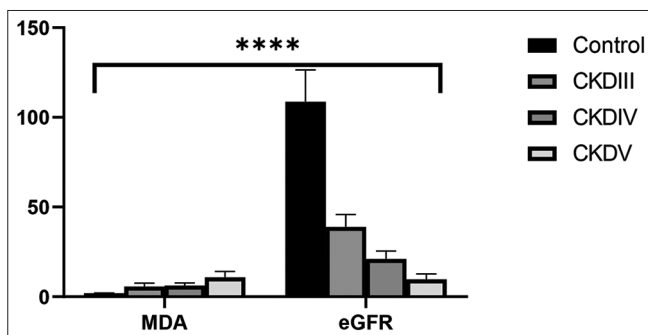


Figure 2: Comparative analysis of MDA (Umol/L) and eGFR (eGFR (mL/min/1.73m²)). Multiple comparison analysis was done with the help of Sidak Multiple comparison test. ($P < 0.0001$)

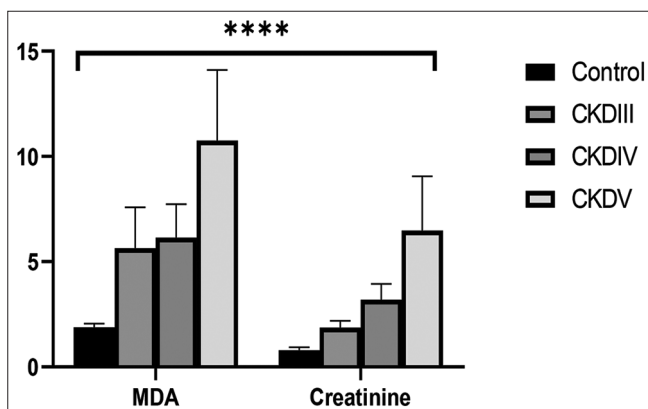


Figure 3: Comparative analysis of MDA (Umol/L) and creatinine (mg/dL). Multiple comparison analysis was done with the help of Sidak multiple comparison test ($P < 0.0001$)

accumulates inside the cell due to lipid peroxidation and during synthesis of thromboxane and prostaglandins. MDA attacks various macromolecules, causing changes in their normal physiological role.¹⁰ MDA can combine with nucleic acids resulting in formation of adducts with toxicity.¹⁴ MDA can also induce frameshift mutations.¹⁵ Moreover, MDA can react with lysine group to form

lysine-lysine bond.¹⁶ In our study, the serum MDA levels were significantly different between the groups of CKD. It showed an increasing trend with increase in disease severity. We found out that it was lowest in the control group, relatively higher in Stages III and IV and highest in CKD V stage. Various studies have reported elevated serum MDA levels in CKD patients compared to healthy controls.¹⁷⁻¹⁹ The study has also documented negative correlation between MDA levels with GFR in patients with different CKD stages.²⁰ In addition, studies have also shown that MDA levels show a direct association with CKD 1-5 stages.²¹ Studies have also reported greater titer of serum MDA in patients on hemodialysis.^{20,22} The level of serum MDA was lower in transplant patients in comparison of dialysis patients.²³ However, MDA was higher in HD patients as compared to healthy controls.^{24,25} Another study reported decreased MDA level after kidney transplantation. Another investigation reported that elevated MDA level can contribute to cardiovascular complications.²⁶ One study focused on the comparison of plasma total anti-oxidant capacity and lipid peroxidation in hemodialysis patients before and after treatment. Results showed that MDA level was higher in HD patients when compared to normal controls.²⁷ Another study aimed to highlight the association of OS in CKD with that of dialysis modality revealed that lipid peroxidation was far more pronounced during hemodialysis as compared to continuous ambulatory dialysis.²⁸ All these previous findings suggest are more or less in conjunction with our results are assert that MDA (an oxidant biomarker) can be used as markers in all stages of CKD.

Finally, MDA is a low molecular weight, water-soluble compound so it is expected that there would be some filtration by the glomerulus and excretion by the kidney, and recently, the MDA-TBARS complex has been characterized in urine from healthy control.

The increased MDA level in CKD group may therefore point that insufficient kidney function with decreased capacity to excrete OS or will further enhance OS and leads to high level of MDA.

Limitations of the study

The study consisted of only oxidative stress biomarker and for better understanding of oxidative burden in chronic renal failure, anti-oxidant parameters should also be analyzed.

CONCLUSION

The case-control study was an attempt to estimate the level of OS associated with lipid peroxidation using MDA

as a biomarker. Study revealed that MDA production is directly proportional to worsening of kidney function. Hence, anti-oxidant intervention is required for lowering oxidative burden in CKD patients. However, the present study was limited in its scope as only one biomarker was under investigation. To obtain a more comprehensive account of OS in CKD, many more biomarkers need to be incorporated. Nevertheless, the present study gives a reliable background for more detailed study.

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