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Original Research Article

Oxidative stress markers in chronic kidney disease patients with hearing lossReshma S^{*1}, Kavitha Ashok Kumar², Soundarya³, Ashok Kumar J⁴, Sushith⁵, Prathima M B⁵ and Madan Gopal Rajan⁵¹Department of Biochemistry, A J Institute of Medical Sciences & Research Center, NH – 66, Mangaluru, India²Department of Otorhinolaryngology, International Medical School, Management & Science University, Malaysia, India³A J Institute of Medical Sciences & Research Center, NH-66, Mangaluru, India⁴Department of Biochemistry, International Medical School, Management & Science University, Malaysia, India⁵Department of Biochemistry, A J Institute of Medical Sciences & Research Center, NH-66, Mangaluru, India

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Department of Biochemistry,
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NH – 66, Mangaluru, India***Article History:****Received:** 05/03/2017**Revised:** 12/05/2017**Accepted:** 16/05/2017**DOI:** <https://doi.org/10.7439/ijbr.v8i5.4120>**Abstract****Introduction:** Chronic kidney disease (CKD) is a disease complex which is highly associated with wide range of progressive complications. The imbalance between the pro-oxidant and antioxidant factors generates a state of oxidative stress which worsens the inflammatory conditions in the patients. The oxidative stress has been known to play a role in the complications associated with chronic kidney disease. One such complication is sensorineural hearing loss which contributes to morbidity in chronic kidney disease.**Materials and Methods:** A cross sectional comparative study comprising of 30 patients with chronic disease and 30 healthy controls were recruited for the study. Routine biochemical parameters like serum urea, creatinine, random blood sugar, hemoglobin were assessed. The oxidant status was assessed by measuring serum malondialdehyde (TBARS). Total antioxidant capacity was measured by ferric reducing ability of plasma (FRAP). Hearing loss was documented by pure tone audiometry.**Results:** Blood urea was elevated (99.50 ± 35.76) in cases significantly (p value < 0.001). Serum creatinine was also elevated significantly in the cases (8.44 ± 2.96). It was found that 22 cases were found to have moderate to severe hearing loss. Blood urea levels had a significant positive correlation with MDA ($p < 0.05$) in patients undergoing dialysis presenting with hearing loss.**Conclusion:** In the present study, it was observed that hearing loss was documented in patients with chronic kidney disease. The oxidant antioxidant status revealed that a significant number of cases had a decreased total antioxidant capacity and oxidative stress marker malondialdehyde was increased in cases though not significant. This could imply that oxidative stress may play a role in the pathogenesis of hearing loss in chronic kidney disease.**Keywords:** Oxidative stress markers, chronic kidney disease, hearing loss, total antioxidant capacity.**1. Introduction**

Chronic kidney disease (CKD) is a public health problem, with rising incidence and prevalence. The structural pathogenesis of CKD include tubular atrophy, interstitial fibrosis, glomerulosclerosis, renal vasculopathy and reduced renal regenerative capability. These characteristics may be caused by the gradual loss of renal

function through the development of mitochondrial dysfunction and increasing oxidative stress.[1]

Oxidative stress represents an imbalance between the production of reactive oxygen species (ROS) and the detoxification of their reactive intermediates. Hydroxyl radicals, superoxide anions, hydrogen peroxide, and singlet

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oxygen are the ROS generated by mitochondria and are regarded as the toxic metabolites of cellular metabolism [2]. Studies have warranted the role of oxidative stress in uraemia, hemodialysis and peritoneal dialysis is known to contribute to the oxidative stress and reduction in the levels of antioxidants [3]. During the pathogenesis of CKD, perturbations in oxidant levels in the kidney, promote renal cell apoptosis, decreased regenerative ability of cells and fibrosis[4]. Free radicals produced in the body have short half-lives, therefore in most cases oxidative stress is measured by specific end-products of the process. Malondialdehyde (MDA) is one such end-product generated by lipid peroxidation and has been used extensively to demonstrate increased oxidative stress during CKD. The production of free radicals is usually in balance with the availability of antioxidant enzymes and systems.

The incidence of sensorineural hearing loss among patients with chronic kidney disease is considerably higher than in the general population. The general consensus in audiometric findings among patients with CRF claims a high frequency hearing loss [5]. The presence of hearing loss and the associated type is the most common method to investigate the effects of hearing loss in renal disease [6]. The cochlea and kidney share similar physiological aspects with respect to the active transport of fluid and electrolytes and also antigenicity[7]. Various factors have been attributed for the hearing loss that include mainly haemodialysis treatment, ototoxic medications, electrolyte disturbances, alterations in peripheral and central nervous systems [8].

Over the last few years researchers have studied the possible mechanisms of sensorineural hearing loss that is caused due to loss of cochlear hair cells or neurons. The major factors mediating hearing loss are due to metabolic damage, apoptosis in inner ear sensory cells; also recent observations have stressed the fact that oxidative stress could further damage inner ear by producing endothelial dysfunction in the cochlear microcirculation.

The current study therefore aimed at evaluating the effects of oxidative stress markers on hearing loss in patients with chronic kidney disease.

2. Materials and methods

A cross sectional comparative study was carried out at a tertiary care hospital in Mangalore for duration of 6 months. The study group comprised of 30 cases diagnosed with chronic kidney disease undergoing hemodialysis; 30 healthy age and sex matched controls. The age groups of the subjects were

An oral informed consent was taken from the study subjects before the collection of sample. The ethical

clearance was obtained from the institutional Ethical Review Board.

5ml of random venous blood sample was collected. Collected blood was subjected to centrifugation. The clear serum obtained after centrifugation was used for the following biochemical investigations: 1) Serum urea measured by urease method. 2) Serum creatinine by kinetic Jaffes method. 3) Random blood glucose by glucose - oxidase peroxidase method. 4) Malondialdehyde by Thiobarbituric acid reactive substances (TBARS) estimated by the method described by Wilbur *et al* [9]. 5) Total antioxidant capacity by using FRAP (ferric reducing ability of plasma) assay [10]. 6) Pure tone audiometry was done for evaluation of hearing impairment.

2.1 Statistical analysis

Data was analysed using IBM SPSS ver. 20. Independent sample t test was done to compare the two groups. Data is represented as Mean± standard deviation. Pearson's correlation analysis was done for oxidative stress markers in patients with hearing loss undergoing renal dialysis. P < 0.05 was statistically significant.

3. Results

Following the inclusion criteria a total of 30 controls and 30 cases were enrolled for the study. The table 1 shows the baseline characteristics as well as the parameters analysed for the study. The mean age of cases was found to be 44.10±9.45 which was comparable with the control group (41.37±8.84). The gender ratio was found to be 1.1:1 in both the groups. Amongst the cases there were 18 patients who were found to be having hypertension and 15 patients were found to be having diabetes. The mean hemoglobin was less compared to the control group owing to the hemodialysis status and also decreased erythropoietin synthesis in the cases. Blood urea was elevated (99.50±35.76) in cases significantly (p value <0.001). Serum creatinine was also elevated significantly in the cases (8.44±2.96).

Table 1: Baseline characteristics of the two groups

Parameter	Controls (n=30)	Cases (n=30)	p value
Age	41.37±8.84	44.10±9.45	0.252
Gender Males n (%)	17 (56.7)	16 (53.3)	0.795
Hypertension – n (%)	0	18 (60)	
Diabetes – n (%)	0	15 (50)	
Hemoglobin (g/dL)	12.94±0.93	10.50±2.15	<.001*
Random Blood Glucose (mg/dL)	93.37±11.39	125.73±53.81	<.001*
Blood Urea (mg/dL)	23.10±6.21	99.50±35.76	<.001*
Serum Creatinine (mg/dL)	0.93±0.21	8.44±2.96	<.001*
TAC	0.35±0.19	0.19±0.08	<.001*
MDA (µmol/L)	1.4±0.70	2.18±2.11	0.061

Data represented as Mean±SD; TAC=total antioxidant capacity; MDA=malondialdehyde; *p<0.001 was statistically significant

Table 2: Audiometry findings of patients with chronic kidney disease & Controls

Audiometry	Controls	Cases
Normal	30 (100%)	8 (26.7%)
Hearing loss	0	22 (73.3%)

$\chi^2 = 34.73$; p -value $<.001$

Table 2 shows the audiometry findings for the cases and controls. It was found that 22 cases were found to have moderate to severe hearing loss.

Table 3: Correlation of oxidative stress markers with various parameters in patients with hearing loss on dialysis

Parameter	TAC		MDA	
	r value	p value	r value	p value
Blood Urea (mg/dL)	-0.226	0.312	0.550	$<0.05^*$
Serum Creatinine (mg/dL)	-0.178	0.428	0.224	0.316

p -value < 0.05 is considered statistically significant

Table 3 shows the correlation of oxidative stress markers with renal function tests in those patients undergoing dialysis presenting with hearing loss. It was found that Blood urea and serum potassium levels had a significant positive correlation with MDA.

4. Discussion

The current study aimed at investigating the oxidative stress markers on hearing loss in patients with chronic kidney disease. Chronic kidney disease induces a slow and progressive decline of kidney failure. It occurs gradually over weeks, months, years leading on to end stage renal disease.

High blood pressure is one of the leading causes of kidney disease. G-protein coupled receptors and Calcium dependant kinases are responsible for control of blood pressure. Mutations cause changes in receptors causing hypertension [11]. In this study, 60% of the cases were hypertensive.

CKD is associated with insulin resistance and in later stages decrease in insulin degradation. Glucose homeostasis is altered to a great extent in patients with diabetic kidney disease. Decrease in glucose filtration and excretion and inflammation induced insulin resistance are predisposing factors to hyperglycemia [12]. In this study 50% of cases were diabetics.

Anaemia is the complication of CKD, as erythropoietin which is required for the process of erythropoiesis is reduced during the disease process. In this study, there was significant decrease in haemoglobin in the cases (10.50±2.15).

Measurement of urea and creatinine have been used to assess have been used to assess the functioning of kidney. An abnormal concentration of these indicates the pathological processes of renal failure [13]. In this study we found a significant rise of serum urea and creatinine owing the chronic pathological process of the disease.

The uremic toxins may be the source of oxidative stress in chronic kidney patients. There was significant decrease in the total antioxidant levels in the cases. This was in accordance with the study by D. R. Suresh *et al*[14]. CKD being a pro-oxidant state with degree of intracellular and extracellular oxidant damage is related to severity of renal failure [15]. FRAP assay is a novel method to assess the total antioxidant capacity and a useful indicator to regulate damage caused due to reactive oxygen species. Malondialdehyde, a 3- carbon aldehyde produced by free radical attack on the biological membranes. In this study there was a rise in MDA levels though not statistically significant in the cases owing to the smaller study group.

The audiometry findings in the patients with CKD showed that a significant number (73.3%) were affected with hearing loss. Various studies have documented the occurrence of hearing loss in chronic kidney disease. Johnson and Mathog noted high frequency hearing loss in hemodialysis patients [16]. Charachon *et al* reported 75% in the patient group with hearing loss [17]. The various theories on hearing loss in CKD documents the main site of lesion in the cochlea based on the findings on audiometry. Intense metabolic activity is known to increase the production of free radicals and products of lipid peroxidation. Antioxidants partially protect the sensory cells in the organ of Corti from stress induced degeneration [18].

In this study it was observed there was a significant correlation between serum urea and MDA levels in patients presenting with hearing loss. This reflects the increased ROS formation and its relationship between uremic toxins and hearing loss. A negative correlation between serum creatinine and total antioxidant capacity but it was not statistically significant.

Prolonged oxidative stress induces delay and continued cochlear injury. In response to apoptosis, ROS generation leads to inflammation and production of pro-inflammatory cytokines IL-6 and tumor necrosis factor [19].

5. Conclusion

Hearing loss was demonstrated in the patients with Chronic kidney disease by pure tone audiometry. The role of oxidative stress is well documented as a pathogenetic feature in hearing loss. Antioxidant levels as measured by Total antioxidant capacity was found to be significantly lowered in cases indicating a possible imbalance in patient's antioxidant status contributing to oxidative stress. Oxidant

marker MDA were higher in cases but was not statistically significant owing to the reduced sample size.

So, this calls for a larger study group to demonstrate the relationship between oxidative stress markers in hearing loss in chronic kidney disease in order to understand the pathogenesis and further management.

Conflict of Interest: None

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