ORIGINAL ARTICLE

Early Detection of Dwindling Cochlear Sensitivity in Patients with Chronic Kidney Disease

Debayan Dey[1], Shilpa C[2], Sandeep S[3], Manjunath S Shetty[4]

Abstract

Introduction: Chronic kidney disease (CKD) is a recognized global public health issue. The burden of CKD is even greater in developing countries like India as compared to developed countries. CKD affects multiple organ systems, including the auditory system. The cochlea and kidney also share certain anatomical resemblance at an electron microscopic level and similar antigens.

Materials and methods: A cross-sectional observational study with sixty CKD patients and 20 age-matched controls to establish a relationship between stage 3, stage 4, and stage 5 of CKD and degree of hearing loss. These patients underwent a complete clinical evaluation, including blood investigation and audiometry, and categorized into stages 3, 4, and 5 of CKD based on estimated glomerular filtration rate values and compared to the control group.

Results: The most common etiology identified was hypertensive CKD affecting 42 cases. Tinnitus was the most common symptom. The pure-tone audiometry (PTA) findings of both ears showed increased hearing thresholds in CKD patients as opposed to the control group. As the disease progressed from stage 3 to stage 5, the hearing loss also increased across all frequency. A significant correlation between duration of disease and mean PTA of patients was noted in our study. As the disease progressed from stage 3 to stage 5, distortion-product otoacoustic emissions (DPOAE) sound noise ratio values in both ears decreased, indicating cochlear hypofunctionality across all frequencies.

Conclusion: We suggest a routine DPOAE evaluation at least once in 6 months for patients who are newly diagnosed or are receiving treatment for CKD to pick up outer hair cell abnormality early.

Keywords: Chronic kidney disease, Distortion product otoacoustic emissions, Hearing loss, Pure-tone audiometry, Sensorineural hearing loss.

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Introduction

Chronic kidney disease (CKD) is a recognized global public health issue. Although developed countries have a reasonably well-defined CKD burden, increasing researches speculate that the burden of CKD is even greater in developing countries.[1] Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD as kidney damage or glomerular filtration rate (GFR) <60 mL/minute/1.73 m^2 for 3 months or more, irrespective of the cause.[2] CKD causes irreversible damage to kidneys and/or reduction in kidney function. This leads to a further decline in the function of kidney.[3] Multiple organs are affected by CKD; complications result from side effects of the drugs used to treat the disease itself. Aggregation of uremic toxins and extended duration of hemodialysis (HD) causes damage to the auditory system with other organ systems.[4] Estimation of hearing loss and its type is the most prevalent method implemented in the investigation of the outcome of the auditory system in kidney dysfunction.[5]

The etiopathogenesis of sensorineural hearing loss (SNHL) in CKD patients described in the literature includes osmotic changes causing the loss of outer hair cells, endolymphatic space collapse, and atrophy with edema of the specialized auditory cells. The cochlea and kidney also share certain anatomical resemblance at an electron microscopic level and similar antigens.[6] Various metabolic disorders have been associated with hearing loss due to direct or indirect effect on the cochlea. Cochlea has complex and terminal blood supply, and subtle changes in vascular supply affect stria vascularis and outer hair cells. Hyperuricemia has been recently implicated in cardiovascular diseases by causing vascular calcification and hypertension and hence leads to indirect cochlear injury.[7]

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Although studies are available that established the prevalence of SNHL in CKD by using pure-tone audiometry (PTA), more research is required to observe the reverberation of CKD on distortion product otoacoustic emissions (DPOAE). Taking into account the outcome of decreased hearing in CKD patients and the diverseness in presentation, type, mechanism, and prognostic outcome, we conducted this study to evaluate hearing loss in patients with CKD and identify the possible factors responsible for hearing loss. This study also aims to find an association between the extent of hearing loss with duration and grading of CKD and substantiate that patients on HD should be screened for early detection of hearing loss.

Materials and Methods

Cross-sectional observational study conducted over 1.5-year period included sixty CKD patients obtained by consecutive sampling and

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20 age-matched controls. Our inclusion criteria included: (1) age range 15–60 years, (2) hearing impairment after the occurrence of renal failure, (3) bilateral type A tympanogram, (4) no prior history of ear surgery, (5) no history of diabetes or noise exposure, and (6) no tympanic membrane perforation or tympanosclerosis.

Patients underwent a detailed evaluation in Nephrology unit and ear, nose and throat outpatient department (ENT OPD). They were subjected to PTA, IA (impedance audiometry), and DPOAE. Nephrological investigations included serum urea, serum creatinine, and serum electrolytes. The patients on presentation were categorized into three groups depending on their CKD stage. Modification of Diet in Renal Disease (MDRD) Study equation was used to calculate estimated glomerular filtration rate (eGFR). Patients with eGFR ranging between 59 and 30 mL/minute/1.73 m^2 belonged to stage 3, those ranging between 29 and 15 mL/minute/1.73 m^2 belonged to stage 4, and stage 5 included patients whose eGFR was less than 15 mL/minute/1.73 m^2. A hearing threshold of more than 20 dB (decibel) in PTA was defined as any hearing loss. In DPOAE, a sound–noise ratio (SNR) value of 6 or more was considered pass.

Results

Our study comprised sixty CKD patients as defined by KIDGO and 20 healthy age-matched controls. Of sixty CKD patients, there were 43 males and 17 females with age ranging from 18 to 59 years. The average duration of kidney disease in each stage of CKD was found to be 1.6, 3.05, and 4.05 years for stage 3, stage 4, and stage 5, respectively (*p*-value 0.001). Twenty out of sixty patients required regular HD. All twenty of these patients belonged to stage 5 with average duration of HD being 2.25 years.

The most common complaint among our study population was tinnitus reported in 23 cases followed by decreased hearing in 12 cases (Fig. 1). The most common etiology identified was hypertensive CKD affecting 42 cases followed by chronic glomerulonephritis (CGN) in 8 cases. Other etiology included polycystic kidney disease (4), obstructive nephropathy (2), and unknown causes (4).

The mean eGFR for stage 3 was found to be 42.2 mL/minute/1.73 m^2, while stage 4 and stage 5 had a mean eGFR of 20.6410 mL/minute/1.73 m^2 and 8.7575 mL/minute/1.73 m^2, respectively.

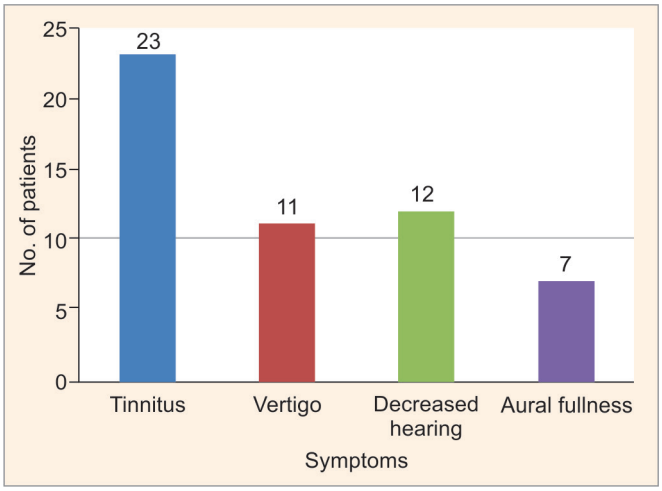


Fig. 1: Symptoms

The PTA findings of both right and left ears showed increased hearing thresholds in CKD patients as opposed to the control group. As the disease progressed from stage 3 to stage 5, the hearing loss also increased across all frequencies. This difference was found to be significant (p <0.005). Hearing loss significantly increased with increasing frequency as shown in Figures 2A to D.

Out of 60 right ears evaluated, SNHL was found in 22 ears. Similarly out of 60 left ears, 22 ears had SNHL. At higher frequencies (6 and 8 KHz), more number of patients was found to have SNHL. Both right and left ears showed a positive correlation between hearing loss and severity staging of the CKD, i.e., as the disease progressed, the hearing got worse. A significant correlation between duration of disease and mean PTA of patients was noted in our study (p <0.005).

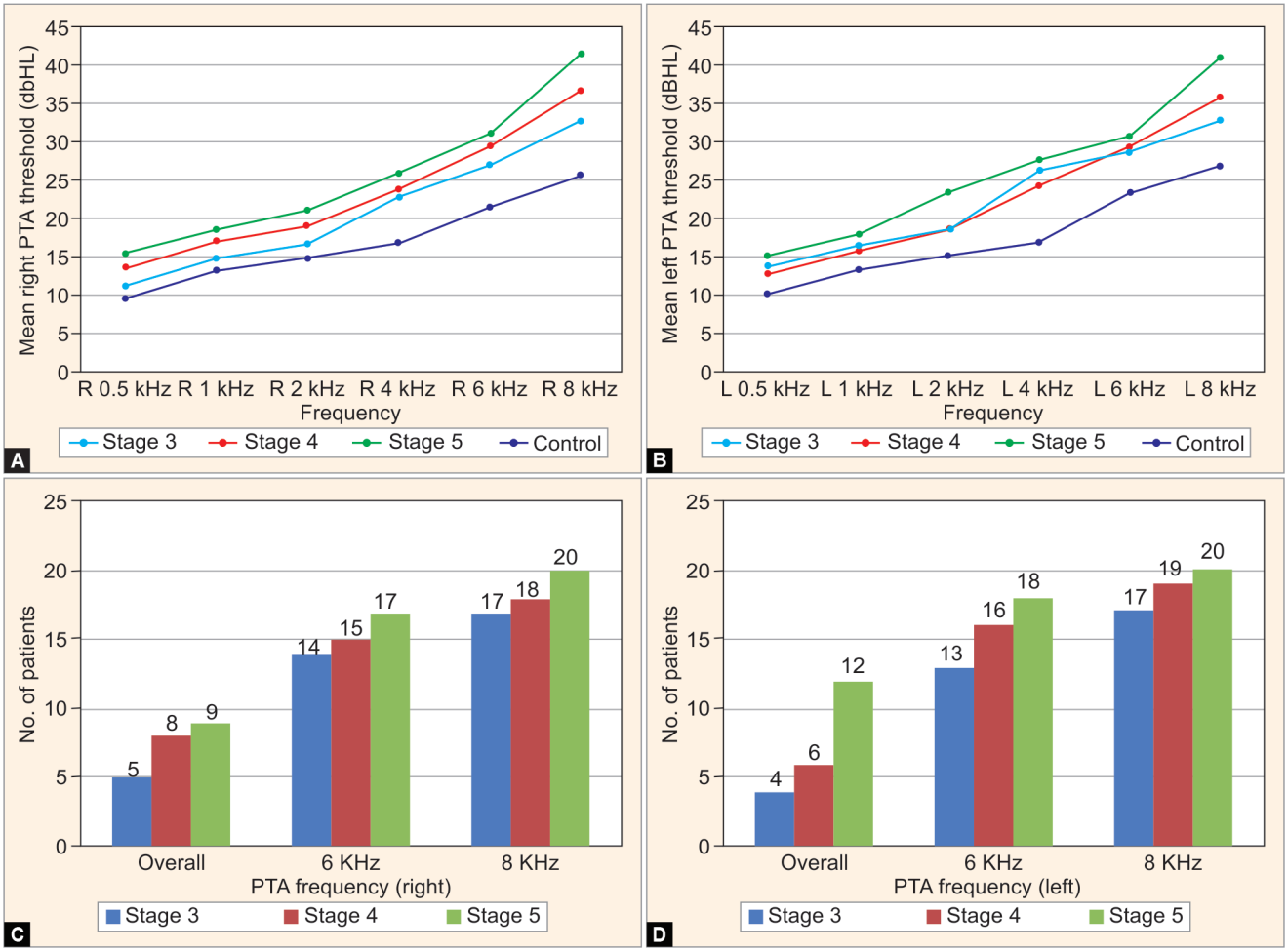
The DPOAE findings of the right and left ears showed decreased SNR values in CKD patients as opposed to the control group. As the disease progressed from stage 3 to stage 5, the SNR values also decreased, indicating cochlear hypofunctionality across all frequencies. This difference was found to be significant (p <0.001). The SNR values were significantly low in higher frequency as depicted in Figures 3A to D. Thirty-one out of 60 right ears and 28 out of 60 left ears were reported as "Refer" in DPOAE. The number of referred cases increased with an increase in staging of CKD. Both right and left ears showed a positive correlation between cochlear hypofunctionality and severity staging of the CKD.

Discussion

The burden of CKD is escalating worldwide. India, being a developing country, is faced with multiple challenges.[8] According to the first report of Indian CKD registry, the most common cause of CKD is attributed to diabetic nephropathy (31%) and rightly so as India is considered to be the diabetic capital of the world. It results due to the interactions between metabolic and hemodynamic pathways, which are often disturbed in the setting of diabetes. CGN contributes to 13.8% CKD cases followed by hypertensive glomerulosclerosis accounting for 12.9% of CKD cases. Other causes like autosomal dominant polycystic kidney disease and obstructive uropathy constitute about 2.6 and 3.4% cases of CKD, respectively.[9]

In our study, we observed hearing thresholds of patients in each of the CKD stages across different frequencies and compared it to our control group. We found a general trend that there is a significant hearing loss in each of the CKD staging. With an increase in disease duration, the eGFR decreases leading to an upstaging of CKD. The severity of hearing loss increases as the disease progresses. The higher frequencies are first to be affected with a significantly poor hearing thresholds. The hearing in this high frequency also worsens with the disease progression. Seventeen patients out of sixty CKD patients had bilateral SNHL and ten CKD patients had unilateral SNHL. Out of 120 (36.6%) ears subjected to PTA, 44 had SNHL. Ninety-three ears (77.5%) and 111 ears (92.5%) were found to have SNHL at 6 and 8 kHz frequencies. OAE are a measure of the cochlear sensitivity, and they reflect the outer hair cell function of the cochlea. The SNR value is indicative of the functionality of these hair cells. We found out of 120 ears tested 54 ears came as "Refer," accounting for 45% of the cases. The higher frequencies are worse affected in terms of SNR values.

All CKD patients were found to have a significantly lower SNR values when compared to controls. We also found outer hair cell dysfunction in some CKD patients in spite of having normal hearing thresholds. This could imply that the changes in inner ear due to



Figs 2A to D: Pure-tone audiometry

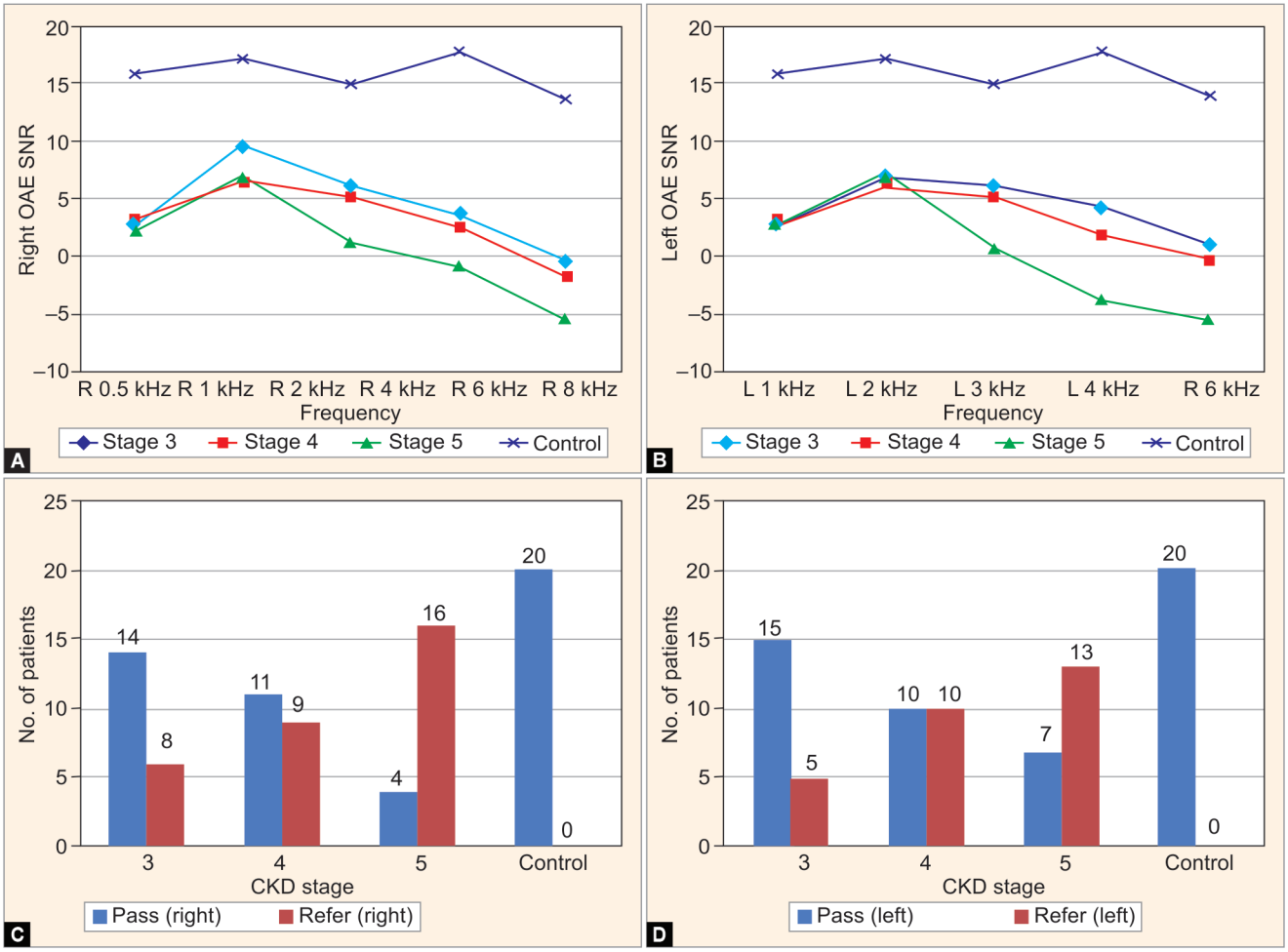
CKD are first reflected in DPOAE as outer hair cells (OHC) dysfunction even before patients' hearing is affected. This could also explain why patients with CKD most commonly complain of tinnitus. This not only indicates the dysfunctionality of the outer hair cells but also suggest a link between the progression of the disease and cochlear damage due to an electrolyte imbalance. The finding of the study by Renda et al. on the pediatric population with CKD report is similar to the finding of our study. We found the SNR values to peak around 2–3 Hz following which a sharp decline in these values were noted as the frequency increased.

Alport first reported an association of hearing loss in patients with CKD in year 1927.[10] Ransome et al., in the year 1969 suggested the role of ototoxic compound used in the treatment of CKD to be the cause for SNHL among these patients.[11] Yassin et al. in 1970 suggested that hyponatremia in CKD patients is the cause for hearing loss.[12] Bergstorm et al. in 1973 pointed out that drugs causing ototoxicity often cause nephrotoxicity, and ototoxicity is more prevalent in patients with decreased renal function.[13]

Multiple etiological factors have been suggested that lead to hypoacusis in CKD patients. Ototoxic drug usage, electrolyte dysbalance, elevated blood pressure, and even HD itself are a few causes. Brookes et al. suggested a role of vitamin-D deficiency in SNHL among patients with CKD. A considerable reduction in the levels of Na+-K+ ATPase in the cochlea of guinea pigs that were uremic was identified by Alder et al. They then suggested that Na+-K+ ATPase levels in cochlea and serum creatinine have an inverse correlation. They also thought that Na+-K+ ATPase enzyme inhibition could be a contributing factor in cochlear dysfunction and hearing loss among uremic patients.[5]

Cochlear striae vascularis and kidney share the similar functions of water homeostasis and acid-base balance, systemically by renal function and locally in the inner ear; therefore, they share similar antigens making them susceptible to immunological factors and ototoxic drugs. Those patients with carrier and channel proteins gene mutations frequently complain of hearing dysfunction and present with altered systemic hydro-electrolytic and acid-base balances. Similar gene regulations are seen during embryogenesis of the ear and kidney, and mutation in these genes plays a crucial role in differentiation, formation, and functioning of the ear and kidney.[14–16] These resemblances between kidney and inner ear justify the toxic nature of drugs of certain classes in these two organs. Furosemide acting on ascending limb of loop of Henle is an oto-toxic loop diuretic frequently used in CKD patients, inhibits apical Na-K Cl2 transporter. Strial epithelium shows the presence of an isoform of this ion transporter and is important for endolymphatic secretion.

Use of diuretic is beneficial and efficacious in the treatment of CKD patients. They act by reducing extracellular fluid (ECF)



Figs 3A to D: DPOAE

volume; lowering mean blood pressure, and potentiating the actions of other antihypertensive like angiotensin II receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, and other antihypertensive medications. They help in decreasing the risk of cardiovascular accident in CKD patients. Choice of diuretic is dependent on the GFR and CKD grade, to reduce ECF volume. The Na+-K+-2Cl- co-transporter is inhibited by the loop diuretics in the thick ascending limb of the loop of Henle.

According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines, loop diuretics are strongly recommended in all stages of CKD and are the most commonly used diuretic. Furosemide is the most commonly used diuretic, being cheap and with moderate potency but with ototoxic effects. We suggest the use of torsemide, which is more potent and less ototoxic instead of furosemide. We also suggest the limited use of aminoglycoside antibiotics in patients with CKD.[17]

Disabling hearing impairment, disregarding the age at which it develops, has catastrophic consequences. In general, it affects interpersonal communication, psychosocial well-being, quality of life, and economic independence. We conclude that outer hair cell damage is the first sign of an impending cochlear dysfunction. Thus, we suggest a routine OAE evaluation at least once in 6 months for patients who are newly diagnosed or are receiving treatment for CKD to pick up outer hair cell abnormality early. Once DPOAE abnormality is detected, we could then subject these patients for a follow-up PTA. This protocol helps us to decrease the cost of investigations for identifying high-risk groups who might develop hearing loss with progression of the disease and also mold a treatment protocol for CKD with a limited use of ototoxic drugs if not completely avoided in such patients. A strict regulation of serum electrolytes, especially serum potassium and serum urea and creatinine, might flatten the progression curve of SNHL with time.

Once hearing loss is detected in these patients, they could be prescribed hearing aid so as to remove any barriers in interpersonal communication and psychosocial well-being without diminishing the quality of life any further than already caused by CKD. As every human being aspires for a better quality of life, our proposed protocol might help these patients to lead an improved life without embarrassment, social isolation, psychiatric disturbance, depression, and difficulties in relationships with partners and children as commonly seen with hearing loss.

Conclusion

Hearing loss in CKD patients not only adds to the morbidity of the disease but also further reduces the quality of life. Early diagnosis of hearing loss and the at-risk population in CKD patients will help to improve the quality of life. We suggest screening of all CKD

patients with OAE at the time of presentation to estimate a baseline cochlear function. If the DPOAE is reported as "Refer," we suggest a PTA evaluation to estimate the degree of hearing loss and judicious use of ototoxic drugs in these patients to prevent a further decline in hearing. These patients should be followed up every 6 months with PTA to identify any further hearing loss. If the patient records a bilateral "Pass," we suggest a repeat DPOAE every 6 months. For patients with hearing loss, we recommend the use of a hearing aid.

Ethical Approval

This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants in the study.

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