Characterization of Hearing Loss in Adult Patients With Nondialysis Chronic Kidney Disease

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Objective: To confirm the association between chronic kidney disease and sensorineural hearing loss in non-dialysis non-diabetic patients and to establish the audiological profile of these patients indicating the possible location of the auditory damage.
Study Design: Cross-sectional study.
Setting: Tertiary referral center.
Patients: Patients between 18 and 60 years old with chronic kidney disease, without diabetes mellitus and without personal history of otology disease, were compared with a healthy control group pared by sex and age to establish differences between their audiological profile.
Interventions: Pure tone audiometry (PTA), transient evoked otoacoustic emissions (TEOAEs), distortion products otoacoustic emissions (DPOAEs), and auditory brainstem responses (ABR) were performed in both groups.
Main Outcome Measures: Mean and standard deviation of PTA auditory thresholds, TEOAEs reproducibility, DPOAEs level/noise, and ABR absolute latency and interwave latency were measured, and compared using linear mixed models.
Results: Fifty one cases were included and compared with 51 healthy volunteers. The audiometric profile found in patients with chronic kidney disease was a sensorineural hearing loss in 4 to 8 kHz frequencies in the PTA, a decrease in the TEOAEs reproducibility and a decrease in the DPOAEs level. An enlargement in the V wave absolute latency and III to V and I to V interwave latency in the ABR were also found but within normal range.
Conclusions: There is an association between chronic kidney disease in non-dialysis non diabetic adults patients and sensorineural hearing loss, affecting high frequencies and having the cochlea as the main site of auditory damage.
Key Words: Auditory brainstem responses—Chronic kidney disease—Otoacoustic emissions—Pure tone audiometry—Sensorineural hearing loss.
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BACKGROUND

Hearing loss has been associated with several diseases and organ-specific disorders such as diabetes mellitus (DM), systemic arterial hypertension (SAH), ischemic heart disease (IHD), chronic kidney disease (CKD), smoking, and dyslipidemia (1–5).

Chronic kidney disease (CKD) was first associated with hearing loss in 1927 when Alport (6) described hearing loss associated with familial kidney disease (7). However, it was not until the 1980s that several studies were performed to demonstrate the incidence and the potential mechanism of auditory dysfunction in patients with CKD (8). The incidence of hearing loss in patients with CKD ranges between 46 and 77% (8–10).

The kidney and the stria vascularis of the cochlea share physiologic, ultrastructural, and antigenic similarities (8,10–12). It has been suggested that common physiologic mechanisms involving fluid and electrolyte shifts in stria and kidney might explain the association between hearing loss and CKD (10,11).

Recently, another theory considered that the relationship between CKD and hearing loss is due to endothelial dysfunction produced by chronic subclinical inflammation caused by CKD along with an increase in oxidative stress, provoking damage to the stria vascularis of the inner ear with subsequent loss of the endocochlear potential (8,13–15). In addition, overexpression of the sympathetic system, caused by the neurohormonal mechanisms of renal failure and the similarity between renal and cochlear microcirculation strongly supports the idea

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of sensorineural hearing loss in CKD due to vasomotor alterations (8,13–15).

All the current evidence about the audiological profile of patients with CKD is derived from studies in the pediatric population (16–21), adult patients with advanced CKD on renal replacement therapy (8,9,12,22–28), or adult patients with CKD due to DM (associated in several studies as an independent risk factor for hearing loss (1–4)). Moreover, most of the studies measure the audiologic status of the patients using only one or two audiological tests.

The aim of this study was to confirm the association between chronic kidney disease and sensorineural hearing loss specifically in non-dialysis and non-diabetic adult patients, to establish the audiological profile of these patients with a complete audiological test battery, and to indicate the possible location of the auditory damage.

METHODS

Study-Population

We performed a cross-sectional study that included patients between 18 and 60 years old with CKD. The CKD stages included were from stage 2 to stage 4, ranging from 89 to 15 ml/min/1.73 m^2 of glomerular filtration rate (GFR). The patients were recruited during 1 year (2017–2018) from the Nephrology Department. The study was approved by the Ethics Committee.

The preferred measure of kidney function was the estimated glomerular filtration rate (eGFR). The eGFR was obtained using the four-variable Modification of Diet in Renal Disease (MDRD) Study Equation: GFR (ml/min/1.73 m^2) = 186 $\times$ (serum creatinine)$^{-1.154}$ $\times$ (age)$^{-0.203}$ $\times$ 0.742 (if women).

The patients included in our study were non-diabetic and have no personal history of otologic disease. Selection criteria are detailed in Table 1. This selection criterion eliminates probable confounding variables that might affect the audiological status, trying only to measure the effect of CKD.

The control group were patients with dysphonia from the Voice Unit of the Otolaryngology Department without history of otologic and renal disease or risk factors associated.

The case group and the control group audiological results were analyzed taking into consideration the mean of both ears (right and left). This mean was analyzed with the rest of variables but always having controls and cases as subjects not each ear as an independent observation.

The case group was compared with the control group paired by sex and age to establish differences between their audiological profiles, and to rule out sex and age as possible confounding variables. Moreover, to test the statistical significance of variable linked to disease in response variables, we estimated linear mixed models including as explanatory factors age and sex.

TABLE 1. *Detailed selection criteria for this cross-sectional study searching for a correlation between chronic kidney disease and hearing loss in non-dialysis adults patients*

Case Group Selection Criteria
Adults aged between 18 and 60 years old
History of chronic kidney disease stage 2 to 4
No diabetes mellitus
No otologic infection or disease
No family history of hearing loss
No ototoxic drug usage
No history of noise exposure
No smoking history
No history of otologic surgeries
No history of neurologic diseases associated with hearing loss: cerebrovascular accident, multiple sclerosis, Chiari malformations, etc.

Audiologic Performance Testing

Normal middle ear status was confirmed. It was assessed by otoscopy by an experienced otologist.

The audiological profile included four tests: pure tone audiometry (PTA), transient evoked otoacoustic emissions (TEOAEs), distortion products otoacoustic emissons (DPOAEs), and auditory brainstem responses (ABRs).

PTA was performed using a GSI 61 audiometer (Grason-Stadler Incorporation, Denmark) with Telephonics TDH-39 earphones. PTA thresholds were measured from 250 to 8000 Hz using the American Speech and Hearing Association guidelines.

TEOAEs and DPOAEs were obtained using the computer-based IL292 (software version 5, Otodynamics Ltd., Hatfield, UK).

TEOAEs were performed with clicks at 80 dB sound pressure level (SPL). The global reproducibility and response level of the TEOAES were measured at 1, 1.5, 2, 3, and 4 kHz frequencies.

For DPOAEs two simultaneous pure-tone signals were presented to the ear at two different frequencies (f1 and f2, where $f2 > f1$). The two stimuli were mixed acoustically and delivered to a probe, which was sealed with a foam tip into the external ear canal. The probe fitting check and the two-tone adjustments were performed before each measurement session. DPOAE data were collected using the DP-gram format. Recordings were obtained with a frequency ratio f2/f1 fixed at 1.22.

The ABR were recorded with four electrodes attached with adhesive and a conductive paste. The active electrode was placed on the top of the forehead, the ground electrode was placed below the active electrode in the low forehead and the two reference electrodes were placed on each mastoid process.

A double-channel recording was obtained with an Integrity V500 system (Vivosonic Inc., Toronto, Canada). The stimuli used consisted of clicks with a stimulus rate of 37.7/s at 80 dB hearing level (nHL). If waves I, III, and V could not be discerned, a higher intensity (maximum of 90 dB nHL) was used. The analysis time was set at 10 ms. Trials of at least 2,000 noise adjusted sweeps were performed to ensure reproducibility of the traces. The right and left ears were stimulated separately, and proper masking was applied to the ear not being tested.

Latencies of waves I, II, III, IV, and V and interpeak latencies I to III, III to V, and I to V were measured and recorded for statistical analysis.

A group of 51 (102 ears) healthy adult volunteers (except for dysphonia) audiologically normal and with no past medical history of kidney disease or hearing loss, selected on a case-matched basis for age and sex, served as the Control Group. PTA, TEOAEs, DPOAEs, and ABR were performed with the same audiological protocol and in the same conditions.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences IBM SPSS version 25.0 (Valladolid, Spain) and R Statistical Package v3.6 (R Foundation for Statistical Computing, Vienna, Austria). The following parameters were entered into statistical analysis: 1) cases PTA

TABLE 2. *Etiologies of chronic kidney disease found in the study*

	Number	Percentage
Chronic glomerulonephritis	19	37.25%
Obstructive nephropathy	15	29.41%
Hepatorenal polycystic disease	8	15.70%
Unknown origin	6	11.76%
Interstitial nephritis	3	5.88%
Total	51	100%

thresholds and each frequency level versus controls, 2) cases TEOAE global level and reproducibility and each frequency level and reproducibility versus controls, 3) cases DPOAE levels and noise at Distortion Product gram (DP-gram) versus controls, 4) cases ABR latencies and interpeak latencies versus controls.

Numerical variables were summarized with means and standard deviations. To test differences linked to disease in response variables, we estimated linear mixed models including as explanatory factors age and sex. In these models both ears were also included as a within-subject effect. And p-values <0.05 were considered as statistically significant

RESULTS

In our study, 51 patients (102 ears) with chronic kidney disease were evaluated. The mean of the two ears in each patient was used for comparison.

The patient's age range was from 18 to 60 years with a mean age of 44.51 ± 11.63 years. The 47.1% (24/51) were women while the 52.9% were men (27/51).

The principal etiology of CKD was chronic glomerulonephritis (37.25%) followed by obstructive nephropathy (29.41%). All the etiologies found in the study are described in Table 2.

The mean GFR was 55.07 ± 19.40 ml/min/1.73 m^2 having a CKD Grade 3 as the most prevalent renal failure stage.

If we defined hearing loss as having a mean auditory threshold more than 25 dB in the 500, 1000, 2000, and 4000 kHz frequencies, the 23.6% of the patients have at least mild hearing loss. However, when analyzing the pattern of hearing loss in high frequencies by measuring a high frequency threshold (HFT), including the 4000, 6000, and 8000 Hz frequencies, the incidence of hearing loss significantly increased from 23.6 to a 58.9%.

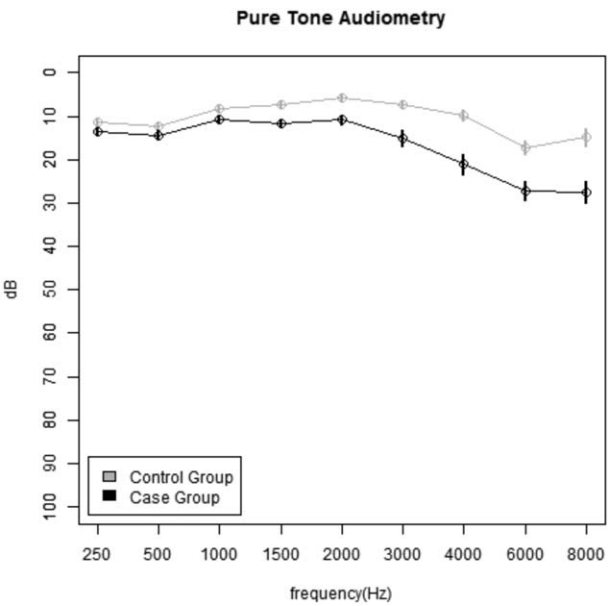

FIG. 1. Representative pure tone audiometry (PTA): comparison between chronic kidney disease patients (case group) and control group. Each PTA frequency mean value in decibels (dBs) is shown as well as error bars that represent the standard error of the mean, so the inter subject variability is revealed.

Moreover, the differences of mean PTA in high frequency thresholds between patients and controls were found to be statistically significant: 25.29 ± 15.62 dB versus 13.90 ± 10.16 dB ($p < 0.001$) and especially at 8 kHz frequency with a mean of 27.60 ± 17.80 dB versus 14.90 ± 13.89 dB ($p < 0.001$). The global PTA threshold and each PTA frequency mean value and standard deviation (SD) are detailed in Table 3 and Figure 1.

The TEOAEs global level and reproducibility was inferior in the CKD group compared with the control group: 5.67 ± 4.87 dB versus 9.29 ± 3.48 dB and

TABLE 3. *Pure-tone audiometry: comparison between chronic kidney disease (CKD) and control group*

	CKD Group (n = 102 ears)		Control Group (n = 102 ears)		
Frequency	Mean(dBs)	SD	Mean (dBs)	SD	p-Value
250 Hz	13.53	7.02	11.42	6.23	0.147
500 Hz	14.36	7.48	12.40	5.72	0.198
1000 Hz	10.83	6.98	8.14	5.19	0.042
1500 Hz	11.62	6.80	7.45	5.67	0.002
2000 Hz	10.83	8.10	5.78	5.01	<0.001
3000 Hz	15.05	12.92	7.25	6.81	<0.001
4000 Hz	21.13	16.59	9.85	8.95	<0.001
6000 Hz	27.16	15.99	17.20	11.04	<0.001
8000 Hz	27.60	17.80	14.90	13.89	<0.001
HFT[a]	25.29	15.62	13.90	10.16	<0.001

[a]HFT (high frequency Threshold): includes 4000, 6000, and 8000 Hz frequencies.
SD indicates standard deviation.

TABLE 4. *Transient evoked otoacoustic emissions (TEOAEs) levels (dB) and reproducibility (%): comparison between chronic kidney disease (CKD) and control group*

	CKD Group (n = 102 ears)		Control Group (n = 102 ears)		
	TEOAEs Levels (dB)		TEOAEs Levels (dB)		
Frequency	Mean	SD	Mean	SD	*p*-Value
1000 Hz	10.12	6.27	11.75	5.30	0.185
1500 Hz	11.74	6.42	14.93	5.16	0.010
2000 Hz	7.91	6.54	12.01	4.68	<0.001
3000 Hz	5.91	6.83	12.49	4.13	<0.001
4000 Hz	2.48	5.73	9.44	4.18	<0.001
Globallevel[a]	5.67	4.87	9.29	3.48	<0.001
	TEOAEs Reproducibility (%)		TEOAEs Reproducibility (%)		
1000 Hz	79.11	24.96	85.64	22.09	0.193
1500 Hz	85.06	20.04	93.09	9.82	0.018
2000 Hz	74.25	25.09	88.69	14.93	0.001
3000 Hz	60.64	33.45	91.50	9.07	<0.001
4000 Hz	37.47	34.89	84.86	13.37	<0.001
Globalrepro[b]	73.95	25.87	87.91	9.37	0.001

[a]Global TEOAEs Level (dB): includes 1000, 1500, 2000, 3000, and 4000 Hz frequencies.
[b]Global TEOAEs reproducibility (%): includes 1000, 1500, 2000, 3000, and 4000 Hz frequencies.

$73.95 \pm 25.87\%$ versus $87.91 \pm 9.37\%$ and this difference was more evident in high frequencies, especially at 4 kHz with 2.48 ± 5.73 dB versus 9.44 ± 4.18 dB and $37.47 \pm 34.89\%$ versus $84.86 \pm 13.37\%$. The global TEOAEs level and reproducibility and each frequency level and reproducibility mean value and SD, are detailed in Table 4.

In the Distortion Product gram (DP-gram), the emission levels were greater than the noise floor throughout the testing frequencies in both patients and healthy subjects. The DPOAE amplitude levels of the patients were significantly lower than the DPOAE amplitude levels of the control group in the frequencies greater than 2 kHz ($p < 0.001$). There was a remarkable decline in the DPOAE amplitudes in high frequencies, especially at 6 kHz. The global DP-gram comparing cases and controls with the mean level and noise value of each frequency (f2) is represented in Figure 2.

ABR revealed statistical significant results comparing patients and controls only in wave V absolute latency, and in the interpeak latency III to V and I to V. Differences in the absolute latency of V wave between groups were: cases 5.712 ± 0.255 ms versus controls 5.554 ± 0.135 ms ($p < 0.001$), in the interpeak latency III to V with less power: cases 1.921 ± 0.181 ms versus controls 1.829 ± 0.195 ms ($p = 0.014$), and in the interpeak latency I to V with a major difference: cases 4.150 ± 0.248 ms versus controls 4.002 ± 0.174 ms ($p = 0.001$). The global absolute latency of each wave (I, III, and V) and the interpeak latencies (I–III, III–V, and I–V) mean value and SD are shown in Table 5 and Figure 3.

Discussion and Conclusion

The prevalence of hearing loss measured with PTA in mid frequencies in our patients was 23.6%, which is below the international literature (24,25,29–31). This may be due to the exclusion of advanced chronic kidney disease in the study. However when considering a high frequency threshold (4–8 kHz) the prevalence increased from 23.6 to 58.9% reaching the prevalence rates previously reported (10,12,32).

Otoacoustic emissions are thought to be a byproduct of the cochlear amplifier and their presence indicate outer hair cells normal function (33,34). Furthermore, it is now

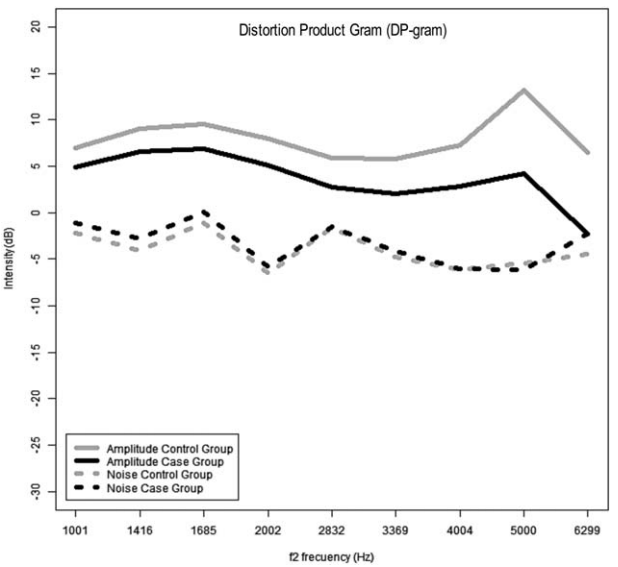

FIG. 2. Distortion product gram (DP-Gram): comparison between chronic kidney disease patients (case group) and control group. Each distortion product otoacoustic emissions (DPOAEs) mean amplitude and mean noise value in decibels (dBs) of each frequency (f2) is represented.

TABLE 5. *Auditory brainstem responses (ABR) wave latency (ms) and interpeak latency (ms): comparison between chronic kidney disease (CKD) and control group*

	CKD Group (n = 102 ears)		Control Group (n = 102 ears)		
	ABR (ms)		ABR (ms)		
	Mean	SD	Mean	SD	*p*-Value
Wave latency					
I	1.555	0.126	1.553	0.111	0.845
III	3.791	0.212	3.726	0.146	0.125
V	5.712	0.255	5.554	0.135	<0.001
Interpeak latency					
I–III	2.225	0.190	2.173	0.137	0.158
III–V	1.921	0.181	1.829	0.195	0.014
I–V	4.150	0.248	4.002	0.174	0.001

well established that OAEs are more sensitive to inner ear dysfunction than PTA or ABRs (19,26).

In our study, the level and reproducibility of the TEOAEs of the cases were significantly lower than the control group ($p < 0.001$), including certain patients with a PTA within normal range. This might be considered as an incipient auditory damage shown in the TEOAEs before it is clinically evident in the PTA.

In DPOAEs the amplitude of our patients with CKD was significantly lower than that of the control group in the frequencies greater than 2 kHz. Thus, our results indicate that in adult patients with CKD the ability of the cochlea to generate DPOAE appears to be lower to a similarly aged and gendered control group.

These findings are consistent with other reports in the literature. Renda et al. (21) in their study with patients between 6 and 18 years of age, divided into three groups: patients with CKD without treatment with hemodialysis, patients with hemodialysis, and a control group. DPOAEs levels and signal-to-noise ratios were measured. Significantly lower DPOAEs levels and signal to noise ratio in all frequencies in both the hemodialysis and non-hemodialysis groups were observed when compared with the control group.

The ABRs are a reliable instrument to demonstrate retrocochlear disease. Antonelli et al. (27) found in their study that patients with CKD in hemodialysis had an enlargement in the interpeak latency I to III after controlling the age as a possible confusing variable. Aspris et al. (28) indicated that wave V absolute latency and III to V and I to V interpeak latencies were significantly prolonged in patients with CKD in hemodialysis

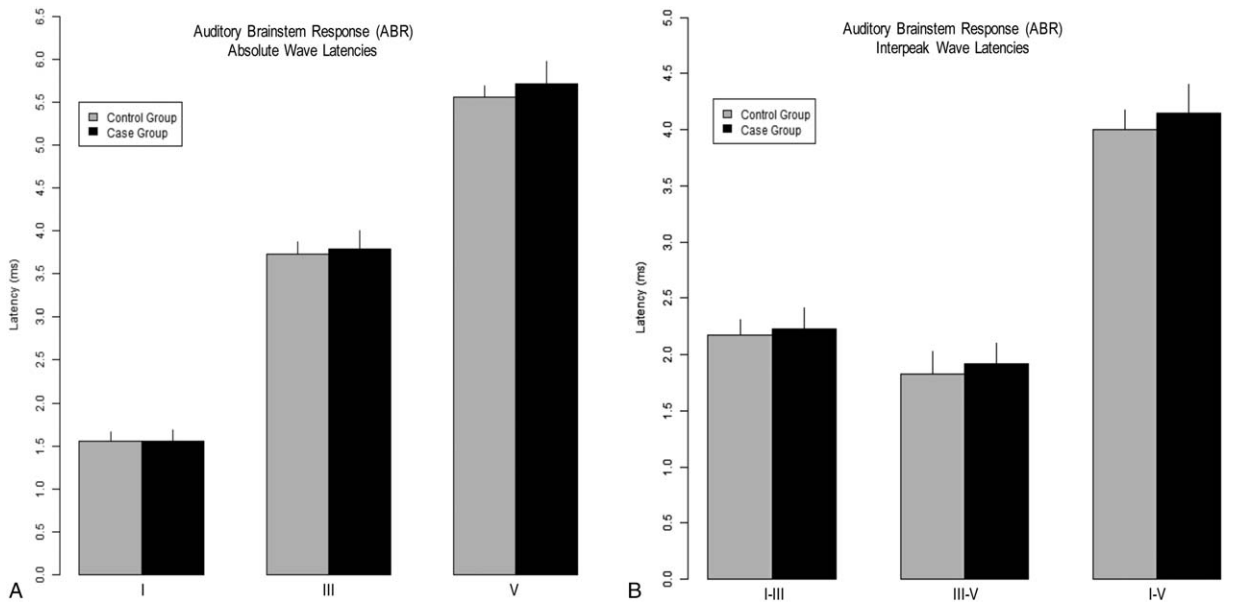

FIG. 3. Auditory brainstem responses (ABR). Comparison between chronic kidney disease patients (case group) and control group. *A*, The mean of each absolute latency wave: I, III, and V in milliseconds (ms) are shown with error bars that represent the standard error of the mean. *B*, The mean of each interpeak latencies: I to III, III to V, and I to V in milliseconds (ms) is revealed with their error bars that represent the standard error of the mean.

compared with a control group. They concluded that a possible damage in the ascending auditory pathway could be caused due to uremic neuropathy.

In our study, an enlargement in the V wave absolute latency and in the III to V and I to V interpeak latency in the ABRs was observed between groups. Although there were statistically significant differences, these findings were within normal range. A retrocochlear disease due to CKD could not be confirmed with this study and future researches are needed.

A high frequency sensorineural hearing loss in adult patients with CKD was demonstrated in this study. This association was confirmed after removing the possible effect of hereditary or congenital syndromes, ototoxic drug usage, noise exposure, and history of otologic disease.

DM was excluded as an important confusing variable. At the present time, DM is the most frequent cause of CKD and DM has been accepted as an independent risk factor for hearing loss (1–4). Moreover, we decide not to include patients with advanced CKD in hemodialysis because several studies, although it is controversial, have suggested that hemodialysis is a risk factor for the development of sensorineural hearing loss due to an osmotic disequilibrium (24,35–38). Therefore, we tried to measure only the effect of CKD with a complete audiological test battery which includes the cochlea and the auditory ascending pathway.

Limitations of our study are a small case-group sample size due to the strict selection criteria applied, and that it is a cross-sectional study with a level of evidence inferior to any prospective or randomized-controlled trial. Despite the fact, we had a case-matched control group and the variables sex and age were statistically controlled, it should have been taken into consideration a reference for comparison as the international standard ISO 1990 (39) for describing what is a normal hearing threshold for both sexes at various ages.

In conclusion, there is an association between non-dialysis, non-diabetic chronic kidney disease adult patients, and sensorineural hearing loss. The audiological profile of CKD patients shows a significantly lower response in high frequencies of the pure-tone audiometry and in the otoacoustic emissions level and reproducibility, having the cochlea as the main site of auditory damage. Further prospective and larger sample size studies are needed to confirm this association and audiological profile.

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