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Audio-vestibular Evaluation of Children with Chronic Kidney Disease

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Abstract: Background: Chronic kidney disease (CKD) and hemodialysis (HD) cause malfunction of multiple organs, including auditory and vestibular systems. Although the etiology is not definitely described, multiple factors have been proposed. **Objectives:** Assessing the audio-vestibular system of Egyptian children with CKD and on regular HD. **Methods:** A prospective cohort study conducted upon 100 children divided into: Group 1 (30 CKD patients), group 2 (20 patients with CKD on regular HD), group 3 (20 patients with CKD evaluated at initial HD and 6 months later) and group 4 (30 healthy children as controls). Standard and high-frequency pure tone audiometry (PTA), otoacoustic emissions (OAEs) and combined vestibular evoked myogenic potentials (com-VEMPs) done for all subjects. **Results:** Sensorineural hearing loss (SNHL) found in 29%, 36% and 11% of patients in groups 1, 2 and 3 respectively. High frequency PTA showed reduced detectability and higher thresholds at higher frequencies than controls with increased number of patients having SNHL after HD (group 2, 3) with statistically significant correlation between PTA and duration of HD. OAEs and com-VEMPs tests showed abnormal results in CKD and HD patients with higher sensitivity than PTA. **Conclusions:** Both auditory and vestibular pathways are affected in children with CKD and on regular HD. High frequency PTA, OAEs and com-VEMPs should be done routinely in children with CKD regardless the disease stage and on early HD.
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Keywords: Audio-vestibular system, chronic kidney disease, hemodialysis, Egyptian children

1. Introduction:

Chronic kidney disease (CKD) is a condition related to irreversible kidney damage that progress to end stage renal disease (ESRD) [1]. Kidney and cochlea are closely linked together with antigenic similarity between glomerular basement membrane and striavascularis of the inner ear, physiologic mechanisms involving fluid and electrolyte shifts in striavascularis of cochlea and glomeruli might explain the association between hearing loss and CKD [2-4]. The etiology of hearing loss in CKD patients are electrolyte disturbances, uremia, hypotension, hypoxia, altered pharmacodynamics of ototoxic drugs, atrophy of specialized auditory cells, neuropathy and in hemodialysis (HD) patients; wide blood pressure fluctuation during HD session, accumulation of dialysate contaminants [5]. The vestibule is a sensitive organ that reacts to metabolic disturbances through damage to its vascular endothelium [6]. Normal hearing level was defined as hearing intensities lower than 16 dB. 15 dB is the upper limit for normal hearing in children between (2-18 years) so hearing loss (HL) means hearing threshold >15dB [7]. Pure tone audiometry (PTA) is commonly used to assess the hearing function of children with only one limitation which is that; subclinical hearing loss cannot be identified using it. Otoacoustic emissions (OAEs) known to be sensitive to early cochlear dysfunction, thus sensitively identifying a subclinical hearing loss than PTA [8].

Aim of the work: Considering the impact of CKD on different body systems including the audio-vestibular system, this study was designed to evaluate it in children with CKD and on regular HD.

2. Materials and Methods:

This prospective cohort study carried out upon Egyptian children with CKD and on regular HD at Pediatric Nephrology and Dialysis Unit, Tanta University Hospitals between October 2016 and April 2019.

Subjects' selection: 100 subjects included in this study, 70 CKD patients (5-18 years) classified to three groups (Gs): **G1** 30 non-dialytic CKD patients with glomerular filtration rate (GFR 16-89ml/min/1.73m²), **G2** 20 ESRD patients on regular HD > 6 months and **G3** 20 ESRD patients evaluated at initial HD and 6 months later (GFR ≤15 ml/min/1.73 m^2). **G4** 30

healthy children as control group matched for age and sex. We excluded from the study, children with history of otological diseases, ear trauma, received ototoxic drugs, syndromes of hearing abnormalities and renal disease as ciliopathies or family history of hearing loss.

HD description (G2 and G3): Patients were dialyzed on a Fresenius 4008-B dialysis machine (Fresenius SE & Co. KGaA, Bad Homburg, Germany) at a blood flow rate of [2.5 × BW (kg)] + 100 ml/min, using polysulphane hollow fiber dialyzers suitable for the surface area of the patients (F4 0.7 m^2, F5 1.0 m^2, F6 1.2 m^2) with bicarbonate dialysis bags.

History and examination: Age, sex, CKD etiology, ototoxic drugs, otolgical diseases, HD vascular access and duration were taken. All children clinically examined (weight, height and blood Pressure). ***Routine Laboratory*** **data:** Blood urea, serum creatinine, complete blood count, serum total calcium, phosphorus, sodium, potassium, albumin, cholesterol and parathyroid hormone.

Audi-vestibular system evaluation: All subjects undergo both standard pure-tone audiometry and extended high-frequency testing:

1. Basic audiological evaluation included: Pure tone audiometry (PTA) at frequencies of 0.25-8KHz in addition to extended high frequency at 10, 12,16KHz and speech audiometry [speech reception threshold (SRT) and speech discrimination scores (SD%)] using GSI- 61 audiometer (Grason Stadler, USA). Pure tones were delivered using TDH-39 headphones for frequency range 250-8000Hz, while, circumaural headphone was used for the extended high frequencies testing. Immittancemetry (tympanometry and acoustic reflex thresholds) had done using (Interacoustic AT235 tympanometry).

2. Otoacoustic emissions (OAEs): were elicited using non-linear click stimuli at stimulus intensity 80dB of 80μs duration, at a rate of 19/s within a time window of 20 msec. TEOAEs were analyzed by recording 260 sweeps in one session and averaged within 5 frequency bands centered at (1, 1.5, 2, 3 and 4 kHz) using Smart-EPs of intelligent Hearing System (IHS, USA). Ear tip was securely positioned in the external auditory canal to each ear separately. Ear tip was securely positioned in the external auditory canal to each ear separately and patients were instructed to remain still and quiet during testing in a quiet room.

3. Combined vestibular evoked myogenic potentials (com-VEMPs) were conducted for simultaneous recording of both cervical (CVEMPs) and ocular VEMPs (OVEMPs). Nine electrodes were used for recording of com-VEMPs. For recording CVEMPs, two active electrodes were placed on the middle third of the contracted sternocleidomastoid muscle in the neck on each side. Two reference electrodes were placed on the middle third of both clavicles. For recoding of o-VEMPs two active electrodes were placed just inferior to each eye, about 1cm below the center of the lower eyelid. Two reference electrodes were placed about 1- 2cm below the corresponding active electrodes below each eye. One ground electrode was placed over the forehead. The subject was asked to rotate his head to the opposite side of recording with flexing the head approximately 30º forward to contract the SCM while looking upward at a distant target in the midline from the eyes. The eye position was measured as a vertical visual angle of approximately 30º- 35º above horizontal. Stimulation of right ear leads to recording of the right CVEMPs (ipsilateral) and left OVEMPs (contralateral) and vice versa as regards left ear stimulation.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Chi-square test for categorical variables, to compare between different groups Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5, Kruskal Wallis test For abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons, Wilcoxon signed ranks test For abnormally distributed quantitative variables, to compare between two periods. Mann Whitney test For abnormally distributed quantitative variables, to compare between two studied groups, F-test (ANOVA) For normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons Paired t-test For normally distributed quantitative variables, to compare between two periods Student t-test For normally distributed quantitative variables, to compare between two studied groups. McNemar and Marginal Homogeneity Test Used to analyze the significance between the different stages (P value < 0.05 is significant*).

3. Results:

Demographic data of the studied groups shown in table 1, according to CKD cause; glomerulonephritis was the most common cause of CKD (53.3%) followed by obstructive uropathy (23.3%) in group 1, while the hypoplastic and aplastic kidney diseases together with obstructive uropathy was the most common cause of CKD in HD groups (G2 and G3). 50% of patients in HD group (G2) was on dialysis for <20 months, 45% for (20-40) months and 5% for >40 months. A-V fistula was the

commonest HD vascular access (65%) used in our HD patients (G2 and G3).

Table 1: demographic data:

	G1 CKD patients (n= 30)	**G2 HD patients >6m (n= 20)**	**G3 HD patients ≤6m (n= 20)**	**G4 Controls (n= 30)**	**p**
Age (years) Median (IQR)	11.0 (7.0 – 14.0)	13.0 (9.0 – 15.0)	9.50 (7.0 – 15.0)	10.50 (10.0 – 12.0)	0.349
Sex (Male / female)	1.7/1	1.5/1	1.8/1	1.5/1	0.799
Weight (Kg) Mean ± SD	35.87 ±11.25	42.80 ± 12.04	36.30 ± 12.23	34.25 ± 6.54	0.040*
p_1	0.932	0.028*	0.905		
Sig. bet. Grps	P_2=0.106, P_3=0.999, P_4=0.209				
Height (cm) Mean ± SD	137.37 ±13.38	143.65 ± 9.31	138.10 ± 9.09	141.60 ± 7.48	0.121
Systolic BP (mmHg) Mean ± SD	104.0 ± 12.76	121.0 ± 13.34	119.0 ± 18.04	101.0 ± 7.12	0.001*
p_1	0.801	0.001*	0.001*		
Sig.bet. Grps	P_2=0.001*, P_3=0.001*, P_4=0.960				
Diastolic BP (mmHg) Mean ± SD	69.0 ± 9.23	79.50 ± 10.50	79.0 ± 12.52	64.0 ± 4.98	0.001*
p_1	0.001*	0.002*	0.998		
Sig. bet. Grps	P_2=0.165, P_3=0.001*, P_4=0.001*				
Etiology of CKD: 1. Glomerulonephritis 2. Obstructive uropathy 3. Hypoplastic kidney 4. Thrombotic microangiopathy (TMA) 5. Chronic pyelonephritis 6. Nephrocalcinosis 7. Polycystic kidney	16 (53.3%) 7 (23.3%) 5 (16.7%) 0 1 (3.3%) 0 1 (3.3%)	4 (20%) 5 (25%) 5 (25 %) 1 (5%) 2 (10%) 3 (15%) 0	2 (10%) 8 (40%) 8 (40%) 2 (10%) 0 0 0		0.005*
HD duration (months) Median (IQR) **<20 m** **20 – 40 m** **>40 m**		14 (6.0 – 30.0) 10 (50%) 9 (45%) 1 (5%)	6 m		
Vascular access in HD patients: **1.** A-V fistula **2.** Jugular venous catheter **3.** Permanent catheter **4.** Femoral venous catheter		20 (100%) 0 0 0	6 (30%) 6 (30%) 6 (30%) 2 (10%)		0.001*

Comparison between routine laboratory data of studied groups (Blood urea, serum creatinine, complete blood count, serum total calcium, phosphorus, sodium, potassium, albumin, cholesterol and parathyroid hormone) shown in table 2.

As regard PTA; CKD patients (G1) had normal peripheral hearing up to 10 KHz then SNHL was found at 12 KHz and 16KHz. ESRD patients on regular HD (G2) had normal peripheral hearing up to 8 KHz followed by SNHL at extended higher frequencies. ESRD patients at initial HD (G3) had normal peripheral hearing up to 8 KHz followed by SNHL at extended higher frequencies and controls (G4) had normal peripheral hearing at all frequencies as shown in table 3 and figure 1. Patients with ESRD evaluated before and after HD (G3) showed significantly improvement in some frequencies (low frequencies) after HD but worsening occurred at extended high frequencies from 10 KHz (figure 2). SNHL was in 29%, 36% and 11% of patients in groups 1, 2 and 3 respectively with increased SNHL% after HD (figure 3, 4).

Table 2: laboratory data:

	Group 1 CKD patients (n= 30)	**Group 2 HD patients >6m (n= 20)**	**Group 3 HD patients ≤6m (n= 20)**	**Group 4 Controls (n= 30)**	**p**
Urea (mg %) Median (IQR)	50 (36.0- 82.5)	150 (142.5 – 187.5)	185 (160 – 200)	23.5 (20.0 -25)	0.001*
P_1	0.001*	0.001*	0.001*		
Sig bet.Grps	P_2=0.001*, P_3=0.001*, P_4=0.359				
Creatinine (mg %) Median (IQR)	1.0 (0.7 -1.23)	5.0 (5.0 – 5.45)	6.0 (5.0 – 6.0)	0.7 (0.6 - 0.8)	0.001*
P_1	0.011*	0.001*	0.001*		
Sig. bet. Grps	P_2=0.001*, P_3=0.001*, P_4=0.229				
Hb (g %) Mean ± SD	11.13 ± 0.93	9.60 ± 1.23	8.50 ± 1.41	11.96 ± 0.76	0.001*
P_1	0.017*	0.001*	0.001*		
Sig. bet.Grps	P_2=0.001*, P_3=0.001*, P_4=0.008*				
Platelets (x10^{-3}) Mean ± SD	200.1 ± 28.30	197.2 ± 31.09	189.0 ± 33.23	244.0 ± 64.58	0.001*
P_1	0.001*	0.002*	0.001*		
Sig. bet. Grps	P_2=0.996, P_3=0.816, P_4=0.934				
TLC (x10^{-3}) Median (IQR)	11 (9.0 -12.0)	11 (9.08 – 12.0)	10.15 (9.0 – 13.0)	12.3 (12- 13.0)	0.001*
P_1	0.001*	0.001*	0.002*		
Sig. bet. Grps	P_2=0.965, P_3=0.790, P_4=0.839				
Calcium (mg %) Mean ± SD	9.57 ± 0.90	8.09 ± 0.69	7.72 ± 0.61	10.32 ± 0.18	0.001*
P_1	0.001*	0.001*	0.001*		
Sig. bet.Grps	P_2=0.001*, P_3=0.001*, P_4=0.278				
Phosphorus (mg%) Mean ± SD	5.59 ± 1.40	6.87 ± 1.89	6.86 ± 2.01	4.95 ± 0.53	0.001*
P_1	0.337	0.001*	0.001*		
Sig. bet. Grps	P_2=0.018*, P_3=0.019*, P_4=1.000				
Sodium (mEq/L) Mean ± SD	137.70 ± 3.82	133.90 ± 2.92	133.80 ± 3.37	138.90 ± 2.38	0.001*
P_1	0.462	0.001*	0.001*		
Sig. bet. Grps	P_2=0.001*, P_3=0.001*, P_4=1.000				
Potassium (mEq/L) Mean ± SD.	4.11 ± 0.72	4.76 ± 0.69	5.58 ± 0.47	4.17 ± 0.41	0.001*
P_1	0.954	0.001*	0.001*		
Sig. bet. Grps	P_2=0.001*, P_3=0.001*, P_4=0.001*				
PTH (pg/ml) Median (IQR)	60 (30 - 112.5)	525(400 - 600)	600 (550 - 700)	30 (25- 35)	0.001*
P_1	0.016*	0.001*	0.001*		
Sig. bet.Grps	P_2=0.001*, P_3=0.001*, P_4=0.419				
Albumin (g %) Mean ± SD.	3.23 ± 0.59	3.51 ± 0.51	3.40 ± 0.45	4.15 ± 0.33	0.001*
P_1	0.001*	0.001*	0.001*		
Sig. bet. Grps	P_2=0.210, P_3=0.626, P_4=0.900				
Cholesterol (mg %) Median (IQR)	150 (100-167.5)	110 (100 – 150)	120 (100 – 140)	95 (80 – 100)	0.001*
P_1	0.001*	0.001*	0.001*		
Sig. bet. Grps	P_2=0.365, P_3=0.647, P_4=0.683				

There was statistically significant difference between group (2 and 3) when compared with control as regard speech recognition threshold and discrimination score but no statistically significant

difference between group 1 and controls, there was higher speech recognition threshold in patients after hemodialysis median before HD 10 and increased after HD 15.0 (P=0.025*) with no significant in discrimination score (P=0.157). There is statistically significant difference between CKD groups and control as regard acoustic reflex threshold (immitancemetry) at 1000, 2000 and 4000 frequencies (figure 5) with no significant difference between before and after HD. Transient evoked otoacoustic emissions (TEOAEs) were absent in 9 cases in group 1 (15%), in 10 cases (25%) in group 2 and in 13 cases in group 3 (32.5%) and present in 100% of control group. There was statistically significant difference was found between the CKD groups and control as regards TEOAEs (P=0.001*) (figure 6) There was increased number of absent TEOAEs in patients after 6m of hemodialysis in group 3(before 32.5% after 57.5%) (P=0.008*) (figure 7).

Combined vestibular evoked myogenic potentials (Cervical and ocular VEMP) done showed that; CVEMP was absent in 45%, 62.5% and 50% of group 1,2 and 3 respectively while OVEMP was absent in 38.3%, 75% and 40 % of group 1,2 and 3 respectively with statistically significant difference between the CKD groups and controls (P=0.001*) (figure 8). There was increased number of absent CVEMPs (before 50% after 80%) (P=0.012*) and OVEMPs (before 40% after 90%) (P=0.001*) in patients after HD (figure 9).

Table 3: Pure tone audiometry (PTA)

Pure Tone Audiometry	**Group 1 CKD patients (n 30) (60 ears)**	**Group 2 HD patients >6m (n 20) (40 ears)**	**Group 3 HD patients ≤6m (n 20) (40 ears)**	**Group 4 Controls (n 30) (60 ears)**	**p**
PTA 250 Median (IQR)	15.0(10.0 – 20.0)	20.0(15.0 – 28.75)	20.0(15.0 – 25.0)	15.0(15.0 – 15.0)	0.001*
P_1	0.658	0.006*	0.001*		
Sig.bet.Grps	P_2=0.002*, P_3=0.001*, P_4=0.373				
PTA 500 Median (IQR)	15.0 (10.0 – 20.0)	20.0 (10.0 – 25.0)	15.0 (10.0 – 20.0)	15.0 (10.0 – 20.0)	0.178
PTA 1000 Median (IQR)	15.0 (10.0 – 15.0)	20.0 (10.0 – 25.0)	10.0 (10.0 – 18.75)	10.0 (10.0 – 15.0)	0.001*
P_1	0.004*	0.001*	0.016*		
Sig.bet.Grps	P_2=0.004*, P_3=0.838, P_4=0.004*				
PTA 2000 Median (IQR)	10.0 (10.0 – 15.0)	17.5 (11.25 – 25.0)	15.0 (10.0 – 20.0)	5.0 (5.0 – 10.0)	0.001*
P_1	0.001*	0.001*	0.001*		
Sig.bet.Grps	P_2=0.005*, P_3=0.466, P_4=0.061				
PTA 4000 Median (IQR)	10.0 (10.0 – 20.0)	20.0 (15.0 – 25.0)	15.0 (5.0 – 27.50)	5.0 (0.0 – 10.0)	0.001*
P_1	0.001*	0.001*	0.001*		
Sig.bet.Grps	P_2=0.017*, P_3=0.664, P_4=0.010*				
PTA 8000 Median (IQR)	15.0 (10.0 – 35.0)	25.0 (15.0 – 45.0)	20.0 (10.0 – 40.0)	10.0 (5.0 – 15.0)	0.001*
P_1	0.001*	0.001*	0.001*		
Sig.bet.Grps	P_2=0.033*, P_3=0.733, P_4=0.101				
PTA 10000 Median (IQR)	20.0 (10.0 – 40.0)	40.0 (20.0 – 50.0)	20.0 (16.25 – 37.5)	22.5 (15.0 – 30.0)	0.001*
P_1	0.469	0.001*	0.672		
Sig.bet.Grps	P_2=0.001*, P_3=0.284, P_4=0.005*				
PTA 12000 Median (IQR)	40.0 (11.25 – 50.0)	60.0 (41.25 – 70.0)	30.0 (21.25 – 50.0)	35.0 (20.0 – 45.0)	0.001*
P_1	0.066	0.001*	0.318		
Sig.bet.Grps	P_2=0.001*, P_3=0.519, P_4=0.001*				
PTA 16000 Median (IQR)	60.0 (11.25 – 70.0)	70.0 (51.25 – 80.0)	40.0 (26.25 – 58.75)	37.5 (30.0 – 45.0)	0.001*
P_1	0.001*	0.001*	0.034*		
Sig.bet.Grps	P_2=0.001*, P_3=0.379, P_4=0.001*				

Table 4: Comparison of speech audiometry between the different studied groups

Speech audiometry	Group 1 (n= 30) (60 ears)	Group 2 (n= 20) (40 ears)	Group 3 (n= 20) (40 ears)	Group 4 (n= 30) (60 ears)	p
Speech recognition threshold (Db) Median (IQR)	10 (10- 15)	20 (15 - 25)	10 (10 - 20)	10 (10 - 10)	0.001*
P_1	0.005*	0.001*	0.001*		
Sig.bet.Grps	P_2=0.001*, P_3=0.272, P_4=0.001*				
Discrimination score % Median (IQR)	100	96 (96-100)	100 (97- 100)	100	0.001*
P_1	0.055	0.001*	0.002*		
Sig.bet.Grps	P_2=0.001*, P_3=0.149, P_4=0.003*				

In HD patients (G2, 3), there was statistically significant positive correlation between PTA (SNHL %) and levels of urea (r=0.754, P=0.001*), creatinine (r=0.626, P=0.001*), cholesterol (r=0.349, P=0.027*), phosphorous (r=0.468, P=0.002*) and PTH (r=0.588, P=0.001*). In HD patients (G2, 3), there was statistically significant negative correlation between PTA (SNHL %) and HD duration (r= -0.542, P=0.001*), albumin (r= -0.694, P=0.001*), calcium (r= -0.457, P=0.003*), sodium (r= -0.423, P=0.041*).

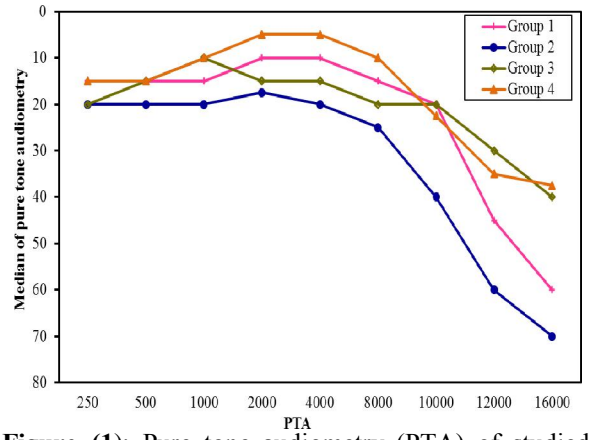

Figure (1): Pure tone audiometry (PTA) of studied groups

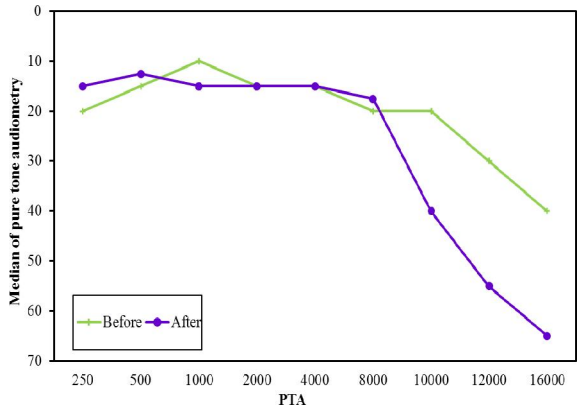

Figure (2): PTA before and after HD in G3

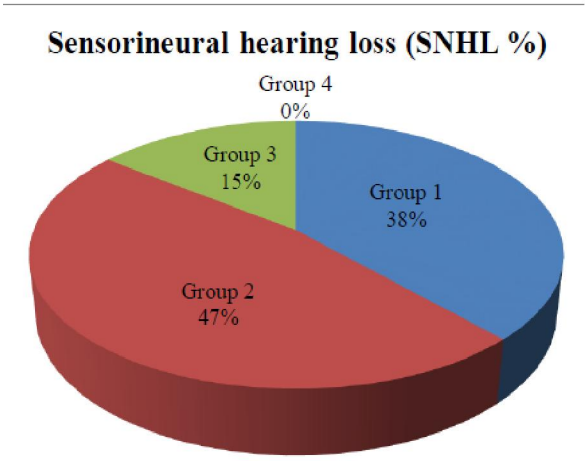

Figure (3): SNHL % of studied groups

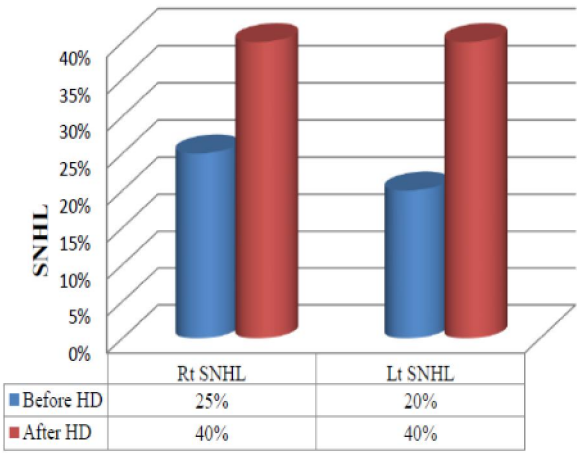

Figure (4): SNHL% after HD in G3

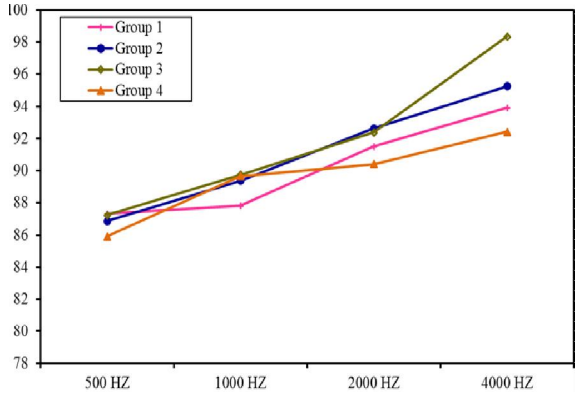

Figure (5): Acoustic reflex threshold (Immitancemetry) of studied groups

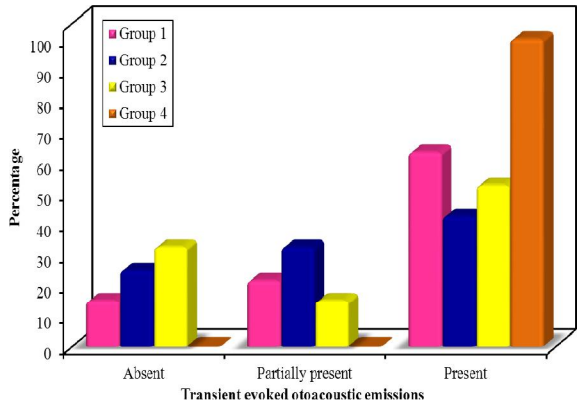

Figure (6): Transient evoked otoacoustic emissions (TEOAEs) of studied groups

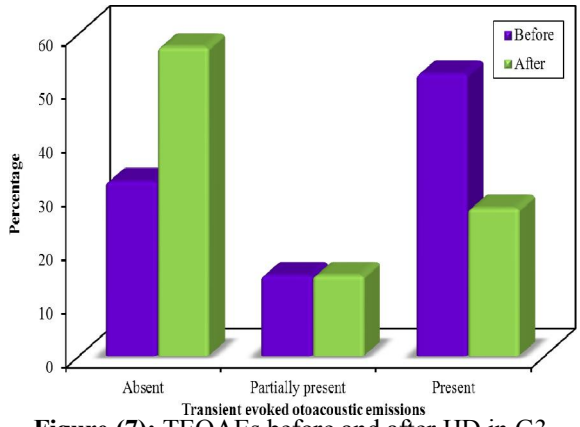

Figure (7): TEOAEs before and after HD in G3

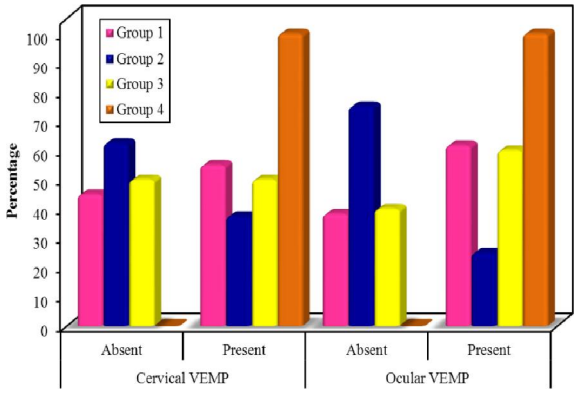

Figure (8): Combined vestibular evoked myogenic potentials (Cervical and ocular VEMP) of studied groups

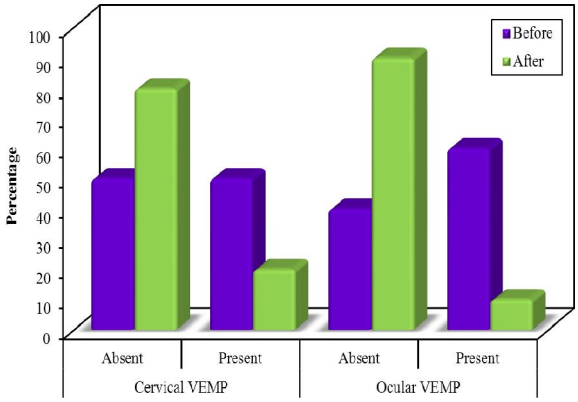

Figure (9): Before and after HD Cervical VEMP and Ocular VEMP in G3

4. Discussion:

The main causes of CKD in children are congenital abnormalities of kidney and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis (e.g. lupus nephritis, Alport syndrome) and renal ciliopathies [9]. Whereas structural causes predominate in the younger patients, the incidence of glomerulonephritis (GN) increases in those older than 12 years, CAKUT and hereditary nephropathies are responsible for about two thirds of all cases of CKD in developed countries, while acquired causes predominate in developing countries [10]. In the present study; glomerulonephritis, obstructive uropathies and hypoplastic kidney diseases were the most common causes of CKD.

All subjects of this study had normal middle ear function confirmed with otoscopic examination and tympanometry. Pure tone audiometry showed that all subjects in group 4 had normal peripheral hearing while 29%, 36% and 11% of patients in group 1, 2 and 3 respectively had SNHL which indicate the relation between chronic kidney disease and SNHL, this explained by similarity between antigens of kidney

and cochlea, water and electrolytes disturbances or a component of the uremic neuropathy which improved after renal transplantation [11] and this is consistent with Jishana et al [12], Saeed et al [13] and El-Anwar et al [8] studies.

The present study showed increased SNHL % after 6 months of initial HD which attributed to the osmotic disequilibrium induced by HD leading to endolymphatic system collapse, edema and atrophy of the labyrinth. Fidan et al [14] Meena et al [11] showed that, SNHL occurred more frequently in CKD children who require dialysis than in normal controls as the HD duration increases, the chances of developing SNHL and degree increases [15].

In the present study, SNHL % was higher in HD patients with A-V fistula (26 cases) 61.5%, than patients using CVC (14cases) 35.7%, this may be explained by limitation of nephrotoxic antibiotics use in our HD unit to guard against CVC infection also the more osmotic disequilibrium which occurred with A-V fistula.

In this work, hearing thresholds were evaluated with standard PTA in addition to the high frequency audiometry. Results of standard PTA showed significant decrease of hearing threshold between HD groups (2 and 3) when compared to controls at 250 and 500Hz and with significant negative correlation to HD duration this is consistent with Sharma et al study [16] which showed that hearing threshold worsens at low frequency (250 Hz) as the duration of disease increases. Other frequencies (1000-8000Hz) showed significantly elevated hearing thresholds in all groups with CKD when compared to controls with significant difference between group 2 (patients on dialysis) and the other 2 groups. Additionally, high frequency audiometry showed more affection at frequencies higher than 8000Hz in patients with CKD especially in group 2 with no significance between group 1 and 2. Similar elevated hearing thresholds mainly at the high frequencies were reported by Gatland et al [17] and Peyvandi et al [18] which showed that, hearing loss was more obvious in higher frequencies. Its prevalence and severity increased with chronicity of renal failure and HD.

Administration of ototoxic drugs (aminoglycosides and furosemide), Aluminum from the use of antacids in the treatment of hyperphosphatemia or dialysate water contamination toxicity and amyloid materials accumulation in prolonged HD also have a role in hearing loss [19, 20]. On the other hand El-Anwar et al [8] showed that; the duration of HD treatment, biochemical and hematological parameters did not have a significant impact on hearing loss. Stavroulaki et al [21] showed no significant changes in PTA thresholds were encountered in renal patients before and after a HD session.

OAEs were absent in 15%, 25% and 32.5% of group 1, 2 and 3 respectively despite of their normal hearing sensitivity in both ears. These findings support the previous observation of OAEs sensitivity to subtle cochlear pathology before the observed elevated hearing thresholds. Similar results were reported by Samir et al [22] and Pandy et al [23] that showed low frequency impairment in OAEs that may be explained with that chronic renal failure is characterized by disturbed sodium and potassium blood levels. Consequently affection of their levels in the inner ear perilymph and endolymph is expected with subsequent poor coupling of energy from the foot plate of stapes to the hair cells [24]. HD had a significant effect on OAEs when compared patients before and after HD in group 3 and this is consistent with Samir et al [22] which showed that there is significantly higher degree of cochlear dysfunction among patients on HD as compared to those on conservative treatment, especially if frequent intense osmotic pressure changes occur [25]. These events were interpreted as alterations caused by osmotic disequilibrium (endolymphatic hydrops) associated with HD by migration of edema fluid into the intercellular and intracellular spaces of the stria vascularis, hair cells and supporting cells [19].

Combined VEMPs (CVEMP and OVEMP) were used to assess the otolith function in this study. Results showed absent cervical VEMPs in about 45%, 62.5% and 50% of ears in group 1, 2 and 3 respectively. This is consistent with Sazgar et al [26] which showed that there was a significant difference between the presence and absence of VEMP waves in ESRD patients when. These VEMPs findings suggested pathology in the vestibulospinal tract as CKD may be associated with a disturbance in the blood level of Na and K. In turn, this will affect their concentration in the perilymph and endolymph leading to subsequent poor coupling of energy from the saccular macula to the hair cells (OHCs) [27, 28]. Moreover, changes sympathetic control of blood pressure can occur in CKD and could affect the blood supply of the inner ear resulting in cochleovestibular dysfunction [26].

As regards the results of OVEMPs, they were absent in about 38%, 75% and 40% of the cases in study groups 1, 2 and 3 respectively. Results of the CVEMPs suggest impaired otolith function (saccule and utricle) and or their innervations (inferior or superior vestibular nerves) in either ipsilateral (CVEMPs) or contralateral (OVEMPs) side of stimulation. Similar VEMPs results were reported by Sazgar et al [26].

In our study it was found that hearing thresholds worsen with electrolyte disturbances as low sodium level and this agreed with Meena et al [11] who found that Patients with SNHL over 70 db had significantly low sodium and higher potassium and chloride values. This signifies the role of electrolyte disarray in causing SNHL. This may be explained with a significant reduction of Na+, K+ activated ATPase in the inner ear of uremic guinea-pigs. They also reported an inverse correlation between serum creatinine levels and Na+, K+ activated ATPase. As the Na+, K+ activated ATPase in the cochlea is important for maintaining cationic gradients; they suggested that inhibition of this enzyme system may be a contributing factor in inner ear dysfunction among uremic patients [27-29].

In the present study it was found that hearing thresholds worsen with high levels of urea and creatinine and this is consistent with Seo et al [5] who showed that serum creatinine could be important independent contributing factos of disturbed cochlear function. But not agreed with Meena et al [11], who found that the levels are similarly raised in cases of CRF with or without SNHL. Therefore, it cannot predict the occurrence of SNHL and all patients of CRF with SNHL having raised blood urea level but number of patients does not increases with the increasing level of blood urea.

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Conclusions:

Both auditory and vestibular pathways are affected in children with CKD and on regular HD. High frequency PTA, OAEs and com-VEMPs should be done routinely in children with CKD regardless the disease stage and on early HD.

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