Article

Correlation between blood urea nitrogen level and cochlear outer hair cell function in non-dialysis chronic kidney disease patients

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Abstract

Background: Hearing loss due to impaired cochlear function, which results from increased blood urea nitrogen (BUN) level, is one of the important clinical problems in chronic kidney disease (CKD) patients with uremia. This study aims to determine correlation between blood urea nitrogen (BUN) levels and cochlear outer hair cell (OHC) dysfunction in non-dialysis stage 3-5 CKD patients so that the BUN levels may also be used to determine the presence of cochlear OHC dysfunction.

Design and methods: An observational analytic study with a cross sectional design and consecutive sampling. This study was conducted from November 2019 to February 2020 at the Department of Internal Medicine, Soetomo Hospital, Surabaya, Indonesia, and Otorhinolaryngology-Head and Neck Surgery Department, Soetomo Hospital, Surabaya, Indonesia. Non-dialysis CKD patients who met the inclusion and exclusion criteria were subjected to a Distortion Product Otoacoustic Emissions (DPOAE) test to assess cochlear OHC function at the Otorhinolaryngology-Head and Neck Surgery, Soetomo Hospital, Surabaya.

Results: Female patients were in larger number than male patients in a ratio of 1 : 2. Most of the patients were between 51-60 years of age. DPOAE distribution was refer in 25 patients (83.3%) and pass in 5 patients (16.7%). The highest pass was at 2000 Hz in 24 patients (80.0%), while the refer results were mostly at 12,000 Hz in 29 patients (96.7%). The highest average signal to noise ratio (SNR) was at 2000 Hz and 4000 Hz (12.77 dB and 11.13 dB), while the lowest at 11,000 Hz and 12,000 Hz (1.60 dB and 1.03 dB). Pearson's correlation test on DPOAE results did not show a significant correlation ($p>0.05$) between BUN levels and impaired cochlear OHC function.

Conclusions: There was no correlation between increased blood urea nitrogen levels and cochlear outer hair cell function disorders in non-dialysis patients with CKD stage 3-5.

Introduction

Hearing loss is the most commonly found disability in the world, with a prevalence of 5% of the world's population, which equals to 466 million people.[1] Chronic kidney disease (CKD) contributes to the high prevalence of hearing loss, reaching 45% to 80%.[2-4] Chronic kidney disease may cause malfunctioning of several organs, including the auditory organs and the vestibular system.[2]

The high prevalence of hearing loss in CKD patients is an aspect that needs to be considered in the management of CKD patients, so it is necessary to carry out monitoring with hearing tests.[5] Chronic kidney disease is strongly suspected as a cause of sensorineural hearing loss. However, a study on this subject revealed controversial results.[6] Several studies of CKD patients had successfully demonstrated the presence of hearing impairment, mainly due to impaired cochlear function, but many other studies had found no evidence.[2,6]

A study by Seo *et al*. found a significant correlation between hearing loss and risk factors for blood urea nitrogen (BUN), glomerular filtration rate, urine albumin, urine creatinine, systolic and diastolic blood pressure with $p<0.05$.[7] A study Krishnan *et al*.,in 89 patients with CKD found a significant correlation between sensorineural hearing loss with CKD stage and age, but not significant with BUN values, serum creatinine, hemoglobin, sodium, potassium and serum calcium.[8]

In chronic kidney disease the body fails to excrete the waste protein metabolism, resulting in high concentrations of urea, creatinine and uric acid.[9] Urea increases serum osmolarity, resulting in a different osmotic gradient between endolymph and perilymph fluid. The osmotic effect of urea causes a decrease in the amount of endolymph fluid, which can affect hearing.[10] In uremic conditions, there is inhibition of the action of the cochlear sodium potassium adenosine triphosphatase (Na+/K+ATPase) pump, which results in a decrease in endococcal potential.[11] Inhibition of Na+/K+ATPase will reduce endococcal potential and cause disruption of water osmosis regulation to cells so that the cells become edema until lysis.[12] Osmotic change causes outer hair cell (OHC) damage, endolymphatic space collapse, edema and cochlear support cell atrophy.[13]

The otoacustic emission examination (OAE) has a sensitivity of 95% and a specificity of 90% so it is sensitive for the detection of cochlear dysfunction. OAE examination is widely used to evaluate OHC function because it is objective, accurate, having specific frequency, automatic, easy procedure, non-invasive, fast and

Significance for public health

One of the most commonly found disabilities in the world is hearing loss, which has a prevalence of 5% of the world population or affecting 466 million people. One that contributes to the prevalence of hearing loss is Chronic Kidney Disease (CKD). Its contribution to hearing loss prevalence may reach 45% to 80%. This is because CKD itself may cause malfunctions of some organs, including auditory organs. Therefore, early detection of hearing loss among patients with CKD is necessary by determining correlation of a kidney disease marker, the blood urea nitrogen (BUN), and cochlear Outer Hair Cell (OHC) dysfunction. The otoacoustic emission examination (OAE) should be used to detect cochlear dysfunction as it has 95% sensitivity and 90% specificity. It was expected that by the finding of correlation between BUN levels and cochlear OHC dysfunction in CKD patients, possible hearing loss of these patients can be anticipated early.

practical.[14] Hearing loss in CKD patients is generally subclinical, with normal ANM results, but the distortion product otoacoustic emissions (DPOAE) results are abnormal.[15]

Therefore, it is necessary to conduct a study to prove the correlation between the function of the outer hair cell cochlea based on DPOAE examination and blood urea nitrogen levels in CKD patients at Soetomo Hospital, Surabaya, Indonesia.

Design and methods

This study has been conducted under the authorization of the Ethic Committee of Soetomo Hospital, Surabaya, with ethical clearance number 1661/KEPK/XI/2019.

This study was an analytic observational study with a cross-sectional design. The research sample was CKD stage 3-5 patients aged 18-60 years who came for treatment at the Internal Medicine Clinic, Soetomo, Surabaya, Indonesia, from November 2019 to February 2020, with a normal tympanogram. Patients who underwent regular hemodialysis, worked in noisy places or had been exposed to explosions, had experienced head trauma, had a family history of hearing loss, had a hereditary disease (Alport's syndrome), used long-term ototoxic drugs (e.g., aminoglycosides, cytostatics and quinolones), had a history of fever that caused hearing problems (Mumps, Rubella, and Meningitis), had a neurological disease that could cause hearing loss (multiple sclerosis), and heavy smoking were excluded.

The samples involved comprised 30 patients and subjected to DPOAE examination using GSI Corti brand made in Denmark at a frequency of 1500 Hz to 12000 Hz. The examination result criteria were pass and refer for each frequency based on the signal to noise ratio (SNR) value. The SNR value on DPOAE obtained from the difference in DP amplitude was compared with the noise floor (NF) at each frequency. SNR value ≥6 was regarded as pass and <6 as refer. Age, sex, and laboratory data were taken from medical record data with a maximum time span of 1 month from the DPOAE examination. Data analysis used Pearson's correlation test with 95% confidence intervals.

Results

Results showed that there were more female patients than males. Ratio between male and female patients was 1:2 (Table 1). The age distribution of the samples showed that most of the patients belonged to 51-60 years age group, consisting of 17 patients (56.7%), followed by 41-50 years age group of 9 patients (30.0%). The youngest age was 30 years old, while the oldest was 60 years. The mean age of the study sample was 49.23 (+8.09 years) (Table 1). DPOAE distribution showed refer in 25 patients (83.3%) and pass in 5 patients (16.7%) (Table 2). The distribution of DPOAE results for each frequency showed that the highest pass was at the frequency of 2000 Hz in as many as 24 patients (80.0%) and the smallest at the frequency of 12,000 Hz in only 1 patient (3.3%). The most refer results were at the frequency of 12,000 Hz in as many as 29 patients (96.7%). The results of DPOAE examination based on the value of the signal to noise ratio (SNR) for each frequency showed the highest average SNR was at the frequencies of 2000 Hz and 4000 Hz, i.e. 12.77 dB and 11.13 dB, while the lowest average SNR was at frequencies of 11,000 Hz and 12,000 Hz, i.e. 1.60 dB and 1.03 dB. Pearson's correlation test did not show a significant correlation between BUN levels and impaired cochlear OHC function based on the DPOAE results; p-values >0.05 were obtained at all frequencies (Table 3).

Discussion

Chronic kidney disease is a multi-organ dysfunction characterized by a slow but progressive decline in kidney function.[16] The correlation between kidney function and hearing loss has been extensively studied, but the results are controversial.[6] Various factors are thought to cause hearing loss in CKD, including the presence of the same antigen to the kidney and cochlea that causes autoimmunity, impaired transport of electrolytes through membranes, or the presence of uremic toxins.[17] Chronic kidney disease can cause malfunctioning of several organs, including the auditory organs and the vestibular system.[2] Chronic kidney disease causes sensorineural hearing loss due to damage to the level of sensory organs and neurons.[18] The results showed that there were more female patients than male patients with a ratio of 1: 2. The results of this study were in accordance with the prevalence data of CKD patients, ie. 67% female patients and 33% male patients.[19] A study by Hill et al., (2015) found that 38 out of 51 studies showed that the prevalence of CKD incidence in females was higher than that in males. The prevalence of CKD stage 3-5 was found in females was as much as 12.1% (10.6-13.8%) while in males 8.1% (6.3-10.2%).[20] This finding differed from the results of the study by Singh *et al*. who compared hearing function in stage 3 to 5 CKD patients. The study found that patients undergoing conservative therapy and hemodialysis 40% were female and 60% were male.[18] A study by Acharya and Nayak found a ratio of male patients to female patients of 4:1.[21] A study by Singh *et al*. found no correlation between the severity of hearing loss in CKD patients and sex.[18] Sex is not a major risk factor for chronic kidney disease because it is also influenced by race, genetic factors, and environment. Chronic kidney disease is a multifactorial disease. Some of the factors that make women more likely to develop chronic kidney disease are preeclampsia, urinary tract infections, lupus, and cervical cancer.[22]

This study showed an increase in the incidence of CKD with

Table 1. Sex and age distribution of the patients with CKD stage 3-5.

Age (years)	Sex		Total	
	Male	Female	N	%
≤30 years	0	1	1	3.3
31-40	1	2	3	10.0
41-50	5	4	9	30.0
51-60	4	13	17	56.7
Total	10 (33.3%)	20 (66.7%)	30	100
		Mean±SD (min-max)	49.23±8.09 (30-60)	

increasing age. Most CKD patients were in 51-60 years age group, consisting of 56.7% of the patients. The highest prevalence of CKD in Indonesia is in the age group 45 to 64 years. At the age of less than 25 years the prevalence was 2.57%.[23] Increasing age will affect the anatomy, physiology and cytology of the kidneys. After 30 years of age the kidneys will experience atrophy and the thickness of the renal cortex will decrease by about 20% every decade. Other changes that occur with age include thickening of the glomerular basement membrane, expansion of the glomerular mesangium and the occurrence of extracellular matrix protein deposits, causing glomerulosclerosis.[22]

The results of this study were similar to those of Vilayur's study, as cited by Yamamoto *et al.*, who found that the prevalence of CKD in those aged 50-59 years was 4.2% and increased to 52.2% at the age of 80-99 years.[24] In this study, the age was limited to 60 years to avoid prebiacusis bias, so we could not observe the prevalence at those over 60 years of age. Gabr *et al.*'s study found no statistically significant difference between groups of normal people, CKD patients with or without hemodialysis based on sex and age with p>0.01.[16]

Table 2. DPOAE examination results based on correlations of all frequencies.

DPOAE results	CKD Stages 3-5	
	n	%
Refer	25	83.3
Pass	5	16.7
Total	30	100

Chronic kidney disease has a high prevalence of hearing loss up to 80%, with the location of the main lesion, based on ABR examination, in the cochlea and some in the retrochoclea.[3,6,13] Based on OAE examination in CKD patients, cochlear dysfunction showed a varying prevalence from 40% to 95.65.[14-16,25] A study by Govender *et al.* in 50 CKD stage 1-5 patients showed impaired cochlear function at high frequency at stage 3-5 CKD. Subclinical hearing loss was present in 50% of the patients, in whom DPOAE results were abnormal, but ANM was normal. Distortion product otoacoustic emissions can detect initial cochlear damage, making it superior to audiometry as a screening tool.[15] The high prevalence of hearing loss is an aspect that needs to be considered in the management of CKD patients.[5] Hearing loss in CKD is associated with impaired cochlear function primarily due to damage to cochlear hair cells.[4] Several studies have found abnormal OAE results but with normal ANM. These findings support OAE sensitivity to detect abnormalities in the cochlea before the hearing threshold develops in CKD patients.

In this study we obtained the prevalence of cochlear OHC function disorders based on DPOAE results in non-dialysis stage 3-5 CKD patients. We obtained refer results in 25 patients (83.33%). A research by Pandey, as cited by Hong *et al*. obtained the results of DPOAE showing that refer status was found in 63.04% of 23 patients (46 ears) of CKD, and the transitory evoked otoacoustic emission (TEOAE) examination revealed refer status in 95.65% of the patients. A follow-up examination using ABR to evaluate the retrochoclea found no retrochoclear involvement. A total of 65.21% of patients had abnormalities in the cochlea.[25]

The causes of hearing loss in CKD are still being debated. One of the factors that are thought to play a role in the pathophysiology of hearing loss in patients with CKD is associated with uremia.[26]

Table 3. Correlation between cochlear outer hair cell function and the BUN value.

Frequency	SNR Mean±SD (min-max)	Cochlear OHC function status	n (%)	BUN level		r (p)
				Mean±SD	(Min-Max)	
1500 Hz	9.40±6.58 (0-21)	Pass	21 (70.0%)	68.86±30.86	(20-117)	-0.317
		Refer	9 (30.0%)	88.67±35.56	(38-144)	(0.088)
2000 Hz	12.77± 7.56 (1-30)	Pass	24 (80.0%)	69.46±33.15	(20-144)	-0.218
		Refer	6 (20.0%)	96.17±24.20	(77-137)	(0.246)
3000 Hz	9.77±7.22 (0-23)	Pass	17 (56.7%)	73.12±31.74	(20-117)	-0.058
		Refer	13 (43.3%)	77.00±35.83	(26-144)	(0.761)
4000 Hz	11.13±8.48 (0-25)	Pass	17 (56.7%)	76.00±33.15	(20-117)	0.051
		Refer	13 (43.3%)	73.23±34.15	(26-144)	(0.787)
5000 Hz	8.87±7.98 (0-26)	Pass	17 (56.7%)	77.24±35.23	(20-144)	0.095
		Refer	13 (43.3%)	71.62±31.00	(26-137)	(0.617)
6000 Hz	6.10±7.81 (0-24)	Pass	11 (36.7%)	67.64±38.50	(20-117)	-0.054
		Refer	19 (63.3%)	78.95±29.74	(38-144)	(0.775)
7000 Hz	5.53±8.70 (0-32)	Pass	10 (33.3%)	69.70±38.04	(20-117)	-0.085
		Refer	20 (66.7%)	77.35±30.96	(29-144)	(0.656)
8000 Hz	3.27±7.79 (0-33)	Pass	5 (16.7%)	77.00±38.39	(22-117)	-0.030
		Refer	25 (83.3%)	74.36±32.73	(20-144)	(0.874)
9000 Hz	3.07±6.94 (0-26)	Pass	5 (16.7%)	58.80±36.19	(22-110)	0.220
		Refer	25 (83.3%)	78.00±32.18	(20-144)	(0.242)
10000 Hz	3.13±7.41 (0-34)	Pass	6 (20.0%)	83.17±37.51	(22-117)	-0.129
		Refer	24 (80.0%)	72.71±32.35	(20-144)	(0.497)
11000 Hz	1.60±5.40 (0-27)	Pass	2 (6.7%)	87.50±31.82	(65-110)	-0.105
		Refer	28 (93.3%)	73.89±33.48	(20-144)	(0.583)
12000 Hz	1.03±4.26 (0-23)	Pass	1 (3.3%)	110.00±0.00	(110-110)	-0.201
		Refer	29 (96.7%)	73.59±32.92	(20-144)	(0.286)

In chronic kidney disease there is a decrease in kidney excretory function and causes a buildup of protein metabolism waste, resulting in high concentrations of non-protein nitrogen, especially urea, creatinine and uric acid. Toxic metabolic waste causes tissue damage and malfunctioning of several organs, including the cochlea.[15,27] The amount of urea in the blood is determined by the protein diet and the ability of the kidneys to excrete urea. In damaged kidneys, urea will accumulate in the blood. Serum urea levels reflect the balance between production and excretion. The BUN value may increase if protein is consumed in large quantities. However, excess urea will be excreted into the urine so that there is no significant increase in plasma urea.[27]

Adler's study, cited by Shomashekara *et al*. reported that in uremic conditions there was a reduction in Na+/K+ adenosin triphosphatase in the ear. Inhibition of action on this enzyme may be the cause of hearing loss, because Na+/K+-activated ATPase in the cochlea plays an important role in maintaining the balance of cationic gradient. Impaired balance of cationic gradient of endolymphatic fluid may have negative impact on hearing.[28] A study by Govender, as cited by Saeed *et al*., regarding cochlear function in CKD stage 1-5 patients found a significant difference between BUN level and decreased cochlear function in patients with CKD stage 3-5.[15] A study by Meena, as cited by Boateng *et al*. on 50 CKD patients compared to normal people, found an increase in BUN levels in CKD patients with sensorineural hearing loss, but there was no increase in the number of CKD patients related to the increase in BUN levels.[3] In a study by Somashekara *et al*. on 60 CKD patients, CKD group with hearing loss showed an increase in BUN and serum creatinine levels, but there was no significant correlation.[29]

This study did not find a significant correlation between impaired cochlear OHC function and increased BUN level. This study was in accordance with Kusakari's study, as cited by Fufore *et al*., which reported that inner ear disorders were not correlated with BUN and serum creatinine level or with urea nitrogen, creatinine, potassium, sodium, calcium, and serum glucose levels.[26] A research by Reddy *et al*. reported that hearing loss was not correlated with age, sex, BUN, serum creatinine, blood glucose levels, diastolic blood pressure, and hemoglobin ($p>0.05$), but it had correlation with disease duration ($p=0.001$).[13] In this study we found impaired cochlear OHC function in 83.3% of non-dialysis CKD stage 3-5 patients, but found no significant correlation with increased BUN. DPOAE examination at each frequency in non-dialysis CKD stage 3-5 patients showed refer category mostly at a frequency of 12,000 Hz as much as 96.7% and a frequency of 11,000 Hz as much as 93.3%. The pass category was moslty at a frequency of 2000 Hz, as much as 80.0%. The results of this study indicated that OHC function disorder was more frequent at high frequencies, starting from the frequency of 6000 Hz.

A study of Seo *et al*. used a large sample size of 5,226 patients, and they found differences in BUN levels ($p <0.001$) between CKD patients with hearing loss and without hearing loss. Multiple linear regression analysis of hearing threshold with several parameters of renal function showed that there was no significant correlation between BUN and hearing loss ($p=0.08$) in CKD patients. Patients who had eGFR of <60 had a worse hearing threshold than patients with eGFR of >60. With multiple logistic analysis the significant result was obtained (OR, 1.25; 95% CI, 1.12–1.64; $p<0.001$).[7] High urea condition affects the function of various organ systems and patients with CKD may experience various complications due to chronic renal dysfunction or the body's adaptation mechanisms to disturbed body homeostasis.[30]

Increased plasma urea indicates renal failure in filtration function. The condition of kidney failure is characterized by very high plasma urea levels above 50 mg/dl, which is known as uremia.[27] Urea increases serum osmolarity, resulting in differences in osmotic gradient between inner ear fluids. The presence of urea transporters-A (UT-A) and UT-B in pillar cells and Deiters cells plays an important role in the urea transport system between endolymph and perilymph. The osmotic effect of urea causes a decrease in the amount of endolymph fluid, which can affect hearing.[10] In addition to causing osmolarity disorders, cochlear fluid, urea toxins can also cause hearing loss through uremic neuropathy of the auditory nerve.[30]

Conclusions

No correlation was found between increased blood urea nitrogen levels and cochlear outer hair cell function disorders in non-dialysis patients with CKD stage 3-5.

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