Cochlear Impairment in Individuals with Chronic Renal Dysfunction - A Systematic Review

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CERTIFICATE

This is to certify that this dissertation entitled **‘Cochlear Impairment in Individuals with Chronic Renal Dysfunction - A Systematic Review’** is a bonafide work submitted in part fulfilment for degree of Master of Science (Audiology) of the student Registration Number: 20AUD013. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru
August, 2022

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CERTIFICATE

This is to certify that this dissertation entitled **'Cochlear Impairment in Individuals with Chronic Renal Dysfunction - A Systematic Review'** has been prepared under my supervision and guidance. It is also been certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled **'Cochlear Impairment in Individuals with Chronic Renal Dysfunction - A Systematic Review'** is the result of my own study under the guidance a faculty at All India Institute of Speech and Hearing, Mysuru, and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru,
August, 2022

Registration No. 20AUD013

Dedication

This dissertation is dedicated to my parents.

This work would not have been possible without their patience & understanding.

Thanks for your great support and love…

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Abstract

This systematic review aims to see the effect of chronic renal dysfunction on individuals hearing ability. This review compares the effect of haemodialysis (which is a procedure to restore the functioning of your kidney) and chronic kidney disease (It is a disorder where the kidneys capacity gradually declines) on hearing. The study used a detailed exploration of the major databases (e.g. Pubmed Central, Semantic Scholar, Science Direct, and Google Scholar) to archive the objectives of the systematic review. The retrieved articles were assessed in two stages: title and abstract screening, followed by a full-length article review. Twelve articles were selected after the full length article review out of 19 shortlisted articles.

Chronic renal function is a leading cause of morbidity and mortality, especially in the later stages of disease. Most of the studies taken for the systematic review, found that reduced hearing acuity is common in individuals with chronic renal insufficiency. It is observed that whether conservatively or haemodialyzed, hearing acuity was observed to be diminished in CRF patients. Hence, haemodialysis may not be hazardous to hearing impairment in CRF patients. While reduced hearing acuity is common in people with chronic renal insufficiency, haemodialysis may not be harmful to hearing. Therefore, it is needed that Regular screening for hearing loss should be included in the routine care of CKD patients in order to improve their quality of life.

Chapter 01

Introduction

The auditory system is one of the most essential sense organs that allows humans to be aware of sound and helps to connect to their surroundings. Both the peripheral and the central auditory systems, which together make up the auditory system, must function properly for effective and healthy hearing. There are various causes which can result in sensori-neural hearing loss (SNHL) such as noise exposure, aging, ear and brain infections, ototoxic drugs, trauma, neoplasms, systemic conditions like Meniere's disease, autoimmune illness, neurologic problem, vascular or hematologic disorders, bone abnormalities, endocrine disorders and idiopathic SNHL (Odeh et al., 2015). Typically, ageing or noise-induced hearing loss come to mind when considering the causes of hearing loss, but more recently published studies revealed that the greater incidence of hearing loss among CKD patients has long been documented and is being confirmed by investigations (Doshad & Kuchhal, 2014). In fact 54% of people with CKD experienced hearing loss, compared to just 28% of people without the condition. According to Renda et al. (2015) the major cause of the reported hearing loss in individual with CKD is assumed to be Kidney failure, not haemodialysis.

The progressive loss of kidney function is the hallmark of chronic kidney disease. Body will not be able to entirely rid itself of toxins when a person's kidneys stop functioning properly. As a result, these substances build up in one's blood stream and cause health issues. Dysfunctioning of auditory system is frequently observed in chronic kidney disease (CKD) patients. It is widely acknowledged that a variety of metabolic, electrolytic, and hormonal problems can cause harm to the inner hair cells of the cochlea. Since Grahe's (1924) publication, it has been clear that patients with nephritis frequently experience inner ear impairment. Additional research on hearing loss in people with kidney disease followed the initial discovery that there is a connection between renal failure and hearing loss in Alport syndrome patients (Renda et al., 2015).

Hearing loss in children can get worse over time, making it more difficult for them to engage with others and increasing their risk of social isolation, violence, low self-esteem, and depression (Renda et al., 2015). The body's organ systems, including the hearing and balance systems, almost all are affected by chronic renal failure (CRF) (Naderpour et al., 2011). Between the kidney and the cochlea, there are a number of similarities in terms of anatomy, physiology, immunology, pharmacology, and pathology (Reads, 2014). Even though exact cause of this dysfunction is unknown, several explanations have been presented. Disturbance of electrolytes, high serum urea level, hypotension, dysfunction of hair cells, atrophy of particular auditory cells, neuropathy, also in few patients, hemodialysis and Some of its problems, such high blood pressure variations and the buildup of pollutants in dialysate water, are thought to be its etiopathologies (Naderpour et al., 2011). When our kidneys are unable to perform their duty to maintain the health of our body, hemodialysis is a blood purification technique that restores renal function by eliminating fluid and waste from our blood. The auditory system will be harmed by the deposition of renal excretion and continuous hemodialysis. Several investigations conducted both in the United States and elsewhere have shown that a variety of major illnesses can affect our hearing. Compared to people without renal dysfunction, hearing loss is more prevalent in children and adults with chronic renal failure. According to published studies, hearing loss is unrelated to age or gender and gets worse as the length of renal failure increases (Peyvandi & Ahmady, 2013). Because of the development of peritoneal dialysis, chronic haemodialysis, and other conservative treatments, renal patients and people with CKD live longer and have a higher quality of life (Nikolopoulos et al., 1997). Nonetheless, this elongation of life has resulted in new issues, or at the very least, it has allowed us to detect, evaluate, and treat significant health problems in these individuals (Nikolopoulos et al., 1997).

In 1964, Beaney observed that 28% of his renal patients had issues with their ears, noses, and throats, while Nikolopoulos et al. (1997) reported that, 30.4% of the participants experienced sensorineural hearing loss. The majority of these people showed no symptoms of genetic diseases. Since then, several studies have looked into how the kidney and cochlea are connected, but the findings have prompted serious discussion over the etiology, severity, and type of loss.

Various studies have shown that individual under haemodialysis treatment frequently complain about some degree of hearing loss. A study done by jamaldeen et al. (2015) indicate that 41.7% patients experienced diminished hearing, in that majority of the patients had only mild degree of loss, so the author concluded that CKD is still a likely cause of hearing loss and Patients who have CKD are more likely to experience hearing loss. By this time there have been ample number of research focused on the link between CRF and dialysis with hearing loss in adult patients (Naderpour et al., 2011). Most CRF patients had sensorineural hearing loss, which is noted to be more prevalent in literature with moderate to severe degrees of involvement for higher frequencies (Reads, 2014).

Otoacoustic emissions (OAE) are a quick, reliable, and non-invasive technique to examine the integrity of the outer hair cell, which is an indication that the cochlea is functioning normally. With the help of these emissions, it is possible to monitor changes in the cochlea, such as those that occur in people who are taking ototoxic medications or undergoing hemodialysis. Samir et al. (1998) found that children with CKD had lower TEOAE response and lower reproducibility and 50% of patients showed partial or absent TEOAE responses. Renda et al. (2015) indicated that pure tone threshold at 8 kHz was affected more than the other frequencies in both ears. DPOAE amplitudes and signal to noise ratio were substantially lower in children with CKD even when thresholds were within normal levels, suggesting markedly reduced cochlear activity.

The auditory brainstem response (ABR) measures neuronal activity from inferior colliculus to the cochlea in the ascending auditory pathway. ABR is used in the clinical practice to assess auditory sensitivity as well as otoneurological anomalies in the auditory nerve and auditory brain stem. Aspris et al. (2008) found prolongation of absolute and interpeak latencies except at I-III interpeak latency in ABR examination of CRF patients. Naderpour et al. (2011) also demonstrated abnormalities of wave V latency, in ABR testing of individuals with persistent hemodialysis. As there have been a lot of research that have reported on it that individual with CRF, there is a real risk of auditory impairment, hearing tests should be performed on individuals with CRF regularly, ototoxic drugs should be avoided as much as possible, and hearing aids should be fitted for rehabilitation when called for (Reads, 2014).

There is a need to gather data on the prevalence of hearing loss and symptoms that go along with it in people with chronic renal dysfunction in order to raise awareness among professionals about the prevalence of hearing loss in people with CRF. Many patients report hearing loss after hemodialysis, and the majority of studies show that people with CKD are at a greater risk than the general population to develop auditory impairment. Early identification is therefore advantageous for persons with chronic renal failure since it can stop further hearing loss and improve their quality of life.

1.1 Need of the study

Hearing loss in CKD patients has been linked to haemodialysis and a substantial number of studies have documented it. Additionally, patients with CKD have a higher frequency of SNHL than the general population. According to a sizable population based study by Vilayur et al. (2010) moderate CKD is associated with a significant prevalence of hearing loss of 54%. Many individual complain about diminished hearing following haemodialysis. Therefore, along with their general health, the patient with chronic renal failure needs to have their hearing loss examined. Regular screening for hearing loss should be included in the routine care of CKD patients.

Several investigations into the effects of haemodialysis yielded inconsistent results, with a significant number stating that hemodialysis has no function in hearing loss linked with CKD. Thus, despite a plethora of studies on hearing loss in chronic kidney disease, unsolved issues about the function of haemodialysis persist. Hence, the current study intends to review available literature on the prevalence and degree of hearing loss in individual with CKD. The findings of this systematic review will also aid in creating awareness among audiologists about the link between renal disease and hearing loss.

1.2 Aim of the study

This study aimed to perform a systematic review of association of cochlear impairment with chronic renal dysfunction.

1.3 Objective of the study

1. To assess the prevalence of hearing loss and accompanying symptoms in people with chronic renal failure.
2. To study the effect of hemodialysis on hearing loss.
3. To investigate the link between chronic renal failure and hearing loss.

1.4 Research questions

This review's research questions are based on the PICO/PECO framework. i.e.

- Population - individual with chronic kidney disease
- Evaluation - auditory brainstem response, pure tone audiometry and otoacoustic emission.
- Comparison - with non-kidney disease individual.
- Outcome - diagnosis of hearing loss.

This review attempts to address the following questions:

- What is the prevalence of hearing loss and associated symptoms in individuals with chronic renal dysfunction?
- What consequence does haemodialysis have on hearing loss?
- What is the association between chronic renal failure and hearing loss?

Chapter 2

Methods

Scientific articles focusing on hearing loss in individuals with CKD were gathered from detailed exploration of the major databases to archive the objectives of the systematic review. The systemic review was carried out in conjunction with the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines (PRISMA statement) (PAGE et al., 2021). Before arriving at the articles that were evaluated for the systematic review, various database have been screened based on several criteria. The detailed procedure for the article selection processes is described below.

2.1 Eligibility criteria

Eligibility criteria are inclusion and exclusion criteria that determine which articles are included and omitted from the systematic review. The following are the criteria for this systematic review.

2.1.1 Inclusion criteria

- Articles should include human participants of any age and gender.
- Only manuscripts in English language were reviewed.
- Articles that are published in the peer reviewed journals were included.

2.1.2 Exclusion criteria

- Articles involving animal participation were excluded.
- Articles which are a single case study, case series, short communications, letter to the editor, and systematic reviews were excluded.

- Articles including information about pathologies other than chronic renal dysfunction were excluded.
- Articles with poor methodological quality were rejected.

2.2 Information sources

Articles from different peer-reviewed journals were searched in various databases like Pubmed Central, Semantic Scholar, Science Direct, and Google Scholar. The systematic review only includes information or articles taken from these four databases. Further, manual searches were conducted to find other relevant studies in reference and citation lists.

2.3 Search strategy

Many authors and researchers refer to chronic kidney disease as chronic renal dysfunction, therefore both words are included in the search process. Hence, different keywords, related search phrases, derivatives, and MeSH words related to the study were used with Boolean operators such as 'AND,' 'OR,' and 'NOT.' The keywords used during the search process were as follows:

Chronic kidney disease OR chronic renal dysfunction AND hearing loss OR cochlear impairment OR pure tone audiometry OR Auditory brainstem response OR Auditory evoked potential OR ABR. Filters in many databases have been set to eliminate or limit the incidence of irrelevant items.

2.4 Selection process

The articles included in the review were selected based on whether they matched the inclusion criteria outlined in the eligibility criterion. Each article is checked with the review keywords and inclusion and exclusion criteria in mind. The article that did not match the requirements for inclusion was removed from the study. The selection procedure was carried out separately by two authors, who were followed by a third author if a conflict of interest was discovered. For the data selection approach, the articles were title screened first, then abstract screened, and finally full text screened. Prior to title screening, duplicate detection was performed using the reference management system "Rayyan- intelligent systematic review" software. Following the detection of duplicates, the remaining articles were title screened, with relevant articles being shortlisted based on the title, followed by abstract screening. Again, articles were shortlisted based on the abstract, with articles meeting the inclusion criteria being selected for full text screening and articles that did not fulfil the inclusion criteria being eliminated from the systematic review process. Table 3.2 summarizes the articles that have been included in the review process which include methods, result, discussion and conclusion.

2.5 Data extraction

Two authors separately conducted the initial search across all of the abovementioned electronic databases, using Boolean operators and keywords, and the results from various databases were combined using a reference management system- "Rayyan- intelligent systematic review". The articles from the Pubmed and semantic scholar databases were selected and downloaded in the form of a bib file, whereas the data from Science Direct was downloaded in the form of the RIS file format created by research information systems. Another file type, the ENW file designed by Thomas Reuters for Endnote citation manager, was used to download articles from the Google Scholar database, and all of the articles downloaded in various forms were uploaded to the reference management system described above. After uploading the articles in the reference management system at a time, the selection process was carried out, beginning with duplication detection and then screening of the title, followed by abstract screening and full text screening, as stated in the selection process. A complete Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for research selection is shown in Figure 3.1.

2.6 Methodological quality appraisal

A methodological quality evaluation was performed on the studies cited in the systematic review. The National Institute of Health (NIH) Quality assessment tool for Observational Cohort and Cross-Sectional studies was used to assess the risk of bias in selected studies which assesses research design, population, sample bias, information collecting, variables, blinding, and dropout’s important criteria. The tool consists of various questions that can be responded as 'yes', indicating a low risk of bias, and 'no,' indicating a high risk of bias. However, if there are disagreements or if there is confusion due to insufficient information, it is replied as 'NR' (not reported). Based on the above mentioned criteria, an overall grade of 'good,' 'fair,' or 'poor' is assigned. Each study was evaluated independently. The quality assessment tool for observational cohort and cross-sectional studies is detailed in Table 3.3.

Chapter 03

Results

The present study is intended to conduct a systematic review of cochlear impairment in individuals with chronic kidney disease. The articles were selected based on the inclusion and exclusion criteria, as well as the research question formulated according to the PICO/PECO framework.

3.1 Search results

A total of 13,060 results were identified across four databases, with 1080 of them being deleted as a duplicate, remaining 11,980 articles were subjected to title screening. Based on title screening, 45 full-text articles were selected, whereas 11,935 were rejected as they failed to fulfil the criteria for inclusion for this systematic review. Out of these 45 articles, 26 were excluded during the abstract screening, and the remaining articles were accepted for full text screening. Based on the full-text, seven articles were removed as they were either written in a language other than English, were exempted from haemodylasis therapy, provided a treatment option other than haemodylasis, or included irrelevant study population (the study population had comorbidities such as diabetes, hypertension, and so on). Hence, 12 publications were selected in the data extraction and final review procedure. Figure 3.1 depicts a complete Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for article selection.

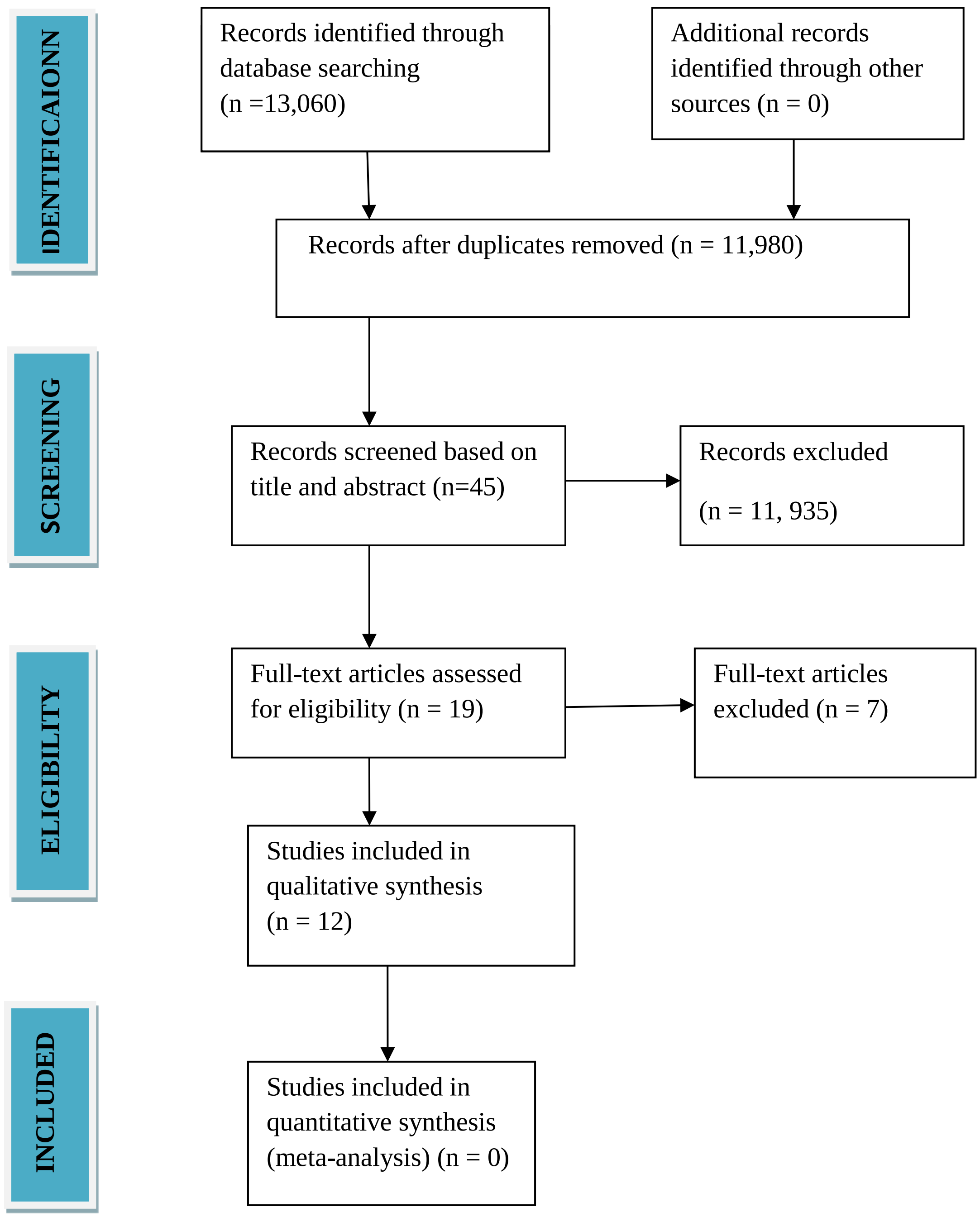

Figure 3.1 PRISMA flow chart for representation of the items screened, included and excluded in the systematic review.

The articles, which are excluded in the full text screening stage, are mentioned in the Table 3.1, with reason.

Table 3.1

Reasons for the exclusion of articles

Author and Year	Title	Reason for exclusion
Barbara et al., 1981	Hearing impairment associated with chronic renal failure	The study evaluated the hearing abilities of kidney transplant patients.
LaVonne Bergstrom and Patricia Thompson, 1983	Hearing loss in pediatric renal patients	The study evaluated the hearing abilities of patients undergoing renal transplantation.
Sharma et al., 2011	A study on hearing evaluation in patients of chronic renal failure	The effect of haemodialysis on hearing was not explained in this study.
Jamaldeen et al., 2015	Prevalence and patterns of hearing loss among chronic kidney disease patients undergoing haemodialysis	Participants who were taking ototoxic medication were included.
Bendo et al., 2015	Hearing evaluation in patients with chronic renal failure	The inclusion of participants with high blood pressure.
Reddy et al., 2016	Proportion of hearing loss in chronic renal failure	In this study effect of haemodialysis were not observed.
Mudhol and Jahnavi, 2019	Hearing Evaluation in Patients with Chronic Renal Failure	In this cross sectional study haemodialysis treatment were not included.

3.2 Study characteristics

Individuals with chronic renal disease served as the experimental group in all 12 studies; hearing thresholds were compared between pre and post hemodialysis sessions in five studies (Gatland et al.,1991; Nikolopouloset al., 1997; Jakic et al., 2010; Doshad & Kuchhal, 2014; Saeed et al., 2018); CKD patients (HD were not given) were compared with age and gender matched healthy individuals in five studies (Samir et al., 1998; Naderpour et al., 2011; Renda et al., 2015;Reads C., 2014; Sobh et al., 1999); and in two studies, both the control and pre and post HD groups were taken (Mahmmod, F. M., 2006; Aspris et al., 2008).

The goal of all included studies were to identify the incidence of hearing loss in individuals with chronic kidney disease, as well as rationale for hearing loss whether it is disease condition or haemodylasis therapy. Table 3.2 summarizes the articles that have been included in the review process which include methods, result, discussion and conclusion.

Table 3.2

An overview of the research articles selected for systematic review

SN.	Author and Year	Title	Method	Results	Discussion and conclusion
1	Gatland et al., 1991	Hearing loss in chronic renal failure-hearing threshold changes following haemodialysis	Sixty-six individuals from the renal unit were randomly recruited for the study. None of the individual had a history of loss or exposure to loud Noise before the onset of CRF. There were 44 male and 22 female among the 66 cases investigated. The age of the participants, which ranged from 25 to 65. Fifty-one patients were on haemodialysis, seven were on continuous ambulant peritoneal dialysis, five were on a strict diet, and three had their kidneys transplanted. To reflect a substantial change in hearing, a difference of 10 dB in one or	Low (125 & 250 Hz), moderate (500, 1 & 2 kHz), and high (4 & 8 kHz) frequency losses were recorded. Low frequency loss was found in 41% of ears examined, whereas high frequency loss was seen in 53%, with the middle frequencies being spared in 15% With dialysis. There was little variation in middle as well as high frequency thresholds. In individuals with chronic renal failure, the results demonstrate low and high frequency hearing loss, with the medium speech frequencies being preserved.	The findings reveal that individuals with chronic renal failure have low and high frequency hearing impairments, with the mid frequencies being spared. In this study, Low frequency thresholds of 125 and 250 Hz were measured. According to the author, this is the only study that measures hearing at 125 Hz. Earlier studies has not revealed a low frequency loss.

			more frequencies in pre- and post- dialysis audiograms was used.		
2	Nikolopoulos et al., 1997	Auditory function in young patients with chronic renal failure	In this study, 46 teenagers and adults with renal failure ranging in age from 3 to 13, were investigated. Twenty-two patients had pre-end stage renal disease, with 15 receiving haemodialysis and 9 receiving continuous ambulatory peritoneal dialysis. Exclusion criteria include Alport disease and other hereditary or congenital syndromes. PTA (at 250 to 8 kHz), tympanometry and acoustic reflex were used to evaluate hearing.	The current study found that 41.3 percent of young renal patients had hearing impairment, with the majority of them (30.4 percent) of the total 46 children evaluated having this impairment of unknown origin. The hearing loss was mostly in the high frequencies. This study found before and after haemodialysis, the audiometric results did not alter statistically significantly.	The findings of this study show that impaired hearing acuity is common in young individuals suffering from chronic renal insufficiency but before and after haemodialysis, the audiometric results did not alter statistically significantly.
3	Samir et al., 1998	Transient otoacoustic emissions in children with chronic renal failure	The study examined 34 children having chronic renal failure age range from 6.5 to 16 years. Out of these, 27 patients received regular haemodialysis for an average of 2 years, and 7	Four patients (11.76 %) reported a mild conduction hearing loss, while five patients (14.7 %) showed moderately severe high frequency SNHL on both	In this study reduced incidence of hearing loss is most likely due to their younger age. This underlines the importance of investigating hearing loss in

			patients received conservative management for an average of 3 years. Patients who have previously consumed extended courses or high dosages of ototoxic medications, congenital hearing loss were prohibited from participation. PTA, speech audiometry, and tympanometry were included for basic audiological assessments. TOAE ILO88 was performed on children with hearing level of 25 dB or below. Twenty healthy, age and gender matched children, were evaluated in the same way as a control group.	sides. One of the SNHL patients was receiving conservative therapy, while the others were receiving haemodialysis. TOAE testing was performed on 25 people who had normal pure tone threshold. In 8% of the patient's ears no response was obtained, however not in any of the controls. In 38% of cases, a partial response was obtained (12% were on conservative treatment and 26 % on haemodialysis versus 10 % in controls). Those on haemodialysis showed significantly lower mean overall echo levels and reproducibility than patients on conservative therapy.	chronic renal failure in children, because interference from other causes will be limited. In 46 % of patients' ears, there was a definite deterioration in cochlear function that was not visible on standard audiometry, compared to 10% of controls. This shows uraemic children's higher susceptibility to hearing loss.
4	Sobh et al., 1999	Value of Otoacoustic Emission in	Sixty-three individuals were enrolled in this study. They were divided into three groups.	Pure-tone audiometry found hearing loss in 22.7 % and 15.3 % of individuals in	Finally, whether managed conservatively or haemodialyzed, hearing

		Monitoring Hearing acuity in Chronic Renal Failure Patients	As a control group, Group I had 15 healthy participants. Group II had 22 individuals with CRF who were receiving conservative management. Group III consist of 26 patients with CRF who were receiving haemodialysis (HD) on a regular basis. Patients having a history of ear problems, or injury, noise exposure, diabetes, or who were using ototoxic medicines were excluded from participating. Only people with healthy middle ear function were recruited. Hearing was evaluated using pure tone audiometry and otoacoustic emission (TEOAE). Before beginning HD treatments, these individuals' hearing acuity was evaluated.	groups (II) and (III), respectively. TEOAE recognized more no. of patients with hearing loss as compare to PTA in these individuals; 27.2 % and 19.2 % for response and reproducibility both. When group III was compared to group II, there was a small increase in response and reproducibility; however, this did not achieve statistical significance.	ability was observed to be diminished in CRF patients. Hence, haemodialysis may not be hazardous to hearing impairment in CRF patients. TEOAE increased the percentages of SNHL identification, showing that it is a better approach for evaluating hearing acuity than traditional PTA.

5	Mahmmod, 2006	Effect of hemodialysis on the hearing function of patients with chronic renal failure	At the time of admission, 34 CRF patients enrolled in pure tone audiometry and again after three haemodialysis treatments. Hearing loss was evaluated in decibels at frequencies from 500 to 8000 Hz. The average of the 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz was recorded. A control group of 28 participants who were otherwise clinically healthy and were of similar age and sex were selected had pure tone audiometry done and recorded. Inclusion criteria include consecutive CRF patients who had not received haemodialysis before to the study began.	Hearing loss was detected in 22/34 (67%) of the participants at enrolment and in 27 of 34 (79%) following haemodialysis. The pre-haemodialysis hearing level was between 15 and 60 decibels, with a mean of 37.42 and a post-haemodialysis hearing threshold of 25 to 90 decibels, with a mean of 48.48.The hearing loss of the controls ranged from 10 to 70 decibels, with a mean of 35 decibels. There was a substantial difference in pre- and post-haemodialysis mean values. There was also a link between the post-haemodialysis hearing threshold and the period of sickness.	CRF has a depressing effect on hearing function, as evidenced by the significant incidence of hearing loss at recruitment. However, following three sessions of haemodialysis, present study found a substantial decrease in hearing threshold. According to this article, the hearing threshold of patients with CRF was shown to be lower after three sessions of haemodialysis, could result from alterations in the electrolyte and endolymph fluid composition, as well as possible exposure to aged cellulose acetate dialyzer membranes, so this needs to be confirmed with a temporal bone study.

6	Aspris et al, 2008	Auditory Brainstem Responses in Patients under Treatment of Hemodialysis	The experimental group comprised of 31 individuals age (range 22-74 years) who were on HD for end-stage CKD. HD sessions were done three times a week, each lasting 4 hours. The control group was made up of 31 age and gender matched people. Every patient underwent an ENT evaluation, which included microscopy, to rule out middle ear disease, hearing test using PTA (at 0.5, 1, 2, and 4 kHz frequency), tympanometry, and ABR recordings. Exclusion criteria include Patients with average thresholds at 500, 1, 2, and 4 kHz more than 60 dB HL, and patients who got aminoglycosides previous year. Auditory threshold were measured at 0.5, 1, 2, and 4 kHz frequency. ABRs were	On the initial audiometric examination pre haemodialysis, pure-tone thresholds for the frequencies (500, 1, 2, and 4 kHz) studied were 24.8 (±12.7), 21.7 (±13.0), 22.9 (±15.6), and 31.2 (±21.1) dB HL respectively. On repeat audiometry post haemodialysis, the mean values for the same frequencies were 21.6 (±9.5), 18.7 (±8.8), 21.9 (±12.7), and 35.3 (±22.5) dB HL. Prior to haemodialysis, a comparison of the control and experimental groups' ABR and interpeak latencies revealed significant differences in all measures, except at I–III interpeak latency. Following	The wave I and wave V latencies in the slow repetition rate as well as the wave V latency in the fast repetition rate were greatly reduced in this study, when ABR recordings were compared before and after haemodialysis. According to the study, CRF affects auditory function at all levels of the auditory system. Although conduction times decrease after haemodialysis, hearing function does not return to normal.

			recorded at a sensation level of 80 dB at 10 and 60 Hz repetition rate. A greater intensity (95 dB SL) was utilized if waves I, III, and V could not be identified.	haemodialysis, a comparison of these two group revealed that the two groups were remained significantly different. In the low repetition rate, the experimental group's wave V absolute latency and III-V and I-V interpeak latencies were much longer. At a high repetition rate absolute latencies of waves I and V, as well as I–III interpeak latencies, were lengthened.	
7	Jakic et al., 2010	Sensorineural Hearing Loss in Hemodialysis Patients	The study comprised 66 ESRD patients with a mean age of 51.50 years who were given HD 3 times a week for 4 to 4.5 hours. For both ears, hearing thresholds (HT) were measured for air and bone conduction at frequencies of 0.25, 0.50, 1k, 2k, 4k, 6k, and 8k Hz. Only audiograms of type A were	Mean HT was 26 ±10.50 dB for all frequencies, 19.70 ±8.80 dB for speaking frequencies, and 41.70 ±19.70 dB for high frequencies. HT above 20 dB was reported in 42 patients (63.64 percent) for all frequencies, 22 patients (33.33 percent) for	Majority of the patients, 63.64 percent (42 of 66), experienced sensorineural hearing loss which shows SNHL is common in chronic HD patients. Moreover, there was no association between hearing threshold and time spent receiving HD treatment; which conclude that hearing

			examined. Mean AC threshold was measured for each ear for all frequencies combined, as well as individually for frequencies in the speech region (250 - 4000 Hz) and in the high frequency (6k and 8k Hz).	frequencies in the speaking region, and 56 patients (84.85 percent) for high frequencies. Sensorineural hearing loss was evident in most of the patients however, no significant relationship between HT and HD treatment duration was found.	ability was not harmed by HD. According to the findings of this study, the high frequency hearing threshold of CRF patients having haemodialysis has increased. This might be due to haemodialysis-induced alterations and disease duration. Another possibility is that haemodialysis has accelerated the vascular aging process, and the final theory is that hearing loss in individuals with CRF is followed on by a combination of causes, some of which may have been made worse by haemodialysis, in addition to early vascular ageing.
8	Naderpour et al., 2011	Auditory brain stem response and otoacoustic emission result in children	Twenty-five ESRD patients on haemodialysis, 25 non-dialytic CRF patients and 25 age and sex-matched control subjects	ABR testing revealed that 44 % of dialysis patients exhibited bilateral symmetric enhanced V latency (by 35	In this study, abnormal OAE and ABR result were considerably more in dialysis patient than the other two

		with end-stage renal disease	were evaluated in three groups of children aged 1 - 16 years in this cross sectional study. All of the participants were extensively examined by an ENT experts. Patients having a history of otological disorders, diabetes, ototoxic medications, hearing impairments syndromes (such as Alport syndrome), and mental retardation were excluded from the study. ABR and OAE test were done bilaterally. The audiological tests were performed at least 24 hours after dialysis. The used ABR standards were 90 dB nHL, 30 impulses, click 125 ms half-wave square at frequencies ranging from 1000 to 4000 Hz. The MADSEN Capella Oto Acoustic analyser was used to measure the OAEs.	dB amplitude at frequencies between 1000 and 4000); indicating mild increased hearing thresholds, while ABR was normal in other two group. The same 44% individuals in the dialysis group (who had abnormal ABR) had abnormal OAE testing, as did 4% of patients in the non-dialytic group and none in the control group.	groups. ABR and OAE testing together give a detailed evaluation of a child's hearing system. All dialysis patients who exhibited bilateral elevated wave V latency had an aberrant OAE finding as well. OAE anomalies imply dysfunction of hair cells in the organ of Corti. Bilateral wave V latency that is increased (by 35 dB in the 1 to 4 kHz frequency range) is mostly a reflection of SNHL brought on by cochlear impairment.

9	Doshad & Kuchhal, 2014	Hearing assessment in chronic renal failure patients undergoing hemodialysis	Sixty-three CRF patients age range from 25 to 75 years were enrolled for PTA at the time of admission and three months after beginning haemodialysis. Consecutive CRF individuals who were non-diabetic, had normal ears, and had no history of ear surgical procedure were included. All patients were on maintenance hemodialysis twice a week for 4-6 hours, and the period of CKDs was considered.	The high frequency was shown to be more affected by SNHL than the mid and low frequencies. The incidence of SNHL was shown to increase with duration. At the beginning of the study, 44.4 % of the 63 patients had hearing loss, with 64.28 % having mild hearing loss, 32.14 having moderate hearing loss, and 3.57 having severe hearing loss. At the end of the study, the hearing loss had grown to 55.5 %, with 34.28 percent having mild hearing loss, 54.28 having moderate hearing loss, and 11.49 having severe hearing loss.	This study found that hearing loss was directly related to disease duration. 87.5 % of patients with more than 18 months of disease reported hearing loss, compared to 33.3 percent with six months of disease. In this study of 63 patients with a three-month follow-up, author observed that hearing status did not improve or worsen as a result of dialysis treatments; rather, it remained steady.
10	Reads, 2014	Hearing impairment in patients with Chronic Renal Failure	This prospective cross-sectional research included a total of 120 participants. The trial included 80 patients, 40 of	74.3 % of CRF patients had SNHL (Due to attrition in health, 1 patient in the CRF group had to be removed	Mean thresholds were higher in the CRF and HD groups than in the controls, with a greater increase in the high

			whom had CRF had a mean age of 45.69 ± 16.47 years, and were on conservative treatment, and 40 of whom were receiving HD had a mean age of 49.4 ± 13.36 years. The control group consisted of 40 healthy volunteers with normal renal function who were age and sex matched to the research group. pure tone thresholds were obtained throughout all frequency octaves from 250 Hz to 16000 Hz.	from the study). 77.5 % of the patients on HD had SNHL. Hearing loss was found in 32.5% of the controls. Hearing loss was mostly bilateral in all three groups. In the CRF group, minimal hearing loss was detected in the frequency range of 250 Hz to 2 kHz, and moderate to moderately severe hearing loss was observed in the frequency range of 4 kHz to 16 kHz. In the HD group, there was Mild HL loss in the 250 Hz - 2 kHz frequency range, and moderate HL in the 4 k - 16 kHz frequency range.	frequencies (4000 - 16000 Hz). The course of the illness had no discernible relation with hearing loss. Even though exact cause of hearing loss is not known, the association between CRF and HL has been hypothesized to be based on biophysical similarity among fluid and electrolyte changes in the cochlea's stria vascularis and kidney.
11	Renda et al., 2015	Cochlear sensitivity in children with chronic kidney disease and end-stage renal	The children in this cross-sectional research ranged in age from 6 to 18 years and were classified into three groups: 36 non-dialytic chronic	Audiometric test (PTA and OAE) results revealed that except for 8 kHz bilaterally, there were no noticeable	To measure cochlear activity at various frequencies, the amplitudes and SNRs of DPOAEs were taken even with normal hearing

		disease undergoing hemodialysis	kidney disease (ND CKD) patients, 16 end-stage renal disease (HD ESRD) patients who underwent dialysis, and 30 healthy controls. The study excluded children having a history of otological dysfunction, chronic systemic illness, ear surgery, noise exposure, acute or chronic otitis media, or middle ear effusion. Patients with mild illnesses such as conjunctivitis and dermatitis were included in the age and gender matched controls. Before audiometric testing, otoscopic exams and tympanometry were done. PTA thresholds were measured bilaterally at 0.5-8 kHz (0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz). The f2:f1 (1:22) ratio was used to get DPOAE responses. Both L1	differences among the 3 groups on the PTA. In comparison to the control group, the DPOAE SNRs in the ND CKD as well as HD ESRD groups were significantly lower. SNRs in both ears were lower in the HD ESRD group than in the ND CKD group, especially at frequencies above 4 kHz, although there were no noticeable differences among the ND CKD as well as HD ERSD groups. Both the ND CKD as well as HD ESRD groups had significantly lower DPOAE amplitudes than the control group. In both ears, DPOAE amplitudes were lower (although not substantially) in the HD ESRD group than the	thresholds. In both the ND CKD as well as HD ERSRD groups OAE amplitudes and SNRs were significantly lower than those of the control group. The DPOAE amplitude graph and the SNR graph both displayed down sloping patterns at frequencies higher than 3 kHz and 4 kHz, respectively, suggesting significantly decreased cochlear activity. As in both the ND CKD as well as HD ESRD groups, PTA and DPOAE results were identical, the major rationale of the reported hearing loss in this study was assumed to be kidney failure, not HD.

			and L2 had stimulus intensities of 65 dB.	ND CKD group, particularly at frequencies over 3 kHz.	
12	Saeed et al., 2018	Sensorineural hearing loss in patients with chronic renal failure on hemodialysis in Basrah, Iraq	Study includes 59 patients with CRF on regular haemodialysis for various periods under the age of 50 years. The same professional audiologist performed pure tone audiometry at the time of admission, six months after, and one year after. Hearing thresholds were tested at frequencies ranging from 500 to 8000 Hz, and a hearing threshold of more than 20 dB on average was considered hearing loss.	Thirty nine participants (66.1%) of the participants, had hearing loss initially. Another four individuals experienced hearing loss after 6 months, for a point prevalence rate of 72.9 %. At the end of the 12 month follow-up period, 45 individuals were found to experience hearing loss, with a prevalence rate of 76.3 %. The mean loss of hearing across all frequencies was 29.2 dB HL initially and rose to 35.3 dB HL after 6 months. The mean hearing loss at the end of the study was 36.9 dB HL. At high frequencies, the dominant hearing loss was evident.	This study found that 27.1% of participants' hearing thresholds remained unchanged at the trial's conclusion, 8.5 % improved, and the majority 64.4 % deteriorated. The high incidence of hearing loss at study admission demonstrates CRF's considerable influence on hearing function. Nonetheless, haemodialysis had a significant influence on the hearing threshold at 12 months. The hearing threshold dropped from 29.2 dB at the start of the study to 36.9 dB after a year, which was a very significant change.

3.3 Quality Assessment

Quality assessment tool to determine the risk of bias in selected studies for the systematic review was done using the National Institute of Health (NIH) Quality assessment tool for observational cohort and cross-Sectional studies which includes total 14 questions. All of the included studies had well specified aims and objectives, and also the methodological quality varied from good to fair. None of the study examines different amount or level of exposure. In six of the 12 studies, the exposure was clearly defined (Sobh et al., 1999; Aspris et al., 2008; Jakic et al., 2010; Naderpour et al., 2011; Renda, et al., 2015; Saeed et al., 2018). The results of the studies included in this systematic review were qualitatively summarized to achieve the study's aims and objectives. The findings are further discussed in this systematic review's discussion chapter. Table 3.3 includes details on the quality assessment tool for observational cohort and cross-sectional studies where "YES" indicating low risk of bias, "NO" indicating high risk of bias, and "NR, CD, NA" indicating unclear risk of bias, with the exception of question 13, with "YES" indicates high risk of bias and "NO" indicates low risk of bias.

Table 3.3

Quality assessment of selected articles

Authors / Year	Quality assessment tool for Observational Cohort and Cross-Sectional studies														
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Rating
Gatland et al. (1991)	YES	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	NR	NO	YES	GOOD
Nikolopoulos et al. (1997)	YES	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	NR	NO	YES	GOOD
Samir et al. (1998)	YES	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	NR	NO	YES	GOOD
Sobh et al. (1999)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NR	NO	YES	FAIR
Mahmmod, (2006)	YES	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	YES	NO	YES	GOOD
Aspris et al. (2009)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Jakic et al. (2010)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES	GOOD
Naderpour et al. (2011)	YES	YE	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	FAIR
Doshad & Kuchhal (2014)	YES	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	NR	NO	YES	FAIR
Reads (2014)	YES	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	YES	NO	YES	GOOD
Renda et al. (2015)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Saeed et al. (2018)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NR	NO	YES	GOOD

Chapter 04

Discussion

This systematic review aimed to identify the incidence of hearing loss in individuals with chronic renal dysfunction. Chronic renal dysfunction is a condition in which glomerular filtration rate become less than 60 ml per min for more than three months (Mudhol & Jahnavi, 2019). In order to achieve the objectives 13,060 articles were selected from detailed exploration of the major databases for this systematic review. On the basis of the inclusion and exclusion criteria, 12 studies were chosen. There are several studies on hearing impairment in people with chronic renal disease have been conducted in children, adults, and in elderly individuals. All 12 studies included in the systematic review found hearing impairment in CKD patients either due to kidney disease or haemodialysis. The cochlea and kidney may share antigenicity, as well as a comparable process of active fluid and electrolyte transport achieved by the stria vascularis and glomerulus, respectively. These might be the causes for the same influence of hereditary factors and drug effects on both organs. (Bendo et al., 2015). Hearing loss in CRF has been linked to a number of aetiological causes, including use of ototoxic medicines, electrolyte abnormalities, and hemodialysis therapy. Brookes (1985) hypothesized that vitamin D insufficiency might contribute to hearing loss in renal failure. The changes in hearing in renal disease has also been confirmed in the animal studies. In uremic guinea pigs' inner ears, there was a substantial decrease in Na+, K+-activated ATPase (Adler et al., 1980). The mitochondria of the stria vascularis intermediary cells and endothelial cells were particularly large.

Chronic renal function is a leading cause of morbidity and mortality, especially in the later stages of disease. Each kidney contains up to 1 million nephrons, each of which contributes to the total GFR. In patients with CRF, regardless of the cause of renal injury, nephrons are gradually destroyed. The kidney's intrinsic ability to maintain GFR stability involves excessive filtration and compensatory nephron growth. The adaptive changes in the nephron result in maladaptive consequences, such as an increase in glomerular filtration, which causes glomerular injury. When the renal reserve is exhausted, the plasma levels of urea and creatinine rise. Blood turns toxic, bones start to lose calcification, and neurons start to age, all of which contribute to sensorineural hearing loss.

In four of the 12 studies, haemodialysis has reportedly been linked to hearing loss in people with CKD. The cochlea in haemodialysis patients has been shown to be vulnerable to different injuries, and the patients typically demonstrate some degree of SNHL, however the actual etiological factor(s) remain unknown (Getland et al., 1991). Whereas eight studies found that reduced hearing acuity is common in individuals with chronic renal insufficiency. Aspris et al. (2008) found that latency of V peak significantly improved when ABR recordings were compared before and after haemodialysis, but did not return to normal. According to this study end-stage CRF has an impact on the auditory system's overall structure and function. Although conduction times decrease after haemodialysis, hearing function does not return to normal. Whether conservatively or haemodialyzed, hearing acuity was observed to be diminished in CRF patients. Hence, haemodialysis may not be hazardous to hearing impairment in CRF patients (Sobh et al., 1999). According to Reads (2014), even though exact cause of hearing loss is not known, on the basis of biophysical commonalities in fluid and electrolyte changes in the stria vascularis of the cochlea and kidney, it has been suggested that CRF and HL are associated. Renda et al. (2015) found decreased DPOAE amplitude in CKD patients, implying reduced cochlear activity in these individuals. Hearing loss is becoming more noticeable as patients live longer lives as a result of the enhanced quality of life given by various treatment options for CRF patients (Bendo et al., 2015). If not identified and treated early, this sort of hearing alteration can substantially interfere with good communication, intellectual capacities, and most importantly education (Samir et al., 1998).

The results of the site of lesion test battery indicated that hearing loss are usually sensorineural in nature. Transient Evoked Otoacoustic Emissions (TEOAE) helps in the early identification of ears that are predisposed to hearing loss (Samir et al., 1998). TEOAE are sounds produced by the outer hair cells of the cochlea in response to a transient click. The presence of a TEOAE response indicates that the cochlear amplifier is in proper functioning. Sobh et al. (1999) found that for both the response and overall reproducibility, compared to pure-tone audiometry, TEOAE recognized more patients with hearing loss. Renda et al. (2015) noted that regardless of hearing loss, compared to the control group, cochlear activity was decreased in the CKD as well as HD groups. Abnormal TOAEs were observed more in patients whose blood pressure fluctuated rapidly and widely during haemodialysis. The sympathetic blood pressure control system alters in response to changes in blood pressure, which may affect the blood supply to the cochlea, resulting in cochlear dysfunction. Therefore, to avoid worsening the condition, efforts should be made to minimize blood pressure changes (Samir et al., 1998). According to Getland et al. (1991), hearing loss may be caused by the process of haemodialysis itself, especially if frequent intense osmotic pressure changes occur. Naderpour et al. (2011) suggested that

ABR and OAE testing together give a detailed evaluation of a child's hearing system. OAE abnormalities suggest hair cell dysfunction or loss in the organ of Corti. Whereas, increased wave V latency of ABR primarily represents sensorineural hearing loss caused by a cochlear lesion.

The first objective of this study was to determine the incidence of hearing loss and associated symptoms in individuals with chronic renal dysfunction. All 12 studies included in the systematic review found hearing impairment in CKD patients, even patients experience diminished hearing, in that majority of the patients had only mild degree of loss. Which shows that CKD is still a likely cause of hearing loss and patients with CKD are at a greater risk for hearing loss. Based on this finding, patients with chronic renal failure should be evaluated for hearing loss in addition to their overall condition. To prevent further deterioration, CKD patients should have regular hearing loss screenings as part of their routine care.

The second objective of this study was to determine the effect of haemodialysis on hearing loss. Out of 12 studies selected for this systematic review, four studies have given emphasis that haemodialysis contribute to hearing loss in CKD individuals not the disease (Gatland et al., 1991; Samir et al., 1998; Mahmmod, 2006; & Naderpour et al., 2011). Abnormal OAE and ABR result were considerably more in dialysis patient than the other (Naderpour et al., 2011). Getland et al. (1991) found that the cochlea in haemodialysis patients have shown vulnerability to different injuries, and the patients typically demonstrate some degree of SNHL. Samir et al. (1998) observed that patients on haemodialysis had significantly lower mean overall echo levels and reproducibility than those on conservative therapy.

The final and last objective of this systematic review is to determine the link between chronic renal failure and hearing loss. Out of 12 studies taken for the systematic review, eight of the studies (Nikolopoulos et al., 1997; Aspris et al., 2008; Jakic et al., 2010; Doshad & Kuchhal, 2014; Renda et al., 2015; Reads, 2014; Saeed et al., 2018 & Sobh et al., 1999) found that reduced hearing acuity is common in individuals with chronic renal insufficiency. Sobh et al. (1999) found that whether conservatively or haemodialyzed, hearing acuity was observed to be diminished in CRF patients. Hence, haemodialysis may not be hazardous to hearing impairment in CRF patients. All the studies in detail have been compiled in the summary table included in this systematic review's result section.

Chapter 05

Summary and Conclusions

This study's goal was to conduct a systematic review to identify the incidence of hearing loss in individuals with chronic renal dysfunction. Articles were selected using specific keywords in four databases: Pubmed Central, Semantic Scholar, Science Direct, and Google Scholar. A total of 13,060 results were identified across four databases, with 1080 of them being detected as a duplicate, remaining 11,980 articles were subjected to title screening. Based on title screening, 45 full-text articles were selected, whereas 11,935 were rejected because they did not fulfil the inclusion criteria for this systematic review. Out of these 45 articles, 26 were excluded during the abstract screening, and the remaining articles were accepted for full text screening. Based on the full-text, seven articles were excluded. Hence, 12 articles were included in the data extraction and final review procedure.

The first objective of this study was to determine the prevalence of hearing loss and associated symptoms in people with chronic renal failure. The studies included in this systematic review found following reported prevalence of hearing impairment in CKD patients. Nikolopoulos et al. (1997) investigated the hearing acuity of 46 children and adolescents with renal insufficiency. The study reported that 30.4 % of their patients had sensorineural hearing loss. Jackie et al. (2010) observed that 42 (63.64%) of 66 patients had increased hearing threshold. Doshad and Kuchhal (2014) found hearing loss in 44.4% of the 63 patients studied. In a study of 79 patients with CRF conducted by Reads (2014), SNHL was found in 75.94% of the patients. In a study by Saeed et al. (2008), hearing loss was detected in 39/59 patients, with a prevalence rate of 66.1%.

The second objective of this systematic review was to see effect of haemodialysis on hearing function. Four of the 12 studies selected for this systematic review emphasized that haemodialysis, not the disease, is a factor in CKD patients hearing loss.

The final objective of this systematic review is to determine the link between chronic renal failure and hearing loss. Most (eight) studies included in the systematic review discovered that while reduced hearing acuity is common in people with chronic renal insufficiency, haemodialysis may not be harmful to hearing.

It can be concluded that along with an evaluation of their general condition, a patient with CRF should also have their hearing tested. Regular screening for hearing loss should be included in the routine care of CKD patients. Patients with chronic renal failure can benefit from early detection because it can enhance their life quality and minimize additional hearing loss.

5.1 Implications of the study

Majority of the studies included in the systematic review discovered that reduced hearing acuity is common in people with chronic renal insufficiency.

The impact of this systematic review are as follows:

1) It throws light on probable causes of cochlear impairment in individuals with chronic kidney disease.

2) It helps to improve the understanding of the need of regular screening for hearing loss in people with chronic kidney disease.

5.2 Future directions

A test battery approach should be developed to detect the hearing loss early in patients with kidney problems. High frequency tone bursts may be used in ABR studies to assess the high frequency range and differentiate which frequency is affected first and most by this disorder.

5.3 Limitation of the study

The current systematic review has limitation in predicting the potential cause of hearing loss when age, ototoxicity and noise exposure coexist in an auditory system.

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APPENDIX

NIH Quality assessment questionnaire template used as quality analysis in the current systematic review study.

Criteria	**Yes**	**No**	**Other (CD, NA, NR)***
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome ifit existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to theoutcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently acrossall study participants?			
12. Were the outcome assessors blinded to the exposure statusof participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured andadjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

*CD, cannot determine; NA, not applicable; NR, not reported.