EFFECT OF AGE ON DISTORTION PRODUCT OTOACOUSTIC EMISSIONS AT EXTENDED HIGH FREQUENCIES

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MANASAGANGOTHRI,

MYSURU-570006

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CERTIFICATE

This is to certify that this dissertation entitled **"Effect of Age on Distortion Product Otoacoustic Emissions at Extended High Frequencies"** is the bonafide work submitted in part fulfilment for the degree of Master of Science (Audiology) of the student, Registration Number: P01II21S0065. This has been carried out under the guidance of the institute's faculty and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru
September 2023

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CERTIFICATE

This is to certify that this dissertation entitled **"Effect of Age on Distortion Product Otoacoustic Emissions at Extended High Frequencies"** has been prepared under my supervision and guidance. It is also 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 **"Effect of Age on Distortion Product Otoacoustic Emissions at Extended High Frequencies"** is the result of my study under the guidance of **Mr Saravanan P.,** Assistant Professor in Audiology, Department of Audiology, 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
September 2023

Registration No
P01II21S0065

Dedicated To

Maa Santoshi, Mummy-Papa (Lifeline), Dr. Onkar Sir (Enlightener), Bhaiya (Strength), Harshu, Vihan, Nissy (BFF), Chandra Prakash (CP, fav) and Saravanan Sir (Guide) for Their Constant Support and Encouragement in Pursuing My Degree.

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Abstract

Introduction

The inner ear is most susceptible to the ageing effects. The anatomical changes like loss of sensory hair cells, loss of spiral ganglion cells and atrophy of stria vascularis lead to changes in cochlear functions and cause age-related hearing loss. Distortion Product Otoacoustic Emissions (DPOAEs) are a good indicator for interpreting the age effects but are usually recorded at up to 8000 Hz frequencies in routine audiometric testing. OAEs are proven more sensitive to cochlear insults than pure tone audiometry. The origin of both DPOAEs at EHF and conventional frequencies is via a similar biological mechanism in the inner ear.

Aim of the study

The present study aimed to see the effect of age on the DPOAEs at conventional extended high frequencies.

Objectives

This study assesses and compares the DPOAEs parameters at conventional frequencies to the DPOAEs parameters at extended high frequencies across different age groups and evaluates the association between the extended high-frequency thresholds and DPOAEs at conventional and extended high frequencies across different age groups.

Materials and Methods

Extended high-frequencies Audiometry (9000-16000 Hz) and DPOAEs from 500-16000 Hz were recorded on eighty adult (160 ears) participants with normal hearing sensitivity. The participants were 15-55 years old, with an equal number of males and females. The participants were further categorised into four groups to see the age-related changes: Group I (15 – <25 years), Group II (25-<35 years), Group III (35-<45 years) and Group IV (45-55 years).

Results

The results showed a significant difference between the four groups for extended high-frequency thresholds and DPOAEs parameters (amplitude and SNR) at conventional and EHF ($p < 0.05$). A statistically significant reduction in EHF thresholds was observed in group II than I at 16000 Hz frequencies. The decline was observed from group III onwards and became poorer in group IV for EHF thresholds. However, the thresholds were comparatively better for group III at frequencies 9000,1000 and 11500Hz than group IV. No significant difference was observed for EHF DPOAEs in Groups I and II (except at 16000 Hz) and III and IV. Group IV (45-55 years) was significantly different from the other three groups for conventional frequencies. A weak negative correlation was observed between the DPOAE parameters and EHF thresholds.

Conclusions

This study suggests an effect of age on EHF DPOAEs before the EHF thresholds for frequencies 9000, 10000 and 11500 Hz. The EHF thresholds and DPOAEs start deteriorating from below 30 years onwards, with a rapid decline above 35 years. EHF DPOAEs can be used in clinics to identify early ageing signs and as a screening tool, as it is less time-consuming.

CHAPTER- I

INTRODUCTION

Otoacoustic emissions (OAEs) are the echoes produced by the cochlea. These emissions are transferred through the middle ear and then to the outer ear meatus, where they can be measured (Kemp, 1978). The generation of OAEs is a hallmark of inner ear health and OHCs' non-linearity. OAEs are the property of healthy cochlea, which usually function as they are generated by the selectivity of active frequency and the non-linear elements within the partition, for which the critical components are the outer hair cells (Kemp, 2002). The diagnostic importance of OAEs has been explained as a non-invasive objective measure used to forecast audiometric status when a behavioural audiogram is not easily obtained (Dorn et al., 1998). Because of their relative simplicity, better sensitivity, and objectivity of technique, the OAEs are a suitable means for monitoring cochlear function (Gates & Mills, 2005).

Among the evoked OAEs, distortion product otoacoustic emissions (DPOAEs) are always produced when there is a mechanical non-linearity (Kemp, 2002). It is a type of emission found in all normal-hearing individuals. The simultaneous presentation of two pure tones closely spaced in frequency elicits DPOAEs. DPOAEs responses are majorly considered distortion emissions since they originate from the cochlea at a frequency not present in stimuli that elicit OAEs. When DPOAEs overlap along the basilar membrane, they derive from the non-linear interaction between the travelling waves of the lower frequency (f1) and higher frequency primary tone (f2). The distortion product frequencies are computed combinations of the f1 and f2 frequencies, and the most remarkable and broadly studied DPOAEs occur at the 2f1-f2 frequency in humans (Dreisbach et al., 2006).

Additionally, it has been shown that decreased DPOAEs levels correlated with outer hair cell destruction, which is supported by histological findings and demonstrates that outer hair cells contribute to the production of DPOAEs (Brown et al., 1989).

The DPOAEs recording has become a rapid and objective test to examine the cochlea and middle ear status and is widely used in hearing clinics. In humans, most DPOAEs studies have used conventional frequencies (≤ 8KHz); however, hearing at extended high frequencies (EHF) is most susceptible to cochlear damage. The origin of both DPOAEs at EHF and conventional frequencies is via a similar biological mechanism in the inner ear (Dreisbach & Siegel, 2001). Due to the emergence of EHF DPOAEs in the range of 9,000 to 16,000 Hz frequencies, changes in hearing preceding hearing loss in conventional audiometric frequencies (250 to 8000 Hz) could be ruled out in the initial stages (Dreisbach et al., 2006; Dreisbach & Siegel, 2005). Previous studies have shown that monitoring the cochlea's high-frequency regions is crucial for detecting noise-induced or ototoxicity-induced and age-related hearing loss, which initially affects the higher frequencies and then proceeds to lower frequencies. The emergence of EHF DPOAEs in clinical procedures directly correlates with these findings in clinical settings (Dunckley & Dreisbach, 2004). A novel objective approach for the early identification of high-frequency hearing loss may thus be established because EHF DPOAEs measurements assess the cochlear health in the basal region of the human cochlea. Jedrzejczak et al. (2022) showed that the decrease in EHF DPOAEs is related to hearing loss, and 16000 Hz can identify preclinical reductions in hearing levels. DPOAEs at EHF can also identify heterozygous individuals with Gap Junction Protein Beta-2 gene mutation even before clinical manifestation in audiometry is observed (de Mello et al., 2014).

Age-related changes are significantly associated with lower DPOAEs amplitude (Uchida et al., 2008a). The results of several studies also point out that the effect of age on DPOAEs measurements is independent of peripheral hearing loss, which is estimated by conventional audiometry (Ortmann & Abdala, 2016). A decline in the production of OAEs with ageing may reflect ongoing OHC deterioration brought on by the ageing process (Uchida et al., 2008b). According to a study by Lee et al. (2012), age-related cochlear damage starts as early as the third or fourth decade of life, more in the basal part of the cochlea that cannot be detected appropriately by conventional clinical measures. Threshold estimation using a standard audiometric frequency range (up to 8 kHz) showed no clinically significant reduction throughout life. Contradictory to that, DPOAEs growth functions measured in the identical frequency range showed apparent decay as early as the age of 30 years, mainly for the moderate stimulus levels (Glavin et al., 2021a). The basilar membrane displays linear response growth at low stimulus levels, a compression "knee" or bend-over section at intermediate stimulus levels, and compressive development at rising stimulus levels during the DPOAEs I/O test. The wide dynamic range of human hearing is primarily the result of this non-linear growth (Dorn et al., 1998).

The authors conducted a study in the participants with an age range of 10-65 years. The authors concluded that the ageing effect in DPOAEs is seen as a reduction in amplitude, which is more seen explicitly in the two highest test frequencies, 6 and 8 kHz (Poling et al., 2012). Early ageing weakens non-linear cochlear expressions, such as the DPOAEs and the DPOAEs I/O functions, that become linearised. The findings imply that changes in compressive non-linearity with ageing may decrease hearing's dynamic range and worsen signal processing in older listeners (Ortmann & Abdala, 2016). Even though the DPOAEs distortion component is present, it is weaker in older and middle-aged adults, especially at high frequencies. These level deductions are evident even in audiometrically similar groups, indicating that hearing loss is not the only contributor to reduced cochlear non-linearity with age (Abdala et al., 2021). Ortmann and Abdala (2016) reported a steeper DPOAEs growth rate at conventional frequencies in middle-aged listeners, indicating the cochlea's compressive non-linearity degradation. The remarkable ageing effect preserves the reflection-emission levels and significantly reduces distortion-emission levels. This relative pattern of OAEs loss with ageing might serve as a diagnostic indicator for cochlear abnormalities caused by ageing (Abdala et al., 2018).

Age-related alterations in hearing levels occur significantly earlier in the EHFs range, greater than 8 kHz (Lee et al., 2012b). Recently, it has been shown that the EHFs (up to 20 kHz) temporal information can enhance speech-in-speech recognition associated with speech, which is bandlimited to 8 kHz (Trine & Monson, 2020). In the same study, Trine and Monson (2020) also found a significant relationship between speech recognition thresholds (SRTs) and EHFs thresholds. The EHFs temporal insights provide a 0.9 dB improvement in speech recognition. Hearing at EHFs exhibits signs of early auditory ageing (Aziz et al., 2020a). According to Mishra et al. (2022), hearing impairment at EHFs severely affects speech-in-noise recognition, independent of speech frequencies and age. The findings also suggest that the audibility of EHFs contributes to speech-in-noise recognition (Mishra et al., 2022). The early ageing effects are susceptible to the EHFs thresholds, and these threshold alterations are even observed in very young populations (Jilek et al., 2014). EHFs insights are essential for the decision of sound elevation and for resolving front/ back chaos (Trine & Monson, 2020). Many studies have reported a relationship between EHF impairment and loss of performance in speech-in-noise (Hunter et al., 2020;

Lough & Plack, 2022; Valiente et al., 2016). EHF thresholds are also helpful in providing knowledge about hair cell loss at lower frequencies (Valiente et al., 2016; Škerková et al., 2023).

Across the entire frequency range, it has been reported that two different ageing processes impact the hearing thresholds: the slower process occurring at low frequencies and the faster process at higher frequencies. These findings suggest that extended high-frequency loss may have already happened when the initial traditional pure tone audiogram (0.25-8 kHz) indicates age-related hearing loss (Lee et al., 2012; Uchida et al., 2008). The rapid ageing process begins at ages 51, 47, 46, 36 and 30 years for frequencies 6, 8, 10, 11, and 12.5 kHz, respectively (Lee et al., 2012a). EHFs have several roles in auditory disorders (Poling et al., 2012). Clinical hearing impairment can be identified early by EHFs hearing loss. It can hinder hearing and speech understanding, especially in noisy environments (Rodríguez Valiente et al., 2014, 2016). EHFs are also related to age-related hearing loss, noise exposure and ototoxicity. With ageing, hearing levels gradually decline; this loss starts at the higher frequencies and travels down to the lowest frequencies. As a result, the EHFs become vital in age-related hearing impairment as a technique for early investigation of such failure (Best et al., 2005; Hunter, Blankenship, et al., 2020; Hunter, Monson, et al., 2020). Additionally, it has been found that individuals' hearing at EHF deteriorated, starting in their 30s and predominated in their 50s and beyond. Before age 30, EHF's hearing thresholds were less than 26 dB HL. The average threshold values with ageing were up to 75 dB HL (Wang et al., 2021).

The EHF hearing thresholds show early auditory ageing signs. The third decade of human life leads to the deterioration of hearing function with age. In individuals with EHF hearing loss, decreased DPOAEs in the standard frequencies may reflect preclinical cochlear damage (Mishra et al., 2022). DPOAEs can be applied as a preclinical tool to identify early ageing, which has already been reported in the literature. Before any alterations are detected by conventional pure tone audiometry, the decline or absence in DPOAEs amplitude implies hearing loss. According to a recent study, the EHF DPOAEs should be used to detect hearing loss in the extended high-frequency range (Jedrzejczak et al., 2022).

1.1 Need of the study

Early ageing starts from the basal frequencies and then progresses to the apical ones. OAEs can be used as objective tests, a sensitive tool for identifying the subclinical damages in the cochlea. DPOAEs values determine cochlear health as a function of frequency (Poling et al., 2012). Reduction in hearing sensitivity at extended high frequencies may signify preclinical hair cell loss in the conventional frequency range (Mishra et al., 2022). A reduction in the amplitude of DPOAEs reported with ageing is significantly seen even before any change is observed in the pure tone audiometry (Dorn et al., 1998).

EHF DPOAEs are essential in identifying disorders like ototoxicity, noise-induced hearing loss, and cystic fibrosis (de Mello et al., 2014; Dreisbach & Siegel, 2001). Škerková et al. (2023) reported that hearing thresholds at EHF begin to deteriorate from 35 years onwards; initially, the effects are more observed in the high frequencies (14 &16 kHz), and as age increases, the result is observed more in low frequencies. The increase in hearing threshold rate is more rapid in males than females. On the other hand, it is unclear if ageing had a similar impact on the DPOAEs at EHFs. Therefore, further research was required to understand how ageing affects DPOAEs at conventional and EHFs. Understanding the effect of age on DPOAEs at

EHFs could help identify individuals with a greater risk of developing hearing impairment. It could further guide in counselling and follow-up assessments.

1.2 Aim of the study

The present study aimed to see the effect of age on the DPOAEs at conventional and extended high frequencies.

1.3 Objectives of the study

I. To assess and compare the DPOAEs parameters at conventional frequencies across different age groups.

II. To assess and compare the DPOAEs parameters at extended high frequencies across different age groups.

III. To assess the association between the extended high-frequency thresholds and DPOAEs at conventional and extended high frequencies across different age groups.

CHAPTER-II

REVIEW OF LITERATURE

2.1 Origin of DPOAEs

Otoacoustic emissions (OAEs) are the echoes produced by the cochlea. These emissions are transferred through the middle ear and then to the outer ear meatus, where they can be measured (Kemp, 1978). The generation of OAE is a hallmark of inner ear health and OHC's non-linearity. The efferent innervations comprise many fibres that form the central and lateral efferent systems. The medial efferent system is connected to the innervations of outer hair cells, while the lateral system is related to inner hair cells. The release of acetylcholine in the synaptic cleft through the medial olivocochlear efferent tract modulates the motion of outer hair cells (Bonfils et al., 1988). The diagnostic importance of OAEs has been explained as a non-invasive objective measure used to forecast audiometric status when a behavioural audiogram is not easily obtained (Gorga et al., 2005).

Among the evoked OAEs, distortion product otoacoustic emissions (DPOAEs) are always produced when there is a mechanical non-linearity (Kemp, 2002). DPOAEs can be recorded from the ear canal during continuous stimulation with pure tones at fl and f2 frequencies where fl < f2 and the intensity level L1 > L2. The DPOAEs have been linked to the functioning of outer hair cells on the basilar membrane corresponding to the locus 2fl-f2 (de Boer et al., 2005; Gibian & Kim, 1982; Kim et al., 1980). The strongest 2f1- f2 DPOAE were produced by the stimulus frequencies about 20% apart in frequency and fl/f2 ratio of 1.22 (Petersen et al., 2017). It has been shown that decreased DPOAEs levels correlated with outer hair cell destruction, supported by histological analysis, demonstrates that outer hair cells contribute to the production of DPOAEs (Brown et al., 1989). A decline in the production of OAEs with ageing may reflect ongoing OHC deterioration brought on by ageing (Uchida et al., 2008).

2.2 Aging and Auditory System

The prevalence of bilateral hearing loss is around 25% at 70 years of age and rises to 85% at the age of 85 years (Göthberg et al., 2020; Hoff et al., 2018, 2023). According to the latest Global Burden of Disease Studies (GBD 2019 Diseases and Injuries Collaborators, 2020), hearing loss is considered one of the six most important drivers of increasing burden (disability-adjusted life-years) in older adults. In 2015, hearing loss was one of the eight leading causes of chronic disease and injury (Chang et al., 2019). Livingston et al. (2020) show that hearing loss in elderly adults is a potentially modifiable factor that helps reduce the risk of dementia.

According to Schmiedt (2010), the inner ear is more vulnerable to age-related changes among the three parts of the ear. The ageing cochlea has undergone the following two most noticeable physiological changes: an increase in the auditory nerve's action potential (CAP) and a decrease in cochlear endolymphatic potentials (EP) (Gates & Mills, 2005). According to recent research, the main contributing factor to age-related hearing loss (ARHL) is metabolic/strial presbycusis or degenerative alterations in the lateral wall and stria vascularis (Ohlemiller, 2009). Increased thresholds of the auditory nerve's compound action potential, a sign of asynchronous firing of the fibres, are another physiological defect in the ageing cochlea (Gates & Mills, 2005). The peripheral and central auditory systems experience pathological and physiological changes with age (Hoth, 1996). Further research is required to comprehensively address underlying mechanisms and determine whether early hearing loss detection can delay or arrest late-life cognitive decline or dementia

(Jayakody et al., 2018). Screening for hearing loss in a senior population could benefit hearing and general health (Gates & Mills, 2005).

2.3 Ageing and DPOAEs

The OAEs are a suitable means for monitoring cochlear function because of their relative simplicity, better sensitivity, and objectivity of technique (Gates et al., 2002; Mills et al., 2000). According to Collet et al. (1990), ageing affects OAEs and is linked with the alteration of cochlear biomechanics and hair cell loss. There is a reduction in the DPOAEs amplitude with ageing because of the decrease in endocochlear potential, reduced prestin activity, and preserved hair cell bundle function (Lai & Bartlett, 2015). Several studies suggest that with an increase in age, the amplitude of DPOAEs decreases, mainly observed in the high frequencies (Bonfils et al., 1988; Brown et al., 1989; Lasky et al., 1992).

In a study by Glavin et al. (2021), the authors aimed to see the effect of ageing on DPOAE in individuals with clinically normal hearing sensitivity. The authors took 199 individuals with an age range of 10-65 years and found an apparent decline in DPOAE growth function beginning in the third decade of life, and this decline is greatest at the cochlear base. So, there is a need for further research where hearing-related monitoring and treatment precede communication difficulties. Another study also found similar results that independent of the hearing thresholds, DPOAEs deteriorate with age. The authors concluded that in future, DPOAEs could be a promising tool to assess the ageing effects before any change in hearing sensitivity (Uchida et al., 2008). The ageing effect in DPOAEs is seen as a reduction in amplitude, which is more seen explicitly in the two highest test frequencies, 6 and 8 kHz. Early ageing weakens cochlear expressions of non-linearity, such as the DPOAE and the

DPOAE I/O functions that become linearised (Poling et al., 2012). The remarkable ageing effect conserves the reflection-emission levels and significantly reduces distortion-emission levels. This relative pattern of OAE loss with ageing might serve as a diagnostic indicator for cochlear abnormalities caused by ageing (Abdala et al., 2018).

2.4 Ageing and Extended High-frequency Thresholds

According to a study by Lee et al. (2012), age-related cochlear damage starts as early as the third or fourth decade of life, more in the basal part of the cochlea that cannot be detected appropriately by conventional clinical measures. Threshold estimation using a standard audiometric frequency range (up to 8 kHz) showed no clinically significant reduction throughout life. Brant and Fozard., (1990) conducted a longitudinal study with males aged 20 to 95 years and found that hearing loss in males 70 and older is greatest at the highest frequencies. Many older adults with hearing loss remain untreated or undiagnosed until the damage does not reach the conventional frequencies (Brant & Fozard, 1990). A cohort study was conducted with a mean age of 71.1 years by Rigters et al. (2018) and found that the mean progression of hearing loss was 0.29 and 1.35 dB/year at conventional audiometric frequencies.

Pure tone audiometry is a standardised behavioural test to assess hearing acuity at conventional frequencies (250 to 8000 Hz). The frequency range for human hearing extends from 20 to 20,000 Hz, which explains that conventional pure tone audiometry (PTA) is not an effective tool for assessing the entire frequency range of human hearing. Due to this limitation of conventional audiometry, it is suggested to use extended high-frequency audiometry (EHF), which evaluates frequencies from 9,000 to 20,000 Hz. Age-related alterations in hearing levels occur significantly earlier in the EHF range, greater than 8 kHz (Lee et al., 2012). Across the entire frequency range, it has been reported that two different ageing processes impact the hearing thresholds: the slower process occurring at low frequencies and the faster process at higher frequencies. These findings suggest that extended high-frequency loss may have already occurred when the initial traditional pure tone audiogram (0.25-8 kHz) indicates age-related hearing loss (Lee et al., 2012; Uchida et al., 2008). The rapid ageing process begins at ages 51, 47, 46, 36 and 30 for frequencies 6, 8, 10, 11, and 12.5 kHz (Lee et al., 2005). Recently, it has been shown that the EHF (up to 20 kHz) temporal information can enhance speech-in-speech recognition associated with speech, which is bandlimited to 8 kHz (Trine & Monson, 2020). In the same study, Trine and Monson (2020) also found a significant relationship between speech recognition thresholds (SRTs) and EHF thresholds. The EHF temporal insights provide a 0.9 dB improvement in speech recognition. Hearing at EHF exhibits signs of early auditory ageing (Aziz et al., 2020a). According to Mishra et al. (2022), hearing impairment at EHF severely affects speech-in-noise recognition, independent of speech frequencies and age. The findings also suggest that the audibility of EHFs contributes to speech-in-noise recognition (Mishra et al., 2022). The early consequences of ageing are highly sensitive to the EHF thresholds, and even in young populations, age-related EHF threshold alterations are observed (Jilek et al., 2014). EHF insights are essential for the decision of sound elevation and for resolving front/ back chaos. Many studies have reported a relationship between EHF impairment and loss of performance in speech-in-noise. EHF hearing loss is believed to be a hallmark of subclinical hair cell loss in the conventional frequencies and often precedes threshold elevation in the traditional frequencies. EHF thresholds are also helpful in providing knowledge about hair cell loss at lower frequencies.

EHFs have several different roles in auditory disorders. Clinical hearing impairment can be identified early by EHF hearing loss. It can hinder hearing and speech understanding, especially in noisy environments (Valiente et al., 2014). EHFs are also related to age-related hearing loss, acoustic trauma, and ototoxicity. With ageing, hearing levels gradually decline; this loss starts at the higher frequencies and travels down to the lowest frequencies. As a result, the EHFs become vital in age-related hearing impairment as a technique for early investigation of such failure (Best et al., 2005a; Hunter et al., 2020). The study also showed that speech localisation cues are provided by audible speech energy at EHF to eliminate front/back confusion (Best et al., 2005b). Additionally, it has been found that individuals' hearing at EHF deteriorated, starting in their 30s and predominated in their 50s and beyond. Before age 30, EHF's hearing thresholds were less than 26 dB HL. The average threshold values with ageing were up to 75 dB HL (Wang et al., 2021). Several authors reported a significant hearing threshold deterioration above 8000 Hz and its effect on speech in noise performance (Rigters et al.,2018; Vielsmeier et al., 2015; Yueh et al., 2010).

2.5 Extended High-frequencies DPOAEs

The origin of both EHF DPOAEs and DPOAEs at conventional frequencies is via a similar biological mechanism in the inner ear (Dreisbach & Siegel, 2001). Dreisbach et al. (2006) and Wagner et al. (2008) checked for the replicability of high-frequency DPOAEs in normal-hearing adults and concluded that higher frequencies were repeatable. These results encourage the exploration of high-frequency DPOAEs measures to be used as an objective test for monitoring ototoxicity in humans. Testing subjects receiving ototoxic therapies is necessary to determine if monitoring high-frequency DPOAEs will successfully predict ototoxic effects.

The findings imply that changes in compressive non-linearity with ageing may decrease hearing's dynamic range and worsen perceptual deficits in older listeners (Ortmann & Abdala, 2016). Even though the DPOAEs distortion component is present, it is weaker in older and middle-aged adults, especially at high frequencies. The cochlea's compressive non-linearity may degrade during early ageing, and the growth rate for DPOAEs amplitude is steeper in middle-aged people (Ortmann & Abdala, 2016). Lonsbury-Martin & Martin (1990) studied 44 ears of 22 adults aged 21-30. It was found that five ears displayed significant decrements in DPOAE amplitudes. The eldest subjects, who were 30 years old, had four out of the five ears that showed high-frequency deficiencies in DPOAE magnitudes. As a result, ageing effects were evident in these older patients through decreases in the amplitudes of the high-frequency DPOAEs and corresponding increases in detection thresholds.

Due to the emergence of EHF DPOAEs in the range of 9,000 to 16,000 Hz frequencies, changes in hearing preceding hearing loss in conventional audiometric frequencies (250 to 8000 Hz) could be ruled out in the initial stages (Dreisbach et al., 2006). Previous studies have shown that monitoring the cochlea's high-frequency regions is crucial for detecting noise-induced or ototoxicity-induced and age-related hearing loss, which initially affects the higher frequencies and then proceeds to lower frequencies. The emergence of EHF DPOAEs in clinical procedures directly correlates with these findings in clinical settings. (Dunckley & Dreisbach, 2004). A novel objective approach for the early identification of high-frequency hearing loss may thus be established because EHF DPOAE measurements are associated with the properties of the basal region of the human cochlea (Ohlms et al., 1990; Tanaka et al., 1990). Jedrzejczak et al. (2022) showed that the decrease in EHF DPOAEs is related to hearing loss, and 16000 Hz can identify preclinical reductions in hearing levels.

2.6 High-frequency audiometry and DPOAE

Early detection and identification of hearing loss can improve quality of life with practical and timely remediation and rehabilitation. In individuals with EHF hearing loss, decreased DPOAEs in the standard frequencies may reflect preclinical cochlear damage (Mishra et al., 2022). A combination of both EHF PTA and high-frequency DPOAEs enables us to evaluate specifically pre-neural peripheral function as well as evaluation of the cochlear base (high-frequency audiometry) (Aziz et al., 2020). According to a recent study, the EHF DPOAEs should be used to detect hearing loss in the extended high-frequency range (Jedrzejczak et al., 2022). Presbycusis of the high frequencies was likely present in the background, which might go unnoticed until the speech frequencies are impacted. EHF PTA is a sensitive and practical method that can diagnose sensorineural impairment earlier than traditional PTA and effectively evaluate cochlear function (Aziz et al., 2020). The authors further concluded that EHF DPOAE should be used as a screening tool, followed by extended PTA testing for confirmation. Valiente et al. (2014) conducted a study on 11 individuals suffering from disorders like Fabry disease; Sinonasal Ca treated with RT+cisplatin, lack of understanding in noisy surroundings, suspicion of genetic hearing loss, etc. The authors performed conventional and extended high-frequency audiometry and found that although these patients showed normal thresholds in conventional PTA, their EHF audiometry was affected.

2.7 Summary

DPOAEs can be applied as a preclinical tool to identify early ageing, which has already been reported in the literature. Before any alterations are detected by conventional pure tone audiometry, the decline or absence in DPOAEs amplitude implies hearing loss. According to a recent study, the EHF DPOAEs should be used to detect hearing loss in the extended high-frequency range (Jedrzejczak et al., 2022). EHF DPOAEs are essential in identifying disorders like ototoxicity, noise-induced hearing loss, and cystic fibrosis (de Mello et al., 2014; Dreisbach & Siegel, 2001). DPOAEs at EHF can also identify heterozygous individuals with Gap Junction Protein Beta-2 gene mutation even before clinical manifestation in audiometry is observed. (de Mello et al., 2014). Elderly persons with hearing loss have higher rates of hospitalisation, death (Fisher et al., 2014), dementia (Fisher et al., 2012) and depression even when known risks for these disorders are considered (Lin et al., 2011). A causal relationship between high-frequency sensorineural hearing impairment and diabetes mellitus has been found (Demeester et al., 2005). EHF loss may indicate impending impairment and can help with diagnosis and hearing health monitoring. There is evidence between EHF loss and issues with speech perception, albeit this relationship may not be causative as EHF loss may instead be a marker for subclinical damage at lower frequencies. In some circumstances, speech perception may depend on EHF information. If a causal relationship exists, amplification in the EHF region would be advantageous if the technological challenges can be resolved (Lough et al., 2022). Škerková et al. (2023) reported that hearing thresholds at EHFs begin to deteriorate from 35 years onwards; initially, the effects are more observed in the high frequencies (14 &16 kHz), and as age increases, the result is observed more in low frequencies. The increase in hearing threshold rate is more rapid in males than females. On the other hand, it is unclear if ageing has a similar impact on the DPOAEs at EHFs. Therefore, more research is required to understand how ageing affects DPOAEs at conventional and EHFs.

CHAPTER III

METHOD

The present study aimed to investigate the effect of age on Distortion Product Otoacoustic Emissions (DPOAEs) at conventional and extended high frequencies.

3.1 Participants

The study was conducted on eighty adult (160 ears) participants aged 15-55 with an equal number of males and females. The participants were further categorised into four subgroups to see the age-related changes. The four subgroups of study participants include Group I (15– <25 years), Group II (25-<35 years), Group III (35-<45 years) and Group IV (45-55 years).

3.1.1 Subject Selection Criteria

The following Inclusion criteria were followed for the selection of participants in all four subgroups:

- The participants with normal otoscopic findings were selected for the study.
- The selected participants had pure tone hearing thresholds of ≤ 25dBHL (ANSI, 1969) in both ears for both Air conduction (250Hz- 8000Hz) and Bone conduction thresholds (250Hz-4000Hz).
- The air-bone gap (ABG) is less than 10 dB. The mean hearing thresholds are shown in Figure 3.1.
- Speech identification scores (≥ 90%) as measured with speech audiometry.
- Participants with no history of any middle ear pathology (ear discharge, ear pain, etc.)

- Individuals with no noise exposure history and no medical conditions like hypertension and diabetes mellitus.
- Individuals with no history of any relevant otological problems or retro-cochlear pathologies.
- Participants with no history or presence of any neurological conditions.

Participants who fulfilled the above criteria were included in the study.

3.2. Test Environment

All the selected participants underwent testing in an acoustically treated room, which satisfies the standards for ambient noise level specified by ANSI S3.1-1999 (R2018).

3.3 Ethical Consideration

All the testing procedures in the present study were performed using a non-invasive approach. The test procedures were clearly explained to the participants before the testing, and written informed consent was also taken from all the individuals for their participation in the study.

3.4 Instrumentation

The following instruments were used for the present study:

- An otoscopic examination was conducted to observe the external auditory meatus and eardrum status.
- The two-channel calibrated Grason-Stadler Inc. AudioStar Pro™ (GSI Audiostar Pro) Audiometer was used to perform threshold estimation in dBHL at the octave frequencies in the conventional frequency range and to carry out speech audiometry.

- The calibration was done in dB SPL to measure the pure tone thresholds at extended high frequencies (9000-16000 Hz).
- The Pure tone audiometry for air conduction threshold estimation was obtained using calibrated TDH 39 headphones at frequencies 250 Hz to 8000 Hz and bone conduction thresholds through a calibrated B-71 bone vibrator at 250 Hz to 4000 Hz.
- The Extended high-frequency audiometry was performed using Sennheiser HDA-200 headphones at 9000 Hz to 16,000 Hz.
- A calibrated Grason-Stadler Inc. Tympstar Pro (GSI Tympstar Pro) Immittance meter was used to perform tympanometry and the acoustic reflex threshold measurements with the probe tone frequency of 226 Hz. Ipsilateral and contralateral acoustic reflexes were measured at 500, 1000, 2000, and 4000 Hz.
- A calibrated Starkey Mimosa OAE DP2000 system measured DPOAEs at conventional and extended high frequencies.

3.4. Procedure

3.4.1 Case History and Otoscopic Evaluation

A detailed case history was obtained from all the subjects to rule out any pathological conditions of the auditory system, noise exposure, and associated medical or neurological history. Visual examination of the external auditory meatus and the eardrum was done using a handheld otoscope to rule out the presence of wax, foreign bodies in the ear canal or external or middle ear pathologies.

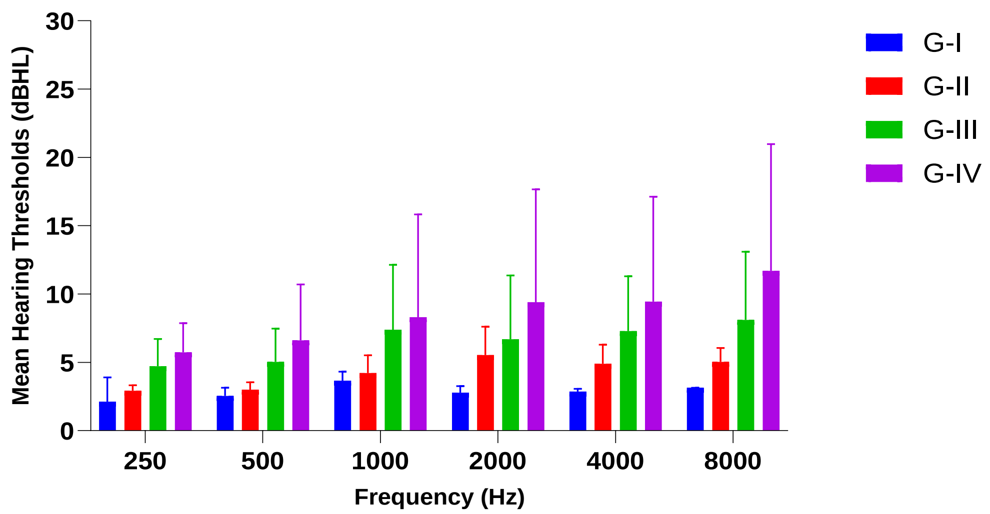
3.4.2 Pure Tone and Speech Audiometry

A Dual-channel calibrated GSI Audiostar Pro audiometer was used for estimating the hearing thresholds in dBHL using the modified Hughson and Westlake procedure (Carhart & Jerger, 1959) for all the participants. TDH 39 headphones were used to obtain the air conduction thresholds at octave frequencies from 250 to 8000 Hz. B-71 bone vibrator was used to measure bone conduction thresholds at 250 to 4000 Hz octave frequencies. The participants were instructed to raise their fingers whenever they heard minimal sound via the transducers.

The participants were asked to repeat the words they heard for speech audiometry. Standardised test materials (spondee words and phonemically balanced words) were used to carry out speech audiometry and to measure both ears' speech identification scores (SIS) presented at 40 dBSL (Ref: SRT level).

Figure 3.1

Mean and SD of air conduction thresholds across age groups



3.5.3 Immittance Evaluation

A calibrated Garson Stadler Inc. Tympstar Pro immittance meter was used to carry out tympanometry and ipsilateral and contralateral acoustic reflex using a probe tone frequency of 226 Hz. External auditory meatus pressure varied from +200 to -

400 daPa. Pure tones recorded ipsilateral and contralateral reflexes at 500, 1000, 2000 and 4000 Hz. The participants were instructed not to move and to swallow during the testing. Immittance audiometry was done to rule out the presence of any middle ear pathology.

3.5.4 Extended high-frequency audiometry

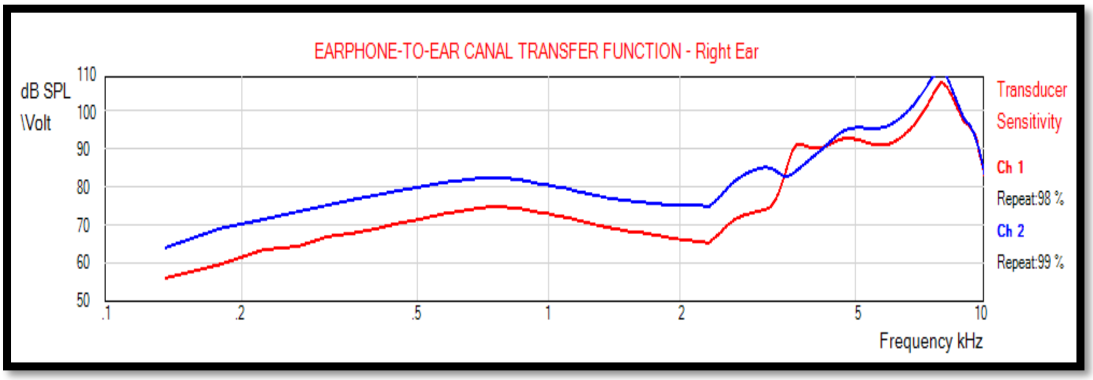
A dual-channel calibrated GSI Audiostar Pro audiometer was used to estimate the extended high-frequency thresholds in dBSPL using the modified Hughson-Westlake procedure (Carhart & Jerger, 1959) for all the subjects. Sennheiser HDA-200 headphones were used to measure the thresholds at 9000, 10,000, 11250, 12500, 14000 and 16000 Hz for both ears. The participants were instructed about the procedure before the threshold estimation and were asked to listen attentively and respond by raising their fingers whenever they heard the tone.

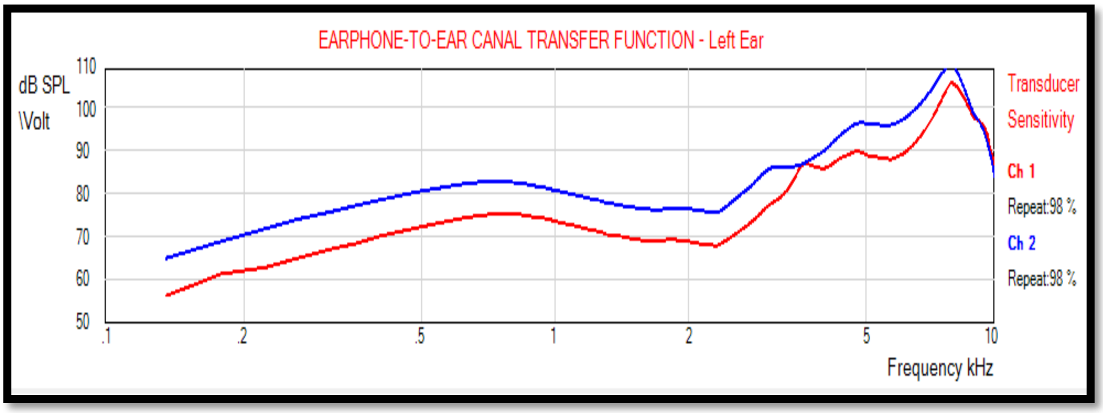
3.5.5 DPOAEs Recording

DPOAEs measurements were carried out using a calibrated Mimosa Acoustics OAE system in a sound-treated room. After ensuring the appropriate probe fitting, each time in ear calibration was performed prior to recording both the conventional and high-frequency DPOAEs. The instrument provided a chirp stimulus via transducers for in-the-ear calibration. The two calibration curves overlapping were required to ensure proper probe fit and reasonable calibration, as shown in Figure 3.2. The probe needed to be fitted again if the reproducibility of the two curves was below 95 per cent, and the test was aborted in between. In the current study, 95 per cent or more reproducibility was considered for all the DPOAE measurements. DPOAEs recording was carried out using the two frequencies, f1(lower frequency) and f2(higher frequency), and two intensities, L1(65 dB SPL) and L2 (55 dB SPL). In humans, the most common distortion product ear occurs at 2f1-f2 with an f2/fl ratio of 1.22. The DPOAEs measurements at 12 frequencies, which includes 500, 1000, 1500, 2000, 4000, 6000, 8000, 9000, 10250, 12500, 14000, and 16000 Hz, were carried out for both ears.

Figure 3.2

In-the-ear calibration for Right and Left ear





The participants were instructed to relax and were informed about the test procedure. They were asked to minimise body movements and not to speak while recording the DPOAEs. The measurements were taken twice, and the average of both was considered as a response. All DPOAEs recordings were analysed using standard OAEs parameters like OAEs amplitude and signal-to-noise ratios (SNRs). The response levels were expressed in dB SPLs, and the SNRs were calculated as the difference in the DPOAEs response level and the noise floor in dB

CHAPTER- IV

RESULTS

The present study investigated the effect of age on extended high-frequency DPOAEs in adults aged 15-55. The study was conducted on eighty adults (160 ears) with an equal number of male and female participants, and they were further divided into four groups based on age. No significant difference in age was observed for the male and female participants across four age groups. The mean, median, standard deviation and interquartile range (IQR*)* of the participants across different age groups are depicted in Table 4.1. The DPOAEs amplitude, signal-to-noise ratio (SNR) and noise floor measurements were carried out in ten different frequencies across 500–16000 Hz to accomplish the study's objectives. The DPOAEs amplitude and SNR were compared across four groups as a part of the between-group analysis. The relationship between pure tone thresholds, DPOAEs amplitude, and SNR was compared via within-group analysis.

Table 4.1:

Mean, Median, Standard deviation and Interquartile range (IQR) of participants across four groups

Groups	Age range (years)	Number of subjects		Mean Age (SD)		Median (IQR)	
		Male	Female	Male	Female	Male	Female
Group I	15- <25	10	10	21.4 (2.19)	20.7 (2.34)	21.7 (3.73)	20.6 (4.07)
Group II	25 - <35	10	10	29.4 (2.10)	29.9 (2.27)	29.4 (3.98)	29.8 (3.32)
Group III	35 - <45	10	10	40.5 (4.38)	39.7 (2.76)	39.6 (5.80)	39.4 (4.95)
Group IV	45 - 55	10	10	50.6 (3.69)	49.3 (2.48)	49.9 (7.49)	49.5 (5.13)

4.1 Statistical Analysis

Statistical Package for the Social Science (SPSS) version 26 software was used for descriptive and quantitative data analysis. The statistical tools that were used to analyse the data were as follows:

- The normality of the data distribution was assessed using the Shapiro-Wilk test.
- Descriptive statistics were conducted to obtain the median and Interquartile range for various parameters of extended high-frequency DPOAEs and EHF thresholds.
- The results of the Shapiro-Wilk test showed that the data was not normally distributed ($p < 0.05$), so non-parametric inferential statistics were administered to the data.
- Between-group comparisons were made using the Kruskal-Wallis test to study the effect of age on DPOAEs amplitude, SNR, extended high-frequency (EHF) PTA and gender across the four age groups.
- A pairwise comparison across all age groups to see which groups differ significantly in DPOAEs amplitude, SNR and extended high-frequency (EHF) thresholds.
- Correlation analysis was conducted using Spearman's rho Coefficient to see the relationship between the EHF PTA and the DPOAEs amplitude and SNR.

The results obtained via different statistical tools are discussed below for all four groups.

4.2. Between-Group Comparison

4.2.1 Noise floor

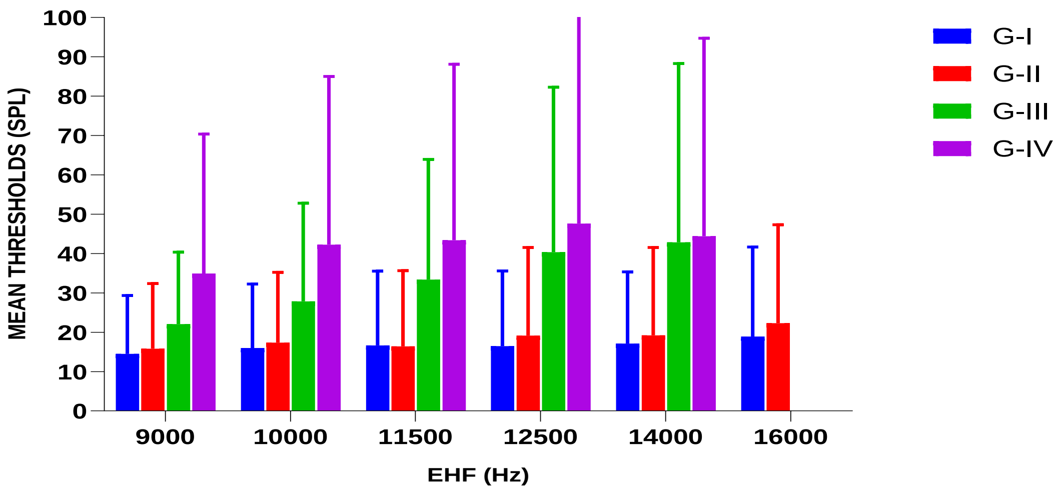
The Kruskal-Wallis test was used to determine whether there was an effect of age on the DPOAEs noise floor across four groups. The results showed no significant difference ($\chi^2(3)$ =4.69, p=0.83) at all conventional frequencies from 500 to 8000 Hz and EHF from 9000 to 16000 Hz across four age groups ($p > 0.05$).

4.2.2. Extended High-frequency Audiometry (EHF)

The hearing thresholds at extended high frequencies were compared in different age groups (Figure 4.1), and the results showed a significant difference at all frequencies from 9000 to 16000 Hz ($p < 0.05$). The hearing thresholds were better at 9000 for all the groups and worsened across frequencies as the age increased, with no responses in Group III (35-<45 years) and Group IV (45-55 years) participants at 16000 Hz.

Figure 4.1

The median and interquartile range of EHF hearing thresholds in SPL across four age groups



The EHF thresholds lie within the 20-95 dB SPL range across four age groups. The Kruskal-Wallis test showed that EHF hearing thresholds across frequencies (9000-16000 Hz) were significantly different across four age groups ($p < 0.05$). Therefore, a pairwise comparison was conducted to see which group differed significantly from the other groups across extended high frequencies. The data analysis showed that Groups I and II significantly differed from Groups III and IV ($p < 0.05$). There was no significant difference between Group I (15- <25 years) and Group II (25 - <35 years) except at 16000 Hz frequency ($p > 0.05$). The last two groups, Group III (35 - <45 years) and Group IV (45 - 55 years), also showed no significant difference across frequencies except at 9000,10000 and 11500 Hz frequency ($p > 0.05$) since the thresholds at 12500, 14000 and 16000 Hz reached near the maximum limits of the audiometer. The details of the pair-wise comparison are shown in Table 4.2

Table 4.2

Pairwise comparison across age groups at extended high frequencies

Frequency (Hz)	Groups											
	GI-GII		GII-GIII		GIII-G1V		GI-GIII		GI-GIV		GII-GIV	
	Test Statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p
PTA 9000	-1.299	.194	-4.381	.000*	-4.122	.000*	-5.680	.000*	-9.802	.000*	-8.503	.000*
PTA 10000	-1.449	.174	-4.747	.000*	-3.808	.004*	-6.195	.000*	-10.003	.000*	-8.555	.000*
PTA 11500	-1.415	.157	-5.023	.000*	-1.689	.002*	-6.438	.000*	-10.127	.000*	-5.023	.000*
PTA 12500	-1.941	.052	-5.222	.000*	-3.221	.091	-7.162	.000*	-10.031	.000*	-8.186	.000*
PTA 14000	-3.141	.077	-5.338	.000*	-2.005	.075	-8.459	.000*	-8.587	.000*	-6.161	.000*
PTA 16000	-4.254	.000*	-5.311	.000*	-	-	-9.322	.000*	-	-	-	-

Note- Group I: 15- <25 years, Group II: 25 - <35 years, Group III: 35 - <45 years, Group IV: 45 - 55 years, p< 0.05 (significance difference)*

4.2.3. DPOAEs Amplitude and SNR at Extended High Frequencies

Figures 4.2 and 4.3 show recording samples of DPOAEs amplitude and noise floor for two age groups.

Figure 4.2

The DPOAEs amplitude and noise floor for Group II: 25 - <35 years

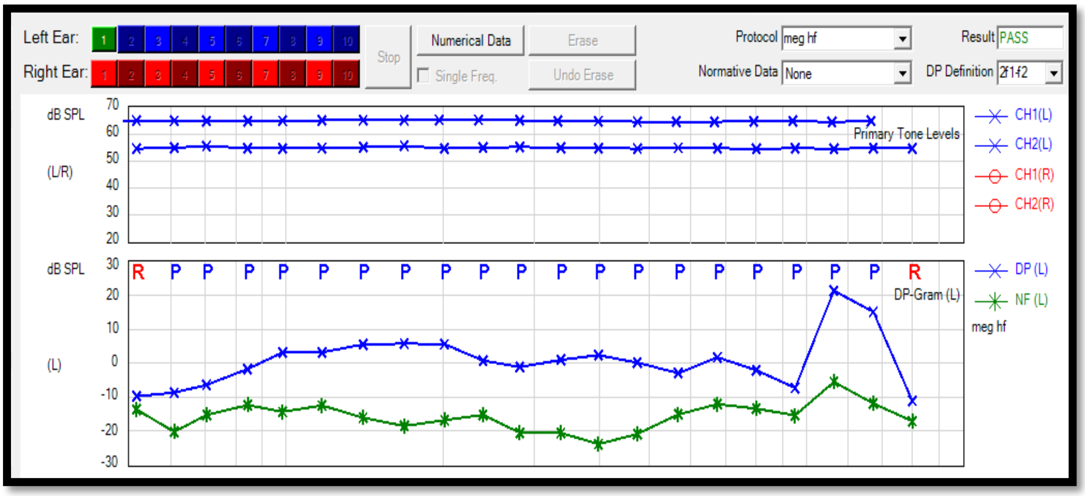
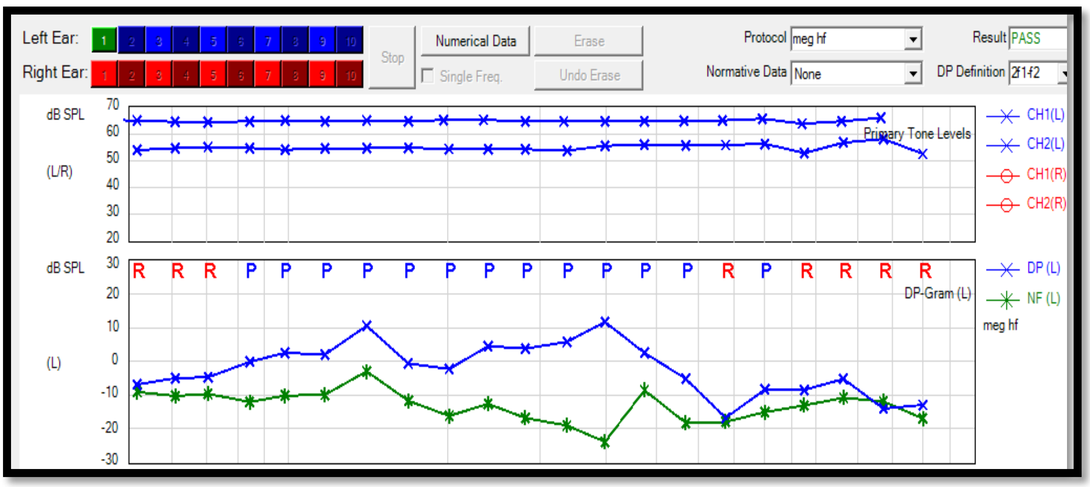


Figure 4.3

The DPOAEs amplitude and noise floor for Group IV: 45 - 55 years



The DPOAEs amplitude for EHF lies within the range of -32 to 17 dB SPL and SNR within -30 to 23 dB across frequencies. The Kruskal Wallis test showed a significant difference across all the extended high frequencies (9000 to 16000 Hz) for DPOAEs amplitude ($\chi^2(3) = 78.19$, p=0.000) and SNR ($\chi^2(3) = 79.32$, p=0.000). The results depicted decreased DPOAEs amplitude and SNR across frequencies with increased age (Figures 4.4 & 4.5).

Figure 4.4

The median and interquartile range for DPOAEs Amplitude at EHF across different age groups

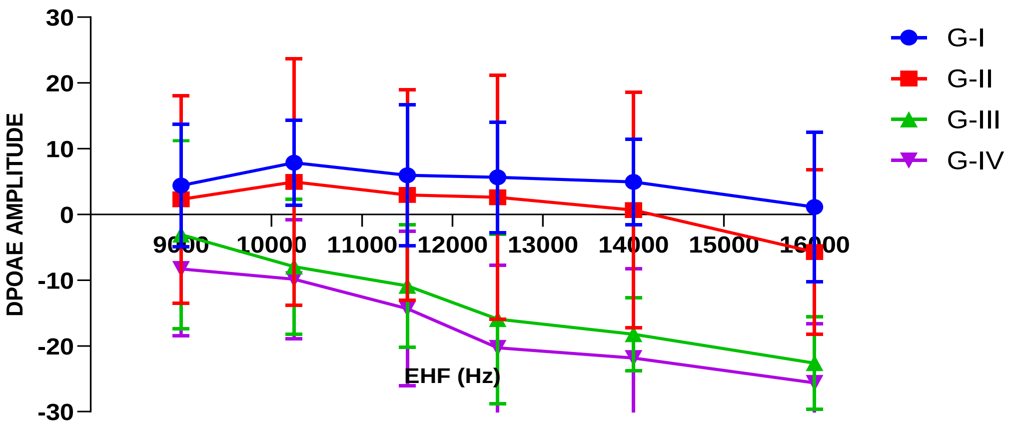
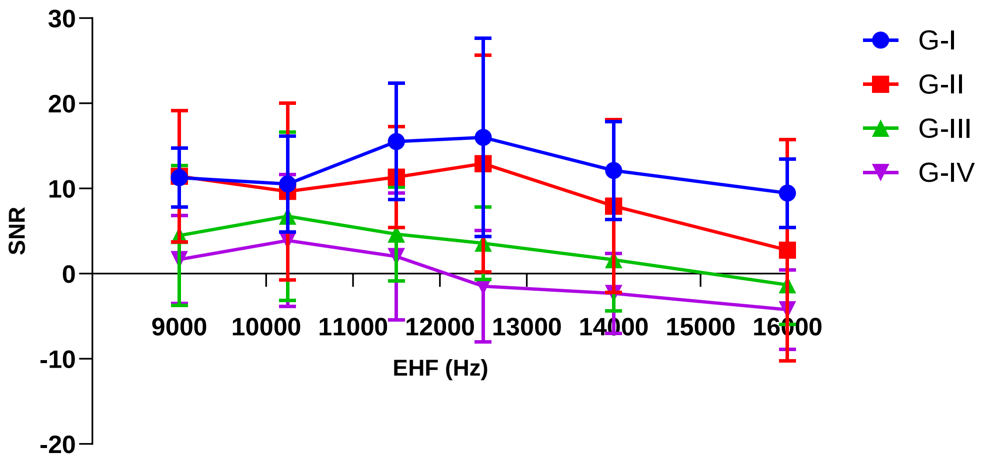


Figure 4.5

The median and interquartile range for SNR at EHF across different age groups



A pairwise comparison was done to see which group differed significantly from the others. For extended high frequencies (9000-16000 Hz), there was no significant difference in DPOAEs amplitude and SNR between Groups I and II (except at 16000 Hz) and Groups III and IV (except at 9000 Hz) (p>0.05). However, Group I and Group II differed significantly from Group III and Group IV for DPOAEs amplitude and SNR in all the test frequencies (p<0.05). The results of pair-wise comparisons are shown in Tables 4.3 and 4.4.

Table 4.3

Pairwise comparison at EHF for DPOAEs Amplitude across the four age groups

Frequency (Hz)	Groups											
	GI-GII		GII-GIII		GIII-G1V		GI-GIII		GI-GIV		GII-GIV	
	Test Statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p
DPOAE 9000	.407	.684	2.968	.003*	3.264	.001*	3.375	.001*	6.639	.000*	6.232	.000*
DPOAE 10250	1.598	.062	2.025	.004*	.391	.696	3.623	.000*	4.014	.000*	1.416	.002*
DPOAE 11500	0.640	.080	3.462	.000*	1.85	.067	6.102	.000*	8.493	.000*	5.853	.000*
DPOAE 12500	.697	.486	5.315	.000*	1.928	.084	6.012	.000*	7.740	.000*	7.043	.000*
DPOAE 14000	1.734	.083	4.584	.000*	.291	.052	6.318	.000*	8.609	.000*	6.875	.000*
DPOAE 16000	4.778	.000*	1.309	.190	1.416	.096	6.087	.000*	8.503	.000*	3.725	.000*

Note- Group I: 15- <25 years, Group II: 25 - <35 years, Group III: 35 - <45 years, Group IV: 45 – 55 years, p< 0.05 (significance difference)*

Table 4.4

Pairwise comparison at EHF for SNR across the four age groups

Frequency (Hz)	Groups											
	GI-GII		GII-GIII		GIII-G1V		GI-GIII		GI-GIV		GII-GIV	
	Test Statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p
SNR 9000	.730	1.00	4.117	.000*	2.419	.016	4.874	.001*	7.269	.000*	6.536	.000*
SNR 10250	.895	.215	2.650	.001*	2.063	.098	2.130	.000*	5.275	.000*	7.713	.005
SNR 11500	2.196	.169	3.507	.000*	2.222	.27	5.703	.000*	7.926	.000*	5.730	.000*
SNR 12500	1.984	.086	4.735	.000*	2.044	.401	6.721	.000*	8.765	.000*	6.779	.000*
SNR 14000	.653	.301	4.400	.000*	1.908	.056	7.054	.000*	8.961	.000*	6.308	.000*
SNR 16000	4.744	.000*	1.023	.002*	2.295	.26	6.768	.000*	9.063	.000*	4.318	.000*

Note- Group I: 15- <25 years, Group II: 25 - <35 years, Group III: 35 - <45 years, Group IV: 45 - 55 years, p< 0.05 (significant difference)*

4.2.4. DPOAEs Amplitude and SNR at Conventional Frequencies (CF)

The DPOAEs amplitude for CF lies within the range of -15 to 30 and SNR within -8 to 34 SPL. The Kruskal Wallis test showed a significant difference across all the conventional frequencies (500 to 8000 Hz) for DPOAEs Amplitude ($\chi^2(3) = 47.83$, p=0.000) and SNR ($\chi^2(3) = 69.34$, p=0.000). The results depicted decreased DPOAEs amplitude and SNR across frequencies with increased age (Figures 4.6 & 4.7).

Figure 4.6

The median and interquartile range for DPOAE Amplitude at CF across different age groups

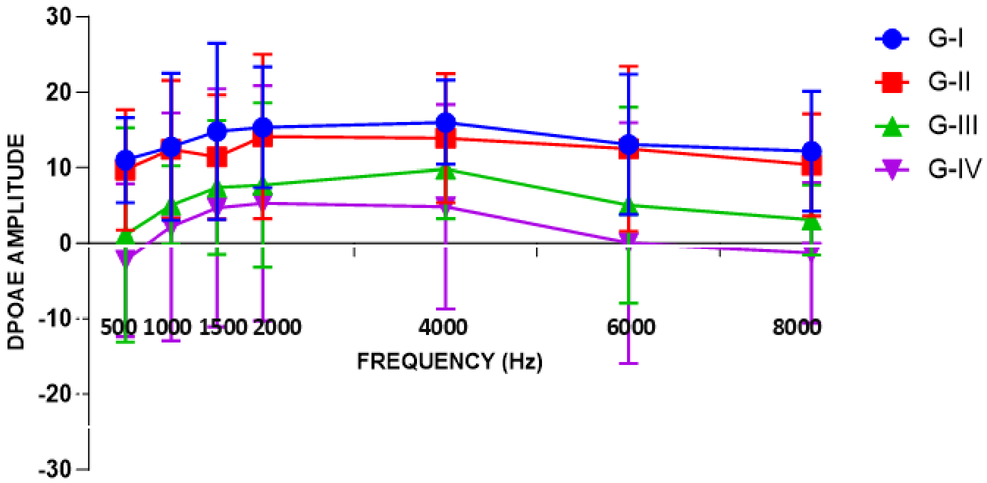
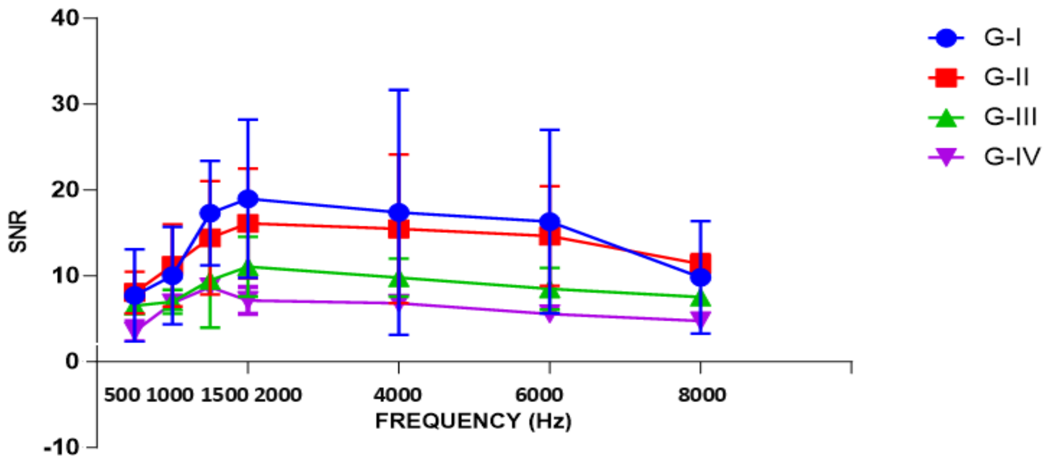


Figure 4.7

The median and interquartile range for SNR at CF across different age groups



A pairwise comparison was done to see which group differed significantly from the others. For conventional frequencies (500-8000 Hz), the data analysis showed no significant difference between Groups I and II ($p>0.05$) for the DPOAEs parameters. Group III differed significantly from Group I and Group II (except at 500, 1000 and 1500 Hz) for DPOAEs amplitude and SNR. Similarly, Group IV differed significantly from other groups for DPOAEs amplitude and SNR (p<0.05). Except for frequencies 500, 1000 and 1500 Hz, Group IV and Group III showed no significant difference (p > 0.05) (Tables 4.5 and 4.6).

Table 4.5

Pairwise comparison at CF for DPOAEs Amplitude across the four age groups

Frequency (Hz)	Groups											
	GI-GII		GII-GIII		GIII-G1V		GI-GIII		GI-GIV		GII-GIV	
	Test Statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p
DPOAE 500	3.790	.790	0.518	.605	1.529	0.126	4.307	.002*	5.836	.000*	2.046	0.41
DPOAE 1000	-.463	.786	-.271	.053	3.912	.201	-.735	.002*	4.646	.000*	4.183	.000*
DPOAE 1500	.321	.748	1.815	.050	4.423	.090	2.136	.003*	6.559	.000*	6.238	.000*
DPOAE 2000	2.558	.061	-.953	.040*	2.968	.003*	3.511	.002*	6.479	.000*	3.921	.000*
DPOAE 4000	1.999	.056	.592	.001*	4.593	.000*	2.592	.007*	7.185	.000*	5.186	.000*
DPOAE 6000	3.489	.097	1.636	.002*	3.016	.000*	5.126	.003*	8.142	.000*	4.653	.000*
DPOAE 8000	2.210	.077	.759	.008	3.834	.000*	2.969	.000*	6.804	.000*	4.593	.000*

Note- Group I: 15- <25 years, Group II: 25 - <35 years, Group III: 35 - <45 years, Group IV: 45 - 55 years, p< 0.05 (significant difference)*

Table 4.6

Pairwise comparison at CF for SNR across the four age groups

Frequency (Hz)	Groups											
	GI-GII		GII-GIII		GIII-G1V		GI-GIII		GI-GIV		GII-GIV	
	Test Statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p	Test statistics	p
SNR 500	2.859	.124	.744	.457	2.905	.094	4.603	.000*	7.508	.000*	3.650	.000*
SNR 1000	1.149	.251	-.110	.913	4.949	.067	-1.258	.020	6.208	.000*	5.059	.000*
SNR 1500	.835	.404	2.893	.074	3.436	.079	3.728	.000*	7.165	.000*	6.330	.000*
SNR 2000	2.869	.148	.999	.009	3.999	.000*	3.868	.000*	7.867	.000*	4.998	.000*
SNR 4000	2.096	.086	1.447	.001*	3.681	.000*	5.543	.000*	9.224	.000*	7.128	.000*
SNR 6000	2.922	.130	3.480	.001*	2.691	.007*	6.402	.000*	9.093	.000*	6.170	.000*
SNR 8000	1.730	.087	2.740	.000*	2.905	.004*	4.470	.000*	7.376	.000*	5.645	.000*

Note- Group I: 15- <25 years, Group II: 25 - <35 years, Group III: 35 - <45 years, Group IV: 45 - 55 years, p< 0.05 (significant difference)*

4.2.5 Gender effect across age groups

The present study reported a gender effect on the EHFs thresholds across the four age groups. There was a significant effect of gender on 9000 Hz in Group II to Group IV ($p < 0.05$). A significant difference was observed for EHF DPOAEs parameters at all frequencies except 16000 Hz in all groups, 12500 Hz in Groups II and III and 11500 Hz in Group IV ($p < 0.05$). Similarly, for conventional DPOAEs, a significant effect of gender was observed at frequencies 2000 and 8000 Hz in groups I and IV and 8000 Hz in Group II.

4.3. Within-group analysis

4.3.1. Correlation Analysis

4.3.1 EHF PTA and DPOAE amplitude

Spearman's rho (ρ) coefficient was computed to assess the relationship between extended high-frequency hearing thresholds and DPOAE amplitude. The correlation analysis was carried out by excluding the hearing thresholds of 16000 Hz frequency for Group IV, as only 3 out of 20 participants showed a response. The results showed a weak negative correlation between the two variables across age groups (ρ (158) = -0.26). An exception with a strong negative correlation was observed for group four (45-55 years) at 10000 and 11500 Hz frequencies.

4.3.2 EHF PTA and SNR

Spearman's rho (r) coefficient was computed to assess the relationship between extended high frequency (except 16000 Hz in group four) and SNR. The results showed a weak negative correlation from 9000 to 16000 Hz for Groups I, II and III (ρ (158) = -0.27).

4.3.3 EHF PTA and conventional frequency (CF) DPOAE Amplitude

Correlation statistics were conducted to see the relationship between EHF PTA and DPOAEs parameters at conventional frequencies (500-8000 Hz). The results implied a weak negative correlation between DPOAE Amplitude and EHF PTA, ρ (158) = -.07, with exceptions observed for Group III at 1500 Hz for all the EHFs where a weak negative correlation was seen (Table 4.7).

4.3.4 EHF PTA and conventional frequency (CF) and SNR

The correlation analysis between EHF PTA and SNR at conventional frequencies showed a weak negative correlation between SNR and EHF PTA, ρ (158) = -.15, with exceptions observed for Group III and Group IV at 1500 and 2000 Hz for all the EHF, where a weak negative correlation was seen (Table 4.8).

Table 4.7

Spearman correlation coefficients for DPOAE at conventional frequencies (CF) across age groups

Age Group (Years)	EHF	DPOAEs at Conventional Frequencies						
		500	10000	1500	2000	4000	6000	8000
15-<25	9000	.070	.126	-.053	-.124	-.067	-.088	-.087
	10000	-.269	.131	.035	-.140	-.053	-.108	-.055
	11500	-.049	.266	-.070	-.203	.065	-.115	-.108
	12500	-.059	.086	-.060	-.027	-.129	-.302	-.401*
	14000	-.070	.014	-.073	-.211	-.039	-.170	-.072
	16000	-.242	-.010	-.197	-.230	-.043	-.159	.010
25-<35	9000	-.186	-.027	-.045	.001	.005	.215	.025
	10000	-.310	.075	-.300	-.185	-.204	-.015	.061
	11500	-.142	.208	-.065	.002	.021	.040	-.100
	12500	.120	.139	.226	.254	-.123	-.060	-.002
	14000	-.122	-.052	.129	.101	-.225	-.304	-.164
	16000	-.157	.241	-.044	-.026	-.114	-.238	-.176
35-<45	9000	-.293	-.254	-.337*	-.300	-.175	-.323*	-.311
	10000	-.346*	-.119	-.453*	-.194	-.114	-.320*	-.319*
	11500	-.527**	-.284	-.367*	-.257	-.228	-.303	-.107
	12500	-.249	-.266	-.315*	-.187	-.241	-.210	-.086
	14000	-.381*	-.232	-.414**	-.350*	-.185	-.173	-.068
	16000	.113	.084	.117	.375*	-.061	.242	.111
45-55	9000	-.265	-.190	-.219	-.256	-.131	-.115	-.105
	10000	-.169	-.071	-.118	-.141	-.019	-.043	-.023
	11500	-.322*	-310*	-.284	-.288	-.209	-.237	-.042
	12500	-.290	-.322	-.351*	-.310	-.213	-.027	.073
	14000	-.241	-.122	-.104	.076	-.151	.039	-.128
	16000	-	-	-	-	-	-	-

Note: *Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed)

Table 4.8

Spearman correlation coefficients for SNR at conventional frequencies (CF) across age groups

Groups	EHF	CF SNR						
		500	10000	1500	2000	4000	6000	8000
15-<25	9000	.151	.122	.050	-.164	-.117	-.097	-.087
	10000	.143	.145	-.044	-.145	-.221	-.050	-.107
	11500	.237	.096	.003	-.235	-.043	-.014	-.056
	12500	.078	-.166	-.049	-.109	-.081	-.302	-.200
	14000	.128	.078	-.044	-.166	-.075	-.203	.054
	16000	-.013	-.023	-.208	-.145	-.116	-.012	.093
25-<35	9000	-.149	-231	.133	.201	.015	.262	.025
	10000	-.253	-.025	.118	-.090	-.094	-.019	.061
	11500	-.012	.245	.206	.057	-.134	.019	-.090
	12500	.019	-.156	.059	.137	-.152	-.019	-.015
	14000	-.113	-.036	-.028	-.049	-.235	-.275	.149
	16000	-.300	-.042	.041	-.096	-.196	-.203	-.084
35-<45	9000	-.232	-.113	-.023	-.300	-.124	-.291	-.237
	10000	-.232	-.017	-.250	-.329*	-.276	-.287	-.438**
	11500	-.384*	-.095	-.339*	-.410**	-.303	-.338*	-.320*
	12500	-.143	-.075	-.281	-.373*	-.290	-.196	-.234
	14000	-.242	-.201	-.230	-.350*	-.311	-.087	-.222
	16000	.217	.138	.018	.277	-.073	.216	-.064
45-55	9000	-.057	-.191	-.304	-463**	-.286	-.259	-.318*
	10000	.064	-.099	-.122	-.355*	-.233	-.114	-.135
	11500	-.163	-.257	-.198	-.337*	-.290	-.207	-.135
	12500	-.326	-.351*	-.239	-.470**	-.363*	-.334	-.273
	14000	.042	.218	-.076	-.292	-.253	-.459	-.378
	16000	-	-	-	-	-	-	-

Note: *Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed)

CHAPTER-V

DISCUSSION

The present study aimed to investigate the effect of age on Extended high frequencies (EHF) across four groups ranging between 15-55 years. The study's objectives were to compare DPOAEs parameters at EHF and Conventional frequencies and to see the association between EHF thresholds and DPOAEs at EHFs and conventional frequencies across the four age groups. The results obtained in the present study are discussed below.

5.1. Effect of age on Extended High Frequency (EHF) Pure tone thresholds

Much literature has reported that hearing tends to deteriorate with age, and the effect is observed more on high frequencies than on low frequencies (Aziz et al., 2020; Gates & Mills, 2005; Kim et al., 2019; Silva & Feitosa, 2006). The human temporal bone's histopathological data also revealed a substantial age-related reduction of outer and inner hair cells, particularly in the cochlear base (Seidman et al., 2002; Wu et al., 2021).

The present study measured EHF hearing thresholds (9000, 10000, 11500, 12500, 14000 and 16000 Hz) for four different age groups. This study showed a significant deterioration in hearing thresholds from Group III (35- < 45 years) in all EHFs with no response at 16000 Hz compared to Group I and II. The worst thresholds were observed for Group IV, aged 45 to 55, with no responses at 14000 and 16000 Hz. However, even for Group II (25-<35), the thresholds were significantly higher at 16000 Hz than Group I.

The study’s findings are similar to those previously reported in the literature. Wang et al., 2021 conducted a study measuring EHF thresholds for participants aged

21-70. The authors reported that subjects below 30 years have responses up to 16000 Hz. EHF thresholds deteriorate from 35 years onwards and worsen above 50 years, with no responses for frequencies above 14000 Hz. A study that measured both conventional and EHF thresholds concluded that EHF thresholds decline as a function of age from 30 years onwards for frequencies above 16000 Hz (Maccà et al., 2015). As the age increases, the ability to respond to EHF decreases, and the decline is observed more from 35 years onwards (Škerková et al., 2023).

According to Lee et al. (2012), two separate ageing processes exist, operating on two different time scales: slow and rapid. The slow process is primarily active for the lower frequencies below 8000 Hz. This is why the decline in hearing thresholds is not observed during early ageing for conventional frequencies. On the other hand, the rapid process is primarily active for frequencies beyond 11000 Hz and in subjects aged 30 years. This phenomenon explains why ageing results in progressive degeneration of hair cells in the cochlea at EHF. Another reason for reduced hearing sensitivity at EHFs with ageing is devascularisation associated with atrophy and acellularity of the spiral ligament and stria vascularis. This devascularisation leads to the thickening of the walls of the associated structures, mainly at the extreme basal end of the cochlea (Johnsson & Hawkins, 1972; Jorgensen, 1961). Several authors reported that reduced endocochlear potential affects the inner ear's sensory structures and leads to altered physiology of the supporting structures. Due to this, oxidative stress is caused, affecting the mitochondrial membrane proteins and disturbing calcium homeostasis, which, in turn, accelerates the rapid process of deteriorating hearing at EHF (Jayakody et al., 2018; Roth, 2015; Tavanai & Mohammadkhani, 2017; T. et al., 2003).

In summary, the results of the present study indicate EHF thresholds start deteriorating from 35 years onwards (Group III), with no responses in Group IV (45-

55 years) for frequencies above 14000 Hz. However, the decline at 16000 Hz was also observed in Group II (25-<35).

5.2 Effect of Age on Extended High Frequency (EHF) DPOAE Parameters

There is enormous literature that shows that the DPOAEs decline with age due to loss of compressive non-linearity of the cochlea, hair cells, spiral ganglion, etc., for conventional frequencies between 6000 and 8000 Hz (Murthy & Kalyan, 2013; Seidman et al., 2002; Uchida et al., 2008). The present study showed the significant effect of age on EHF DPOAEs. There was a significant difference at the extended high frequencies (9000 to 16000 Hz) for DPOAEs parameters (Amplitude and SNR). There is no observed significant difference in DPOAEs parameters for Group I and Group II (except at 16000 Hz) and Group III and Group IV (except at 9000 Hz). However, Group I and Group II differed significantly from Group III and Group IV regarding DPOAEs amplitude and SNR.

In humans, most DPOAEs studies have used conventional frequencies (≤ 8KHz); however, hearing at extended high frequencies (EHF) is most susceptible to cochlear damage. The origin of both EHF DPOAEs and DPOAEs at conventional frequencies is via a similar biological mechanism in the inner ear (Dreisbach & Siegel, 2001). Several authors have reported the effect of age at conventional frequencies for DPOAEs parameters (Cilento et al., 2003; Glavin et al., 2021; Uchida et al., 2008; Ueberfuhr et al., 2016). According to Ortmann & Abdala (2016), due to the changes in compressive non-linearity of the cochlea, there is reduced amplitude in the middle-aged group (mean age 52) for conventional DPOAEs. The authors, Uchida et al. (2008), state a deterioration in DPOAEs amplitude with ageing independent of hearing sensitivity. It has also been reported that the decline in conventional frequencies

DPOAEs amplitude begins around 40 years of age before any observed changes in hearing thresholds (Husen & Author, 2020; Murthy & Kalyan, 2013).

Aziz et al. (2020) reported that the sensitivity and specificity of EHF DPOAEs in detecting high-frequency presbycusis were 72.3% and 49.3%, respectively. The details regarding the clinical utility of EHF DPOAEs are very well explained in a study by (Poling et al., 2012). The authors have also reported a good repeatability of EHF DPOAEs to provide preclinical information regarding disorders like ototoxicity, NIHL, and so on (Dreisbach et al., 2006; Dreisbach & Siegel, 2005; Dunckley & Dreisbach, 2004). However, limited studies have been conducted to show the effect of age on EHF DPOAEs.

The present study's findings showed that the deterioration in DPOAEs parameters started as early as 35 years. However, a statistically significant decline at extremely high frequency (16000 Hz) was also observed for Group II (25-<35).

The present study reported a gender effect on the EHFs threshold across the age groups. There was a significant effect of gender on 9000 Hz in Group II to Group IV ($p < 0.05$). A significant difference was observed for EHF DPOAE parameters at all frequencies except 16000 Hz in all groups, 12500 Hz in Groups II and III and 11500 Hz in Group IV ($p < 0.05$). Similarly, for conventional DPOAEs, a significant effect of gender was observed at frequencies 2000 and 8000 Hz in groups I and IV and 8000 Hz in group II. According to Lee et al. (2012), the gender effect was observed on pure tone thresholds at EHF, DPOAEs at conventional and extended high frequencies could be due to the differences in the ear canal length and volume in males and females, which could have led to such differences.

5.4. Relationship between EHF Pure tone Thresholds and DPOAEs at conventional and extended high frequencies

The present study showed a weak negative correlation between EHF thresholds and the DPOAEs parameters for conventional and EHFs. A similar finding was reported by Schmuziger et al. (2005). The authors reported a weak negative correlation between EHF PTA and conventional DPOAEs. This weak negative correlation was due to the level of the primary tones used in the study for DPOAE recording (65/55). Because of this level, the sensitivity of the basal region increases for potential minor pathologies and further increases the strength of association between high-frequency threshold and DPOAE. Hunter et al. (2020) did a study by compiling different findings on EHFs and reported a low correlation between DPOAEs and EHF thresholds. The authors stated that age-related changes in the cochlea alter DPOAE levels before their manifestation in hearing threshold change.

Most studies compared EHF Pure tone Thresholds and DPOAEs at conventional and extended high frequencies for the normal and disordered population. According to Reavis et al. (2008), the EHF audiometry is more precise in identifying disorders associated with high-frequency hearing loss than the conventional DPOAEs. A similar finding was reported by Maccà et al. (2015). In a study by Arnold et al. (1999), the authors found out about the influence of EHF audiometry on conventional DPOAEs. The authors reported that with early ageing, there is a decline in EHF hearing thresholds and conventional DPOAEs at frequencies 6000 and 8000 Hz.

Poling et al. (2012) measured the EHF thresholds and the EHF DPOAEs. The authors concluded that EHF DPOAEs are a good tool for diagnosing early ageing hearing loss, and the strength increases when combined with EHF audiometry. Aziz et al. (2020) and Valiente et al. (2016) also reported that a combination of both EHF audiometry and EHF DPOAE help us to evaluate the cochlear base, specifically pre-neural peripheral function. The authors further concluded that EHF DPOAEs can be a good screening tool with a confirmation via EHF audiometry. The effect of early ageing is more pronounced in EHF DPOAEs, followed by EHF audiometry (Mishra et al., 2020). The present study reported a weak negative relationship between EHF thresholds and DPOAE parameters at conventional and extended high frequencies.

The results of the present study suggest that age's effect is similar for EHF DPOAEs and EHF thresholds. Both start deteriorating from Group II (25-< 35 years) at 16000 Hz. However, the deterioration was observed more from Group III (35-<45 years) onwards, with no responses at 16000 Hz. A significant decline for Group IV was seen from 14000 Hz with no response at 16000 Hz. Also, the thresholds for Group III were comparatively better at 9000, 10000 and 11500 Hz than Group IV, while there was equal deterioration for DPOAEs parameters for both groups. There is a weak negative correlation between EHF thresholds and DPOAEs parameters. Also, there exists a gender effect for EHF thresholds and DPOAEs parameters at EHF and CF across age groups.

To conclude, the deterioration in EHF thresholds starts from 16000 Hz (25-<35 years), followed by 14000 Hz (35-<45) and worse above 45 years of age. The DPOAEs amplitude and SNR were better for Group I > II> III and Group IV, almost similar to Group III. This proves that EHF DPOAEs can be a good tool to assess the age effects and for early diagnosing the disorders affecting the basal region of the cochlea. EHF DPOAEs can be a good screening tool as it is less time-consuming, and the findings can be further confirmed with EHF audiometry. EHF DPOAEs can predict basal part damage of the cochlea way before the conventional DPOAEs. Follow-ups will be earlier and can further help in early management.

CHAPTER-VI

SUMMARY AND CONCLUSION

The present study is conducted to see the effect of ageing on extended high frequencies (EHF) DPOAEs in individuals having normal hearing sensitivity in Conventional/standard pure tone audiometry. There were 80 (160 ears) participants, aged 15-55 years, and further divided into four subgroups. The three objectives of the study were: a) assess and compare the DPOAE parameters at conventional frequencies across different age groups, b) assess and compare the DPOAE parameters at extended high frequencies across different age groups, and c) assess the association between the extended high-frequency thresholds and DPOAEs at conventional and extended high frequencies across different age groups.

EHF audiometry (9000-16000 Hz) and the DPOAEs at 500-16000 Hz frequency are conducted to achieve the study's objectives.

The results of the present study showed significant differences for every parameter except noise floor at all frequencies across age groups. For EHF audiometry, a significant difference is observed across the age groups. Group I and Group II differed significantly from Group III and Group IV. The first two groups, Group I (15- <25 years) and Group II (25 - <35 years showed no significant difference across frequencies, except at 16000 Hz. There was no observed significant difference between Group III (35 - <45 years) and Group IV (45 - 55 years) ($p>0.05$) except at 9000, 1000 and 11500 Hz frequency. Similarly, there was no significant difference in DPOAEs Amplitude and SNR between Group I and Group II (except at 9000 Hz) and Group III and Group IV (except at 16000 Hz). However, Group I and Group II differed significantly from Group III and Group IV for DPOAEs amplitude and SNR. For conventional frequencies (500-8000 Hz), the data analysis showed no significant difference between groups I and II ($p>0.05$) for the DPOAEs parameters. Group III differed significantly from Group I and Group II (except at 500, 1000 and 1500 Hz) for DPOAEs amplitude and SNR. Similarly, Group IV differed significantly from other groups for DPOAEs amplitude and SNR ($p<0.05$). Except for frequencies 500, 1000 and 1500 Hz, Group III and Group IV showed no significant difference ($p > 0.05$). Spearman correlation coefficient showed a weak negative correlation between EHF thresholds and the DPOAEs parameters at EHF and conventional frequencies across age groups. This reduction may be due to the rapid process of degeneration at EHF, devascularisation, reduced oxidative damage, or reduced endocochlear potential, as reported in the literature (Johnsson & Hawkins, 1972; Lee et al., 2012; Roth, 2015).

The conclusions of the present study suggest that age affects EHF DPOAEs before the EHF thresholds and can be used in clinics to identify early ageing signs. The deterioration can be seen before any change appears in the standard frequencies. The EHF thresholds and DPOAEs start deteriorating from below 30 years onwards for frequencies above 16000 Hz, with a rapid decline above 35 years. The study's clinical implications include early monitoring of EHF hearing loss caused by disorders like ototoxicity, noise-induced hearing loss, and cystic fibrosis. Also, understanding age's effect on DPOAEs at EHFs can help identify individuals with a greater risk of developing hearing impairment. It can further guide in early management, counselling, and follow-up assessments.

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