FREQUENCY TUNING OF CERVICAL AND OCULAR VESTIBULAR EVOKED MYOGENIC POTENTIAL IN INDIVIDUAL WITH DIABETIC AND NON-DIABETIC

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This Dissertation is submitted as a part of fulfillment

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CERTIFICATE

This is to certify that this dissertation entitled **"frequency tuning of cervical and ocular vestibular evoked myogenic potential in individual with diabetic and non-diabetic"** is the bonafide work submitted in partfulfillment for the degree of Master of Science (Audiology) of the student Registration Number: 17AUD031. This has been carried out under the guidance of the faculty of the institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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This is to certify that this dissertation entitled **"frequency tuning of cervical and ocular vestibular evoked myogenic potential in individual with diabetic and non-diabetic** has been prepared under my supervision and guidance. It is also being 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 **"frequency tuning of cervical and ocular vestibular evoked myogenic potential in individual with diabetic and non-diabetic"** is the result of my own study under the guidance of Dr. Sujeet kumar Sinha, Reader in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore, and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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Dedicated to Papa, Amma, Chhotu &Sujeet sir, the best guide in the whole world, and to all the participants of my study.

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Abstract

Aim of the study: The aim of the study was to assess the frequency tuning of cervical vestibular evoked myogenic potential and ocular myogenic potential in individual with non diabetic and with diabetes.

Method: A total of 52 participants in the age range of 35 to 65 years participated in the study. Further, they were categorized in to two groups based on their medical history as non diabetic and diabetes. Frequency tuning were assess using cVEMP and oVEMP at 250HZ,500Hz, 750Hz, 1000Hz, 1500Hz and 2000Hz at 125 dBSPL tone burst stimuli.

Results: The result showed that there is no significant difference in the frequency tuning of cVEMP and oVEMP in individual with non diabetic and with diabetes. There is a significant more amplitude of the cVEMP and oVEMP in the individual with non diabetic compare to diabetes.

Conclusions: The study indicates a lesser prevalence of cVEMP and oVEMP in individuals with diabetes. However, there is no change in tunning of cVEMP and oVEMP in individuals with diabetes.

Keyword: Cervical vestibular evoked myogenic potential, Ocular myogenic potential,

Diabetes, non diabetic, Frequency tuning,

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Chapter-1

Introduction

The sensory organ of the vestibular comprises of otolith organ; saccule, utricle, and six semicircular canal (anterior, posterior and lateral). Semicircular canal responds to rotational movement, and saccule and utricle respond to change in the head position with respect to gravity. The function of otolith organ is assessing by the vestibular myogenic evoked potential (VEMP). There are two types of VEMP, Cervical vestibular evoked myogenic potential (cVEMP) and ocular vestibular myogenic evoked potential (oVEMP). These potentials are short latency response which is elicited by placing a surfaced electrode in response to high level of acoustic stimulation. VEMP testing is done to assess to change in vestibular organs.

The cervical VEMP (cVEMP) assess the function of the saccule and inferior vestibular nerve. cVEMP has been used for diagnosing of sacculocollic pathway in different types of disorder such as Meniere's disease (Sinha, Shankar &Govindaswamy, 2015), Noise induced hearing loss (Kumar, Vivarthini, &Bhat, 2010),age related change (Singh, Kashyap, Supreetha&Sahana, 2014), severe to profound hearing loss (Bansal, Sahni, &Sinha, 2013),individual with vestibular neuritis, (Govender, Rosengren&Colebatch, 2011),individuals with auditory neuropathy spectrum disorder,(Singh, Sinha, & Barman, 2016),Individuals with Diabetes Mellitus (Sahu&Sinha, 2015), Superior canal dehiscence syndrome (Zuniga &Janky, 2013).

The ocular VEMP (oVEMP) assess the function of the utricle and superior vestibular nerve. oVEMP has been used for diagnosing of occulocollic pathway in different types of disorder such as Meniere's disease (Sinha, Shankar &Govindaswamy, 2015),severe to

profound hearing loss (Bansal, Sahni, &Sinha, 2013),individual with vestibular neuritis(Govender, Rosengren& Colebatch, 2011),individuals with auditory neuropathy spectrum disorder (ANSD),Singh, Sinha, & Barman,2016),Individuals with Diabetes Mellitus,(Sahu&Sinha, 2015), Benign Paroxysmal Positional Vertigo (Singh & Barman, 2015), vestibular schwannoma (Chiarovano, Darlington, Vidal, lamas &Waele, 2014), differential diagnosis of brainstem and cerebral lesion, (Su & Young, 2011), Superior canal dehiscence syndrome (Zuniga &Janky, 2013).

1.1 Need for the study

1.1.1 *Need for vestibular studies in Diabetes mellitus:*

Diabetes mellitus is a chronic metabolic condition characterized by an increase in blood glucose levels resulting from the inability of the body's to produce insulin, resist insulin action, or both (Silva, Lin, Staecker, Whitney &Kluding, 2016). Myers et al. (1985) found morphological and structural changes in the peripheral vestibular system in animals with experimentally induced diabetes. Diabetes leads to an overproduction of extracellular matrix and a higher incidence of lysosomes and lipid droplets in the connective tissue of the utricle and the saccule. The extracellular matrix leads to impaired diffusion of oxygen, nutrients, and waste products in diabetic animals. Large portion of disrupted myelin sheath lamellae, thinning of the myelin sheath and reduce the diameter of the axon fiber in the vestibular nerve, Hair cell degeneration also has been noticed in diabetic animals (Myers et al. 1985). The level of type 1 hair cell degeneration was higher in the saccule, suggesting that the saccule may be more susceptible to pathology in diabetes. People with diabetes have significant physical limitations because of decreased proprioception and loss of light

touch, visual acuity, contrast sensitivity, and depth perception may increase both the risk and the recurrence of falls in people with diabetes.

Maia and Camos (2005) reported that individuals with diabetes show vestibular symptoms such as dizziness, tinnitus, and hearing impairment. The authors reported that angiopathy and neuropathy caused by diabetes leads to vestibule cochlear problems in diabetes individuals. Makishimaand Tanaka (1971) demonstrated that demyelination of peripheral nerves of diabetes extremity and indications of abnormalities of myelin metabolism. They demonstrated that there was a demyelination of auditory nerve by differentiation of myelin sheath with small affections to axon and fibrosis of perineurum, severe atrophy of spiral ganglion with loss of cell of basal turn and medium turn of the cochlea, in addition to decrease in number of nervous fibers on the spiral lamina in diabetes individuals. Looking at the literature, various studies have demonstrated anatomical and physiological changes in humans and animal's vestibular system. However, there is a dearth of information on various physiological tests conducted in humans to assess the vestibular system.

1.1.2. Need for study of Vestibular evoked myogenic potentials

Kumar, Vivarthini, and Bhat (2010) examined the vestibular evoked myogenic potential in 55 ears with noise induced hearing loss. Kumar et al (2010) reports absence of VEMP in 16 ears, prolonged latency of VEMP in 19 ears, normal VEMP findings in 20 ears. Therefore, VEMP was absent or abnormal 67% of the individual with noise induced hearing loss.

Singh, Kashyap, Supreetha and Sahana (2013) reported age-related changes in sacculocollic response parameters. Total 280 volunteers within the age range of 10-85

years participated for the study. Result of the study demonstrated a steady change in response rate and amplitude with advancing age past 5th decade (50-60 a long time). And latency of P13 and N23 was increased, whereas the threshold worsened with advancing age after 50 years. Bansal, Sahni, and Sinha (2013) on Cervical and ocular vestibular evoked myogenic Potentials in Individuals with Severe to Profound Hearing Loss. Result showed that cVEMP was absent in 100% of subjects in individuals with severe to profound hearing loss, oVEMP was present in 100% of the control and 66% of the experimental group. There was no connection between cVEMP and oVEMP in a person with severe to profound hearing loss.

Sinha, Shankar and Govindaswamy (2015) examined on cVEMP and oVEMP test results in Individuals with Meniere's disease. The result demonstrated that out of 33 ears with Meniere's disease, 29 ears had no response on cVEMP, 23 ears had no response on oVEMP. The normal ear both cVEMP and oVEMP were absent in 5 ears, cVEMP was absent and oVEMP was present in 13 ears, cVEMP was present and oVEMP was absent in 1 ear, whereas both cVEMP and oVEMP were present in 6 ears in individuals with Meniere's disease.

Singh, Sinha, and Barman (2016) examined otolith mediated neural reflexes through cervical vestibular myogenic evoked potential(cVEMP) and ocular vestibular evoked myogenic potentials(oVEMP) in individuals with auditory neuropathy spectrum disorder (ANSD). Result demonstrated that there was a significant prolongation of later peaks and inter-peak latency intervals and significantly reduced amplitudes compared to the controls. cVEMP & oVEMP both showed larger asymmetry ratios compared to the controls, but only cVEMP asymmetry ratio reached a statistically significant level. There

was no significant relationship between cVEMP and oVEMP response prevalence with the presence of vestibular symptoms.

Singh and Barman (2015) examined the effectiveness of oVEMP Potential in finding posterior semicircular canal benign paroxysmal positional vertigo. Total 60 participants participated in this study, 30 individuals with unilateral posterior canal BPPV and 30 age-and gender-matched healthy controls. The results demonstrated that there was significant smaller amplitude in ear with BPPV as compared to non-BPPV and normal ears. However in 5 BPPV participant in affected ears the amplitude was larger as compared to unaffected ears. Also, there was a significant larger interaural amplitude ratio in individual with BPPV as compared to normal ears.

Govender, Rosengren and Colebatch (2011) examined air conduction and bone conduction cervical vestibular myogenic evoked (cVEMP) and ocular vestibular evoked myogenic potential (oVEMP) in individual with vestibular neuritis. cVEMP and oVEMP were recorded using air-conduction and bone-conducted conduction in 63 participants. The result demonstrated that the AC evoked cVEMP showed slight abnormalities but less than the AC evoked oVEMP and lateral impulses showed high rate of abnormalities for both reflexes. But forehead produced low rates of abnormalities for both reflexes and response amplitudes were smaller from the affected ear. Thus, it is evident that the VEMP is useful in assessment of sacculocollic & otolith ocular pathway dysfunction in individuals with various vestibular disorders. However there is a dearth of information regarding the same in individual with diabetes.

Sahu and Sinha (2015) on assessment of sacculocollic pathway in15 individuals with diabetes mellitus and 15 were non diabetic within the age range of 40-60 years. Result

demonstrated that cVEMP was present 100% in individual with control group as well as with diabetes mellitus group. There was no significant difference in amplitude of P1-N1 complex between the normal and diabetes groups. However further studies are required to explain the pattern of sacculocollic pathway & otolith ocular pathway in individual with diabetes.

1.1.3. *Need for studying tuning of cVEMP and oVEMP*

The tuning of cVEMP and oVEMP has been recently demonstrated as one of the important diagnostic tool in diagnosing the secular and utricular disorders in individuals with secular and utricular disease. Piker, Jacobson, Burkard, McCaslin, and Hood (2013) examined the effects of age on the tuning of the cVEMP and oVEMP in 36 participants in the age range of 22-78 years. cVEMP and oVEMP were recorded using125Hz, 250Hz, 500Hz, 750Hz, 1000 Hz, 1500 Hz, and 2000 Hz tone burst stimulus. The results demonstrated that 750Hz and 1000Hz represent the age related changes better than 500 Hz stone burst stimulus.

Jerin, Berman, Krause, Wagner and Gürkov (2014) examined Ocular vestibular evoked myogenic potential frequency tuning in certain Meniere's disease. Total 58 participants participated in this study, 39 patients with Meniere's disease confirmed by MRI and 19 age- matched healthy controls were participated.oVEMP were recorded using 500Hz and 1000Hz air conduction tone burst. Results demonstrated that 500/1000 Hz amplitude ratio was significantly smaller in Meniere's ears when compared to unaffected ears of Meniere's patients and healthy controls. There is a dearth of information on cVEMP and oVEMP tuning in individuals with diabetes mellitus and hence this study was taken.

AIM OF THE STUDY

The aim of the study was to study the pattern of cVEMP and oVEMP in individual with diabetes mellitus.

OBJECTIVES OF THE STUDY

1. To study the effect of diabetes mellitus in cVEMP & oVEMP tuning.
2. To study the effect of duration of diabetes mellitus in cVEMP & oVEMP tuning.

Chapter-2

Review of literature

Inner ear consists of cochlea and vestibular which is responsible for the hearing and balance. Both the system cochlea and vestibular are close to each other because both organs share the same cavity called the membranous labyrinth. So if there is any problem in the cochlea it leads to problem in the vestibular also. The sensory organ of the vestibular comprises of otolithic organ; saccule, utricle, and six semicircular canal (anterior, posterior and lateral). Semicircular canal responds to rotational movement, and saccule and utricle respond to change in the head position with respect to gravity.

Function of saccule and utricle of the vestibular system is assessed using the vestibular evoked myogenic potential. There are two types of vestibular evoked myogenic potential: cervical vestibular evoked myogenic potential and ocular vestibular myogenic potential. Vestibular evoked myogenic potentials is a short latency response which can be recorded by using the surface electrode. Cervical vestibular evoked myogenic potential is an excitatory response. It assesses the saccule and inferior vestibular nerve. Ocular vestibular evoked myogenic potential is inhibitory response. It assesses the utricle and superior vestibular nerve. It helps in identifying the different types of vestibular pathology like perilymphatic fistula, superior semicircular canal dehiscence, Meniers disease; begin paroxysmal positioning vertigo, vestibular Labyrinthitis, vestibular neuritis, noise induced hearing loss, auditory neuropathy spectrum disorder, diabetes mellitus, age related changes, vestibular schwannoma, vestibular nerve compression and multiple sclerosis etc.

2.1 Applications of vestibular evoked myogenic potentials

2.1.1 Noise induced hearing loss

El-Salam et al. (2017) assessed the function of saccule using cVEMP in 40 subjects exposed to noise during their work. cVEMP was recorded using click stimulus which was presented at 95dBnHL.They found that there was significant prolonged latency of P13 and N23 peaks in individuals exposed to noise. The authors concluded that chronic noise exposure damages the vestibular system especially the saccule in addition to cochlear damage.

Elbeltagy&Galhom (2017) assessed the saccular function in 40 subjects with noise induced hearing loss. They found that c-VEMP was absent in 12 (30%) ears, the latencies of P1 and N1 peak was prolonged and the peak-to-peak amplitude was reduced in 16 (40%) ears in individuals exposed to noise.. VEMP results were normal in 12 (30%) ears in the individual with noise induced hearing loss. The authors concluded that noise can cause damage to the vestibular system, especially the sacculocollic pathway. Dalgic et al (2015) analyzed the electrocochleography (ECoG) and cervical vestibular evoked myogenic potential (cVEMP) in 20 participants with noise-induced hearing loss. They divided the patients into two groups based on averaged thresholds at 4, 6, and 8 kHz; whereby, group 1 had a threshold higher than 68.3 dB HL, whereas group 2 had threshold lower than 68.3 dB HL. So they found that group 2 had a significantly higher number of patients with abnormal cVEMP values (63% versus 28%). The authors also reported that cVEMP was abnormal in participants who reported with vestibular symptoms.

Akin et al. (2012) examined the effects of noise exposure on the cervical vestibular evoked myogenic potential (cVEMP) in 43 individuals with asymmetric noise-induced

sensorineural hearing loss (NIHL).Authors found that 33% of the noise-exposed participants had abnormal cVEMPs, whereas cVEMPs were present and symmetrical in 100% of the age-matched controls, and cVEMP threshold was greater in the noise-exposed group than in the control group. Abnormal cVEMPs occurred most often in the ears with poorer hearing (or greater NIHL), and the noise-exposed participants who had abnormal cVEMPs had poorer high-frequency pure-tone thresholds (greater NIHL) and greater interaural high-frequency pure-tone threshold differences than the noise-exposed participants with normal cVEMPs.

Kumar et al. (2010) evaluated vestibular evoked myogenic potentials (VEMP) in 30 subjects (55 ears) with noise-induced hearing loss. They found that VEMP was absent in 16 (29.0%) ears, the latency was prolonged and the peak to peak amplitude was reduced in 19 (34.6%) ears and VEMP results were normal in 20 (36.4%) ears. They concluded that the possibility of vestibular dysfunction, specially the saccular pathway, is high in individuals with noise induced hearing loss.

Wang et al. (2007) examined vestibular system in 20 patients with chronic noise-induced hearing loss, using caloric, and vestibular-evoked myogenic potential tests. They found that Caloric and vestibular-evoked myogenic potential tests revealed abnormal responses in 9 (45%) and 10 (50%) patients, respectively. However, when both results were considered together, the abnormal rate reached 70% (14 of 20). The hearing threshold of 4 kHz significantly associated with vestibular-evoked myogenic potential results, but not with caloric responses. So they conclude that patients with bilateral 4-kHz notched audiogram and hearing threshold of 4 kHz > 40 dB may show abnormal (absent or delayed) vestibular-

evoked myogenic potentials, indicating that the vestibular part, especially the sacculocollic reflex pathway, has also been damaged.

2.1.2 Vestibular evoked myogenic potentials in severe to profound hearing loss

Said (2014) studied otolith function in 30 children with normal hearing and50 children with varying degrees of bilateral SNHL. They found that abnormal VEMP was found in 72% of HI children, but this percentage varied according to the different etiologies, 56.5, 84, and 75% for heredofamilial, acquired, and unknown, respectively. Bilateral saccular affections were more common than unilateral. HI children with profound HL had the highest percentage of both bilateral and unilateral saccular affections in the absence of VEMP.

Rosengren and Colebatch (2006) studied VEMP in 14 patients with severe to profound bilateral hearing loss were stimulated via a B71 bone-vibrator above the mastoid with bone-conducted tone bursts (500 Hz, 6 ms) at fixed levels above their individual vestibular evoked myogenic potential (VEMP) thresholds. They found that 7 out of 14 patients had suitable VEMPs to the maximal stimulus. P10 and N15 potentials were present in each of these 7 patients, but were absent in patients with absent VEMP responses. So they concluded that normal P10 and N15 potentials can be recorded from patients with bilateral profound hearing loss using bone-conducted acoustic stimulation.

2.1.3 Meniere's disease

Dabiri et al. (2017) examined the saccular function using VEMP test in different groups of 100 Meniere's disease. They categorized the Meniere's disease as possible, probable or definite Meniere's disease groups. They found that there was a significant relationship between the severity of hearing loss and absence of VEMP test. Most of the

cases with severe hearing loss were not recorded the VEMP. However, there wasn't any relation between the pattern of hearing loss and absence of VEMP. They concluded that VEMP test could be a valuable diagnostic clue especially in patients with definite Meniere's disease.

Salviz et al. (2015) examined otolith function in 30 subjects with unilateral Meniere's disease (MD) and 18 age-matched controls using cVEMPs and oVEMP testing using bilateral AC tone burst stimulation of 500Hz and 1000 Hz. So they found that in healthy controls and unaffected ears, 500 Hz was better than 1,000-Hz in both oVEMP and cVEMPs, while ears with MD responded to 1,000-Hz better than 500-Hz in oVEMP. In cVEMPs tests, affected ears responded to 500-Hz and 1,000-Hz equally. Amplitude ratios of 1,000/500 Hz in both oVEMP and cVEMPs were successful in differentiating affected ears from unaffected ears and healthy controls.

Kim et al. (2013) studied the vestibular evoked myogenic potential in 41 definite unilateral Meniers disease. They found that in 41 definite unilateral Meniers disease (MD), the prevalence of cervical VEMP abnormality in the inter-aural difference (IAD) ratio was 34.1%. When compared with 33 normal subjects, the VEMP of MD patients showed low amplitude and a similar latency. The mean IAD ratio in MD was 23%, which was significantly different from that of normal subjects. As the stage increased, the IAD ratio significantly increased. Abnormal IAD ratio showed a decrease in hearing over time compared to those with a normal IAD ratio so they conclude that the IAD ratio can be used to assess the stage of MD. An abnormal IAD ratio may be used as a predictor of poor hearing outcomes in subjects with early stage MD.

Murofushi et al. (2011) studied the otolith function in 20 patients with unilateral Meniere's disease (MD), 6 patients with unilateral vestibular neuritis (VN), and 7 healthy subjects. So they found that patient with MD did not show a significant association between their oVEMP and cVEMPs findings When the MD patients were classified into four stages based on their hearing levels, the patients showed abnormal findings at earlier stages on cVEMPs than on oVEMP tests. While all 6 VN patients showed abnormal findings on oVEMP, only 2 patients showed abnormal cVEMPs. So they concluded that the oVEMP predominantly reflects utricular functions while cVEMPs reflects saccular functions.

2.1.4 Benign paroxysmal positioning vertigo

Chen et al. (2019) studied otolith function using VEMP in 42 patients with BPPV after mTBI. They found that there were abnormal cVEMP and oVEMP responses in patients in the recurrent BPPV group after mTBI and patients in the non-recurrent BPPV group after mTBI, and there was no significant difference between both groups in cVEMP and oVEMP. But oVEMP abnormalities in recurrent BPPV group after mTBI are significantly higher than those in non-recurrent BPPV group after mTBI. Therefore, they concluded that secondary utricular dysfunction may be a potential pathogenesis of recurrence of traumatic BPPV.

Martinez and Amaro (2018) evaluated otolith function in 79 patients with BPPV, 67 patients with posterior semi-circular canal BPPV and 60 healthy subjects. They found that BPPV group had abnormal cervical VEMPs in 49.25% of patients compared to 16.67% in the control group. Ocular VEMPs were altered in 61.19% of the patients and 6.67% of the healthy subjects. Abnormal ocular VEMPs in patients with recurrent BPPV were statistically

significant. So they conclude that Utricular and saccular dysfunction in BPPV patients is higher s than in healthy individuals.

Singh and Apeksha (2016) evaluated the function the otolith organs through cVEMPs and oVEMP in 31 individuals with posterior canal BPPV and 31 age and gender–matched control group using 500Hz tone burst. So they found that there was no significant group difference on any of the cVEMPs parameters. And similar trend was noticed for the latency-related parameters of oVEMP. But the peak-to-peak amplitude was significantly smaller in the affected ears of individuals with BPPV than their unaffected ears and the ears of healthy control group. The BPPV group showed significantly higher inter-aural amplitude difference ratio than the healthy controls. Thus, they conclude that oVEMP appears to be better suited to clinical investigation than cVEMPs in individuals with posterior canal BPPV.

Hong et al. (2008) studied the otolith function in 53 patients with BPPV and 84 healthy subjects using VEMP. They found that healthy subjects older than 60 years showed significantly more prolonged p13 and n23 latencies and lower amplitude than the other 2 subgroups. 13 subjects showed abnormal responses on the affected side when compared with their age-related control group. They conclude that there was no correlation between VEMP findings and the affected semicircular canal. Patients with BPPV may show abnormal VEMP findings, irrespective of the involved semicircular canal, and age was associated with VEMP results suggesting degeneration of the maculae of the saccule.

2.1.5 Auditory neuropathy spectrum disorder

EL-Badry et al. (2018) evaluate the function of the saccule and inferior vestibular nerve in 38 children with auditory neuropathy spectrum disorder (ANSD)

by using the cVEMP. They found that 35 out of 38 pre-lingual ANSD children had bilateral intact C-VEMP response in terms of amplitude, asymmetric ratio, latency, and inter-aural latency difference that were similar to those in the control children. Only 3 children had bilateral absent C-VEMP response. On the other hand, 11 out of 16 post-lingual ANSD children had bilateral absent C-VEMP response. The remaining 5 children had bilateral intact C-VEMP response that was similar to those in the control children.

Sujeet et al. (2014) studied the function of inferior and superior vestibular nerve involvement through cVEMP in 26 individuals with Auditory Neuropathy Spectrum Disorders. They found that cVEMP was absent most of the subject's also caloric responses showed bilateral hypo-functional responses in most of the participants, which is suggestive of involvement of both the inferior as well as superior vestibular nerve in individuals with auditory neuropathy spectrum disorders.

2.1.6 Semicircular canal dehiscence

Zuniga et al. (2013) examined otolith function in 29 patients with SCDS and control group. They measure the cVEMP thresholds; oVEMP n10 and peak-to-peak amplitudes. They found that cVEMP threshold results showed sensitivity and specificity ranging from 80% to 100% for the diagnosis of SCDS. In contrast, oVEMP amplitudes demonstrated sensitivity and specificity greater than 90%. oVEMP amplitudes are superior to cVEMP thresholds in the diagnosis of SCDS.

Streubel et al. (2001) recorded vestibular-evoked myogenic potentials (VEMP responses) in 10 patients with SCD syndrome which was confirmed by the high resolution CT scan of temporal bone. They found that patients with SCD syndrome have lowered VEMP thresholds. So they conclude that instead of using single test, the diagnosis of SCD

syndrome is best established when the characteristic symptoms, signs, VEMP response, and CT imaging all indicate SCD.

2.1.7 Vestibular neuritis

Shin et al. (2012) studied the (cVEMPs and oVEMPs in 60 healthy controls and 41 patients with acute VN. The VN selectively involved the superior vestibular nerve in 30 patients, affected the inferior vestibular nerve only in 3 and damaged both superior and inferior vestibular nerve branches in 8 patients. Result showing that All 30 patients with superior VN presented normal cVEMPs and oVEMP was abnormal in all patients with superior VN. In patients with inferior VN showed normal oVEMP and abnormal cVEMPs. They conclude that the oVEMP in response to acoustic stimulation may be mediated by the superior vestibular nerve, probably due to an activation of the utricular receptors.

2.1.8 Vestibular schwannoma

Ogawa et al (2018) Compared cervical VEMP evoked by stimulation with Air-conducted sound (ACS) and bone-conducted vibration (BCV) in 33 patients with vestibular schwannoma. So they found that patients with abnormal ACS cVEMP, BCV cVEMP, oVEMP, test results were 78.8%, 75.8%, 78.8%,, respectively. BCV cVEMP did not correlate with ACS cVEMP, but correlated with oVEMP results. So they conclude that BCV cVEMP cannot be used as a substitute for ACS cVEMP.

Taylor et al (2015) examined 50 patients with vestibular schwannoma using a air-conducted cervical- and bone conducted ocular-vestibular-evoked myogenic potentials (AC cVEMPs and BC oVEMPs) VEMP asymmetry ratios, latencies, were used to determine the test sensitivity, relationship with tumour size and the pattern of vestibular nerve involvement. They found that the percentage of abnormalities ranged between 36.2-61.7%.

In 58.3 % of patients, test abnormalities were referable to both superior and inferior vestibular nerve divisions. Selective inferior nerve dysfunction was identified in 10.4% and superior nerve dysfunction in 12.5%. The remaining 18.8% of patients demonstrated a normal test profile. The sensitivity of the battery increased with tumour size and all patients with medium to large (>14 mm) schwannoma had abnormal vestibular test result.

Lin et al (2014) examined oVEMP and cVEMP test in 50 patients with unilateral VS. So they found that oVEMP and cVEMP responses remained significant predictors for tumor size. When the tumor size was less than 2.0 cm, preservation of the function of superior/inferior vestibular nerve indicated by presence of oVEMP/cVEMP response Therefore, both oVEMP and cVEMP tests may serve as supplementary tools for determining treatment option in VS patients.

2.1.9 Vestibular migraine

Kang et al (2016) evaluated 81 vestibular migraine (VM) patients' using vestibular-evoked myogenic potentials (VEMPs), at the initial visit and then evaluated for symptomatic improvement after 6 months. Complete response (CR) was defined as no need for continued medication, partial response (PR) as improved symptoms but need for continued medication, and no response (NR) as no symptomatic improvement and requiring increased dosage or change in medications. At the initial evaluation, 8 of 75 (11%) exhibited abnormal cervical VEMP results, and 20 of 75 (27%) exhibited abnormal ocular VEMP results. Six months later, 63 of 81 patients (78%) no longer required medication (CR), while 18 (22%) still required medication, including 7 PR and 11 NR patients. These results suggest that peripheral vestibular abnormalities are closely related to the development of vertigo in VM patients.

Zaleski et al (2015) studied otolith function in 39 patients with suspected VM and 29 in control patients using 500 Hz tone burst stimuli. Age of headache onset was most often in childhood or adolescence, with dizziness onset occurring later. They found that the rate of bilaterally absent oVEMPs was significantly higher 28% in the VM group compared with the control group (0%). oVEMP amplitude asymmetry ratios were significantly higher for the definite VM and probable VM groups than the control group. 11 patients also had history of concussion; they were significantly more likely to demonstrate bilaterally absent oVEMPs in comparison to the control patients. When VM patients with a history of concussion were omitted from analysis, differences in oVEMP amplitude asymmetry and bilateral oVEMP absence remained significant. There were no differences in the rate of bilateral cVEMP presence or response parameters between VM and control groups .VEMP presentation differs for some patients diagnosed with VM. The higher rates of abnormal oVEMPs may suggest greater vulnerability within the ascending utricular–ocular pathway in patients with VM.

Moallemi et al (2011) studied the vestibular evoked myogenic potential in 25 migraine patients and 26 healthy volunteers using 500 Hz tone bursts at 95 dB nHL. They found that Mean of absolute amplitude and p13 latency values in the migraine group were significantly less and more than the normal group, respectively for absolute amplitude in right and left ears for p13 latency in right ears and left ears). There was no statistically significant difference between the two groups in mean of the n23 latency and also the amplitude ratio. So they concluded that prolonged latency of vestibular evoked myogenic potentials response, vestibulospinal tract in brainstem is probably involved in migraine patients.

Baier et al (2009) assessed otolith function in 63 patients with vestibular migraine and 63 age and sex -matched healthy controls group. They found that 43(63%) patients with vestibular migraine had reduced EMG-corrected VEMP amplitudes compared to the controls. Patients with vestibular migraine indicate that the VEMP amplitudes are significantly and bilaterally reduced compared to those of controls. This electrophysiological finding suggests that both peripheral vestibular structures, such as the saccule, but also central vestibular structures are affected. Thus, beside the brainstem, structures in the inner ear also seem to contribute to vertigo in vestibular migraine.

2.1.10 Brainstem lesion

Guven (2014) studied the vestibular evoked myogenic potential in 50 patients with multiple sclerosis (MS) and 30 healthy control subjects. They found that the p1–n1 and n2–p2 waves were more frequently absent in MS than in control subjects. The mean p1–n1 amplitude was lower in MS than in control subjects. A total of 24/50 MS patients had VEMP abnormalities (absent responses and/or prolonged latencies). VEMP abnormalities were more frequent in patients with vestibular symptom than without vestibular symptoms and with brainstem functional system score (FSS).

Gazioglu and Boz (2012) investigate the otolith function in 62 MS patients and 35 age and sex matched healthy volunteers to assess their relation with clinical and cranial MRI findings. They found that oVEMP mean n1 and p1 latencies and cVEMPs mean p13 latency were significantly prolonged in MS patients. Although the abnormality ratios of both VEMPs were higher in patients with brainstem clinical or MRI lesions, the correlation was not statistically significant. Both ocular and cervical VEMP latencies were significantly correlated with expanded disability status scale. Although there is no significant correlation

with clinical or MRI findings, MS patients show high frequency of abnormality in VEMP tests, especially in oVEMP tests.

Pollak et al (2006) investigated the otolith function in 19 patients with cerebellar ischemic stroke and 15 patients with lower-brainstem ischemic stroke and 53 normal individuals. So they found that there were no latency or amplitude differences ipsilaterally or contralaterally to the lesion. At the individual level, there was no correlation between laterality of lesion and that of P13 or N23 abnormalities in patients with cerebellar strokes; however, there were two patients who presented P13 and N23 latency abnormalities ipsilaterally to the lesion. Cerebellar strokes do not influence VEMPs. Therefore, VEMPs do not appear a suitable tool for assessment of brainstem integrity in patients with posterior fossa strokes.

2.1.11 Diabetes mellitus

Ward et al (2015) studied the vestibular dysfunction in 25 adults with type 2 DM with age range of 50 years of age and older with ≥10-year history of type 2 DM and 25 non-diabetic age-matched controls group . Vestibular function was assessed by VEMPs, testing the saccule and utricle, respectively. . They found that subjects with DM demonstrating 50% otoconial organ impairment (absent ocular VEMP and/or cervical VEMP). Both cervical VEMP peak-to-peak amplitude and ocular VEMP n1 amplitude were also decreased with diabetes 2. They concluded that adults with type 2 DM have poorer performance on tests of vestibular function compared with no diabetic age-matched adults.

Bektas et al (2008) studied the otolith function in 25 NIDDM patients with polyneuropathy (PNP), 13 NIDDM patients without PNP and 21 healthy subjects using click stimulation. They found that VEMP responses were normal in NIDDM patients with or

without PNP. So they concluded that Vestibular evoked myogenic responses (VEMPs) are not affected in non-insulin-dependent diabetes mellitus (NIDDM) patients with or without polyneuropathy.

Chapter-3

Method

The present study aimed at finding out the frequency tunning of the cervical vestibular evoked myogenic potentials and ocular vestibular evoked myogenic potentials in individuals with diabetes.

3.1. Participants

Total 52 individuals within the age range of 35-65 years participated for the study. The participated were divided in to two groups-

Group I: This group included 26 individuals with diabetes mellitus.

Group II: This group included 26 individuals without any diabetes mellitus.

3.1.1. Selection criteria for the participant of group I:

1. All the participants had diabetes mellitus. Diabetes mellitus was confirmed through their medical reports.
2. The participants had either normal hearing sensitivity or various degree of hearing loss.
3. The participants had no history of any middle ear disorders or history of ear discharge, ear pain, ear infection etc.
4. The participants had no history of vestibular problem like vestibulopathy, vestibular neuritis, vestibular Labyrinthitis, vestibular migraine, benign paroxysmal positioning vertigo etc.
5. The participants had no any neurological problem or any history of intake of the Ototoxicity drugs.

3.1.2. Selection criteria for the participant of group II:

1. The participants in this group had no history of diabetes mellitus.
2. Participants in the group had no history of middle ear disorder like ear discharge and/or ear pain, ear infection etc.
3. All participants in the group had no history of vestibular problem like vestibulopathy, vestibular neuritis, vestibular Labyrinthitis, vestibular migraine, benign paroxysmal positioning vertigo etc.
4. All participants in the group had no any neurological problem or history of any intake of Ototoxicity drugs.

3.2 Instrumentation

1. Calibrated 2 channel piano enventis diagnostic audiometer (*Orbiter-922 V-2x, G N Otometrics, Taastrum, Denmark*) with TDH-39(telephonic, 815 Broad Hallow Road, Farmingdale, New York 11735) and bone vibrator B-71 (*Radioear, KIMMETRICS, 22050 Mohawk drive, Smithsburg, MD 21783)* were used to measure the air conduction and bone conduction threshold.
2. Calibrated GSI –Tympstar *(GSI VIASYS Healthcare, Wisconsin, USA*) with probe frequency 226Hz were used to measure tympanometry and Reflexometory.
3. Biologic navigator pro system (*Natus Medical Incorporated, CA, USA*,) with ER-3A inserts ear phones were used for auditory brainstem response, cervical VEMP and ocular VEMP.

3.3 Testing environment

Test was done in the acoustically sound treated room with permissible noise level as per ANSI S 3.1 (1991) standards.

3.4 Procedure

Case history

Case history for each individual was studied thoroughly along with this a dizziness questionnaire was administered.

Pure tone audiometry

Air conduction threshold was estimated between 250Hz to 8000Hz for all the participants by modified Hughson Westlake procedure. BC threshold were estimated between 250 Hz to 4000Hz for all the participants.

Immittance Audiometry

Immittance audiometry was done using 226Hz probe tone fallowed by acoustic reflex were elicited of 500Hz, 1000Hz, 2000Hz, and 4000Hz, both ipsilateral and contralateral stimulation.

Uncomfortable loudness level

Uncomfortable level using ascending method was estimated using speech stimuli.

Auditory brainstem response

Auditory brainstem response was done to rule out retro cochlear pathology in patient with the diabetes mellitus. Electrode placement site were cleaned using gel. Surface electrode were placed using 10-20 conduction paste. Inverting electrode (-) was placed on testing ear mastoid, Non-Inverting electrode (+) was placed on high forehead, and ground on the lower forehead. Inter electrode+ impedances were less than 2 K**Ω** and absolute electrode impedance were less than 5 K**Ω**. Stimulus was click and polarity was rarefaction with the repetition rate of 11.1 /sec and 91.1/sec. Total 1500 stimulus were presented and

obtained response were filtered between 100- 3000 Hz and were analyzed in 12 msec time window

Vestibular myogenic evoked potential:

Vestibular myogenic evoked potential was done to find out the tuning curve of cVEMP & oVEMP. Inter-electrode impedance was 2 KΩ& absolute impedance was 5 KΩs to record the reliable response. The person was asked to seat in an upright position on an adjustable chair.

Cervical vestibular myogenic evoked potential

To find out the tuning of the saccule tone burst stimuli of 250Hz, 500Hz, 750HZ, 1000Hz, and 1500Hz and 2000 Hz were used with the rarefaction polarity with repetition rate of 5.1/sec were presented. Total 200 stimuli were presented. Non-inverting electrode (+) were placed on the midpoint of the sternocleidomastoid muscle of the side being stimulated, Inverting electrode (-) on the sternoclavicular junction and ground electrode on the lower forehead. Intensity of the stimulus was 125dBSPL. Recording were done in the ipsilateral mode with contraction of the sternocleidomastoid muscle in the recording side. The obtained response were filtered between 10Hz -1500Hz and analyzed in a 60 msec time window. Later obtained responses were provided a gain of 500 times.

Ocular vestibular myogenic evoked potential

To find out the tuning of the utricle, tone burst stimuli of 250Hz, 500Hz, 750HZ, 1000Hz, and 1500Hz and 2000 Hz were used with the rarefaction polarity with repetition rate of 5.1/sec were presented. Total 200 stimuli were presented. Non-Inverting electrode (-) were below the inferior to the lower eyelid, Inverting electrode (+) will be immediately inferior to the inverting electrode and ground electrode were placed on the lower forehead.

Intensity of stimulus was 125dBSPL. Recording was done in the contralateral mode with the upper eye gaze. The obtained response were filtered between 0.1Hz -1000Hz and analyzed in a 60 msec time window. Later obtained responses were provided a gain of 500 times.

3.5 Data Analysis

Cervical vestibular evoked myogenic potentials and Ocular vestibular evoked myogenic potentials were recorded at 250 Hz, 500 Hz, 750 Hz, 1000 Hz, 1500 Hz and 2000 Hz. Peak to peak amplitude was calculated for all the frequency. In individuals with normal vestibular system, the amplitude of VEMP is always greater at 500 Hz. If the amplitude was higher at any other frequency compared to 500Hz it was considered to be a shift in tuning of the vestibular evoked myogenic potentials.

Chapter-4

Results

The present study was conducted with an aim of studying the frequency tuning of cVEMP and oVEMP in individuals with diabetic. To achieve the aim of the study, 26 participants with diabetes and 26 participants with non Diabetes were taken. cVEMP and oVEMP was done at 250 Hz, 500 Hz, 750 Hz, 1000 Hz 1500 Hz and 2000 Hz for both the groups. Peak to peak amplitude were calculated in both diabetic and non-diabetic groups for cVEMP and oVEMP for all the frequencies.

4.1 Cervical vestibular evoked myogenic potential

In the Non diabetes group, out of 26 participants cVEMP was present in 14 participants in right ear, 20 participants in left ear at 250 Hz, 21 participants in right ear, 23 participants in right ear and 22 participants in left ear at 500 Hz, 22 participants in right ear and 23 participants in left ear at 750 Hz, 22 participants in right ear and 23 participants in left ear at 1000 Hz, 20 and 22 participants in right and left ear respectively at 1500 Hz, 17 and 22 participants in right and left ear at 2000 Hz respectively.

In the diabetes group, out of 26 participants cVEMP was present in 11participants in right ear, 13 participants in left ear at 250 Hz, 16participants in right ear,15 participants in left ear at 500 Hz, 16 participants in right ear and 16 participants in left ear at 750 Hz, 16 participants in right ear and 16 participants in left ear at 1000 Hz, 15 and 14 participants in right and left ear respectively at 1500 Hz, 13 and 14 participants in right and left ear at 2000 Hz respectively.

Figure 4.1.shows Individual with cVEMP present in both ears in one of the non-diabetic individuals. Figure 4.2.Shows individual with cVEMP absent in both ears in one of the non-diabetic individuals. Figure 4.3.shows cVEMP present in both ears in one of the individuals with diabetes mellitus. Figure 4.4.shows cVEMP absent in one of the individuals with diabetes mellitus.

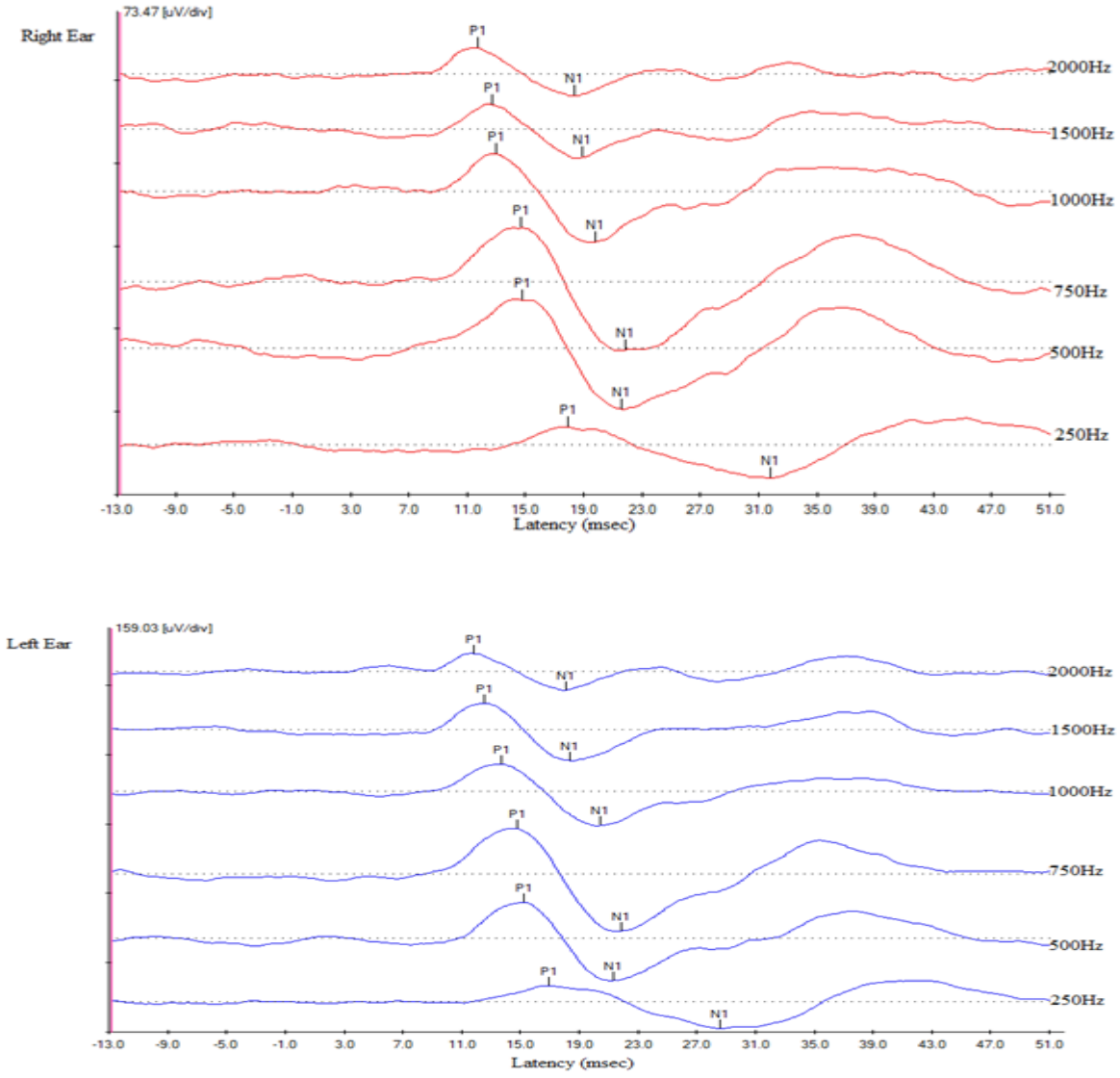

Figure 4.1: cVEMP waveforms in one of the individuals without diabetes mellitus in both ears with presence of cVEMP response.

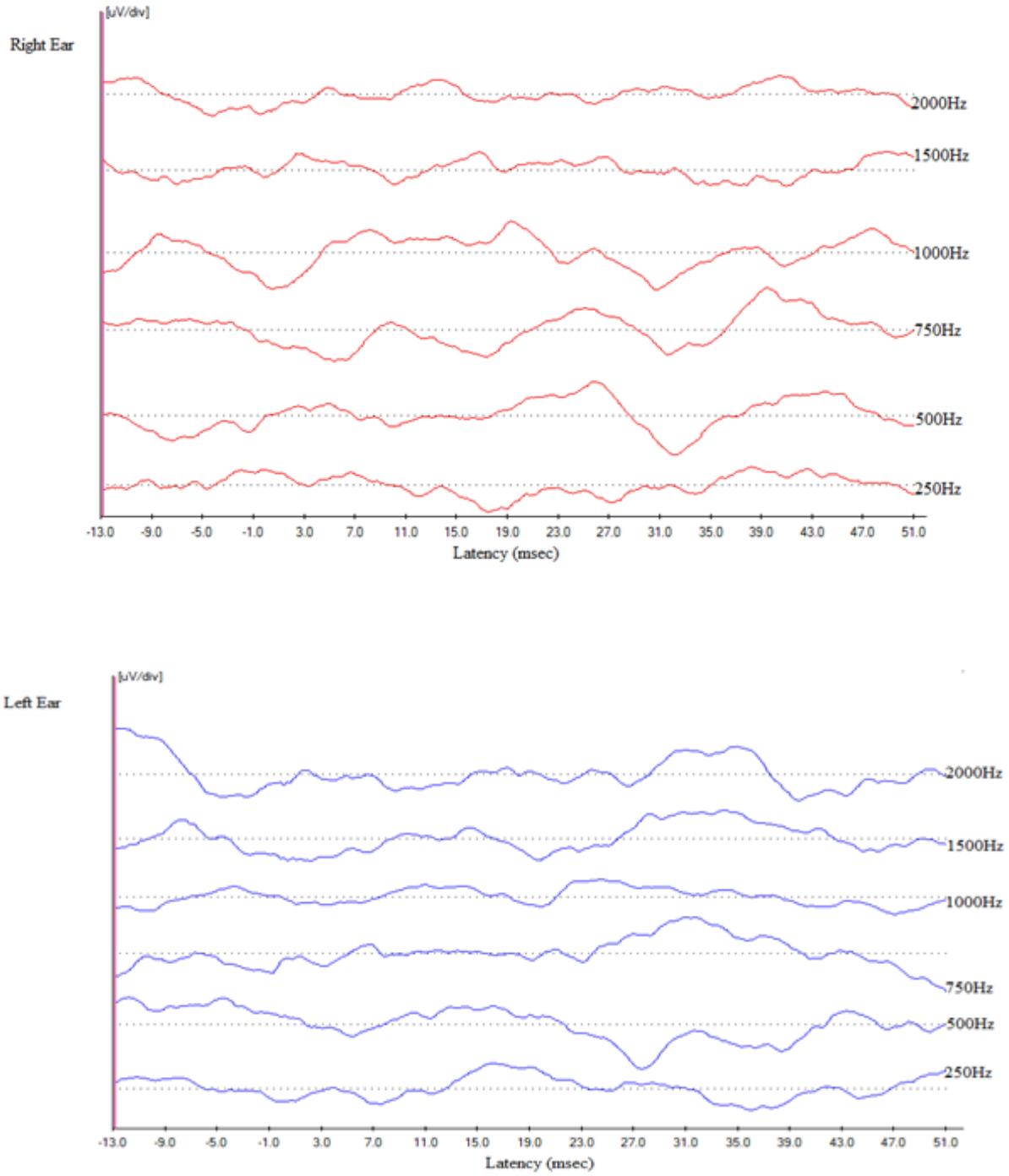

Figure 4.2: cVEMP waveforms in one of the individuals without diabetes with absence of cVEMP in both ears.

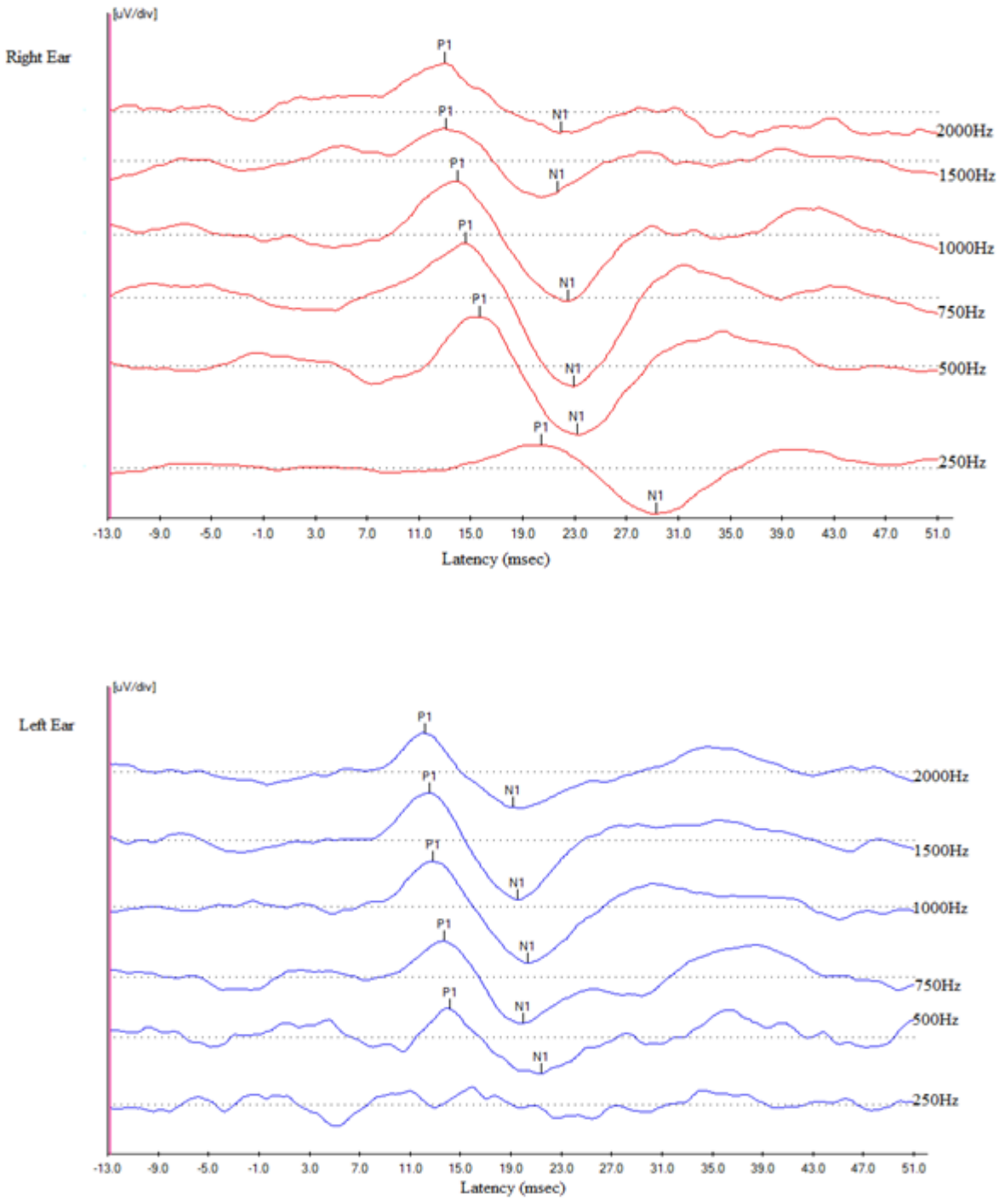

Figure 4.3*: cVEMP* waveforms in one of the individuals with diabetes mellitus in both ears with presence of cVEMP response.

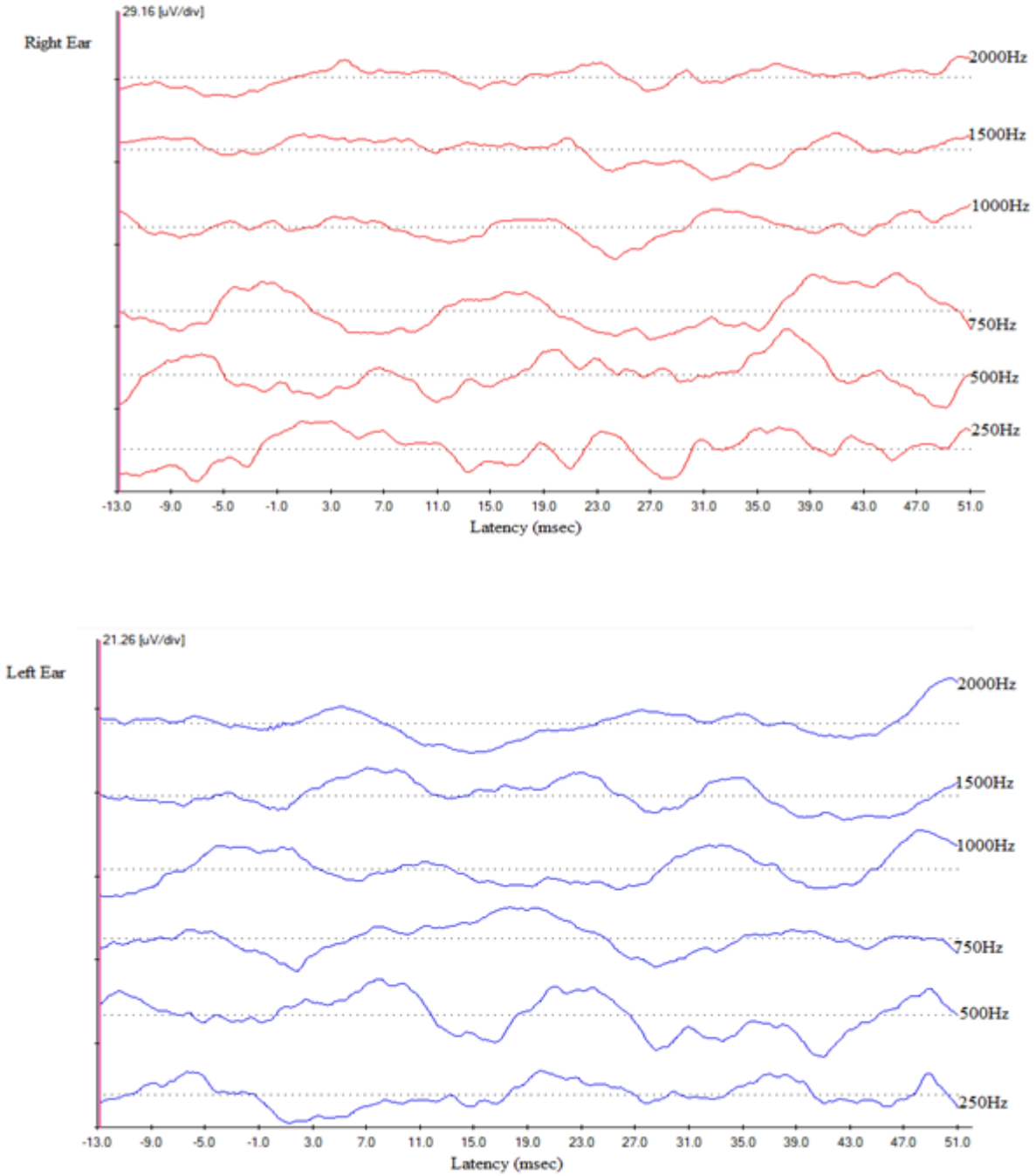

Figure4.4*:* cVEMP waveforms in individuals with diabetes mellitus with absence of responses in both the ears.

Descriptive statistics was done to calculate the mean and the standard deviation of the amplitude of p1-n1 peak for 250 Hz, 500 Hz, 750 Hz, 1000 Hz, 1500Hz, 2000 Hz

frequency. The Mean and standard deviations of non diabetic mellitus group and diabetes mellitus group are shown in Table 4.1 and Table 4.2 respectively for both the groups separately.

Table 4.1

Mean and standard deviation (SD) for cVEMP P1-N1 peak to peak amplitude in right ear and left ear in individuals without diabetes.

Frequency	**Mean amplitude (µV) of right ear**	**SD**	**Mean amplitude (µV) of left ear**	**SD**
250Hz	94.48	91.05	81.49	73.16
500Hz	99.00	88.63	100.29	82.70
750Hz	109.59	85.09	117.16	86.13
1000Hz	95.23	81.31	96.41	77.85
1500Hz	94.59	67.40	74.42	48.92
2000Hz	70.53	54.92	46.73	35.92

Table 4.2

Mean and standard deviation (SD) for cVEMP P1-N1peak to peak amplitude in right and left ear in individuals with diabetes.

Frequency	**Mean amplitude (µV) of right ear**	**SD**	**Mean amplitude (µV) of left ear**	**SD**
250Hz	55.20	46.95	43.81	24.30
500Hz	56.44	47.36	60.32	39.20
750Hz	71.45	52.26	70.94	46.58

1000Hz	63.13	40.85	70.08	44.28
1500Hz	48.98	32.79	52.33	46.37
2000Hz	43.80	24.23	34.94	27.87

It can be seen from Table 4.1 and 4.2 that, cVEMP P1-N1 Peak to peak amplitude of 750Hz was maximum followed by 500Hz compare to other frequency in individual without diabetes. It can also be seen from Table 4.2 that, cVEMP P1-N1 Peak to peak amplitude of 750Hz was maximum followed by 1000Hz compare to other frequency in individual diabetes. While comparing both the tables, it can be seen that the mean amplitude was lesser for individuals with diabetes mellitus when compared to the mean of n1-p1 amplitude in individuals without diabetes mellitus.

To understand the significant differences between left and the right ear cVEMP amplitude for both the groups, Paired sample t-test was performed for both the groups. The results of the paired sample T test in given in Table 4.3 for non diabetic and for diabetes in Table 4.4 respectively

Table 4.3

Paired Sample t test for individual without diabetes mellitus.

Frequency	**T**	**Significance**
250Hz	0.21	0.83
500Hz	0.28	0.78
750Hz	0.32	0.75
1000Hz	0.02	0.98
1500Hz	0.86	0.39
2000Hz	1.13	0.27

Table 4.4

Paired Sample t test for individual with diabetes mellitus.

Frequency	**T**	**Significance**
250Hz	0.94	0.37
500Hz	0.43	0.66
750Hz	0.31	0.75
1000Hz	0.15	0.87
1500Hz	0.54	0.59
2000Hz	1.34	0.20

It can be seen from table 4.3 and 4.4 that there is no significant difference in the P1-N1 peak to peak amplitude of right and left ear of individual without diabetes and individual with diabetes. Hence the data for right ear and left ear in both groups were combined and descriptive statistics was done again to obtain mean and standard deviations for combined right and left ear amplitude of cVEMP. The mean and the standard deviation of the amplitude of cVEMP for the combined data is given in Table 4.5

Table 4.5

Mean and standard deviation of cVEMP amplitude individual without diabetes and individual with diabetes.

Frequency	**Non diabetes mellitus**		**Diabetes mellitus**	
	Mean	SD	Mean	SD
250Hz	84.68	80.10	49.03	36.05

500Hz	98.97	83.94	58.32	42.93
750Hz	110.41	80.07	71.20	48.70
1000Hz	93.59	75.79	66.61	42.06
1500Hz	80.23	57.45	50.65	39.49
2000Hz	56.84	47.34	39.20	26.07

It can be seen from Table 4.5 that mean amplitude of p1-n1 peak was maximum at 750Hz followed by 500Hz in individuals with diabetes mellitus. Overall cVEMP amplitude was lesser in individual with diabetes compare to individual without diabetes. The same can be seen in Figure 4.5.

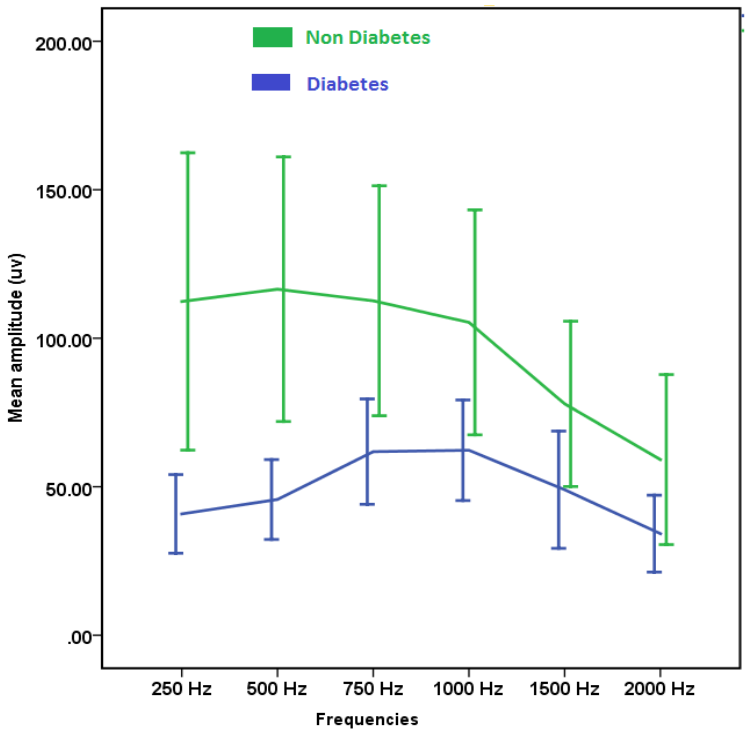

Figure 4.5 Mean amplitude of peak p1and n1 is shown in diabetic and non-diabetic groups from 250Hz to 2000Hz.

To understand the significant differences in mean amplitude of cVEMP within the same groups for different frequencies and across the two groups for P1-N1 amplitude, repeated measure ANOVA with group as between the groups variable was done. Repeated measure ANOVA revealed a significant main effect for the amplitude across different frequencies of cVEMP [F(5,200) =13.45, p=0.00], however there was no significant interaction between groups and amplitude across different frequencies [F (5,200) = 0.59, p=0.70], also repeated measure ANOVA did not show any significant main effect for the two groups[F(1,40)=3.77, p=0.59]. Boneferroni Pairwise comparison was done to understand the difference between different frequencies and the results of the Boneferroni Pairwise tests are given in Table 4.6

Table 4.6

Boneferroni pair wise comparison test.

	250Hz	500Hz	750Hz	1000Hz	1500Hz	2000Hz
250Hz		P <0.05	P<0.05	P>0.05	P>0.05	P>0.05
500Hz			P>0.05	P>0.05	P>0.05	P<0.05
750Hz				P>0.05	P<0.05	P<0.05
1000Hz					P>0.05	P<0.05
1500Hz						P<0.05

From Table 4.6 it can be seen that cVEMP amplitude at 250 Hz was significantly different that 500 Hz and 750 Hz, cVEMP amplitude at 500 Hz, 750 Hz and 1500 Hz was significantly different than 2000 Hz.

4.2 Ocular vestibular evoked myogenic potential:

In the Non diabetes group, out of 26 participants oVEMP was present in 7 participants in right ear, 8 participants in left ear at 250 Hz, 16 participants in right ear, and 15 participants in left ear at 500 Hz, 18 participants in right ear and 18 participants in left ear at 750 Hz, 17 participants in right ear and 18 participants in left ear at 1000 Hz, 15 and 16 participants in right and left ear respectively at 1500 Hz, 13 and 10 participants in right and left ear at 2000 Hz respectively.

In the diabetes group, out of 26 participants oVEMP was present in 3 participants in right ear, 4 participants in left ear at 250 Hz, 12 participants in right ear, 11 participants in left ear at 500 Hz, 14 participants in right ear and 14 participants in left ear at 750 Hz, 14 participants in right ear and 13 participants in left ear at 1000 Hz, 12 and 12 participants in right and left ear respectively at 1500 Hz, 9 and 7 participants in right and left ear at 2000 Hz respectively.

Figure 4.6 shows Individual with oVEMP present in both ears in one of the non-diabetic individuals. Figure 4.7 shows individual with oVEMP absent in both ears in one of the non-diabetic individuals. Figure 4.8 shows oVEMP present in both ears in one of the individuals with diabetes mellitus. Figure 4.9 shows oVEMP absent in one of the individuals with diabetes mellitus.

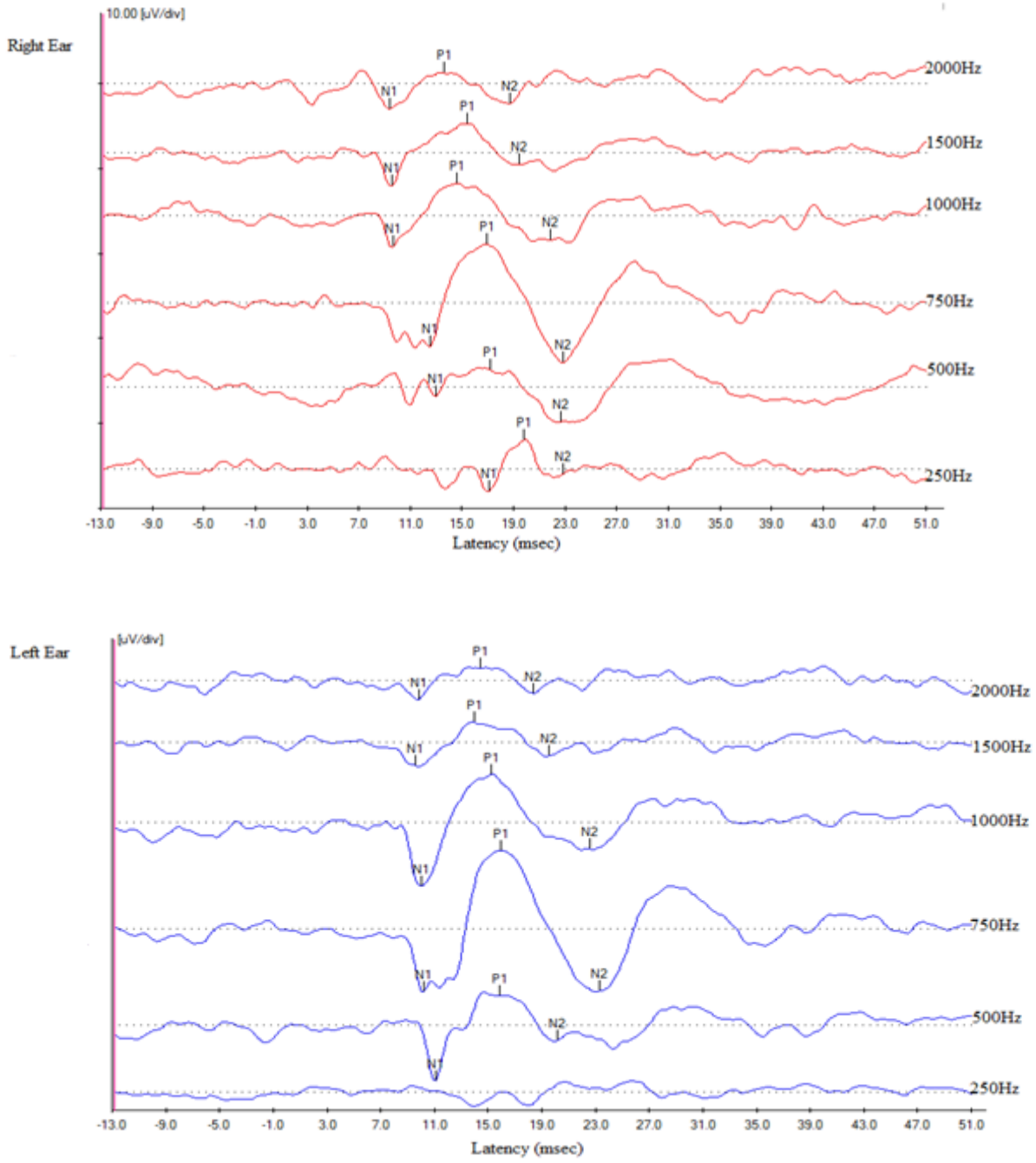

Figure: 4.6 oVEMP waveforms in one of the individuals without diabetes mellitus in both ears with presence e of oVEMP response.

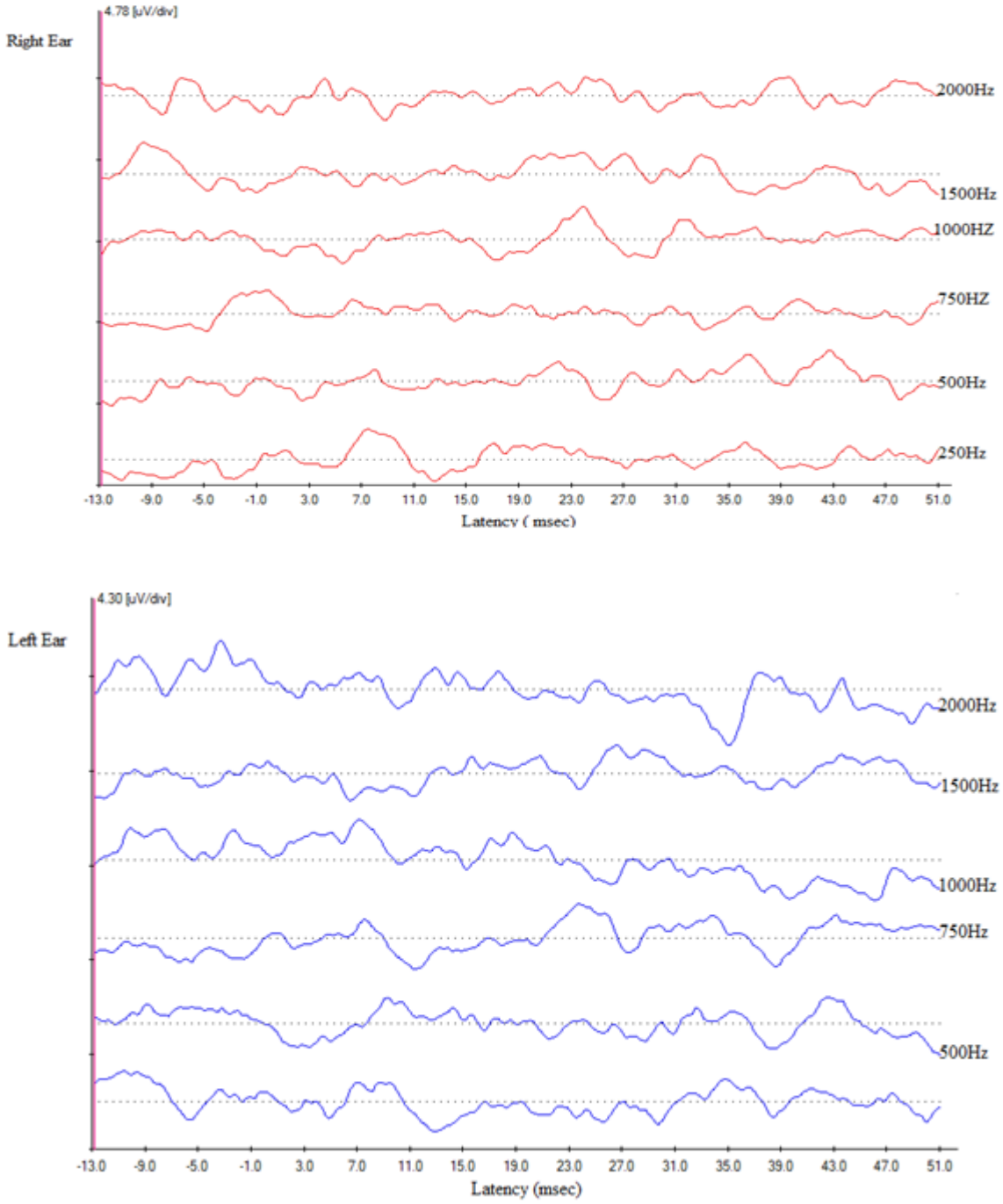

Figure: 4.7 oVEMP waveforms in one of the individuals without diabetes mellitus in both ears with absence e of oVEMP response.

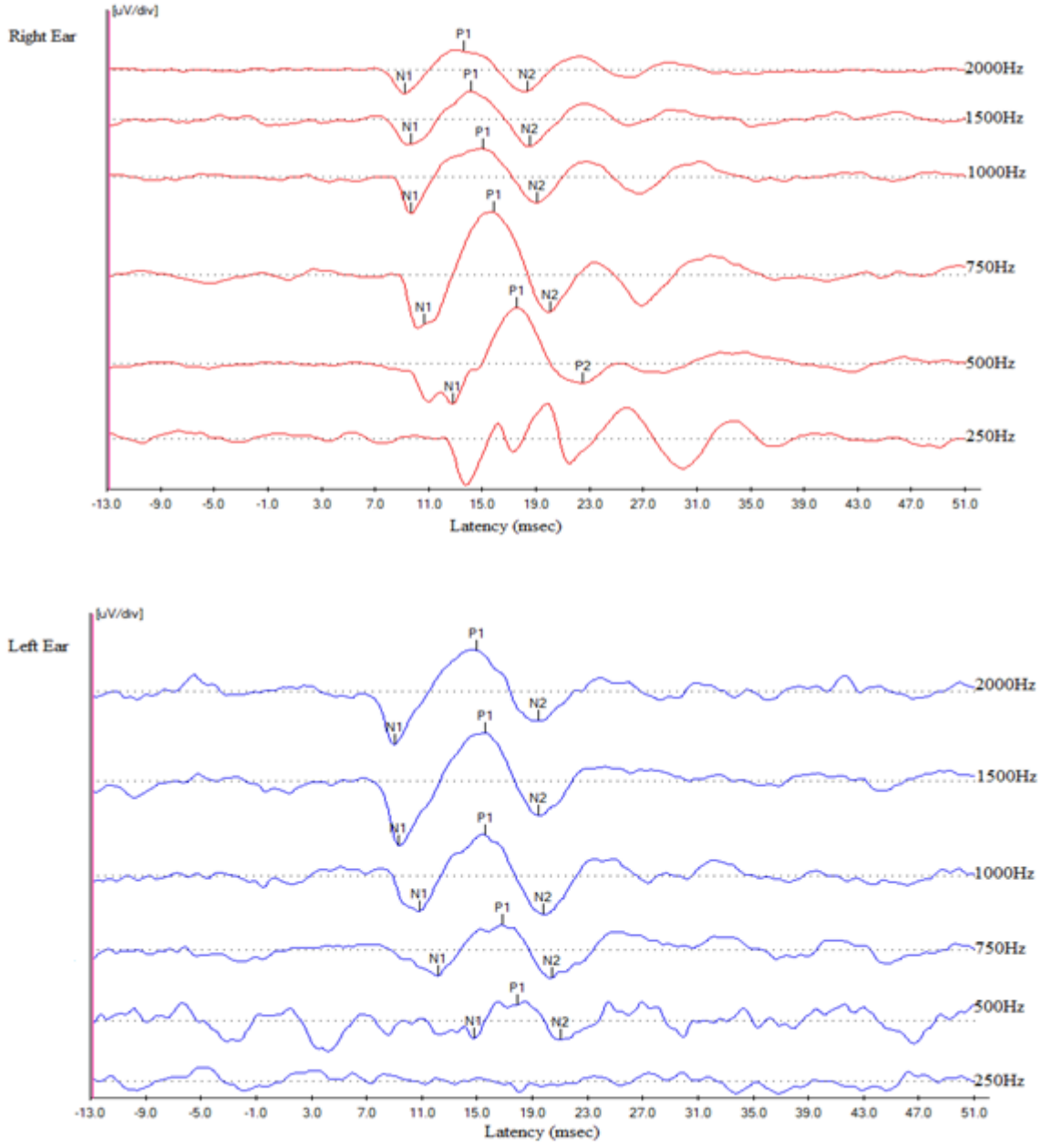

Figure: 4.8 oVEMP waveforms in one of the individual diabetes mellitus in both ears with presence of oVEMP response

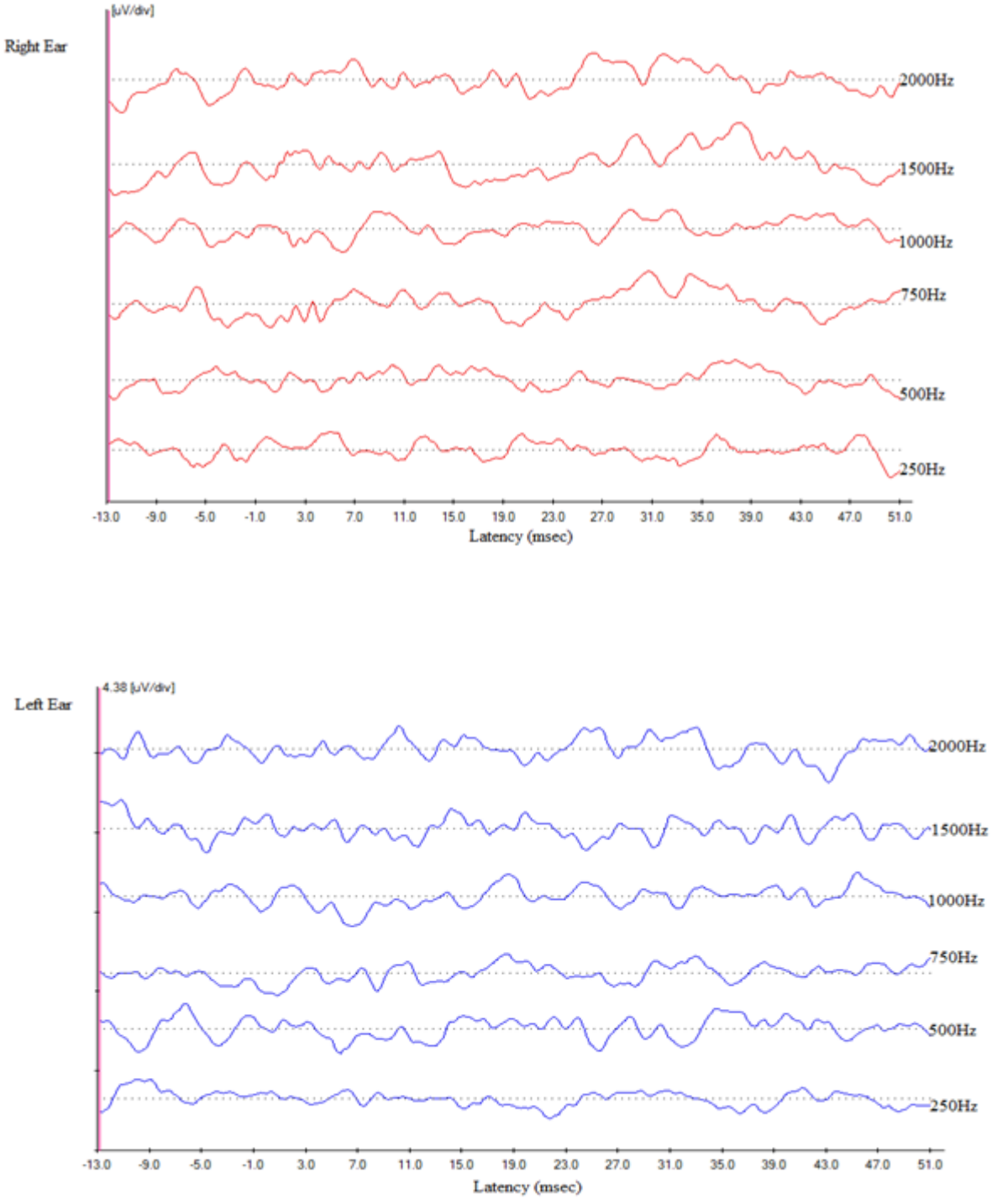

Figure: 4.9 oVEMP waveforms in one of the individual with diabetes mellitus in both ears with absence of oVEMP response.

Descriptive statistics was done to calculate the mean and the standard deviation of the amplitude of n1-p1 and p1-n2 peak for 250 Hz, 500 Hz, 750 Hz, 1000 Hz, 1500Hz, 2000Hz frequency. The Mean and standard deviations of non diabetic mellitus group and diabetes mellitus group are shown in Table 4.7, 4.8 and Table 4.9, 4.10 respectively for both the groups separately.

Table 4.7

Mean and standard deviation (SD) for oVEMP N1-P1amplitude in right ear and left ear in individuals without diabetes.

Frequency	**Mean Amplitude (μv) of right ear**	**SD**	**Mean Amplitude (μv) of left ear**	**SD**
250Hz	6.78	4.82	5.21	3.75
500Hz	5.76	3.43	5.05	2.97
750Hz	8.61	5.07	9.17	6.29
1000Hz	10.06	9.80	8.49	6.34
1500Hz	5.83	4.63	6.00	5.10
2000Hz	3.28	3.01	4.21	2.68

Table 4.8

Mean and standard deviation (SD) for oVEMP P1-N2 amplitude in right ear and left ear in individuals without diabetes.

Frequency	**Mean Amplitude (μv) of right ear**	**SD**	**Mean Amplitude (μv) of left ear**	**SD**
250Hz	6.58	5.81	5.05	5.11
500Hz	8.46	9.90	7.73	7.95
750Hz	11.56	11.33	11.55	13.56
1000Hz	10.30	10.29	9.64	8.71
1500Hz	6.71	5.91	5.78	5.53
2000Hz	3.74	3.52	4.10	3.62

Table 4.9

Mean and standard deviation (SD) for oVEMP N1-P1 amplitude in right ear and left ear in individuals with diabetes.

Frequency	**Mean Amplitude (μv) of right ear**	**SD**	**Mean Amplitude (μv) of left ear**	**SD**
250Hz	2.23	1.35	4.58	2.76
500Hz	5.67	6.24	4.81	3.83
750Hz	7.28	5.83	7.10	6.83
1000Hz	6.32	3.46	7.11	5.12

1500Hz	6.42	4.64	7.65	6.33
2000Hz	5.45	4.15	6.72	3.49

Table 4.10

Mean and standard deviation (SD) for cVEMP P1-N2 amplitude in right ear and left ear in individuals with diabetes.

Frequency	**Mean Amplitude (μv) of right ear**	**SD**	**Mean Amplitude (μv) of left ear**	**SD**
250Hz	2.33	1.17	3.63	2.23
500Hz	4.90	5.53	4.22	3.02
750Hz	7.19	5.50	6.85	6.08
1000Hz	5.45	2.50	6.20	4.72
1500Hz	5.05	3.65	5.74	4.81
2000Hz	4.65	4.06	5.32	3.63

It can be seen from Table 4.7 & 4.8 that, oVEMP N1-P1 & P1-N2 Peak to peak amplitude of 750Hz was maximum followed by 1000Hz compare to other frequency in individual without diabetes. It can also be seen from Table 4.9 & 4.10 that, oVEMP N1-P1 & P1-N12 Peak to peak amplitude of 750Hz was maximum followed by 1000Hz compare to other frequency in individual diabetes. While comparing all the Tables, it can be seen that the mean amplitude was lesser for individuals with diabetes mellitus when compared to the mean of n1-p1 and p1-n2 amplitude in individuals without diabetes mellitus.

To understand the significant differences between left and the right ear oVEMP amplitude for both the groups, Paired sample t-test was performed for both the groups. The

results of the paired sample T test in given in Table 4.11 and 4.12 for Non diabetic and for diabetes in Table 5.7 and 5.8 respectively

Table 4.11

Paired Sample t test of N1-P1 for individual without diabetes mellitus.

Frequency	**T**	**Significance**
250Hz	1.60	0.20
500Hz	1.04	0.32
750Hz	0.24	0.81
1000Hz	0.79	0.44
1500Hz	0.30	0.76
2000Hz	0.21	0.84

Table 4.12

Paired Sample t test of P1 –N2 for individual without diabetes mellitus.

Frequency	**T**	**Significance**
250Hz	1.17	0.32
500Hz	0.56	0.58
750Hz	0.06	0.94
1000Hz	0.18	0.85
1500Hz	0.16	0.87
2000Hz	0.28	0.78

Table 4.13

Paired Sample t test of N1- P1 for individual with diabetes mellitus.

Frequency	T	Significance
500Hz	0.90	0.39
750Hz	0.07	0.94
1000Hz	0.27	0.78
1500Hz	0.83	0.93
2000Hz	0.67	0.53

Table 4.14

Paired Sample t test of P1–N2 for individual with diabetes mellitus.

Frequency	T	Significance
500Hz	0.83	0.42
750Hz	0.32	0.75
1000Hz	0.50	0.62
1500Hz	0.71	0.49
2000Hz	0.59	0.57

It can be seen from Table 4.11, 4.12 & 4.13, 4.14 that there is no significant difference in the N1-P1 & P1-N2 peak to peak amplitude of right and left ear of individual without diabetes and individual with diabetes. Overall oVEMP amplitude was lesser in individual with diabetes compare to individual without diabetes. The same can be seen in Figure 4.11 and 4.12.

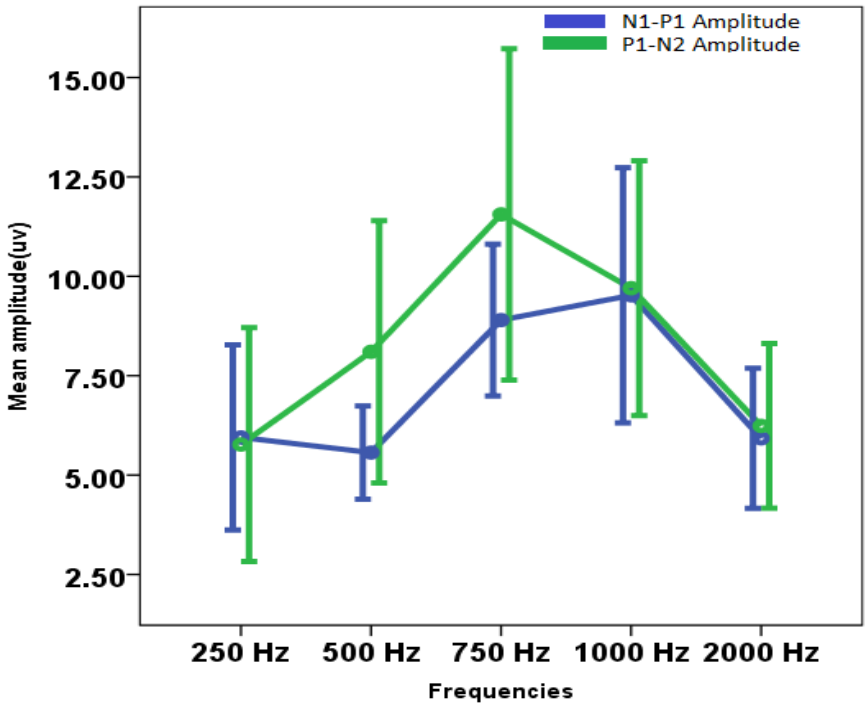

Figure 4.10 Mean amplitude of peak n1-p1 and p1-n2 is shown in non-diabetic groups from 250Hz to 2000Hz.

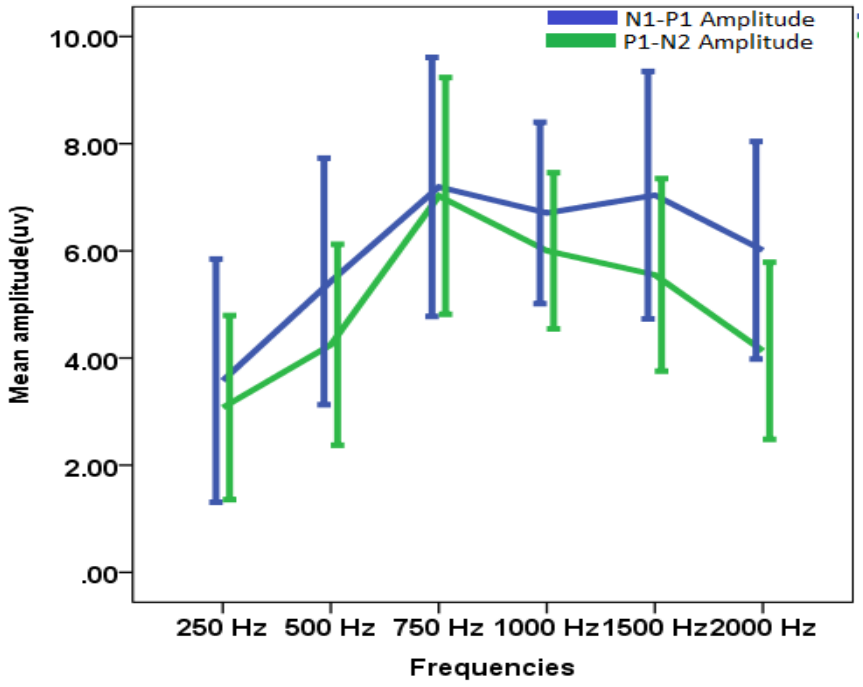

Figure4.11 Mean amplitude of peak n1- p1and p1- n2 is shown in diabetic groups from 250Hz to 2000Hz.

To understand the significant differences in mean amplitude of oVEMP within the same groups for different frequencies and across the two groups for N1-P1 & P1-N2 amplitude, repeated measure ANOVA with group as between the group variable was done. Repeated measure ANOVA revealed a no significant main effect for the amplitude across different frequencies of cVEMP [F(5,50) =2.01, p=0.09], there was also no significant interaction between groups and amplitude across different frequencies [F (5,50) = 1.51, p=0.20], but repeated measure ANOVA showed significant main effect for the two groups[F(1,10)=6.78, p=0.00].

Since the groups showed a significant main effect. Independent Sample‘t’ test was done to compare the amplitude of N1-P1 and P1-N2 peak across different frequency between the two groups. The results of the Independent Sample‘t’ test is given in Table 4.15 below.

Table 4.15

Independent Sample t test of N1-P1 & P1–N2 for individual with diabetes mellitus.

Frequency	**T**	**Significance**
250Hz-N1-P1	1.37	0.18
500Hz-N1-P1	0.14	0.88
750Hz-N1-P1	1.14	0.25
1000Hz-N1-P1	1.47	0.14
1500Hz-N1-P1	0.80	0.42
2000Hz-N1-P1	2.17	0.03
250Hz-P1-N2	1.29	0.21

500Hz-P1-N2	1.74	0.87
750Hz-P1-N2	1.80	0.07
1000Hz-P1-N2	2.19	0.03
1500Hz-P1-N2	0.60	0.54
2000Hz-P1-N2	0.92	0.36

It can be seen from Table 4.15 that there is a significant difference of amplitude of N1-P1 at 2000Hz and P1-N2 at 1000Hz between the two groups. But there is no significant difference of amplitude of N1-P1 at 250Hz, 500Hz, 750Hz, 1000Hz and 1500Hz, also no significant difference of amplitude of P1-N2 at 250Hz, 500Hz, 750Hz, 1500Hz and 2000Hz between the two groups.

To summarise the results, the prevalence of cervical vestibular evoked myogenic potentials and ocular vestibular evoked myogenic potentials was lesser in diabetic individuals compared to the non-diabetic individuals. However, there was no change in the frequency tunning of either cVEMP or oVEMP in individuals with diabetes.

Chapter-5

Discussion

5.1. Vestibular evoked myogenic potentials

cVEMP was present at 250Hz in 61.53%, at 500Hz in 84.61%, and at 750Hz, 1000Hz, 1500Hz and 2000Hz in 86.53%, 86.53%, 80.76%, and 75% respectively in non-diabetic individuals. cVEMP was present at 250Hz in 46.15%, at 500Hz in 59.61, and at 750Hz, 1000Hz, 1500Hz and 2000Hz in 61.53%, 61.53%, 57.69%, and 51.92% respectively in diabetic individuals. In cVEMP, P1-N1 peak to peak amplitude of 750Hz was maximum followed by 500Hz compare to other frequency in individual with non diabetic.

oVEMP was present at 250Hz in 28.84%, at 500Hz in 59.61%, and at 750Hz, 1000Hz, 1500Hz and 2000Hz in 69.23%, 67.30%, 59.61%, and 42.30% respectively in individuals without non-diabetic. oVEMP was present at 250Hz in 13.46%, at 500Hz in 44.23 and at 750Hz, 1000Hz, 1500Hz and 2000Hz in 53.84%, 53.84 %, 48.07%, and 34.61% respectively in individual with diabetic.

Several studies reported vestibular dysfunctioning in individuals with diabetes. Ward et al. (2015) reported that about 50 % of the diabetic individuals had absent oVEMP and cVEMP responses. D'Silva et al. (2017) reported that, 28.9% individuals with diabetes had absent or abnormal cVEMP responses. Abnormal or absent oVEMP were seen in 51.51% diabetic individuals due to increased amount of HbA1c levels. In the present study it can be concluded that absent of oVEMP and cVEMP responses could be due to higher amount and HbA1c cells and causing dysfunctioning of vestibular system.

Perez et al. (2001) reported reduction in the amplitude of p1n1 and prolongation of first wave of VEMP in diabetic individuals due to the functional impairment of vestibular

end organ which could occur because of the accumulation of lipid droplets in the subneuroepithelial connective tissues of the vestibular end organs. Klagenberg et al. (2007) reported that in diabetic individuals 60% of changes occurs in the peripheral vestibular system compared to auditory system. Kamali et al. (2013) reported that, the latencies of p13 showed significant difference between the diabetic group with polyneuropathy, diabetes without polyneuropathy and normal healthy individuals could be indicative of retro labyrinthine pathology whereas, latency of n23 did not show any significant difference between those groups.

Ward et al. (2015) reported significant reduction in the cVEMP peak-to-peak amplitude and in oVEMP n1 amplitude were also reduced in diabetes individuals. Kalkan et al. (2018) reported reduction in the peak-to-peak amplitude of cVEMP (p13-n21) and oVEMP (n10-p15) in diabetic individuals than the normal healthy individuals. Myers and Ross (1987) reported that there was an overproduction of extracellular matrix in the diabetic animals compared to non-diabetic animals and this led to degeneration of scattered type I hair cells in the saccule of diabetic animals and saccule is more vulnerable to diabetes.

Konukseven et al. (2015) reported that, cVEMP and oVEMP, p1 and n1 latencies were prolonged in diabetic individuals compared to prediabetic and control group due to Pathogenesis which can involve degeneration due to sensorial or motor polyneuropathies, which frequently results of type 2 diabetes mellitus. Ibraheem, Hassaan and Mousa (2017) reported dysfunctioning of vestibular system occurs more in type 2 diabetes mellitus and more is seen in insulin treated diabetes compared to orally treated diabetes. Tavakoli et al. (2014) reported the significant difference in the cVEMP parameters of diabetic individuals and the control group due to involvement of central pathway and vestibular end organ.

Myers, Ross, Jokelainen, Graham and McClatchey (1985) have demonstrated vestibular end-organ pathological changes, such as increased capillary diameter of the small blood cells of the utricle and saccule and accumulation of lipid droplets in subneuroepithelial connective tissue cells of these vestibular organs. It is common for capillaries within a capillary bed to vary in size but it is noteworthy that over 25 % of the control capillaries in are under 4 μm in diameter (Myers et al., 1985). The higher viscosity of diabetic blood (Schmid-Schonbein&Volger**,** 1976**)** and the decreased deformability of diabetic red blood cells (McMillan, Utterback& La Puma, 1978**;** McMillan &Gion, 1981; Otsuji, Baba & Kamada 1981) are likely to cause impaired blood flow through such narrow channels. Under these conditions, either the passage of red blood cells would be slowed; reducing oxygen delivery to the tissues, or the mechanical force exerted on the capillary wall would be increased. The latter situation is considered a strong candidate in the development of diabetic microangiopathy (McMillan, 1983) and could explain the increased capillary diameters in the saccules and utricles of the diabetic subjects.

The increased density of capillaries in the saccules and utricles of the diabetic subjects indicates that a vascular proliferation induced by the presence of diabetes and that this proliferation occurs within the first three months of diabetes (Myers et al., 1985). A vascular proliferation such as this would be expected to be a reflection of either an increased oxygen demand by the tissue or alternatively, by a decreased efficiency of oxygen delivery by the capillary bed. No evidence is available to support the former possibility. The latter case is supported by studies which have shown that the glycosylation of hemoglobin in diabetic blood increases the oxygen affinity of the hemoglobin thereby impairing the release of oxygen to the tissues **(**Ditzel, 1976; Bunn, Gabbay and Gallo, 1978**).** Reduced oxygen

delivery by diabetic blood has been challenged (Bunn et al.1978), however, on the grounds that other physiological variables in the blood which influence oxygen release would negate the effect of the increased oxygen affinity of glycosylated hemoglobin. If this is the case, then the possibility of a reduced flow rate, mentioned earlier with regard to elevated blood viscosity, could be an alternative cause of a relative hypoxia of the saccule and utricle leading to a damage of the saccule and utricle and hence absence of cVEMP and oVEMP.

cVEMP peak to peak amplitude of 750Hz followed by 1000Hz in the individual with diabetes. There was no significant difference change in cVEMP frequency tuning of diabetic individuals. In oVEMP, N1-P1 & P1-N peak to peak amplitude of 750Hz was maximum followed by 1000Hz compare to other frequency in individual without diabetes and individual with diabetes. There was no significant difference in oVEMP frequency tuning of in diabetic individuals.

Several studies have reported shift in frequency tunning to a higher frequency in various vestibular pathologies. Jerin, Berman, Krause, Wagner and Gürkov (2014) reported shift of best frequency of cVEMP to 1000 Hz compared to 500 Hz in 58 individuals with Meniere's disease. Taylor et al (2012) assessed tuning of cVEMPs and oVEMPs to air-conducted tone bursts (250–2000 Hz) in 14 patients with superior canal dehiscence (SCD) and 32 healthy controls. They found that for cVEMPs, the most common 'optimal frequency' in control ears (48.2%) was 500 Hz; for oVEMPs, it was 1000 Hz (51.8%). They found a significant interaction between age and frequency, with a shift towards higher-frequency tuning in older subjects.

Piker, Jacobson, Burkard, McCaslin, and Hood (2013) examined the effects of age on the tuning of the cVEMP and oVEMP in the age range of 22-78 years. The tuning of

cVEMP and oVEMP demonstrated as one of the important diagnostic tool in diagnosing the sacular and utricular disorders in individuals with secular and utricular disease.

In the present study, there was no significant change in frequency tunning of cVEMP and oVEMP in individuals with diabetes. This could be because of the fact that in individual with diabetes a large portion of myelin sheath lamellaegets disrupted, thinning of the myelin sheath and reduces the diameter of the axon fiber in the vestibular nerve (Myers et al. 1985). Previous studies have studied the frequency tunning only in pure inner ear pathology. In a pathological condition where both the inner ear and the nerves are involved this kind of change in tunning may not be seen.

Chapter-6

Summary and conclusions

Looking at the literature, various studies have demonstrated that individual with diabetes has anatomical and physiological changes in humans and animal's vestibular system. It was found that individual with diabetes has a large portion of disrupted myelin sheath lamellae, thinning of the myelin sheath and reduces the diameter of the axon fiber in the vestibular nerve; hair cell degeneration also has been noticed in diabetic animals. The present study aimed to find out the Frequency tuning of cervical and ocular vestibular evoked myogenic potential in individual with diabetic and non-diabetic. Total 52 participants in the age range of 35 to 65 years participated in the study. Further, they were categorized in to two groups based on their medical history as non diabetic and diabetes. Frequency tuning were assess using cVEMP and oVEMP at 250HZ,500Hz, 750Hz, 1000Hz, 1500Hz and 2000Hz at 125 dBSPL tone burst stimuli.

The result of the study showed that:

1. The mean cVEMP P1-N1 peak to peak amplitude was higher at 750Hz followed by 500Hz compare to other frequency in individual with non diabetic and oVEMP P1-N1 peak to peak amplitude was higher at 750Hz followed by 1000Hz compare to other frequency with diabetes.
2. There was no significant difference in the cVEMP frequency tuning of individual without diabetes and with diabetes.
3. The mean oVEMP N1-P1 and P1-N2 peak to peak amplitude was higher at 750Hz fallowed by 1000Hz in individual without diabetes and diabetes.

4. There was no significant difference in the oVEMP frequency tuning of individual without diabetes and with diabetes.
5. There was a significant difference in the amplitude of individual without diabetes and with diabetes in the both cVEMP and oVEMP.

Conclusions

The results of the present study indicate that the prevalence of both cVEMP and oVEMP was lesser in individuals with diabetes compared to non diabetic. However, there was no change in the tunning of the cVEMP or oVEMP in individuals with diabetes. To conclude, there may be damage to both the saccule and utricle in individuals with diabetes. Also, there may be damage to the vestibular nerves along with the end organs in individuals with diabetes. Such changes may not lead to a change in tunning of the cVEMP or oVEMP individuals with diabetes.

Implication of the study

This study helps us in understanding the secular or utricular lesions in individuals with diabetes. The findings of the study will help the clinician in understanding the pathophysiology of vestibular damage in individuals with diabetes. Understanding of the pathophysiology will further help the clinician in making a vestibular rehabilitation programme for the individuals with diabetes.

References

Akin, F. W., Murnane, O. D., Tampas, J. W., Clinard, C., Byrd, S., & Kelly, J. K. (2012). The effect of noise exposure on the cervical vestibular evoked myogenic potential. Ear and hearing, 33(4), 458-465.

Baier, B., Stieber, N., & Dieterich, M. (2009). Vestibular-evoked myogenic potentials in vestibular migraine. Journal of neurology, 256(9), 1447.

Bansal, S., Sahni, S., &Sinha, S. K. (2013). Cervical and ocular vestibular evoked myogenic potentials in individuals with severe to profound hearing loss. *Journal of Hearing Science, 3(4),*8-12.

Bektas, D., Gazioglu, S., Arslan, S., Cobanoglu, B., Boz, C., &Caylan, R. (2008). VEMP responses are not affected in non-insulin-dependent diabetes mellitus patients with or without polyneuropathy. ActaOto-laryngologica, 128(7), 768-771.

Bunn, H. F., Gabbay, K. H., & Gallop, P. M. (1978).Glycosylation of hemoglobin relevance to diabetes mellitus.*Science, 200,* 21-27.

Chen, G., Zhao, X., Yu, G., Jian, H., Li, Y., &Xu, G. (2019). Otolith dysfunction in recurrent benign paroxysmal positional vertigo after mild traumatic brain injury. ActaOto-laryngologica, 139(1), 18-21.

Chiarovano, E., Darlington, C., Vidal, P. P., Lamas, G., & de Waele, C. (2014). The role of cervical and ocular vestibular evoked myogenic potentials in the assessment of patients with vestibular schwannoma. *PLoS One, 9(8),* e105026.

Dabiri, S., Yazdani, N., Esfahani, M., Tari, N., Adil, S., Mahvi, Z., &Rezazadeh, N. (2017). Analysis of saccular function with vestibular evoked myogenic potential test in Meniere's disease. ActaMedicaIranica, 55(2), 123-127.

Ditzel, J. (1976). Oxygen transport impairment in diabetes. *Diabetes, 25* (2), 832- 838.

D'Silva, L. J., Lin, J., Staecker, H., Whitney, S. L., &Kluding, P. M. (2016). Impact of Diabetic Complications on Balance and Falls: Contribution of the Vestibular System. *Physical Therapy, 96(3),* 400–409.

EL-Badry, M. M., Gamal, R., &Fawzy, A. (2018). Evaluation of saccular and inferior vestibular nerve functions in children with auditory neuropathy spectrum disorder. *European Archives of Oto-Rhino-Laryngology*, *275*(12), 2925-2931.

El-Salam, N. M. A., Ismail, E. I., & El-Sharabasy, A. E. S. (2017). Evaluation of Cervical Vestibular Evoked Myogenic Potential in Subjects with Chronic Noise Exposure. The journal of international advanced otology, 13(3), 358-362.

Elbeltagy, R., &Galhom, D. (2017). Assessment the effect of noise on the sacculocollic pathway using vestibular evoked myogenic potential. *The Egyptian Journal of Otolaryngology*, *33*(2), 523.

Gazioglu, S., &Boz, C. (2012). Ocular and cervical vestibular evoked myogenic potentials in multiple sclerosis patients. *Clinical Neurophysiology*, *123*(9), 1872-1879.

Govender, S., Rosengren, S. M., & Colebatch, J. G. (2011). Vestibular neuritis has selective effects on air-and bone-conducted cervical and ocular vestibular evoked myogenic potentials. *Clinical Neurophysiology, 122(6),* 1246-1255.

Güven, H., Bayır, Ö., Aytaç, E., Özdek, A., Çomoğlu, S. S., & Korkmaz, H. (2014). Vestibular-evoked myogenic potentials, clinical evaluation, and imaging findings in multiple sclerosis. Neurological Sciences, 35(2), 221-226.

Hong, S. M., Park, D. C., Yeo, S. G., & Cha, C. I. (2008). Vestibular evoked myogenic potentials in patients with benign paroxysmal positional vertigo involving each semicircular canal. *American Journal of Otolaryngology, 29*(3), 184-187.

Ibraheem, O. A., Ramadan Hassaan, M., &Mousa, M. M. (2017).Vestibular profile of type 1 versus type 2 chronic diabetes mellitus. *Hearing, Balance and Communication, 15(3), 133*-144.

Jerin, C., Berman, A., Krause, E., Ertl-Wagner, B., &Gürkov, R. (2014). Ocular vestibular evoked myogenic potential frequency tuning in certain Meniere's disease. *Hearing Research, 310(6),* 54-59.

Kalkan, M., Bayram, A., Gökay, F., Cura, H. S., &Mutlu, C. (2018).Assessment of vestibular-evoked myogenic potentials and video head impulse test in type 2 diabetes mellitus patients with or without polyneuropathy. *European archives of Oto-rhino-laryngology*, *275*(3), and 719.

Kamali, B., Hajiabolhassan, F., Fatahi, J., Esfahani, E. N., Sarrafzadeh, J., &Faghihzadeh, S. (2013). Effects of diabetes mellitus type I with or without neuropathy on vestibular evoked myogenic potentials. *ActaMedicaIranica*, 107-112.

Kang, W. S., Lee, S. H., Yang, C. J., Ahn, J. H., Chung, J. W., & Park, H. J. (2016). Vestibular function tests for vestibular migraine: clinical implication of video head impulse and caloric tests. Frontiers in neurology, 7, 166.

Kim, M. B., Choi, J., Park, G. Y., Cho, Y. S., Hong, S. H., & Chung, W. H. (2013). Clinical value of vestibular evoked myogenic potential in assessing the stage and predicting the hearing results in Meniere's disease. Clinical and experimental otorhinolaryngology, 6(2), 57.

Klagenberg, K. F., Zeigelboim, B. S., Jurkiewicz, A. L., & Martins-Bassetto, J. (2007). Vestibulocochlear manifestations in patients with type I diabetes mellitus. *Brazilian Journal of Otorhinolaryngology*, *73*(3), 353-358.

Konukseven, O., Polat, S. B., Karahan, S., Konukseven, E., Ersoy, R., Cakir, B., &Aksoy, S. (2015). Electrophysiologic vestibular evaluation in type 2 diabetic and prediabetic patients: air conduction ocular and cervical vestibular evoked myogenic potentials. *International Journal of Audiology*, *54*(8), 536-543.

Kumar, K., Vivarthini, C. J., &Bhat, J. S. (2010). Vestibular evoked myogenic potential in noise-induced hearing loss. *Noise and Health, 12(48),* 191-98.

Lin, K. L., Chen, C. M., Wang, S. J., & Young, Y. H. (2014). Correlating vestibular schwannoma size with vestibular-evoked myogenic potential results. Ear and hearing, 35(5), 571-576.

Maia, C. A. S., & de Campos, C. A. H. (2005). Diabetes mellitus as etiological factor of hearing loss. Brazilian journal of otorhinolaryngology, 71(2), 208-214.

Makishima, K., & Tanaka, K. (1971). Pathological changes of the inner ear and central auditory pathway in diabetics. Annals of Otology, Rhinology & Laryngology, 80(2), 218-228.

Martínez, P. P., & Amaro, P. M. (2018). Otolithic damage study in patients with benign paroxysmal positional vertigo with vestibular evoked myogenic potentials. Acta otorrinolaringologica espanola.

McMillan, D. E. (1983).The effect of diabetes on blood flow properties.*Diabetes*, *32* (2), 56-63.

McMillan, D. E., &Gion, K. M. (1981). Glucosylated hemoglobin and reduced erythrocyte deformability in diabetes, *Hormone and Metabolic Research Supplement, 11,* 108-112.

McMillan, D. E., Utterback, N. G., & La Puma, J. (1978). Reduced erythrocyte deformability in diabetes, *Diabetes*, *27 (9)*, 895-901.

Moallemi, M., Hajiabolhassan, F., Fatahi, J., Abolfazli, R., Jalaie, S., &Khamseh, F. (2011). Vestibular evoked myogenic potentials in migraine patients. *Bimonthly Audiology-Tehran University of Medical Sciences*, *20*(1), 16-25.

Murofushi, T., Nakahara, H., Yoshimura, E., &Tsuda, Y. (2011). Association of air-conducted sound oVEMP findings with cVEMPs and caloric test findings in patients with unilateral peripheral vestibular disorders. *Actaoto-laryngologica*, *131*(9), 945-950.

Myers, S. F., Ross, M. D., Jokelainen, P., Graham, M. D., &McClatchey, K. D. (1985). Morphological evidence of vestibular pathology in long term experimental diabetes mellitus: I. Microvascular Changes. *ActaOtolaryngologica, 100*(5-6), 351-364.

Myers, S. F., & Ross, M. D. (1987). Morphological Evidence of Vestibular Pathology in Long-term Experimental Diabetes Mellitus: II. Connective Tissue and Neuroepithelial Pathology. *ActaOto-laryngologica*, *104*(1-2), 40-49.

Ogawa, Y., Otsuka, K., Inagaki, T., Nagai, N., Itani, S., Kondo, T., ... & Suzuki, M. (2018). Comparison of cervical vestibular evoked potentials evoked by air-conducted sound and bone-conducted vibration in vestibular Schwannoma patients. Acta oto-laryngologica, 138(10), 898-903.

Otsuji, S., Baba, Y., &Kamada, T. (1981).Erythrocyte membrane microviscosity in diabetes.*Hormone and Metabolic Research Supplement Series,11,* 97-102.

Perez, R., Ziv, E., Freeman, S., Sichel, J. Y., &Sohmer, H. (2001).Vestibular end-organ impairment in an animal model of type 2 diabetes mellitus. *The Laryngoscope*, *111*(1), 110-113.

Piker, E. G., Jacobson, G. P., Burkard, R. F., McCaslin, D. L., & Hood, L. J. (2013). Effects of age on the tuning of the cVEMP and oVEMP. *Ear and hearing*, *34(6)*, 18-25.

Pollak, L., Kushnir, M., &Stryjer, R. (2006). Diagnostic value of vestibular evoked myogenic potentials in cerebellar and lower-brainstem strokes. *Neurophysiology Clinique/Clinical Neurophysiology*, *36*(4), 227-233.

Rosengren, S. M., & Colebatch, J. G. (2006). Vestibular evoked potentials (VsEPs) in patients with severe to profound bilateral hearing loss. Clinical neurophysiology, 117(5), 1145-1153.

Said, E. A. F. (2014). Vestibular assessment in children with sensorineural hearing loss using both electronystagmography and vestibular-evoked myogenic potential. The Egyptian Journal of Otolaryngology, 30(1), 43.

Sahu, M., &Sinha, S. K. (2015). Assessment of sacculocollic pathway in individuals with diabetes mellitus. *International Journal of Health Sciences Research, 5,* 313-320.

Salviz, M., Yuce, T., Karatas, A., Balikci, H. H., &Ozkul, M. H. (2015). Diagnostic value of frequency-associated vestibular-evoked myogenic potential responses in Ménière's disease. Audiology and Neurotology, 20(4), 229-236.

Schmid- Schonbein, H., &Volger, E. (1976).Red cell aggregation and red cell deformability in diabetes, *Diabetes, 25* (2), 897- 902.

Shin, B. S., Oh, S. Y., Kim, J. S., Kim, T. W., Seo, M. W., Lee, H., & Park, Y. A. (2012). Cervical and ocular vestibular-evoked myogenic potentials in acute vestibular neuritis. *Clinical Neurophysiology*, *123*(2), 369-375.

Singh, N. K., &Apeksha, K. (2016). Efficacy of cervical and ocular vestibular-evoked myogenic potentials in evaluation of benign paroxysmal positional vertigo of posterior semicircular canal. European Archives of Oto-Rhino-Laryngology, 273(9), 2523-2532.

Singh, N. K., & Barman, A. (2015). Efficacy of ocular vestibular-evoked myogenic potential in identifying posterior semicircular canal benign paroxysmal positional vertigo. *Ear and hearing, 36(2),* 261-268.

Singh, N. K., Sinha, S. K., & Barman, A. (2016). Assessment of otolith mediated neural reflexes through cervical and ocular vestibular evoked myogenic potentials in individuals with auditory neuropathy spectrum disorders. *Hearing, Balance and Communication, 14(2),* 77-90.

Singh, N. K., Kashyap, R. S., Supreetha, L., &Sahana, V. (2014). Characterization of age-related changes in sacculocollic response parameters assessed by cervical vestibular evoked myogenic potentials. *European Archives of Oto-Rhino-Laryngology, 271(7),* 1869-1877.

Sinha, S. K., Shankar, K., &Govindaswamy, R. (2015). cVEMP, oVEMP and Caloric Test Results in Individuals with Meniere's disease. *International Journal of Speech & Language Pathology and Audiology, 3(2),* 93-102.

Streubel, Phillip D. Cremer, John P. Carey, Noah Weg, Lloyd B. Minor, S. O. (2001). Vestibular-evoked myogenic potentials in the diagnosis of superior canal dehiscence syndrome. *ActaOto-Laryngologica*, *121*(545), 41-49.

Su, C. H., & Young, Y. H. (2011). Differentiating cerebellar and brainstem lesions with ocular vestibular-evoked myogenic potential test. *European Archives of Oto-Rhino-Laryngology, 268(6),* 923-930.

Sujeet, K. S., Niraj, K. S., Animesh, B., Rajeshwari, G., & Sharanya, R. (2014). Cervical vestibular evoked myogenic potentials and caloric test results in individuals with auditory neuropathy spectrum disorders. Journal of Vestibular Research, 24(4), 313-323.

Tavakoli, M., Talebi, H., ShomeilShushtari, S., MazaheryTehrani, N., &Faghihzadeh, S. (2014). Audiometric results and cervical vestibular evoked myogenic potentials in patients with type I and II diabetes mellitus. *Bimonthly Audiology-Tehran University of Medical Sciences*, *23*(4), 40-48.

Taylor, R. L., Bradshaw, A. P., Halmagyi, G. M., &Welgampola, M. S. (2012). Tuning characteristics of ocular and cervical vestibular evoked myogenic potentials in intact and dehiscent ears. *Audiology and Neurotology, 17(4),* 207-218.

Taylor, R. L., Kong, J., Flanagan, S., Pogson, J., Croxson, G., Pohl, D., & Welgampola, M. S. (2015). Prevalence of vestibular dysfunction in patients with vestibular schwannoma using video head-impulses and vestibular-evoked potentials. Journal of neurology, 262(5), 1228-1237.

Wang, Y. P., & Young, Y. H. (2007). Vestibular-evoked myogenic potentials in chronic noise-induced hearing loss. Otolaryngology—Head and Neck Surgery, 137(4), 607-611.

Ward, B. K., Wenzel, A., Kalyani, R. R., Agrawal, Y., Feng, A. L., Polydefkis, M., ... & Carey, J. P. (2015). Characterization of vestibulopathy in individuals with type 2 diabetes mellitus. *Otolaryngology–Head and Neck Surgery, 153(1),* 112-118.

Zaleski, A., Bogle, J., Starling, A., Zapala, D. A., Davis, L., Wester, M., & Cevette, M. (2015). Vestibular evoked myogenic potentials in patients with vestibular migraine. Otology & Neurotology, 36(2), 295-302.

Zuniga, M. G., Janky, K. L., Nguyen, K. D., Welgampola, M. S., & Carey, J. P. (2013). Ocular vs. cervical VEMPs in the diagnosis of superior semicircular canal dehiscence syndrome. *Otology & Neurotology, 34(1),* 121-28.