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# Brainstem Auditory Evoked Potentials in Type 2 Diabetes Mellitus

*Rajesh Paluru and Devendra Singh Negi*

## Abstract

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Diabetes affects many systems and produces complications in the human body, in those complications one is diabetic central neuropathy. The pathological mechanisms involved in the central neuropathy include chronic hyperglycaemia, hypoglycaemic episodes, angiopathy and blood–brain barrier dysfunction. Diabetic central neuropathy is detected by using of brainstem auditory evoked response (BAER), Visual evoked potential (VEP), somatosensory evoked potential (SEP). These abnormalities are present at different levels and may appear before appearance of overt complications. The central nervous system abnormalities are more frequent in patients with peripheral neuropathy but evoked potentials can be abnormal even in patients without neuropathy. The BAER is a physiological recording technique to study the auditory pathway and does not require subject's attention and generates waves during the first 10 ms after the sound stimulus. Each BAER wave is generated by the activation of a sub-cortical component of the auditory pathway with 90% sensitivity and 70–90% of specificity.

**Keywords:** Brainstem auditory evoked response, central neuropathy, hearing impairment, inter peak latency, type 2 diabetes mellitus

## 1. Introduction

Diabetes mellitus causes both peripheral and central neuropathy, but the peripheral diabetic neuropathy manifestations are more frequently discussed in the literature than the central diabetic neuropathy [1]. The central nervous system has wide, divergent afferent and efferent connections to integrate and transduced the whole body functions like homeostatic adjustments of food intake, energy expenditure, and nutrient metabolism [2].

The auditory nervous system is a complex and intricate structure and performs many tasks in daily life; it analyzes, synthesizes, commands sensory information and carries out decisions; it is measured by using a powerful tool, auditory brainstem evoked response, is capable of both detection and diagnosis of brainstem lesions [3]. The auditory nervous system consists of ascending and descending pathways. Ascending pathway has the classical and non-classical pathways. The classical auditory pathways are known as the tonotopic system because they have

distinct frequency tuning and the neurons are organized anatomically according to the frequency to which they are tuned. Non-classical pathway used the dorsal nuclei of the thalamus and that project to secondary auditory cortex rather than primary auditory cortex. Again the non-classical pathway divided into two separate systems, the diffuse and the polysensory pathways. Descending pathway has the corticofugal and the olivocochlear pathways. Descending auditory pathways are organized mostly parallel to the ascending pathways extending from the cerebral cortex to the cochlear hair cells [4].

Evoked potentials are helpful very much to study the diabetic change in central neural structures [5]. Diabetic central neuropathy is detected by using of brainstem auditory evoked response (BAER), Visual evoked potential (VEP), somatosensory evoked potential (SEP) [5, 6]. These abnormalities are present at different levels and may appear before appearance of overt complications. The central nervous system abnormalities are more frequent in patients with peripheral neuropathy but evoked potentials can be abnormal even in patients without neuropathy. The pathological mechanisms involved in the central neuropathy include chronic hyperglycaemia, hypoglycaemic episodes, angiopathy and blood–brain barrier dysfunction [7].

The BAER is a physiological recording technique to study the auditory pathway and does not require subject's attention and generates waves during the first 10 ms after the sound stimulus. Each ABR wave is generated by the activation of a sub-cortical component of the auditory pathway [8] with 90% sensitivity and 70–90% of specificity [9]. Despite its fall from favor as the initial test of choice in suspected brainstem or VIIIth cranial nerve disease, important clinical roles for BAER still exist. It should be remembered that BAER assess functions of auditory pathways whereas neuroimaging studies examine structure [10].

## **2. Materials and methods**

### **2.1 Research design**

The research design is cross sectional study. The control group included normal subjects, T2DM patients without hearing impairment of either sex, who is not suffering from hearing problems. The sampling technique was sequential sampling.

### **2.2 Participants**

The present study was carried out at Medciti Institute of Medical Sciences (MIMS), Hyderabad, India during the period of 2015 to 2016. This study was approved by institutional ethical committee (FWA00002084; dated 16/03/2015). In this study three groups i.e. WoHI (n = 50), WHI (n = 50) and normal subjects (n = 10) of either sex with an age group of 35–55 were included. The participants were enrolled in the study after acquiring the informed consent.

### **2.3 Inclusion and exclusion criteria**

Type 2 diabetic patients with (WHI) and without (WoHI) hearing impairment, both the gender was included with age limit between 35 and 55 years; minimum duration of diabetes after the diagnosis was 5 years and also ten normal subjects were included as controls.

Participants who had a history of immune/metabolic diseases like hyperbilirubinaemia/kernicterus, polyarteritis nodosa, type 1 diabetes, paraproteinaemias,

anoxia/hypoxia, sarcoidosis, rheumatoid arthritis, uraemia, Guillain-Barré Syndrome, chronic infections like Leprosy, AIDS, Borreliosis, Ramsey Hunt syndrome, using heavy metals like lead, cobalt, mercury; drugs like carboplatin, methyldopa and reserpine; neoplasma/intracranial cystic lesions, chronic middle ear diseases, cranial trauma, ear surgeries, recent surgeries, congenital problems, noise exposure, smoking, alcoholism, hypertension, stroke and hepatic encephalopathy were excluded from the study.

## **2.4 Sample size calculation**

The sample size was calculated in the OpenEpi statistical software. In the pilot study, screening for hearing was carried out for both the ears in fifteen individuals by using pure tone audiometry. In the right ear, 9 out of 15 had a hearing impairment, and 5 out of 9 (55.5%) participants with hearing impairment had diabetes. Out of the 6 (16.7%) individuals without hearing impairment only one had diabetes. Using these values sample size was calculated as 27 each for controls and test. In the left ear, 10 out of 15 had a hearing impairment, and 5 out of 10 (50%) subjects with hearing impairment had diabetes. Out of the 5 (20%) individuals without hearing impairment only one had diabetes. Using these values sample size was calculated as 45 each for controls and test. So in the present study 50 was considered as sample size for each group.

## **2.5 Calculation of BMI**

Height and weight were measured on the subjects in standing position. The weighing scales and the measuring tapes were calibrated periodically. BMI was calculated from the formula,  $BMI = \text{weight (kg)} / \text{height}^2 \text{ (mts)}$ . BMI normal values are below 18.5 (underweight), 18.5–24.9 (normal), 25.0–29.9 (pre obesity), 30.0–34.9 (obesity class I), 35.0–39.9 (Obesity class II) and Above 40 (Obesity class III).

## **2.6 Measurement of HbA1c**

In diabetes, long-term maintenance of blood glucose is important to prevent complications. HbA1c is an indicator of the average glucose concentration in the blood over a period of four months. The HbA1c was measured by using anticoagulated venous blood with latex agglutination inhibition assay (the absence of agglutination is diagnostic of antigen provides a high sensitive assay for small quantities of antigen) with “Rx imola automated analyser (open system)”. Protease enzyme in the hemoglobin denaturant reagent lyses red blood cells and causes hydrolysis of the hemoglobin. The concentration of HbA1c and the total hemoglobin concentrations are measured and HbA1c was calculated as a % of the total hemoglobin concentration. A normal range of HbA1c was 4–6.5% (normal), 6.5–7.5% (target range for those with diabetes), 8–9.5% (high) and greater than 9.5% (very high).

## **2.7 Measurement of pure tone average (PTA)**

The levels of hearing impairment are assessed with the help of Pure Tone Audiometry and obtain pure tone thresholds during air and bone conduction testing. They are recorded graphically on the “audiogram”. The audiogram is graph of a patient’s hearing thresholds across the frequency octaves from 250 Hz to 8000 Hz. The audiogram provides both qualitative and quantitative information about the patient’s hearing loss. Quantitative information tells about degree of loss based on the pure tone average (PTA) of AC thresholds and calculated as decibels (dB). PTA

normal ranges for hearing impairment are –10 to 15 (normal), 16 to 25 (slight), 26 to 40 (mild), 41 to 55 (moderate), 56 to 70 (moderately severe), 71 to 90 (severe), 91 and above (profound). Qualitative information tells about type of hearing impairment and helps in topological diagnosis.

## 2.8 Recording of brainstem auditory evoked response

The BAER is a sequential electrical potential generated in the brainstem and auditory pathway in response to stimulus and is recorded as wave forms from wave I to wave VII and these peaks are generated from different sites of the brainstem auditory pathway. It helps in analyzing presence or absence of hearing loss at the level of central auditory pathway. In the present BAER is recorded by using instrument “Biologic Navigator Pro system AEP Software version 6.3” Natus Medical Incorporated USA, 2013.

### 2.8.1 Stimulus types

An ideal stimulus for eliciting BEAR is a click, which is a brief rectangular pulse of 50–200  $\mu$ s duration with an instantaneous onset. The rapid onset of click provides good neural synchrony, thereby eliciting a clearly defined BAER.

### 2.8.2 Electrode application

Skin must be thoroughly cleaned to remove excess oil, dead skin and dirt to obtain a good contact between skin and electrode. Electrodes are filled with a conducting cream and taped into place. Once the electrodes have been applied, adequacy of contact with skin is assessed by measuring electrical impedance between each electrode pair. For high quality recording, inter electrode impedance  $\leq 5$  k $\Omega$  is acceptable.

### 2.8.3 Processing of electrical activity

Electrical activity picked up by the recording electrodes within the specified time window must be processed through several stages to visualize the BAER waveform. This is because the BAER peaks are of extremely small voltage ( $>1$   $\mu$ V) and are buried in a background of interference (termed ‘noise’), which includes ongoing electroencephalogram (EEG) activity, muscle potentials caused by movement or tension, and 50 Hz power-line radiation. The stages of processing include amplification, filtering, and signal averaging.

### 2.8.4 Amplification and filtering

The small size of the BAER peaks requires amplification to increase the magnitude of the electrical activity picked up by the electrodes. An amplifier gain of  $10^5$  is typically used. The problem of interference obscuring the BAER can be diminished partially by filtering the electrical activity coming from the electrodes. Band pass filters are used to accept energy only within the particular frequency band of interest and reject energy in other frequency ranges. For BAER recording, a filter setting of 30–3000 Hz is recommended to enhance the BAER when testing infants.

Filtering can only eliminate a portion of the interfering noise because of overlap between the frequency content of the BAER and the frequency of the interference. Therefore, another technique, called signal averaging, must be used to further reduce unwanted interference.



### 2.8.5 Signal averaging

The BAER is very small, and even with filtering, it is buried with a background of noise. Signal averaging helps to reduce this noise so that the signal, in this case the BAER, can be detected. Signal averaging is possible because the BAER is time-locked to stimulus onset, whereas the noise interference occurs randomly. That is, the signal occurs at the same points in time following onset of the eliciting stimulus, but the noise has no regular pattern. In signal averaging, a large number of stimuli are presented, and the responses to each of the individual stimulus presentations (termed 'sweeps') are averaged together to obtain a final averaged waveform. By averaging, the random noise tends to cancel out, whereas the evoked potential is retained because it is basically the same in each sweep. The greater the number of stimulus presentations used, the greater the improvement in signal to noise ratio, and the more clearly the BAER can be visualized in the final averaged waveform.

### 2.8.6 Procedure

The patient is made to lie down in a relaxed position with eyes closed so that no auro-palpaberal reflex could be picked up. The portion behind the ear i.e., mastoid on both sides and the forehead are rubbed gently with a conductive gel such that it allows to maintain adequate impedance for the testing. Measures are taken that there no particulars in the testing area that could cause electrical artifacts. Care should also be taken that the wires embedded to the instrument are un-tangled. Considering the test particulars, click stimulus with an alternating polarity are used at intensity levels 80, 70, 60, 50, 40, 30 dB NHL. The filter setting that is set ranges from 150 Hz–1500 Hz, with an epoch time of 10.26 ms and stimulus rate of 11.1/sec and 1024 sweeps of stimulus. The waveform thus displayed post averaging process on the screen is analyzed and the peaks I, III and V are noted. The results thus obtained are analyzed for the final diagnosis considering the absolute latencies of peaks I, III and V and inter peak latencies of I-III, III-V and III-V respectively. Waves I-VII are originated from cochlear nerve, cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body and auditory cortex respectively.

### 2.8.7 Interpretation

IPL I-III is the conduction from the eighth nerve across the subarachnoid space, into the core of the lower pons; normal is 2 milli secs and abnormal is  $\geq 2.4$  milli secs. IPL III-V is the conduction from the lower to the upper pons and possibly into the midbrain; normal is 2 milli secs and abnormal is  $\geq 2.4$  milli secs. IPL I-V is the conduction from the proximal eighth nerve through pons and into the midbrain; normal 4 milli secs and abnormal is  $\geq 4.4$  milli secs.

## 3. Statistical analysis

All the data were expressed as mean  $\pm$  SE. The mean were analyzed by one way ANOVA (Student–Newman–Keuls method). Pearson correlation test was done to see the relationship between right and left ear inter peak latencies of wave I-III, III-V and I-V values in normal subjects, WoHI and WHI groups. Pearson correlation test was done to see the relationship between inter peak latencies I-III, III-V and I-V with age, BMI and HbA1c values in normal subjects, WoHI and WHI groups for both the ears. For all the statistics and graph plotting, SigmaPlot 13.0 (Systat software, USA) was used.  $P < 0.05$  was considered as significant.

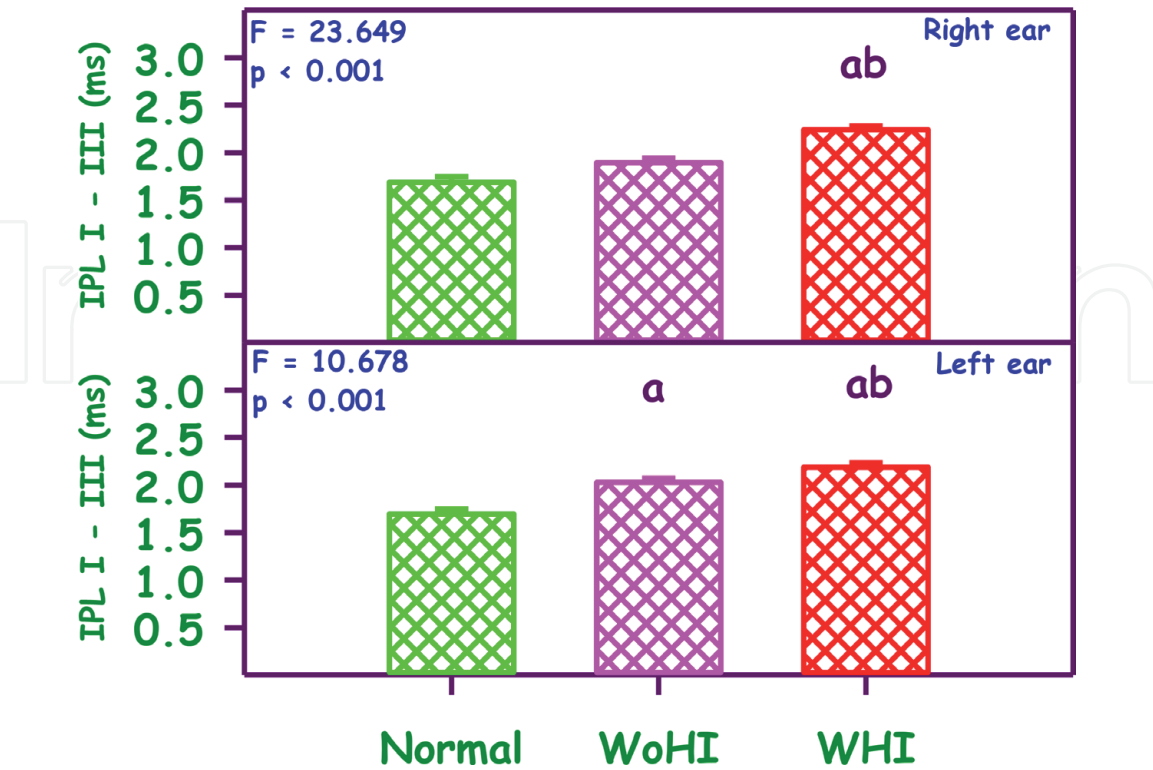
4. Results

The comparison of IPLs I-III, III-V and I-V of both the ears in normal subjects, WoHI and WHI groups were done by one way analysis of variance and it was represented in **Table 1** with their mean and standard error of mean. The comparison of IPL I-III of BAER of both the ears in normal subjects, WoHI and WHI groups were given in **Figure 1**. The IPL I-III of both the ears in WHI group was statistically different from normal subjects and WoHI groups ( $P < 0.0001$ ), this showed that IPL I-III increased in both ears of WHI group. The correlation of IPL I-III values of both the ears in WoHI and WHI groups were given in **Figure 2**. Negative correlation is seen in WoHI group for both the ears ( $P = 0.730$ ), whereas in WHI group it is statistically significant ( $P = 0.050$ ).

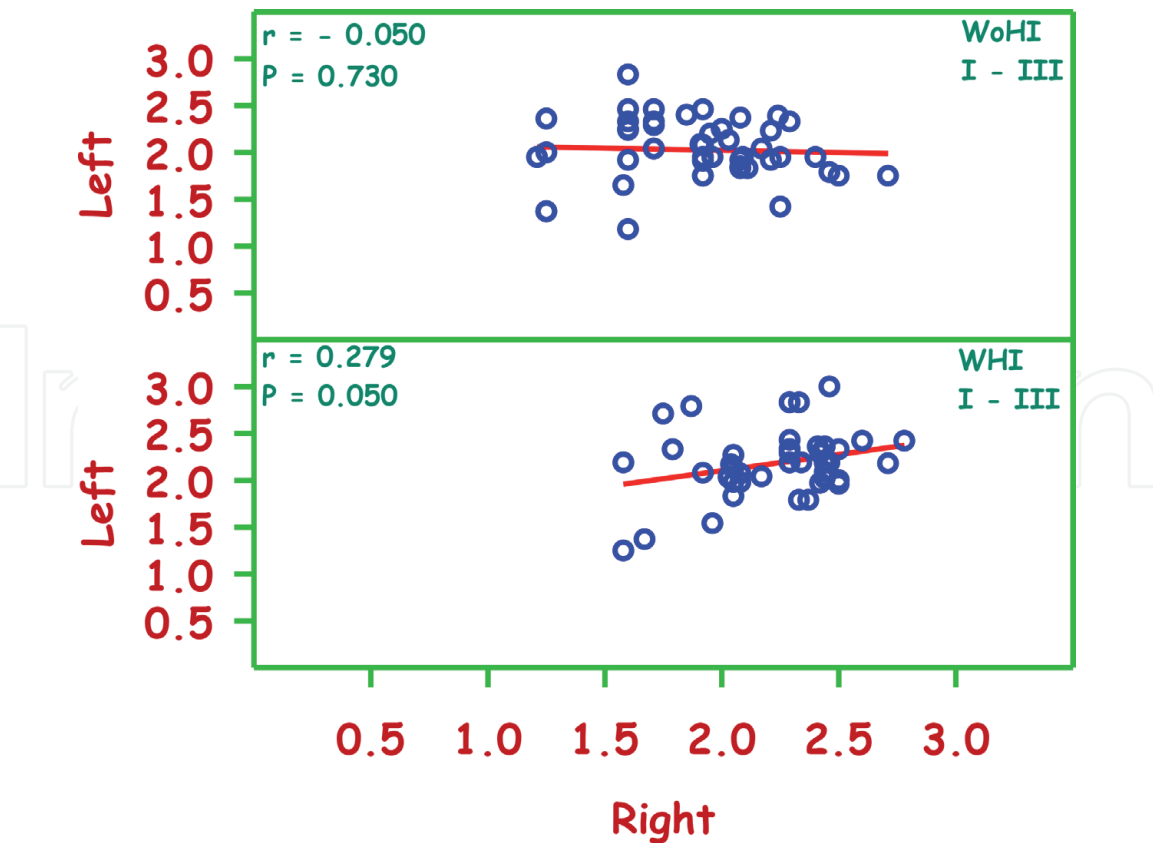
The comparison of IPL III-V of BAER of both the ears in normal subjects, WoHI and WHI groups were given in **Figure 3**. The right ear IPL III-V of WHI group

Parameter	Ear	Normal subjects (Mean ± SEM)	T2DM WoHI (Mean ± SEM)	T2DM WHI (Mean ± SEM)	P-value
IPL I-III (ms)	Right	1.688 ± 0.059	1.895 ± 0.048	2.241 ± 0.039	Given in Figure 1
	Left	1.695 ± 0.056	2.027 ± 0.317	2.187 ± 0.048	
IPL III-V (ms)	Right	1.596 ± 0.044	1.896 ± 0.048	1.930 ± 0.053	
	Left	1.521 ± 0.051	1.818 ± 0.053	1.662 ± 0.038	
IPL I-V (ms)	Right	3.081 ± 0.201	4.083 ± 0.050	4.170 ± 0.058	
	Left	2.919 ± 0.174	3.845 ± 0.052	3.715 ± 0.043	

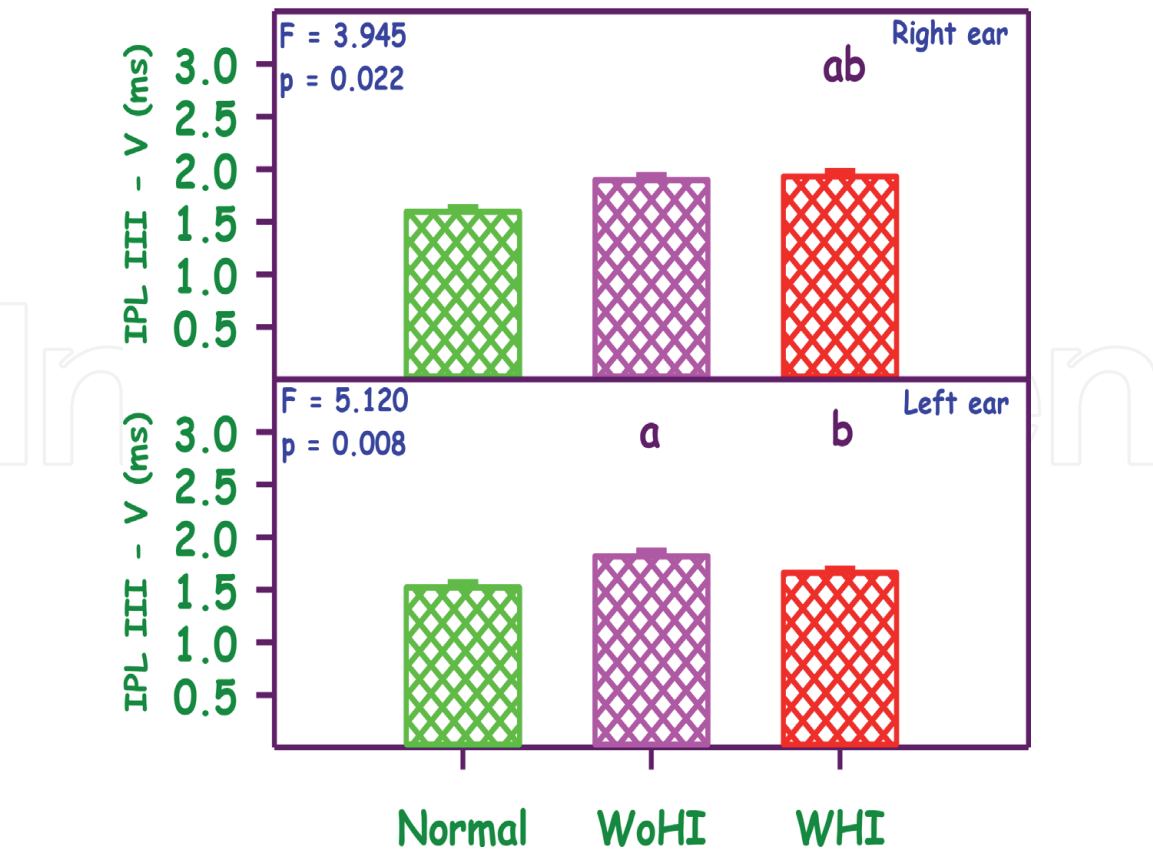
**Table 1.**  
One way analysis of variance of IPLs in normal subjects, T2DM WoHI and WHI groups.



**Figure 1.**  
The IPL I-III in normal subjects, type 2 diabetes without (WoHI) and with (WHI) hearing impairment. Mean + SE ( $n \pm 50$  each in WoHI and WHI groups,  $n \pm 10$  in normal subjects). The 'F' and P values are comparing normal subjects, WoHI and WHI of right and left ear. a – Significantly different from normal subjects; b – Significantly different from WoHI group.



**Figure 2.**  
Correlation of IPL I-III (ms) in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment.  $n = 50$  each. The 'r' and P values are correlating WoHI and WHI right and left ear.



**Figure 3.**  
The IPL III-V in normal subjects, type 2 diabetes without (WoHI) and with (WHI) hearing impairment. Mean + SE ( $n \pm 50$  each in WoHI and WHI groups,  $n \pm 10$  in normal subjects). The 'F' and P values are comparing normal subjects, WoHI and WHI of right and left ear. a – Significantly different from normal subjects; b – Significantly different from WoHI group.

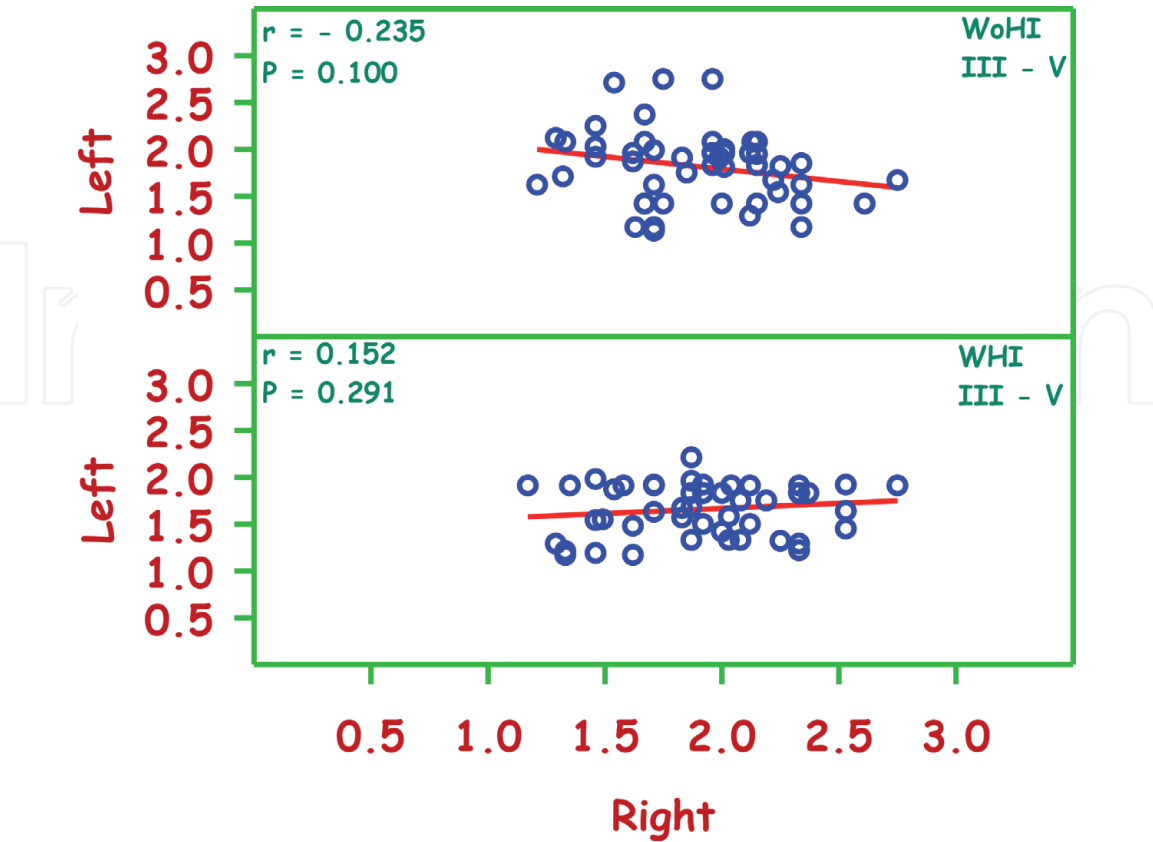


( $P = 0.022$ ) were statistically different from normal subjects, WoHI group. The left ear IPL III-V of WoHI group is significantly different from normal subjects whereas WHI group is significantly different from WoHI group. This showed that IPL III-V increased in both ears of WHI group. The correlation of IPL III-V values of both the ears in WoHI and WHI groups were given in **Figure 4**. No correlation is seen in WoHI and WHI groups for both the ears. Negative correlation is seen WoHI group for both the ears ( $P = 0.100$ ).

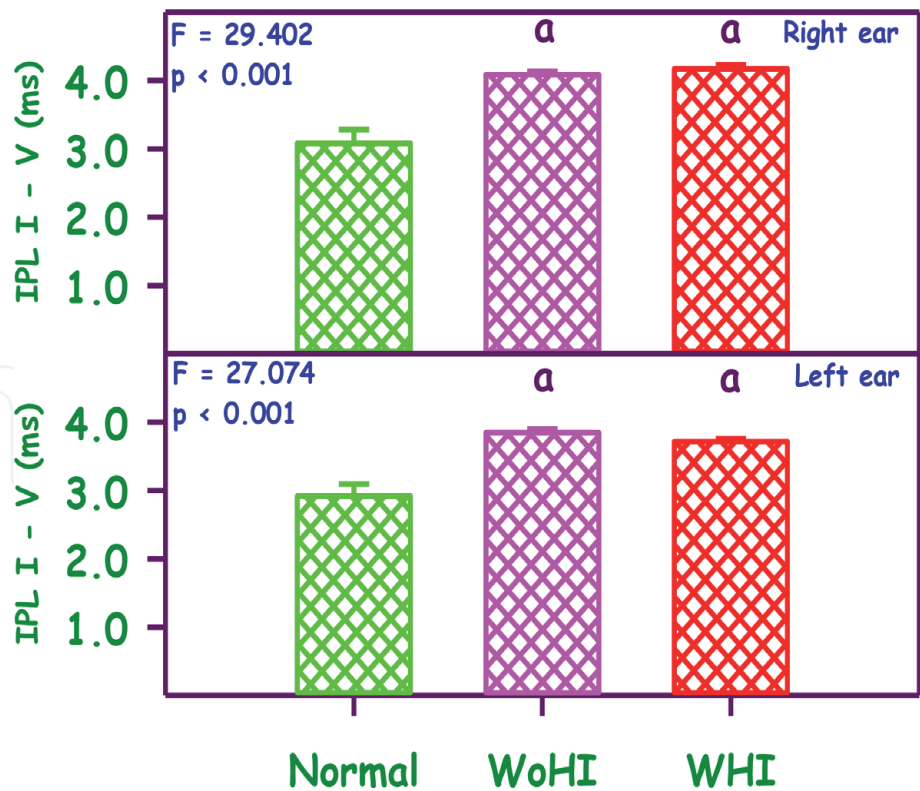
The comparison of IPL I-V of BAER of both the ears in normal subjects, WoHI and WHI groups were given in **Figure 5**. In WoHI and WHI groups ( $P < 0.0001$ ), both the ears showed significant difference from the normal subjects. The correlation of IPL I-V values of both the ears in WoHI and WHI groups were given in **Figure 6**. No correlation was seen in WoHI and WHI groups for both the ears.

The correlation of IPL values and age, BMI, HbA1c values for both the ears in normal subjects were given in **Table 2**. The age, BMI, HbA1c values are not correlated with IPL values in normal subjects. The correlation of IPL values and age, BMI, HbA1c values for both the ears in all subjects were given in **Table 3**. The BMI correlated with the IPL I-V ( $P = 0.003$ ) of both the ears and HbA1c values correlated with IPL I-III ( $P = 0.003$ ), I-V ( $P < 0.001$ ) values of both ears in all subjects. This showed that with increase in BMI and HbA1c values, the IPL values are increased in diabetic subjects.

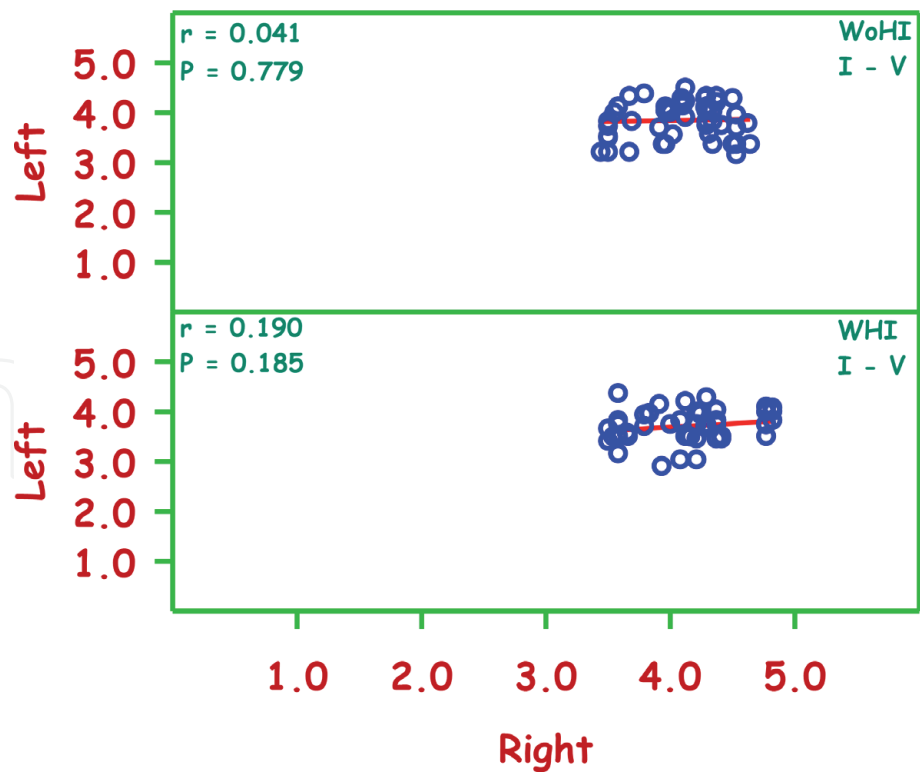
The correlation of IPL I-III, III-V and I-V values and age for both the ears in WoHI and WHI groups were given in **Figures 7–9**. In both the groups IPL I-III, III-V and I-V values were not statistically correlated with age. In the IPL I-III, left ear ( $P = 0.262$ ) of WoHI and right ear ( $P = 0.735$ ) of WHI groups shows negative correlation with age. In the IPL III-V, right ear ( $P = 0.460$ ) of WoHI group shows negative correlation with age. In the IPL I-V, right ( $P = 0.757$ ) and left ( $P = 0.433$ ) ears of WoHI group and left ( $P = 0.826$ ) ear of WHI group shows negative correlation with age.



**Figure 4.** Correlation of IPL III-V (ms) in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment.  $n = 50$  each. The 'r' and P values are correlating WoHI and WHI right and left ear.



**Figure 5.**  
The IPL I-V in normal subjects, type 2 diabetes without (WoHI) and with (WHI) hearing impairment. Mean + SE ( $n \pm 50$  each in WoHI and WHI groups,  $n \pm 10$  in normal subjects). The 'F' and P values are comparing normal subjects, WoHI and WHI of right and left ear. a – Significantly different from normal subjects; b – Significantly different from WoHI group.



**Figure 6.**  
Correlation of IPL I-V (ms) in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment.  $n = 50$  each. The 'r' and P values are correlating WoHI and WHI right and left ear.

The correlation of IPL I-III, III-V and I-V values and BMI for both the ears in WoHI and WHI groups were given in **Figures 10–12**. In both the groups IPL I-III, III-V and I-V values were not statistically correlated with BMI. In IPL I-III,

S.No	Independent variable	Dependent variable	Ear	r-value	p-value
1	Age (years)	IPL I-III	Rt	-0.571	0.084
			Lt	-0.523	0.121
		IPL III-V	Rt	-0.737	0.014
			Lt	-0.499	0.142
		IPL I-V	Rt	-0.705	0.022
			Lt	-0.733	0.015
2	BMI (sq.m)	IPL I-III	Rt	0.742	0.013
			Lt	0.215	0.550
		IPL III-V	Rt	0.523	0.121
			Lt	0.471	0.170
		IPL I-V	Rt	0.549	0.100
			Lt	0.496	0.145
3	HbA1c (%)	IPL I-III	Rt	-0.431	0.335
			Lt	-0.355	0.314
		IPL III-V	Rt	-0.436	0.208
			Lt	-0.282	0.430
		IPL I-V	Rt	-0.392	0.263
			Lt	-0.354	0.315

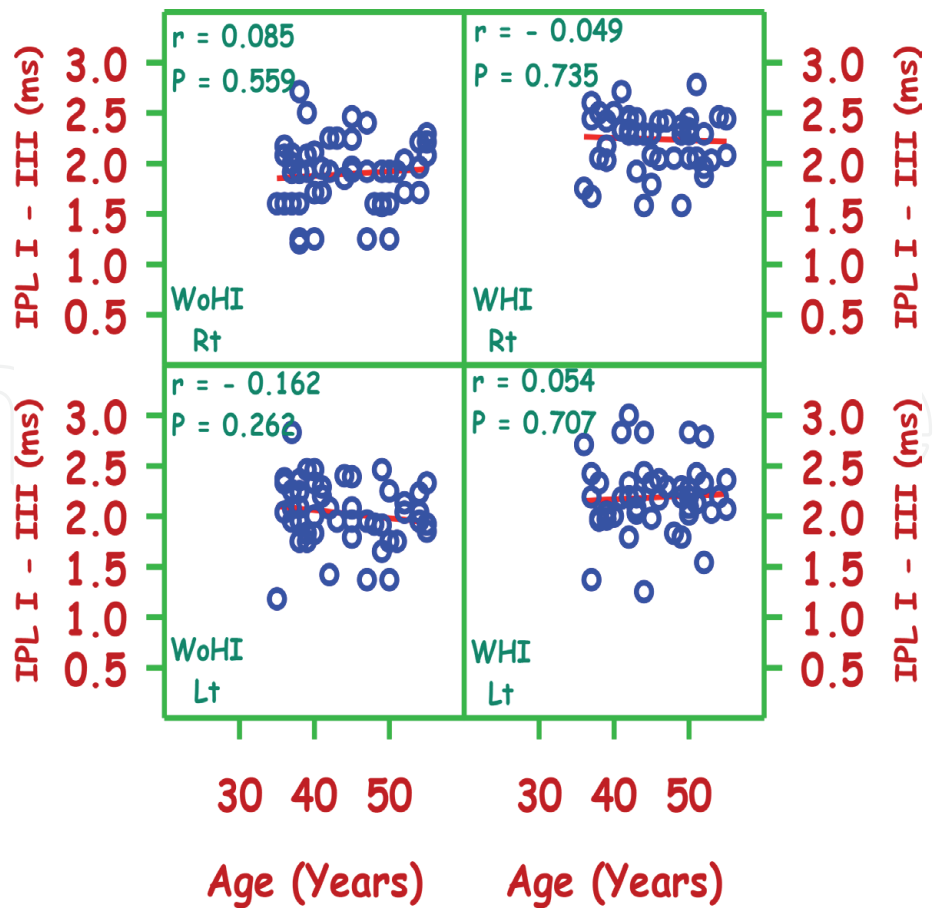
IPLs in milli seconds, Rt – right, Lt – left.

**Table 2.**  
Correlation of independent variables and IPLs in normal subjects.

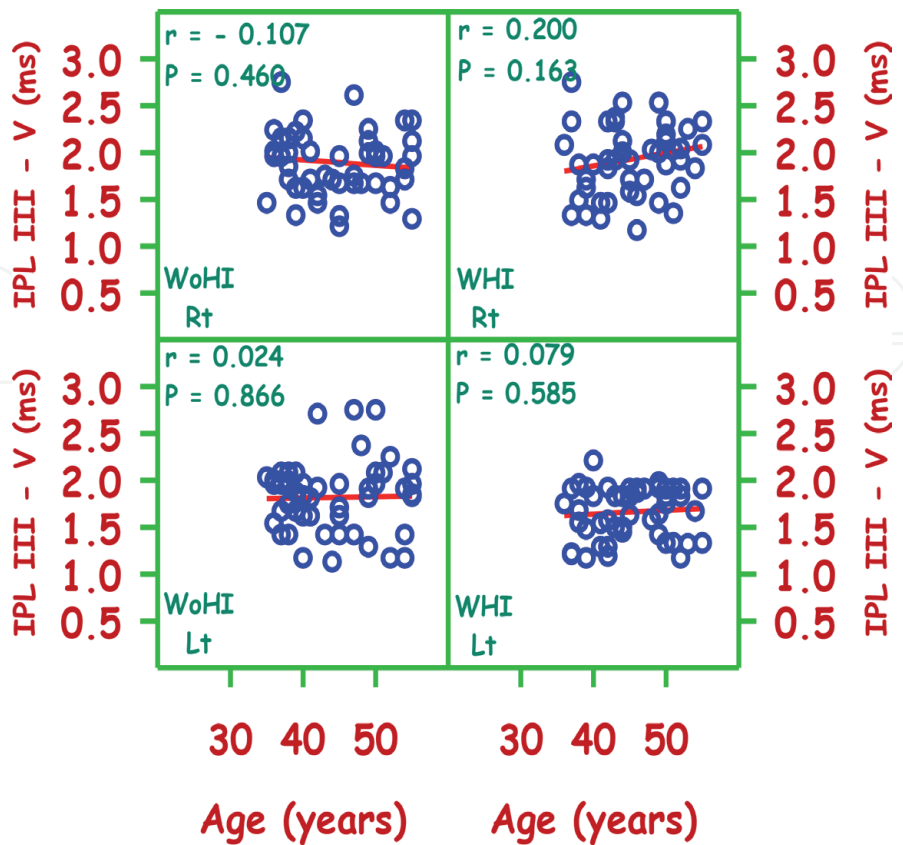
S.No	Independent variable	Dependent variable	Ear	r-value	p-value
1.	Age (years)	IPL I-III	Rt	0.081	0.397
			Lt	-0.002	0.978
		IPL III-V	Rt	0.057	0.550
			Lt	0.032	0.737
		IPL I-V	Rt	0.062	0.516
			Lt	-0.052	0.590
2.	BMI (sq.m)	IPL I-III	Rt	0.095	0.321
			Lt	-0.008	0.931
		IPL III-V	Rt	0.095	0.321
			Lt	-0.008	0.931
		IPL I-V	Rt	0.274	0.003
			Lt	0.210	0.027
3.	HbA1c (%)	IPL I-III	Rt	0.274	0.003
			Lt	0.210	0.027
		IPL III-V	Rt	0.130	0.176
			Lt	0.121	0.208
		IPL I-V	Rt	0.296	0.001
			Lt	0.296	0.001

IPLs in milli seconds, Rt – right, Lt – left.

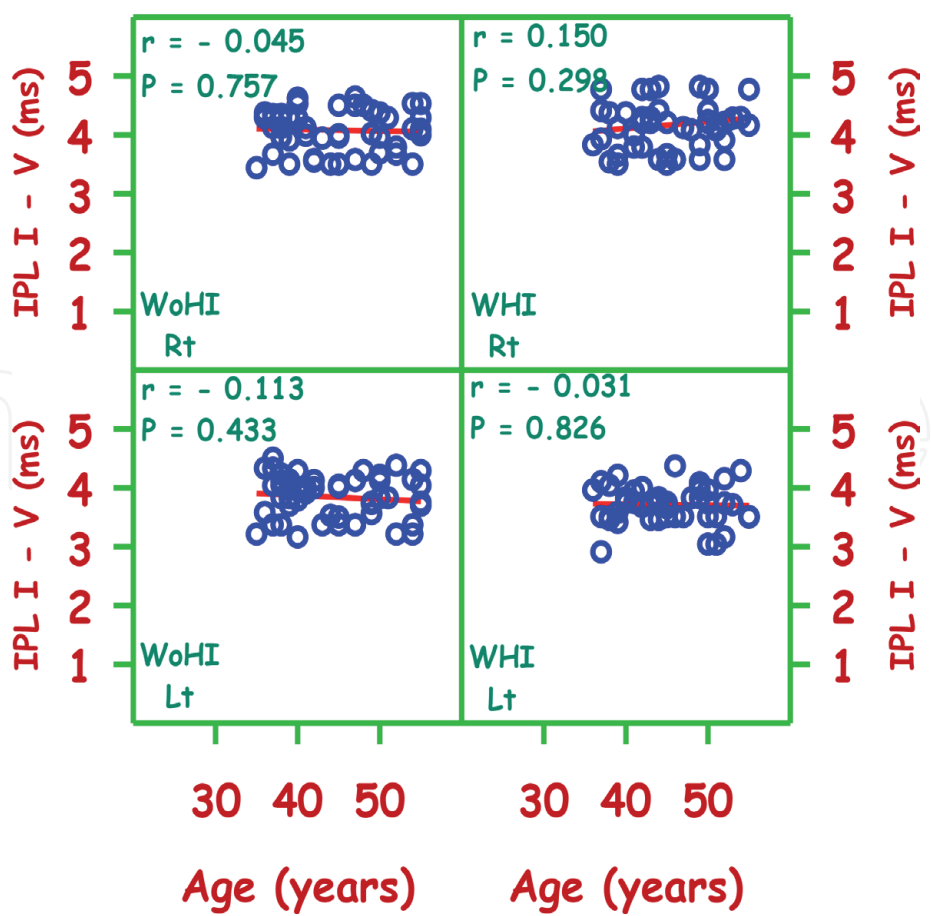
**Table 3.**  
Correlation of independent variables and IPLs in all subjects.



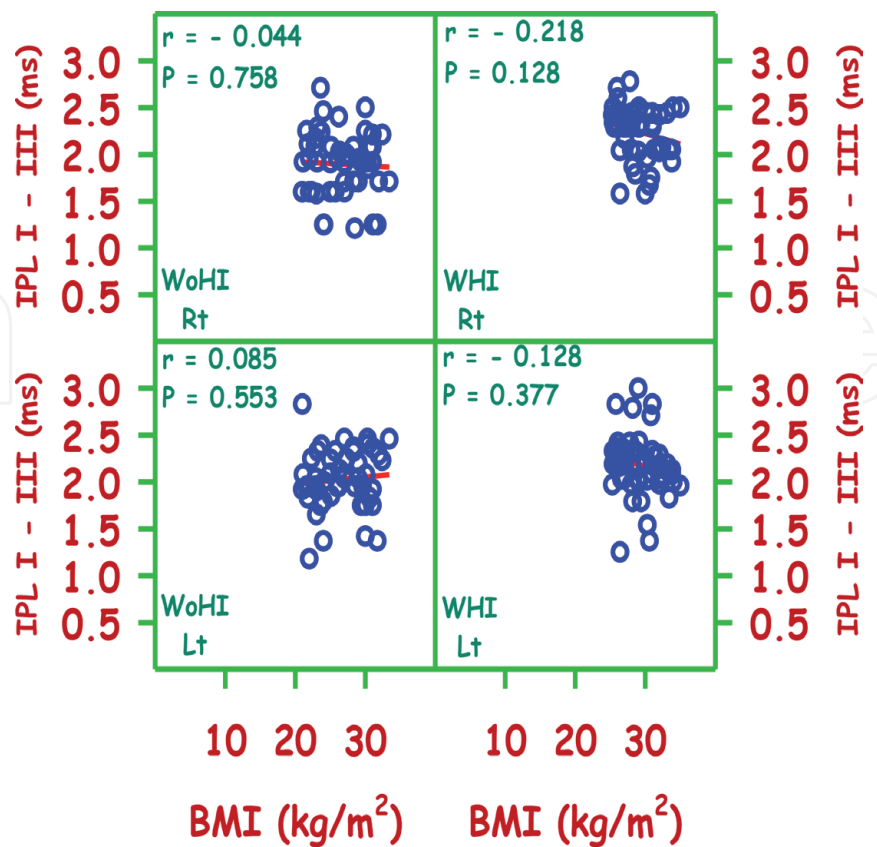
**Figure 7.**  
Correlation of IPL I-III and age in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.



**Figure 8.**  
Correlation of IPL III-V and age in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

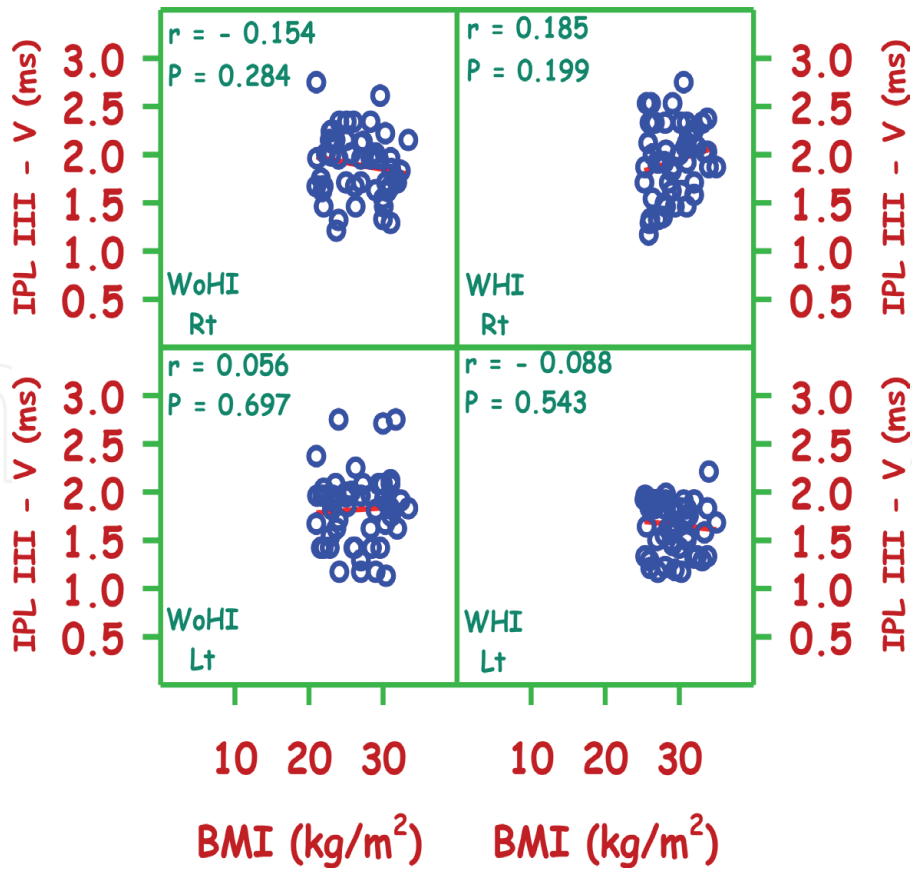


**Figure 9.**  
Correlation of IPL I-V and age in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

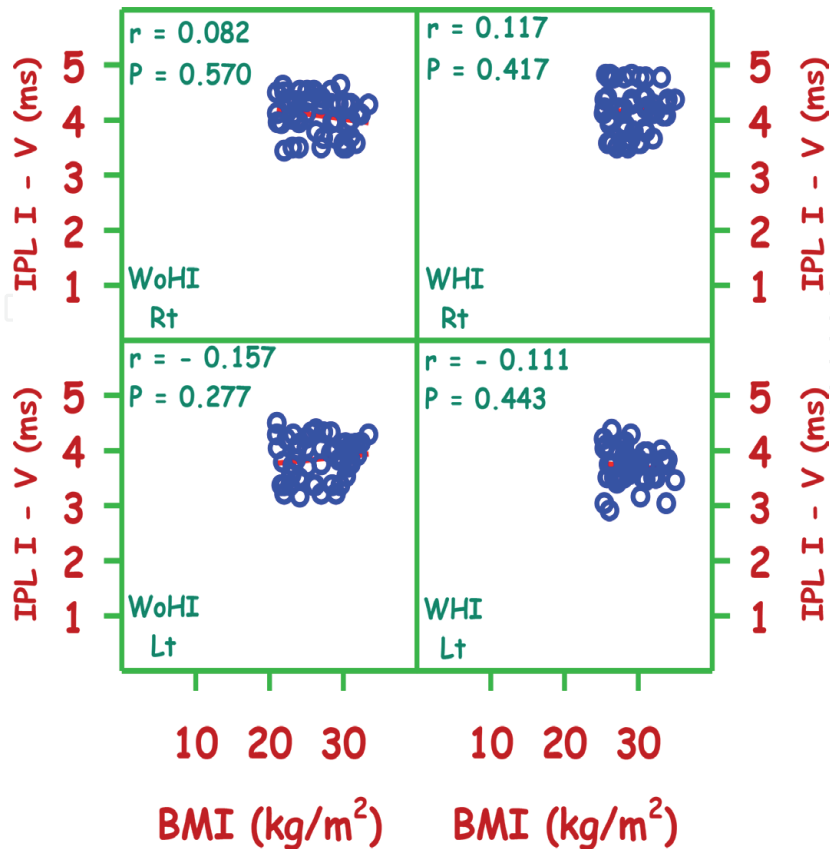


**Figure 10.**  
Correlation of IPL I-III and BMI in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.

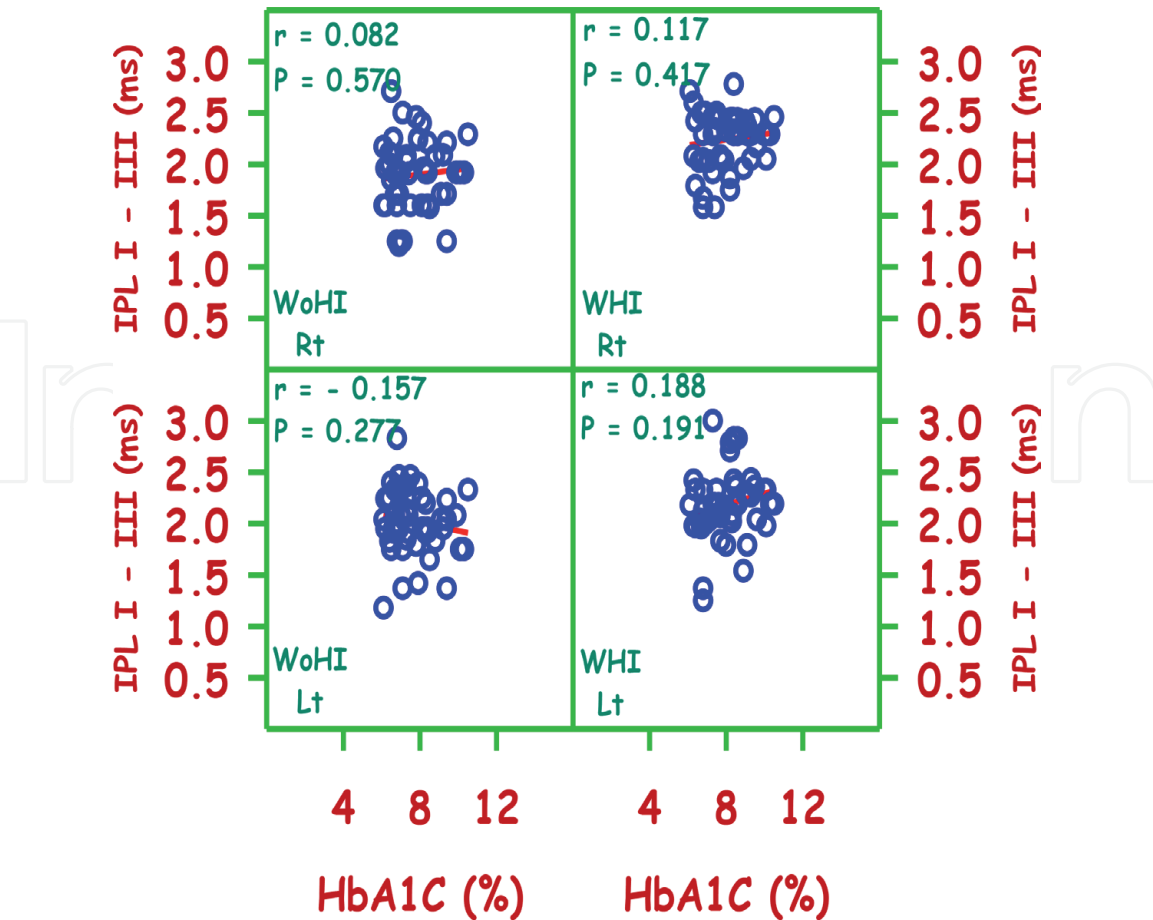




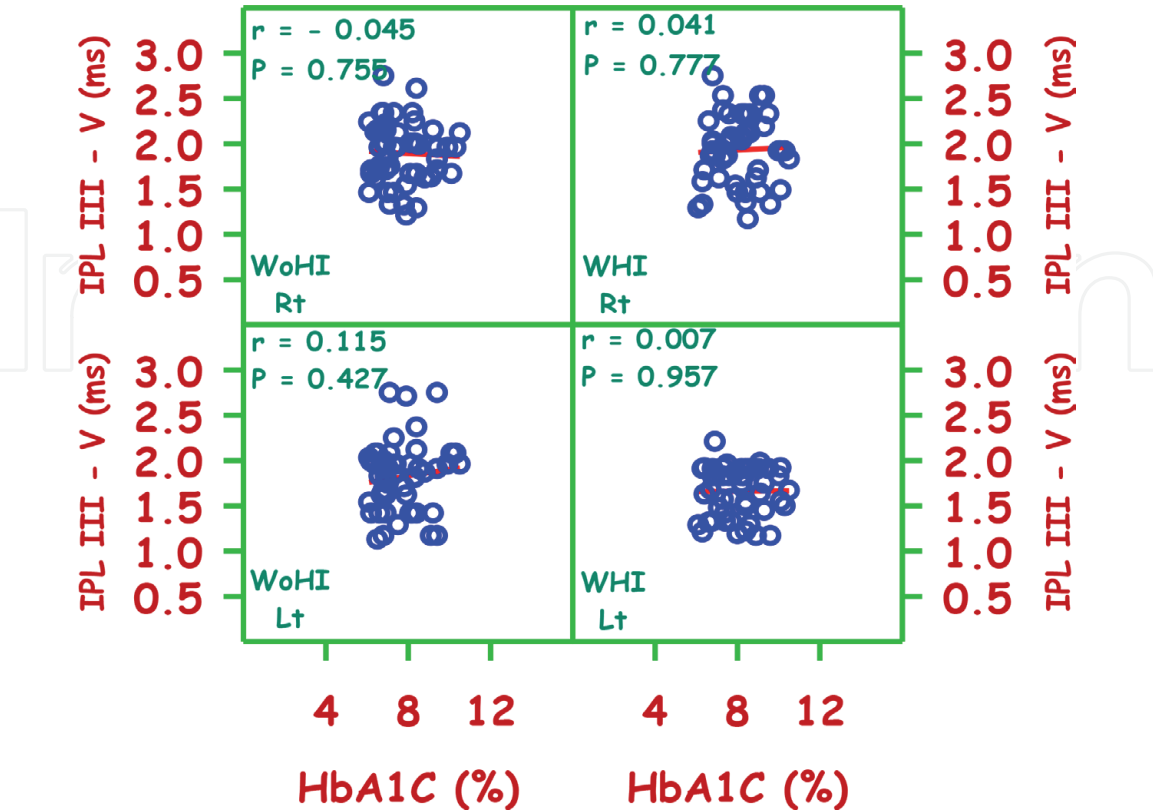
**Figure 11.**  
Correlation of IPL III-V and BMI in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The ‘r’ and P values are correlating WoHI and WHI right and left ear.



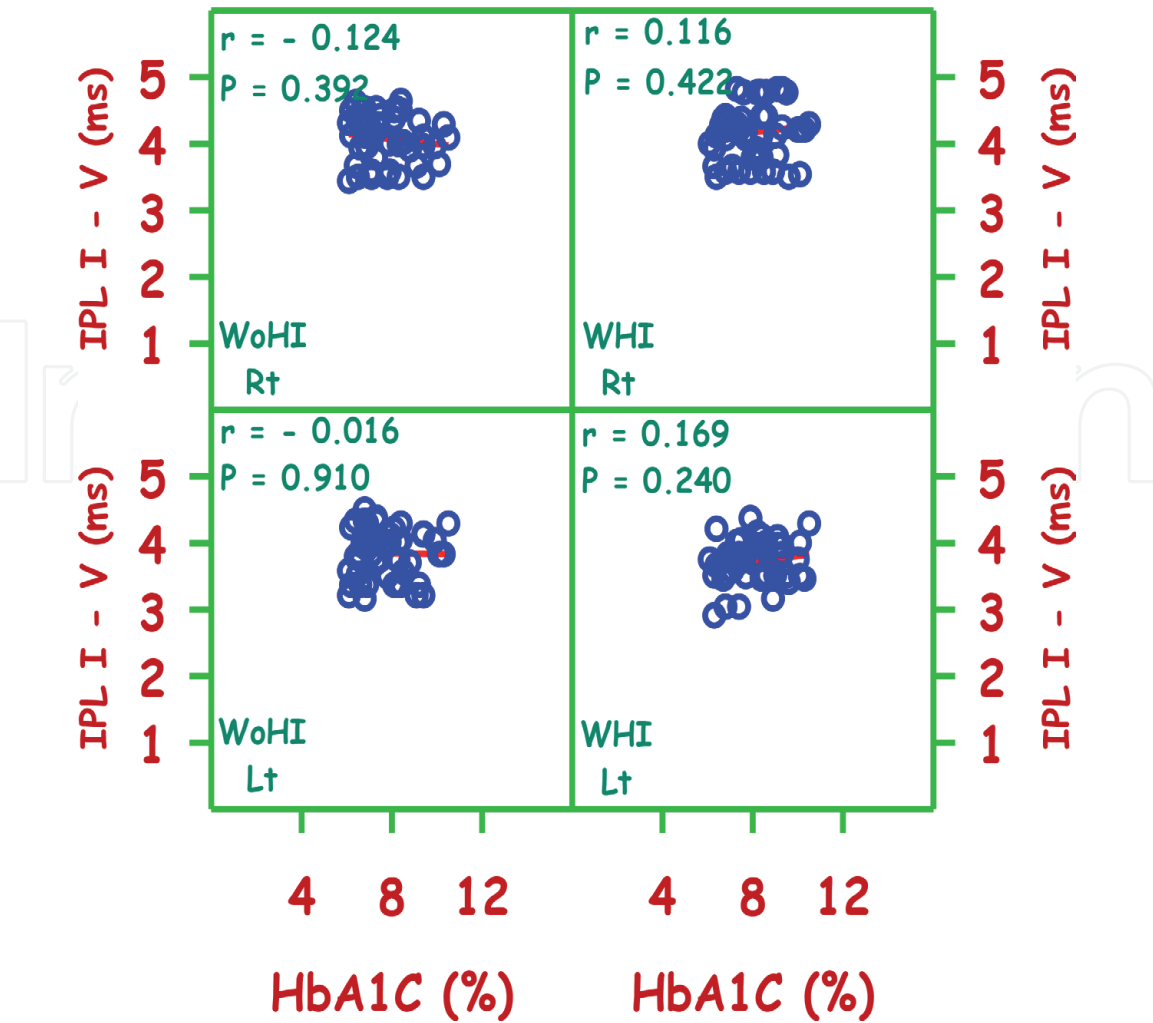
**Figure 12.**  
Correlation of IPL I-V and BMI in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The ‘r’ and P values are correlating WoHI and WHI right and left ear.



**Figure 13.**  
Correlation of IPL I-III and HbA1c in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.



**Figure 14.**  
Correlation of IPL III-V and HbA1c in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The 'r' and P values are correlating WoHI and WHI right and left ear.



**Figure 15.**  
Correlation of IPL I-V and HbA1c in type 2 diabetes, without (WoHI) and with (WHI) hearing impairment. The ‘r’ and P values are correlating WoHI and WHI right and left ear.

the right ear of WoHI ( $P = 0.758$ ) and WHI ( $P = 0.128$ ) group and left ear of WHI ( $P = 0.377$ ) group showed negative correlation with BMI. In IPL III-V, the right ear ( $P = 0.284$ ) of WoHI group and left ear ( $P = 0.543$ ) of WHI group showed negative correlation with BMI. In IPL I-V, the right ear ( $P = 0.179$ ) of WoHI group and left ear ( $P = 0.443$ ) of WHI group shows negative correlation with BMI.

The correlation of IPL I-III, III-V and I-V values and HbA1c for both the ears in WoHI and WHI groups were given in **Figures 13–15**. In both the groups IPL I-III, III-V and I-V values were not statistically correlated with HbA1c. In IPL I-III, left ear of WoHI group shows negative correlation with HbA1c ( $P = 0.277$ ). In IPL III-V, right ear of WoHI group shows negative correlation with HbA1c ( $P = 0.755$ ). In IPL I-V, WoHI group right ( $P = 0.392$ ) and left ( $P = 0.910$ ) ears shows negative correlation with HbA1c.

### 5. Discussion

The BAER is a simple, non-invasive procedure to detect early impairment of auditory nerve and auditory pathway even in the absence of specific symptoms in the diabetic patients. The present study strongly recommended that BAER is carried out in all diabetic patients to detect the involvement of central neuronal pathway and periodic evaluation in of diabetes for early intervention regarding metabolic regulations.

The inter peak latencies of BAER tells about the time required for processing from one site to the next site in the auditory pathway [11]. In the present study, WHI group IPL I-III, III-V and I-V of both ears and left ear IPL III-V increased when compared to the normal subjects and WoHI group. These findings are in line with the previous research who found significant changes in the IPLs of the diabetics when compared to the controls [7, 12–16].

The prolongation of IPLs I-III, III-V and I-V are indicated central conduction delay at the level of brainstem and midbrain in the auditory pathway of diabetics. These prolongations are due to neuropathy at brainstem and midbrain level. These findings are supported by previous research [16]. In the present study, WHI group left ear IPL I-V values are decreased minimally when compared to WoHI group left ear IPL I-V values. Metformin (N, N-dimethylbiguanidine) is a widely used oral hypoglycaemic agent in T2DM; it has a potential anti-ototoxic activity. It prevents oxidative stress induced cell death and inhibition of lipid peroxidation and also scavenges hydroxyl radicals by modulating NADPH oxidase and inhibits apoptotic cascades by increasing the expression of the anti-apoptotic protein Bcl-2 [17]. This is the probable mechanism responsible for the reduced IPL values in the WHI group who are on metformin treatment.

The IPLs I-III, III-V and I-V of both the ears in WoHI and WHI groups were not correlated with the age, BMI and HbA1c values. The present study is contradicting with the previous research [18]. The HbA1c values are not correlated with the IPLs of both ears in WoHI and WHI groups. This finding is in line with the previous research [19–21] and contradicting with other studies [7]. In diabetes, hyperglycaemia results many pathological changes in nervous tissue by apoptosis, nerve energy deficits, intracellular calcium excitotoxicity, glycosylated products, oxidative stress, hypoxia and ischemia [22]. In the peripheral nervous system the myelin sheath and other nerve components are affected by hyperglycaemia [23].

In the present study, BMI and HbA1c values were correlated with the IPL I-III and I-V of both the ears in all subjects; it indicated that, with increase in BMI and HbA1c values the IPL values are increased in diabetic subjects. This finding is in line with the previous research where inter peak latencies were prolonged in uncontrolled T2DM subjects [24]. The inter peak latencies were prolonged in T2DM patients with duration of diabetes more than 7 years [24].

In diabetic neuropathy, hyperglycaemia accumulates diacylglycerol and activates PKC; this PKC causes transcription changes in the contractile proteins fibronectin, type IV collagen, and extracellular matrix (ECM) proteins in neurons and endothelial cells [25]. Due to this the affected neurons had degenerated axons, so that the amplitude of the neural conduction alters and the conduction velocity decreases in that affected nerves [26]. This is one of the reason to increase the inter peak latencies in the hearing impaired persons with T2DM in the present study. The present study is in line with the previous research with prolonged inter peak latencies in the T2DM patients [27, 28]. Another mechanism involved in the reduced neural transmission in T2DM with hyperglycaemia is oxidative stress with reactive oxygen species, these causes dendritic damage in the affected neurons with microglial activation [28–31] with prolongation of inter peak latencies.

Diabetes associated disruption between insulin activity and glucose metabolism results in decreased cerebral blood flow and oxidative glucose metabolism with impairment of neurotransmission. Diabetes has been widely associated with slowly progressive end-organ damage in brain resulting in diabetic neuropathy and/or mild to moderately impair cognitive function, both in type 1 and type 2 diabetic patients. The molecular mechanisms involved in the CNS damage in diabetes are hypothesized that AGEs formation, aldose reductase activity, oxidative stress, activation of protein kinase C and increased hexosamine pathway flux [32].

Chronic hyperglycaemia elicits pathophysiological changes to the nervous system as a result of oxidative stress, nerve energy deficits, decreased Na/K/ATPase activity and decreased neurotrophism. The damage to myelin sheaths and other nerve components as a result of hyperglycaemia occurs prominently in the peripheral nervous system but also in the spinal cord, cranial, optic and vestibular nerves. In the peripheral nervous system major myelin proteins are glycosylated, perhaps making them more prone to the effects of AGE, while in the CNS major myelin proteins are not glycosylated. The glial margin demarcates the boundary of the peripheral and central auditory systems, and is located about halfway between the cochlea and the cochlear nucleus [33]. These findings may explain why the peripheral auditory function was more affected than the central auditory nervous system in the present study. In diabetics, the IPLs I-III and I-V were positively correlated with autonomic score and large sensory nerve dysfunction. The abnormalities of waves III and V indicated an impairment of the auditory brainstem function in diabetic neuropathy [34].

The T2DM affects the cognitive function. The higher concentrations of neuron specific enolase (NSE) protein in long standing T2DM result permanent brain damage and was correlated with poor cognitive performance. Its concentration increased by oxidative stress and neuronal apoptosis and these changes reversed with insulin treatment [35]. In T2DM, the P300 event related potentials (ERPs) revealed early cognitive dysfunction which was not detected by neuro-psychometric test mini mental state examination (MMSE) and it was more prominent when the disease duration more than 5 years. When the T2DM is associated with hypertension, further increases the risk of cognitive impairment [36].

## 6. Conclusion

The present study explains about the inter peak latency changes of the brainstem auditory evoked potentials in T2DM. BAER was performed in normal subjects, WoHI and WHI groups for both the ears. Compared the inter peak latencies I-III, III-V and I-V between normal subjects, WoHI and WHI groups. Correlated age, BMI and HbA1c values with inter peak latencies in normal subjects, WoHI and WHI groups for both the ears. Age, BMI and HbA1c are not correlated with increase in inter peak latencies for both the ears in WHI group. The BMI and HbA1c values were correlated with IPL I-V of both the ears in all subjects.

We focused on functional changes but not anatomical changes. Because, functional changes can happen without any visible anatomical changes. For the assessment of structural changes we need CT or MRI brain which are highly cost, time consuming, radio-hazard and the subject may face inconvenience. However BAER can overcome all these circumstances. India is a country with large number of population with diabetes, insists the necessity to focus on long term hearing loss among them. BAER test is the very feasible method to perform at regular intervals for record. It could help to take necessary action to prevent hearing loss.

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## **Conflict of interest**

The authors declare no conflict of interest.

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