INTRODUCTION

Diabetes mellitus (DM) is recognized as a group of heterogeneous disorders with the common elements of hyperglycaemia and glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action, or both.[1] India is currently, the world leader in terms of diabetic population and it is anticipated that the number diabetic patients in India will reach 79.4 million by the year 2030.[2] The increased morbidity and mortality in diabetics is mainly due to long term micro and macrovascular complications affecting the eyes, kidneys, heart and nerves.[3] There has been a persistent concern about the hearing loss in diabetics, since extensive evidence suggests that deafness might represent a complication of type 2 diabetes mellitus (T2DM).[4,5]

The typical hearing impairment described in diabetics is a bilateral sensorineural hearing loss occurring as a result of neuropathy.[6] Clinically overt neuropathy manifests only after many years of onset of diabetes, but it can be detected much earlier with the help of electrophysiological tests.[7]

Brainstem auditory evoked potentials (BAEP) are recorded from the ear and vertex in response to brief auditory stimulation. They assess the conduction through the auditory pathway up to the midbrain. BAEP comprises of five or more waves occurring within 10 msec of the acoustic stimulus. Their clinical utility has been established in the

### A B S T R A C T

**Background:** Diabetes mellitus is a complex metabolic disorder whose detrimental effects on various organ systems, including the nervous system are well known. **Aim:** This study was conducted to determine the changes in the brainstem auditory evoked potentials (BAEP) in patients with type 2 diabetes mellitus. **Materials and Methods:** In this case-control study, 116 females with type 2 diabetes and 100 age matched, healthy female volunteers were selected. The brainstem auditory evoked potentials (BAEP) were recorded with RMS EMG EP Marc-II Channel machine. The measures included latencies of waves I, II, III, IV, V and Interpeak latencies (IPL) I-III, III-V and I-V separately for both ears. Data was analysed statistically with SPSS software v13.0. **Results:** It was found that IPL I-III was significantly delayed ($P = 0.028$) only in the right ear, while the latency of wave V and IPL I-V showed a significant delay bilaterally ($P$ values for right ear being 0.021 and 0.0381 respectively while those for left ear being 0.028 and 0.016 respectively), in diabetic females. However, no significant difference ($P > 0.05$) was found between diabetic and control subjects as regards to the latencies of waves I, II, III, IV and IPL III-V bilaterally and IPL I-III unilaterally in the left ear. Also, none of the BAEP latencies were significantly correlated with either the duration of disease or with fasting blood glucose levels in diabetics. **Conclusions:** Therefore, it could be concluded that diabetes patients have an early involvement of central auditory pathway, which can be detected quite accurately with the help of auditory evoked potential studies.

**Key words:** Auditory evoked potentials, brainstem dysfunction, diabetes mellitus, interpeak latency, sensorineural hearing loss
assessments of hearing in uncooperative patients, children
and in patients with brainstem disorders. The working
hypothesis in most BAEP studies has assigned waves I, II,
III, IV and V to the segment of the auditory nerve closest
to the cochlea, cochlear nucleus, superior olivary complex,
lateral lemniscus and inferior colliculus respectively.

Many studies have evaluated the association of BAEP
abnormalities and T2DM, but these have given variable
results. There is also a lack of adequate data on BAEP
changes in diabetics in India, mainly because very few
studies have been done here. The present study was
done to assess the BAEP abnormalities in females with
T2DM and also to study the correlation of the observed
abnormalities with the duration of diabetes and fasting
blood glucose levels.

Material and Methods

The study was carried out from 2008-2010 in the Physiology
department of the institute. The subjects were divided into
two groups i.e., (i) the diabetic group and (ii) the control
group. The procedures followed were in accordance with
the ethical standards of the institutional committee on
human experimentation and with the Helsinki declaration
of 1975, as revised in 2000.

Participants

The diabetic group comprised of 116 female patients
attending the Endocrinology Outdoor clinic of the hospital,
while the control group consisted of 100 age matched
female volunteers from among the paramedical and lower
staff of the hospital. Written consent was obtained from
all the enrolled subjects after explaining them the details
of the study in their own language.

Inclusion criteria

Among the first group, those with T2DM, aged 35-50 years
and with no past/present or family history of ear diseases
or deafness were included. The diagnostic method of
T2DM was based on the criteria from the American
Diabetes Association (ADA). None of the diabetics had
a clinically overt neuropathy at the time of study. Among
the controls, non-diabetic, age matched females who had
no past/present or family history of ear disease or deafness
and who were apparently healthy, were included. We did
not include subjects over 50 years of age since this age
group has an increased incidence of presbyacusis, a type
of sensorineural hearing loss.

Exclusion criteria

For both the groups, those females were excluded,
who had a history of head/ear trauma, significant
occupational noise exposure, intake of known ototoxic
drugs (e.g., aminoglycosides) or any other medication
that might affect normal functioning of the nervous
system (e.g., antidepressants, antipsychotics, methyldopa,
etc.), family history of deafness, any ear disease
or any systemic illness that might affect the nervous
system (uraemia, stroke, hepatic encephalopathy, multiple
sclerosis, thyroid disorders, anaemia, meningitis, etc),
any ear surgery, radiotherapy or chemotherapy.

Medical and Biochemical examination

Prior to the BAEP recordings, all the females were subject
to the following:

- Detailed history by way of self-administered
  questionnaires about medical history and lifestyle
- Detailed general physical and systemic examination
- Complete ENT check up by way of otoscopic
  examination, tuning fork tests and audiometry, to rule
  out peripheral hearing loss
- Serum urea, creatinine and fasting blood sugar (FBS)
  levels, which were assessed in the clinical biochemistry
  lab of the hospital.

BAEP Study

It was performed as per the guidelines of the American
Clinical Neurophysiological Society. BAEPs were
recorded with a PC based, RMS EMG EP Marc-II
Channel machine (Recorders and Medicare Systems Pvt.
Ltd. Chandigarh, India). Before starting the test, age was
calculated to the nearest completed year. Standing height
without shoes (in cm) and body weight with minimal
clothing (in kgs), were also noted. The BAEP recordings
were done in a semi-dark room with quiet surroundings.
The subjects were made to sit comfortably in a chair, whose back
was turned towards the recording machine. The participants
were asked to avoid unnecessary movement and to remove
all the metallic ornaments that they were wearing. The
recording method for BAEP is summarised below.

Monaural stimulation (i.e., one ear at a time), in the form
of “broad-band clicks”, the acoustic energy of which is
spread over a wide range of audio frequencies, was given
via headphones at the rates of 11.1 Hz, along with masking
of sounds in the contralateral ear. Two thousand clicks
were averaged by a filter setting of 100 and 3000 Hz. The
clicks were given at an intensity of 60 dB level above the
individual perceptual hearing threshold. Percutaneous
silver disc electrodes were used to record the BAEPs. The
active electrodes were placed at both mastoids; reference
electrode at vertex (Cz), while the ground electrode was
placed on the scalp, in the midline frontal location (Fz).
Electronic impedance was kept below 5 Kohms. Two or
more responses were obtained for both the ears separately,
to show replicability. The BAEP results were interpreted for the latencies of waves I, II, III, IV, V and Interpeak Latencies (IPL) I-III, III-V and I-V.

**Statistical analysis**
The data was analysed statistically by using Statistical Package for Social Sciences version 13.0 (SPSS Inc. Chicago, US). Student’s unpaired t-test was used for the analysis. Pearson’s coefficient was also found between the BAEP waveforms and the duration of the disease and the fasting blood glucose (FBG) levels. The BAEP wave latencies and IPL were dependent variables while both the duration of diabetes and FBG were independent variables.

**RESULTS**
The basic data i.e. age, height and weight did not show any statistical significance between the diabetics and controls (P > 0.05), but there was a statistically highly significant difference between the mean FBG levels of both the groups (P < 0.001), the values being much higher in diabetic females. The duration of T2DM in our subjects ranged from 1-15 years, the mean value being 5.38 ± 6.14 years [Table 1].

Furthermore, since the corresponding mean BAEP wave latencies are comparable between right and left ear (P > 0.05), in both diabetic and control subjects [Tables 2 and 3 respectively] thus, it is clear that the right-left latency asymmetry is within normal limits in both these groups.

A comparison between the mean values of the various wave latencies and IPLs was done separately for both the ears, in diabetics and controls [Table 4]. It was seen that only two measures were significantly higher in diabetics, i.e., the mean latency of wave V and mean IPL I-V, with both right ear (P values for these latencies being 0.021 and 0.0381 respectively) and left ear stimulation (P values being 0.028 and 0.016 respectively). Also, the mean IPL I-III was significantly higher in diabetic females, but only with right ear stimulation (P = 0.028), while it was comparable with control group, with left ear stimulation. None of the differences between the mean latencies of waves I, II, III, IV and mean IPL III-V were statistically significant between both the groups (P > 0.05), with either ear stimulation.

Also, all the BAEP wave latencies showed a non significant (P > 0.05), positive correlation with both the duration of diabetes and FBS levels [Table 5]. However, there is a stronger correlation of BAEP latencies with FBS levels, as suggested by higher ‘r’ values, than with the duration of diabetes.

**DISCUSSION**
The results of our study have shown that wave V and IPL I-V were significantly delayed bilaterally, while the IPL I-III was significantly delayed unilaterally, in females with T2DM.

These results are in complete agreement with those of Konrad Martin et al.,[14] who also reported a significant rise (P < 0.05) in latency of wave V and IPL I-V of T2DM patients. We also agree with results of Al-Azzawi and Mirza,[15] regarding the significant prolongation of
latency of wave V and IPL I-III and IPL I-V in diabetics but disagree regarding the increase in latencies of waves I, III and IPL III-V. Our results are in agreement with the observations of Morales et al.,[16] regarding the significant rise in the latency of wave V and IPL I-V but we are in disagreement regarding their reporting of a significant rise in IPL III-V.

Habib et al.,[17] reported a significant rise in latency of wave V and IPL I-V of T2DM patients, which is in conformity with our study, but their detection of a significant rise in wave I latency as well, in diabetics, shows a disparity with our results.

The significant increase in latency of wave V, IPL I-III and I-V in T2DM, as reported by Gupta et al.,[18] are similar to this study but their additional observations of an increase in wave latency III and IPL III-V, are incongruous with our results. Toth et al.,[19] has also confirmed our findings of a significant increase in latencies of waves V and IPL I-III in T2DM, but their reporting of a significant rise in latencies of waves I, II, III and IPL III-V are in contradiction with our findings.

In the present study, the fact that the latency of waves I and II are comparable between both the groups, suggests that the auditory nerve (Cranial Nerve VIII) transmission is normal in females with T2DM. The delay in latency of wave V and IPL I-III, therefore, points towards a central conduction delay, at the brainstem-to-midbrain level. The increase in IPL I-V may be a result of a prolongation of IPL I-III.[20]

The delay in the central conduction time in DM may be related to the neurodegenerative changes occurring in these patients. The exact mechanism of neuronal degeneration in T2DM is uncertain. However, as suggested by some recent studies, the insulin resistance in T2DM, not only leads to a compromise in the cell survival, metabolism and neuronal plasticity, but also increases oxidative stress and apoptosis of neurons. Also, an increase in the ceramide generation and a subsequent rise in its trafficking across the blood brain barrier, promotes further insulin resistance and neurodegenerative changes in the brain of patients with T2DM.[21]

In our study, there was a non significant positive correlation of all BAEP latencies with both the duration of diabetes and FBG levels. The absence of a correlation between BAEP variables and fasting blood glucose in diabetes would appear to rule out subclinical hypoglycaemia as a source of delay in the transmission time. Also, the absence of a correlation between BAEP abnormalities and duration of diabetes may be attributed to the relatively shorter duration of diabetes in our patients (mean 5.38 ± 6.14 years).

These findings are in agreement with most of the authors worldwide,[22-24] but are in sharp contrast with Gupta et al.,[18] and Fawi et al.,[25] who found a strong correlation of BAEP with duration of diabetes, may be due to the relatively longer duration of diabetes in their study subjects (mean duration >10 years). Some discrepancies between the results of this study and the ones previously mentioned can be explained by the fact that many of these studies have been done on fewer number of participants. Also, since most of the available studies are western, therefore, the consequent difference in the socio-economic, lifestyle

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### Table 4: Comparison of BAEP latencies (in msec) between diabetic and control subjects

| BAEP latencies | Diabetic Group (n=116) Mean±SD | Control Group (n=100) Mean±SD | P value |
|---------------|-------------------------------|-------------------------------|---------|
| **RIGHT EAR** |                               |                               |         |
| I             | 1.64±0.26                     | 1.59±0.19                     | 0.586*  |
| II            | 2.73±0.27                     | 2.72±0.22                     | 0.932*  |
| III           | 3.70±0.26                     | 3.61±0.19                     | 0.648*  |
| IV            | 4.76±0.39                     | 4.76±0.27                     | 0.949*  |
| V             | 5.76±0.32                     | 5.40±0.32                     | 0.021†  |
| I-III         | 2.13±0.29                     | 2.08±0.22                     | 0.028†  |
| III-V         | 1.89±0.29                     | 1.83±0.29                     | 0.861   |
| I-V           | 3.95±0.32                     | 3.84±0.31                     | 0.038*  |
| **LEFT EAR**  |                               |                               |         |
| I             | 1.64±0.24                     | 1.61±0.17                     | 0.764*  |
| II            | 2.77±0.25                     | 2.68±0.23                     | 0.628*  |
| III           | 3.67±0.27                     | 3.63±0.24                     | 0.718†  |
| IV            | 4.77±0.47                     | 4.69±0.32                     | 0.292†  |
| V             | 5.59±0.32                     | 5.35±0.27                     | 0.031†  |
| I-III         | 2.09±0.30                     | 2.04±0.23                     | 0.846†  |
| III-V         | 1.92±0.33                     | 1.91±0.23                     | 0.938†  |
| I-V           | 3.94±0.22                     | 3.83±0.29                     | 0.016†  |

n: No. of subjects, *Non-significant (P>0.05), †Highly significant (P<0.001), SD: Standard deviation

### Table 5: Pearson’s correlation coefficient (r) between the BAEP latencies, FBS levels and duration of disease in females with type 2 diabetes

| BAEP latencies | Duration of Disease | FBG levels |
|---------------|---------------------|------------|
| **RIGHT EAR** |                     |            |
| I             | 0.010               | 0.034      |
| II            | 0.028               | 0.058      |
| III           | 0.029               | 0.192      |
| IV            | 0.136               | 0.220      |
| V             | 0.058               | 0.028      |
| I-III         | 0.009               | 0.390      |
| III-V         | 0.042               | 0.321      |
| I-V           | 0.036               | 0.218      |
| **LEFT EAR**  |                     |            |
| I             | 0.012               | 0.187      |
| II            | 0.069               | 0.101      |
| III           | 0.082               | 0.012      |
| IV            | 0.131               | 0.192      |
| V             | 0.194               | 0.314      |
| I-III         | 0.120               | 0.306      |
| III-V         | 0.801               | 0.118      |
| I-V           | 0.172               | 0.201      |

BAEP: Brainstem auditory evoked potentials, SD: Standard deviation, FBS: Fasting blood sugar. All the r values are non significant for both right and left ear (P>0.05)
and dietary factors of those populations and Indians, might also have influenced the study results.

Keeping in mind the ever increasing prevalence of diabetes worldwide and its long term negative impact on a person’s hearing ability, it is recommended that BAEP testing may be carried out in diabetics with abnormal HbA1c levels and/or those with long standing diabetes. This is the most important clinical implication of this study.

**Study limitations**

One of the limitations of our study was the use of fasting blood glucose (FBG) as an indicator of the chronic glycemic status of T2DM patients. We admit that, the FBG values vary on a daily basis, depending upon the glucose levels in blood and are better indicative of acute glycaemia. HbA1c is a newer and a better parameter to assess chronic glycaemia and long term complications of diabetes. However, due to the higher cost of this test and the poor financial condition of our patients, to which our hospital mainly caters, we were unable to carry out HbA1c testing in all our patients. Also keeping in mind the results of many studies, done worldwide including India,[26-28] that have shown a strong, significant positive correlation of HbA1c and FBG levels in diabetics, we feel that FBG could be considered as an equally effective alternative to HbA1c, in the assessment of chronic glycaemia.

Another limitation might be the relatively smaller sample size of this study, but this was the maximum number of the participants that we could get, who best fulfilled the study criteria, during the duration for which the study was conducted.

**Conclusions and Recommendations**

In this study, significant differences in BAEP latencies were seen between T2DM patients and healthy controls. These abnormalities were attributed to a T2DM associated central auditory dysfunction. This study suggests that if BAEP study is routinely carried out in these patients, then the central acoustic neuropathy can be detected even in the absence of any clinically apparent hearing loss. Therefore, we highly recommend the use of BAEP in diabetic patients. More similar researches are necessary and helpful not only for standardization of BAEP results in diabetics, but also for detecting the association between BAEP abnormalities and severity of diabetes with greater accuracy.

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Baweja, et al.: BAEP in females with type 2 diabetes

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