

The relationship between auditory brainstem response, nerve conduction studies, and metabolic risk factors in type II diabetes mellitus

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Background

Few studies have reported a correlation between auditory brainstem response (ABR) findings and nerve conduction studies (NCSs). The correlation between ABR findings and the metabolic profile of these patients is not well documented in previous studies. The present study was designed to investigate the impact of the disturbed metabolic profile (hyperglyceridemia and hyperlipidemia) in diabetic patients on the peripheral nervous system as well as the auditory brainstem response.

Aim

The present study aimed to detect the effect of diabetic control on the presence of abnormal ABR and/or peripheral nerve affection in Egyptian diabetic patients.

Patients and methods

The study was conducted on two groups: the diabetic group ($n=68$) and the control group, which was matched for age, sex, blood pressure, and BMI ($n=60$). All participants were subjected to clinical assessment, basic audiologic assessment, brainstem auditory evoked potential, NCS, and metabolic profile [serum level of glycated hemoglobin (HbA1c%) and lipid profile].

Results

There was a significant increase in absolute wave latencies of ABR and interpeak latencies (IPLs) in the diabetic group compared with the control group. Twenty-six (38.2%) patients had abnormal ABR values. IPLs (I–III and III–V) were significantly negatively correlated with sensory conduction velocity of the sural, median, and ulnar nerves as well as F-wave latency of the posterior tibial, median, and ulnar nerves ($P=0.01$ and 0.001 , respectively). Moreover, IPL III–V and sural sensory conduction velocity were significantly correlated with HbA1c% and total cholesterol, as well as triglyceride serum levels.

Conclusion

Brainstem dysfunction and ABR changes are common in patients with type II diabetes mellitus. These changes are significantly correlated to NCS parameters on one hand and serum HbA1c% and lipid profile (total cholesterol and triglycerides) on the other hand.

Keywords:

auditory brainstem response, cranial neuropathy, diabetes mellitus type II, glycated hemoglobin, lipid profile, metabolic profile, nerve conduction study, peripheral neuropathy

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Introduction

Diabetes mellitus (DM) is a clinical disorder that causes a variety of metabolic, neurological, and vascular complications [1]. In 2013, 15.6% of the Egyptian population was estimated to have diabetes. This was the second highest prevalence rate in the Middle East and North African region after Saudi Arabia. This percentage is expected to increase to 18.6% in 2035 [2].

The most common complications recorded for diabetes over time are microvascular disorders (retinopathy and nephropathy) and neuropathy (peripheral and central).

DM has been implicated as an independent causative factor of sensorineural hearing loss [3]. Neuropathy, both central and peripheral, is an important complication of type II DM [4]. In general, central neuropathy in diabetic patients is developed later compared with peripheral neuropathy [5]. Many early studies had reported a longer latency of responses in patients with DM than in controls in

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facial nerve conduction study (NCS) and blink reflex study [6,7].

Sensorineural hearing loss could be clinically unapparent in some patients with DM [8,9]. The brainstem auditory evoked potentials (BAEP) is an effective and inexpensive test in the evaluation of brainstem function [10].

Previous studies have been performed to evaluate BAEP in DM patients, but these studies led to controversial results [11,12]. The most common abnormalities in these studies were the lengthening of the latency of waves III and V [13–15]. Moreover, the interpeak latencies (IPLs) I–III, III–V, and I–V of BAEP between diabetic and nondiabetic patients have been reported to have a statistically significant difference in other studies [8,16–20]. However, the correlation between the BAEP findings and NCSs and metabolic profile of those patients were not clear. However, diabetic neuropathy was found to be positively correlated with the most common marker of hyperglycemia and glycated hemoglobin (HbA1c%) [21]. Moreover, several earlier large-scale trials of type II diabetic patients pointed to the observation that early dyslipidemia was a major independent risk factor for the development of diabetic neuropathy [22]. Moreover, recent clinical evidence suggests that dyslipidemia is also associated with diabetic neuropathy. Lipid profiles are commonly abnormal early in the course of type II DM in a temporal pattern and correlates with the presence of diabetic neuropathy [23].

However, the correlation between auditory brainstem response (ABR) findings among type II diabetic patients and these metabolic factors are not well documented in previous studies [19,24,25].

The present study aimed to estimate the relationship between ABR findings and NCS parameters on one hand and metabolic profile among type II diabetic patients on the other hand.

Patients and methods

The present study was conducted on two groups:

First group: 68 type II DM patients (26 men and 42 women) were recruited from the outpatients' clinic of DM at the general Department Internal Medicine in Assuit University Hospital. Their ages and duration of DM ranged from 30 to 68 and 2 to 8 years, respectively. They received oral hypoglycemic agents for DM control.

Second group: 60 healthy volunteers who were matched for age, sex, and BMI were recruited as a control group (20 male and 40 female; age range: 32–68 years).

Participants of both groups were excluded if they; had previous complaints of otological disease detected in the present or past history, were exposed to ear trauma or surgery, presented with acute hearing loss or had a history of noise exposure or ototoxic drug intake, had head trauma, had a history of any medical systemic or neurological diseases, or manifested with diabetic complications (eye, kidney, and cardiac) or had a history of diabetic coma being either hypoglycemic or hyperglycemic within the last 6 months or presented with motor deficit or positive electroencephalography and neuroimaging findings.

All participants signed a written consent for participation in the study. They all underwent the following: history taking, BMI, systemic, cardiac, ophthalmic, and neurological examinations, ECG, laboratory profile, computed tomography of the brain, and neuroelectrophysiology studies (i.e. BAEP, motor, sensory conduction, and F-wave studies).

Laboratory profile included fasting serum glucose, serum HbA1c%, urea, creatinine, and lipid profile (serum cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein).

Basic audiological evaluation

Full history taking and audiological examination were carried out to evaluate any ear disorders and identify wax presence that might impede the exams. Pure-tone and speech audiometry were carried out for each ear using a diagnostic audiometer (Madsen OB 822; Madsen Electronics, Copenhagen, Denmark) with sound delivered through headphones (model Headphones TDH-39, Telephonics; Huntington, NY, United States America).

Tympanometry and acoustic reflex threshold testing were carried out on each ear using a middle ear analyzer (Interacoustics Az26; Interacoustics, Assens Denmark Nihon Kohden model MEB-7102, Nihon Kohden Corp., Tokyo, Japan) to exclude middle ear disease.

Neuroelectrophysiology assessments

Auditory brainstem evoked potentials (BAEP or ABR) were determined using the Nihon Kohden model MEB7102" (Nihon Kohden, Corp., Tokyo, Japan). BAEP was recorded using headphones. The type of sounds used was clicks. The duration of stimulus was

0.1 ms, rate of stimulus was 10 Hz, averaging 2000, and the intensity of stimulus was 90 dB. An active electrode was attached in the zone of scalp (CZ) 5 cm from the vertex; the reference electrode was placed on the ear lobe of the tested ear, and the ground electrode was placed at the midline of the forehead. The waves routinely analyzed in BAEP were numbered (I–V). The absolute latency (stimulus to peak) of each (I, II, III, IV, and V) and IPLs (I–III, I–V, and III–V) were measured.

On the basis of control reference data, the diabetic group was classified into two subgroups, subgroup I with abnormal ABR response and subgroup II with normal ABR response. Diabetic patients with abnormal ABR response are those who had longer wave latency or IPLs of any ABR value, exceeding 2 SD of mean reference values.

Nerve conduction studies

NCS were performed using the conventional procedures and performed using the Nihon Kohden model MEB7102" EMG machine (Nihon Kohden). Motor NCS of the median, ulnar, and common peroneal nerves (CPN) were assessed using standard procedures with surface electrode. A pulse of 0.2 ms duration, at the rate of 1/s at supramaximal intensity was used for stimulation. Motor distal latencies were measured up to M-wave onset. The shape, amplitude, and duration of the compound muscle action potential (CMAP) were measured. The amplitude was measured from peak to peak and the duration from the beginning to the end of the CMAP. Motor conduction velocity (MCV) can be calculated accurately by stimulating two different points along the nerve course and measuring the latency for each response.

The normal limits of MCV and distal latencies were set at ± 2 SD from the mean values of the control group. The CMAP was considered abnormal if the amplitude was below the lowest value found in controls.

For F-wave determination, 10 stimuli were given, and minimal latency value was determined for the median, ulnar, and posterior tibial nerves after stimuli at the wrist or soleus muscle respectively (stimulation at soleus muscle for determination of F-wave and H-reflex of the posterior tibial nerve) and consecutive responses were recorded. The latency to onset of the first deflection from baseline was measured for each trace, and the shortest latency was determined as minimal F-wave latency [26].

Sensory NCS of the median, ulnar, and sural nerves were tested. Sensory nerve action potentials (SNAPs)

were recorded using the antidromic technique using ring electrode. Median SNAPs were recorded from the index fingers, at 14 cm from recording electrode after wrist stimulation. Ulnar nerve SNAPs were recorded from little fingers, at 12 cm from recording electrode. Sural nerve SNAPs were recorded at the lateral malleolus, and stimulation was delivered 14 cm proximally. On the basis of neurological assessment of diabetic patients and their abnormal NCS findings (that exceeding ± 2 SD of mean control values), these patients were classified into two subgroups after fulfilling case definition below.

Confirmed clinical diabetic peripheral polyneuropathy ($n=40$) was defined as the presence of symptoms and signs consistent with distal symmetrical peripheral polyneuropathy and NCS abnormalities in more attribute(s) in at least two anatomically distinct nerves [27].

Subclinical diabetic peripheral neuropathy ($n=28$) was confirmed with abnormal NCS findings that were consistent with distal symmetrical polyperipheral neuropathy with absent diagnostic symptoms or signs on neurological assessment.

Ethics

This study was conducted after approval of the Ethical Committee of Faculty Medicine, Assiut University.

Statistical analysis

Statistical analysis was performed using SPSS (16.0 for Windows; SPSS Inc., Chicago, Illinois, USA). The reference limits from the control group were derived from the mean ± 2 SD. The data exceeding the reference limits were considered to be 'outside reference data'. The diabetic group was classified into two subgroups: abnormal versus normal ABR and clinical versus subclinical diabetic neuropathy. Comparative statistical analysis was performed between study groups and between diabetic subgroups. Categorical variables were compared using the χ^2 -test. Continuous variables within two groups were compared using the independent *t*-test for parametric data and the Mann–Whitney *U*-test for nonparametric data, respectively. Spearman's correlation was performed between ABR and NCSs as well as metabolic profile. Significance was set at *P* less than 0.05 (two-tailed).

Results

No statistically significant difference was found between demographic and clinical data of study groups, as illustrated in Table 1.

In audiometry study, speech discrimination scores were excellent in all participants. Moreover, normal middle ear functions and acoustic reflex thresholds were evident in all.

Overall, absolute latency of ABR waves and IPLs were significantly longer in the diabetic group compared

with the control group ($P=0.0001$). The highest frequency of abnormality was recorded in absolute latency of waves III and V and IPL III–V. Moreover, this significant difference was also found between values of diabetic patients with abnormal ($n=26$) versus normal ABR ($n=42$) response (subgroup I vs. II) ($P<0.01$), as illustrated in Table 2.

Table 1 Demographic and clinical data of study groups

Variables	Diabetic group (N=68)	Control group (N=60)
Age (years)	51.2±14	44.9±14.9
Sex (male/female)	21/47	19/41
Weight (kg)	80.1±13.2	79.3±11.8
Height (m)	1.63±0.06	1.60±0.01
BMI (kg/m ²)	31.4±4.7	31.7±4.7
Systolic blood pressure (mmHg)	134.4±13.3	126.3±5
Diastolic blood pressure (mmHg)	86.7±8.3	81.1±6.5

Independent *t*-test was used for statistical analysis.

NCSs were performed for all participants and revealed significant differences in all NCS parameters between diabetic compared with control values ($P<0.001$). All diabetic patients had either clinical or subclinical diabetic peripheral polyneuropathy ($n=40$ and 28 , respectively). A significant difference was found between NCS parameters of diabetic patients either with abnormal or normal ABR response subgroup versus the control group ($P=0.0001$ for all).

The main significant differences between NCS parameters among diabetic subgroups (I vs. II) were

Table 2 Auditory brainstem response values in the study group and diabetic subgroups

ABR variables	DM (N=68)	Control (N=60)	Patients with abnormal ABR (N=26)	Patients with normal ABR (N=42)
Wave latency (ms)				
Wave I	1.6±0.24 (8) ^{^^}	1.36±0.24	1.72±0.28 [*]	1.51±0.15
Wave II	2.83±0.41 (23) ^{^^}	2.40±0.25	3.04±0.54 [*]	2.6±0.11
Wave III	3.76±0.15 (22) ^{^^}	3.34±0.2	3.75±0.17	3.73±0.14
Wave IV	4.84±0.19 (14) ^{^^}	4.39±0.30	4.94±0.21 [*]	4.77±0.11
Wave V	5.6±0.24 (20) ^{^^}	5.23±0.22	5.81±0.24 ^{**}	5.48±0.14
IPL (ms)				
I–III	2.16±0.29 (3) [^]	1.96±0.17	2.19±0.28	2.06±0.26
III–V	1.91±0.29 (26) [^]	1.83±0.19	2.17±0.15 ^{**}	1.69±0.14
I–V	4.03±0.28 (8) [^]	3.78±0.38	3.93±0.21 [*]	4.11±0.31

Values are expressed as mean±SD. Number of patients with abnormal ABR values in the diabetic group are given in parentheses.

Mann–Whitney *U*-test was used for statistical analysis. ABR, auditory brainstem response; DM, diabetes mellitus; IPL, interpeak latency.

[^] $P<0.01$, ^{^^} $P<0.001$; *P* values of significant difference between mean ABR values among diabetic patients versus control group. ^{*} $P<0.01$,

^{**} $P<0.001$; *P* values of significant difference of mean ABR values between diabetic patient subgroup I versus diabetic patient subgroup II.

Table 3 Nerve conduction study parameters among diabetic patients with abnormal versus normal auditory brainstem response and the control group

Nerve conduction study parameters	Diabetic subgroup I with abnormal ABR (N=26)	Diabetic subgroup II with normal ABR (N=42)	Control (N=60)
Motor conduction velocity (m/s)			
Median nerve	48.95±11.8	53.33±7.7	61.19±6.4
Ulnar nerve	52.87±9.3 [*]	57.84±6.7	61.25±4.7
Common peroneal nerve	42.18±10.6	45.63±4.8	50.95±4.5
Sensory conduction velocity (m/s)			
Median nerve	30.28±7.3	28.50±9.9	56.90±6.20
Ulnar nerve	30.17±11.8	32.81±15.1	67.38±7.6
Sural nerve	21.54±9.8 ^{**}	37.11±11.3	50.66±3.2
F-wave latency (ms)			
Median nerve	32.09±3.2 ^{**}	28±5.8	23.48±3.2
Ulnar nerve	32.56±3.6 ^{**}	27.96±3	23.89±3
Posterior tibial	37.89±5 ^{**}	32.92±2.9	25.87±3.1
H-reflex (ms)	35.89±3.5 ^{**}	31.24±6.4	24.36±1.4

Mann–Whitney *U*-test was used for statistical analysis. ABR, auditory brainstem response. ^{*} $P<0.05$, ^{**} $P<0.001$; *P* values between diabetic subgroups.

Table 4 Correlation between interpeak latencies in auditory brainstem response and nerve conduction study findings

Nerve conduction study parameters	IPL I–III		IPL III–V		IPL I–V	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Motor conduction velocity						
Median nerve	–0.155	0.143	–0.114	0.283	–0.147	0.165
Ulnar nerve	–0.120	0.255	–0.113	0.291	–0.201	0.056
Common peroneal nerve	–0.329	0.002	–0.079	0.461	–0.296	0.005
Sensory conduction velocity						
Median nerve	–0.398	0.000	–0.101	0.351	–0.311	0.001
Ulnar nerve	–0.412	0.000	–0.100	0.352	–0.382	0.000
Sural nerve	–0.376	0.000	–0.231	0.035	–0.357	0.001
F-wave latency						
Median nerve	0.482	0.000	0.210	0.044	0.351	0.001
Ulnar nerve	0.303	0.004	0.217	0.041	0.238	0.025
Posterior tibial nerve F-wave latency	0.390	0.000	0.212	0.049	0.315	0.003
Posterior tibial nerve H-reflex	0.336	0.006	0.296	0.017	0.122	0.334

Spearman's correlation was used for statistical analysis. ABR, auditory brainstem response; IPL, interpeak latency.

Table 5 Metabolic profile among diabetic subgroups

Serum levels	Diabetic subgroup I with abnormal ABR (<i>N</i> =26)	Diabetic subgroup II with normal ABR (<i>N</i> =42)	Patients with clinical diabetic neuropathy (<i>N</i> =40)	Patients with subclinical diabetic neuropathy (<i>N</i> =28)
HbA1c%	8.85±0.76 [*]	6.36±1.8	8.7±0.8 [#]	5.6±1.5
Lipid profile				
Cholesterol (mg/dl)	242.±28.9 [*]	184.6±42.9	239.4±28.1 [#]	171.4±34.9
Triglyceride (mg/dl)	193.2±16.5 [*]	126.1±54.8	194.3±17.1 [#]	116.2±44.3
HDL (mg/dl)	33.1±2.3 [*]	41.4±10.2	32.9±2.2 [#]	45.9±5.2
LDL (mg/dl)	170.4±25.2 [*]	113.6±45.1	168.5±26 [#]	102.9±31.2

Mann–Whitney *U*-test was used for statistical analysis. ABR, auditory brainstem response; HbA1c%, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein. ^{*}*P*<0.001; *P* values of significant difference of mean values of metabolic profile between diabetic patients subgroup I versus diabetic patients subgroup II. [#]*P*<0.001; *P* values of significant difference between mean values of metabolic profile among diabetic patients with clinical versus subclinical diabetic neuropathy subgroup.

found in sural sensory conduction velocity (SCV), MCV of the ulnar nerve, and F-wave latency of all nerves studies (*P*<0.01 and <0.05) (Table 3).

The relationship between auditory nerve pathway changes (IPLs) and NCS parameters was estimated using Spearman's correlation. Significant inverse correlations were found between IPLs I–III, I–V, and measured conduction velocities not latencies, and a positive correlation was found with the F-wave and H-reflexes (Table 4).

Serum HbA1c% and lipid profile were significantly higher in diabetic patients with abnormal than in those with normal ABR response and also in clinical versus subclinical diabetic polyneuropathy, with *P*=0.0001 for both comparisons (Table 5).

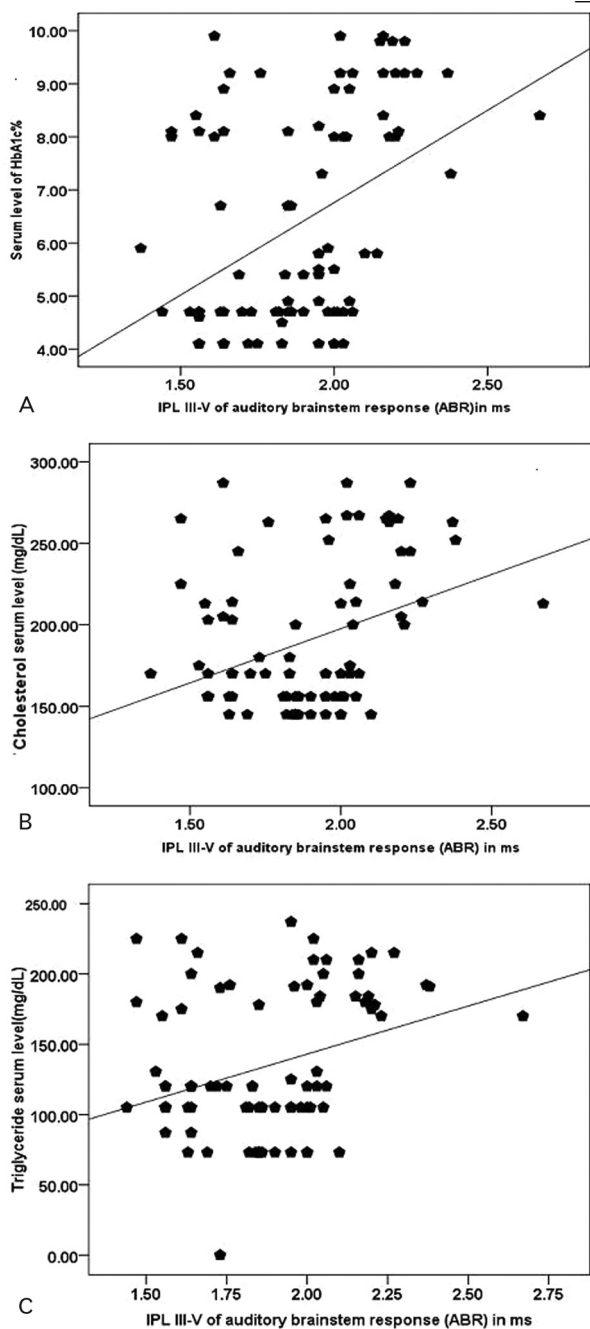
Spearman's correlation was performed between all participant values to confirm the relationship between metabolic profile and IPLs of ABR as well as conduction velocity (CV) of nerve studies.

Figures 1 and 2 showed a significant correlation between metabolic profile and IPL III–V as well as sural CV. HbA1c% was significantly correlated with IPL III–V (*r*=0.447, *P*=0.000) and sural CV (*r*=–0.427 and *P*=0.000) (Figs 1a and 2a). Moreover, serum cholesterol and triglyceride levels were significantly correlated with IPL III–V (*r*=0.314, *P*=0.002; *r*=0.296, *P*=0.004, Fig. 1b and c, respectively) and sural CV (*r*=–0.312, *P*=0.001; *r*=–0.316, *P*=0.001, Fig. 2b and c, respectively).

As regards other IPLs, IPL I–V was significantly correlated with HbA1c% (*r*=0.226, *P*=0.022) and serum level of cholesterol and triglyceride (*r*=0.232, *P*=0.026; *r*=0.120, *P*=0.251, respectively). However, no significant correlation (*P*>0.05) was found between these metabolic parameters and IPL I–III (*r*=0.065 for HbA1c%; *r*=0.081 and 0.122 for serum cholesterol and triglyceride, respectively).

As regards other nerve studies, the metabolic parameters had a significant negative correlation with SCV of the

Figure 1

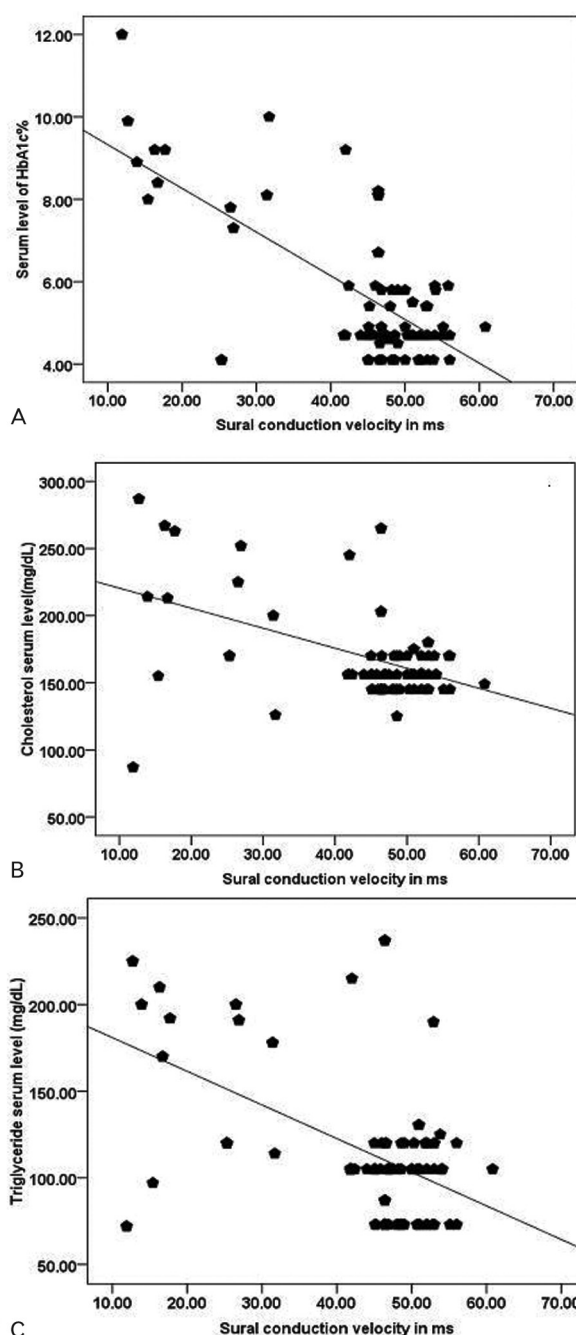


The effect of metabolic profile on interpeak latency (IPL) III-V in auditory brainstem response (ABR) using Spearman's correlation for statistical analysis. IPL III-V was significantly positively correlated with (A) serum glycated hemoglobin (HbA1c%) ($r=0.447, P=0.000$), (B) serum cholesterol ($r=0.314, P=0.002$), and (C) triglyceride ($r=0.296, P=0.004$).

median and ulnar nerves and MCV of CPN ($P=0.0001$) for all and a less significant correlation ($P<0.01$) for serum HbA1c% and cholesterol levels with MCV of the median and ulnar nerves.

Moreover, serum HbA1c% was significantly positively correlated with serum level of cholesterol and triglyceride ($r=0.631$ and 0.615 , respectively; $P=0.0001$ for both).

Figure 2



The effect of metabolic profile on sural conduction velocity (CV) using Spearman's correlation for statistical analysis. Sural CV was significantly negatively correlated with (A) glycated hemoglobin (HbA1c%) ($r=-0.427, P=0.000$), (B) serum cholesterol ($r=-0.312, P=0.001$), and (C) triglyceride ($r=-0.316, P=0.001$).

Discussion

Our results point out to the evident affection of the nervous system of diabetic patients in the form of diabetic neuropathy, affecting the peripheral as well as the central nervous system (CNS). Both are common complications of this metabolic disorder. Subclinical acoustic neuropathic affection of the CNS pathway was recorded as prolonged absolute latencies of wave I with

consecutive delay in absolute latency of waves III and V in ABR study among the diabetic group of patients. These data are consistent with the recorded data of central (acoustic) neuropathy in previous studies on diabetic patients [9,15,19].

The significant difference in IPLs between diabetic patients and controls is partially consistent with the observations of many studies [20,28,29]. Baweja *et al.* [20] observed that IPL I–V was significantly delayed bilaterally, whereas the IPL I–III was significantly delayed unilaterally, in female patients with type II DM. However, Huang *et al.* [28] and Al-Azzawi and Mirza [29] found a significant delay in IPLs I–III and I–V but not IPL III–V among diabetic patients versus the nondiabetic group. This indicates that retrocochlear lower and upper brainstem dysfunction in diabetic patients is associated with mainly delayed central rather than peripheral conduction time of the auditory nerve pathway. They postulated dual pathogenesis of the above findings and suggested that silent lacunar infarct and metabolic disturbance of the brain could be proposed in the form of diabetic angiopathy that could induce cranial (acoustic) neuropathy or brainstem dysfunction, as previously reported by Kurita *et al.* [30]. Our finding of the correlation of hyperlipidemia with the HbA1c% could point to the possibility that the associated dyslipidemia could be a factor in the pathogenesis of central as well as peripheral nervous affection in diabetics.

In the present study, significant differences were recorded in terms of NCS parameters both between the diabetic group or the diabetic subgroup (I or II) and the control group as well as between diabetic patients with abnormal and those without normal ABR response (Table 3). Our findings are consistent with the reported data in previous studies [31,32]. However, Goldsher *et al.* [31] reported abnormal brainstem response in type II diabetic patients with neuropathy in 94% of cases. In contrast, Siddiqi *et al.* [32] found that 52% of type II DM patients had diabetic neuropathy, 92% of whom showed abnormal BAEP, and only 50% of nonneuropathic patients showed abnormal BAEP. These recording data indicate that delay in absolute wave latencies and IPLs by BAEP demonstrates defect at the level of brainstem and midbrain in long-standing type II DM patients on one hand and neuropathy being more pronounced among diabetic patients with abnormal ABR response than in those with normal ABR response on the other hand. Overall, the mentioned data are consistent with previously reported data that stated that

the most common complication of diabetes is peripheral neuropathy, occurring in ~60% of all diabetic patients [33,34].

Significant inverse correlations were found between IPLs I–III, I–V, and CV of all studied nerves, predominantly in lower limbs, and F-wave studies (Table 4). These data are consistent with the study by Huang *et al.* [28], who found that the best correlation was between IPL I–III and MCV in tibial followed by median and sural CV studies. These findings could be explained by 'low NCS velocity in DM, which was more significantly found in lower limb than in upper limb nerve studies because of length-dependent diabetic polyneuropathy'. However, other studies showed the correlation between BAEP findings and SCV of the median nerve and MCV of CPN [16,35]. Moreover, the recorded significant correlation between IPL I–III, IPL I–V, and NCS parameters could point to the possibility that diabetic acoustic neuropathy that manifested with central ABR changes could occur parallel to peripheral neuropathy, as previously reported [18,36]. A recent study also reported that a trend toward an association between evidence of wave IV and the presence of somatic neuropathy or abnormal cardiovascular autonomic tests was observed among patients with type I DM [37]. Overall, these reported findings may suggest early damage of small nerve fibers within the auditory pathway at the pons and midbrain level, lateral lemniscuses, and inferior colliculi, which is in line with evidence that small nerve fibers may be affected first in diabetic neuropathy [38]. However, this difference in recorded data of different studies could be related to the wide spectrum of the disease.

These patients had a significantly higher serum level of HbA1c% and hyperlipidemia, either among diabetic patients with abnormal ABR response or clinical diabetic neuropathy. Confirming these recorded associations, serum HbA1c% level had a significant positive correlation with IPL III–V and the reverse (negative correlation) with CV studies. This significant association between HbA1c% serum level and CV nerve studies are consistent with the findings of Huang *et al.* [39], who reported a significant reduction of CV in poor glycemic control type II DM. Our correlating ABR results with serum level of HbA1c% are consistent with previously reported data [24,40], but it is inconsistent with other studies [19,25] that found no relation between serum HbA1c% and ABR results. These recorded data suggest that poor glycemic control could enhance related metabolic

changes and angiopathy either on peripheral nerves and/or acoustic nerve as well as auditory nerve pathway and brainstem functions. It could affect normal nerve functions and accelerate neuropathy, either peripheral or central [41–43]. The predominant significant correlation with IPL III–V but not IPL I–III values may be attributed to brainstem neurons being more vulnerable to these metabolic disturbances and ischemic changes.

In the present study, diabetic patients who either showed ABR changes or clinical neuropathy had concurrent significant hyperlipidemia compared with the other subgroup. Furthermore, the recorded significant correlation between lipid profile and IPL III–V as well as SCV of the sural nerve, confirms the harmful effect of serum cholesterol and triglyceride either on peripheral nerves as well as the central neural transmission in the auditory nerve pathway. These results are consistent with reporting data of case–control study evaluating patients suffering from hypercholesterolemia and hypertriglyceridemia [44]. Namysłowski *et al.* [44] reported prolonged latencies of the III and V waves, as well as IPLs I–III and III–V, in patients with hyperlipidemia compared with the control group. The hearing affection among these patients could be explained by the postulated microvascular complications. In addition, it is consistent with previously reported data in ABR study by Ben-David *et al.* [45]. However, they found subclinical impairments of brainstem function in hyperlipidemic patients compared with normolipemic patients, probably due to ischemia accelerated by their condition. Previous histopathological studies have shown damaged nerves and vessels of the inner ear of the individuals with diabetes and hyperlipidemia, which have been theorized to be an important causative factor for neuronal degeneration in the auditory system [46,47]. The possible mechanism is that hypercholesterolemia induces phenotypic changes in the microcirculation, which are consistent with oxidative and nitrosative stresses. The superoxides that are generated participate in a number of reactions, yielding various free radicals. This leads to platelet activation and lipid peroxidation, which is involved in the initiation and the progression of the atherosclerotic lesions [48]. Hyperlipidemia also had a harmful effect for progression of peripheral and autonomic diabetic neuropathy as previously mentioned [49,50].

Finally, the correlation between serum levels of HbA1c % and lipid profile confirms the role of poor glycemic

control and concurrent hyperlipidemia in rapid development of diabetic neuropathy in type II DM, as previously reported [23,51]. Both act with synergistic action to induce the following: (i) metabolic disturbances and inflammatory process of oxidative stress that lead to peripheral nerve as well as auditory nerve pathway damage, and (ii) vascular changes in microcirculation and small blood vessels in peripheral nerves and inner ear structures associated with angiopathy leading to peripheral or central neuropathy on one hand and brainstem dysfunction on the other hand.

Conclusion

ABR changes are subclinical and common among type II DM, indicating peripheral and central conduction impairment in auditory nerve pathway. Therefore, early screening of these patients by means of ABR as a noninvasive procedure to detect early impairment of acoustic nerve and CNS pathway involvement, even in the absence of specific symptom, is highly recommended. These ABR changes occur parallel to central as well as peripheral neuropathy, and are associated with poor glycemic control as well as hyperlipidemia in type II DM. Thus, early estimation of metabolic profile and control of hyperlipidemia are mandatory in DM management to ameliorate vascular complication and progression of diabetic peripheral and central neuropathy as well as brainstem dysfunctions.

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Conflicts of interest

There are no conflicts of interest.

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