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ISSN 2544-1361 (online); ISSN 2544-2406
doi: 10.15584/ejcem.2017.3.1

http://www.ejcem.ur.edu.pl/en/
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2017; 15 (3): 185–191

ORIGINAL PAPER

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Infuence of HbA_{1c}, serum lipids, blood pressure and BMI on Auditory Brainstem Response in diabetic patients

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ABSTRACT

Introduction. Impaired hearing organ function including abnormalities in auditory brainstem response (ABR) are more frequent in diabetic subjects compared to the general population. The aim of our study was to assess the impact of selected modifiable factors on ABR latencies in diabetic subjects.

Material and Methods. 58 patients with type 1 and type 2 diabetes, aged <45 years, with diabetes duration <10 years, and without clinically overt hearing impairment or diabetic neuropathy, were included. In all subjects vital signs and blood samples were obtained, and ABR audiometry was performed.

Results. Significantly delayed latencies in ABR were found in patients with total cholesterol <192 mg/dL, with HDL-cholesterol <49.5 mg/dL, with triglycerides >89 mg/dL, with presence of hypertension, and with systolic and diastolic blood pressure >135 and >78 mm Hg respectively. A linear correlation between triglycerides and wave I and III latencies, and between systolic blood pressure and wave III latency were revealed. A relationship between ABR latencies and HbA_{1c}, LDL-cholesterol or BMI was not found.

Conclusions. Several modifiable factors affect functioning of the retrocochlear part of the auditory pathway. If these results were confirmed in further studies, a vast area of possible therapeutic interventions to preserve hearing function in diabetic patients would become available.

Keywords. auditory brainstem response; diabetes mellitus; serum lipids.

Introduction

The prevalence of hearing impairment in diabetic subjects is roughly doubled compared to the non-diabetic population and along with noise exposure and smoking, diabetes can be counted among risk factors of hearing impairment.[1,2] The negative impact of diabetes on auditory organ function has been studied for years and it was also summarized in recently published reviews and meta-analyses.[3-5] In contrary to the non-diabetic population, the prevalence of hearing impairment in diabetic

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

Received: 14.03.2017 | Accepted: 23.06.2017
Publication date: September 2017

Dąbrowski M, Mielnik-Niedzielska G, Nowakowski A. *Infuence of HbA_{1c}, serum lipids, blood pressure and BMI on Auditory Brainstem Response in diabetic patients*. Eur J Clin Exp Med. 2017;15(3):185–191. doi: 10.15584/ejcem.2017.3.1

subjects did not decrease during the three decades of observation in the U.S.[6] One of the clinical manifestations of hearing organ impairment seen in diabetic patients is delayed nerve conduction velocity along the auditory pathway. First described by Jewett et al. in 1970 , evaluation of auditory brainstem response (ABR) became the most commonly used non-invasive electrophysiological test to determine function of the retrocochlear part of the auditory pathway, up to the brainstem level.[7,8] Wave I in ABR arises from the distal part of the auditory nerve (first-order neuron of the auditory pathway), a branch of the vestibulocochlear (VIII) cranial nerve. Wave III reflects activation of the second-order neuron at the cochlear nuclei, while wave V likely originates from the lateral lemniscus.[8] The main abnormalities found in ABR in type 1 diabetes are delayed latencies of wave III and V, and prolonged interpeak latencies III-V and I-V.[4] In type 2 diabetic subjects, there were delayed wave III and V latencies (in this review interpeak latencies were not analyzed).[5]

Among factors affecting hearing function in diabetes the role of its metabolic control has been the most extensively studied. These data are divergent and they are discussed in a small review.[9] Data regarding influence of other mediators on auditory organ function in diabetic populations are scarce. In a population drawn from the National Health and Nutrition Examination Survey (NHANES) diabetes, low HDL-cholesterol, higher BMI and higher CRP level were associated with a higher risk of hearing impairment.[10] In one of the studies HDL-cholesterol, triglycerides and BMI were associated with higher hearing threshold and otoacoustic emission (OAE) abnormalities.[11] Relationships between lipid abnormalities and impaired OAE in diabetic subjects were also described by Erdem et al., while Duck et al. found higher hearing threshold in hypertensive patients with diabetes.[12,13]

Since data regarding associations between serum lipids, blood pressure, BMI, and auditory brainstem responses in diabetic subjects are scarce, we decided to perform this interdisciplinary study to assess the impact of these potential mediators of hearing function on waves and interpeak latencies in auditory brainstem response audiometry in a group of young adult subjects with both type 1 and type 2 diabetes mellitus.

Material and methods

58 diabetic subjects of Caucasian ethnicity, among them 31 patients with type 1 diabetes and 27 with type 2 diabetes, with no history of noise exposure and/or ototoxic medication use, were included. The other inclusion criteria were: age below 45 years, a diabetes history of no longer than 10 years (to avoid advanced diabetic complications), and no clinically overt diabetic neuropathy or hearing impairment present. Among study participants 10 subjects had an early background retinopathy, 2 patients had microalbuminuria, 28 were hypertensive, 17 patients were overweight and 14 were obese. The detailed characteristics of the study group are presented in Table 1.

Table 1. Characteristics of the study participants

Parameter	*Value ± SD*
Gender (n)	
women	21 (36.2%)
men	37 (64.8%)
Age (years)	33.7 ± 7.9
Retinopathy (n)	
normal eye fundus	49
background retinopathy	5
not examined	4
Nephropathy (n)	
normoalbuminuria	49
microalbuminuria	02
not examined	07
Albuminuria (mg/l)	09.9 ± 7.6
BMI (kg/m^2)	26.9 ± 6.7
Lipid profile (mg/dl)	
total cholesterol	182.1 ± 35.6
LDL cholesterol (calculated)	107.2 ± 32.6
HDL cholesterol	052.6 ± 14.6
triglycerides	108.0 ± 69.3
Creatinine (mg/dl)	0.77 ± 0.18
Glycated hemoglobin HbA_{1C} (%)	7.16 ± 1.56
Hypertension (n)	28 (48.3%)
Blood pressure (mm Hg)	
systolic	137.4 ± 17.9
diastolic	081.3 ± 12.1

SD – standard deviation

Study was approved by the Bioethics Committee at Regional Medical Chamber in Rzeszów; Poland. After an informed consent was obtained, in all patients weight, height and blood pressure were measured, and BMI was calculated. Blood samples for fasting serum lipids were obtained in 54 subjects (4 patients were not fasting). Total cholesterol, HDL-cholesterol and triglycerides were measured, while LDL-cholesterol level was calculated using the Friedewald formula.[14] Morning urine samples were analyzed for microalbuminuria in 51 subjects. After vital signs and blood samples were obtained, patients were referred to the Department of Otorhinolaryngology at the Provincial Specialist Hospital in Rzeszów, Poland, where a detailed ear examination by an ENT (Ear-Nose-Throat) specialist was performed to exclude abnormalities of the external and middle ear. Then auditory brainstem response evaluation was carried out in all study participants by trained audiological technicians.

Auditory brainstem response audiometry was performed using a Centor-C analyzer (Racia-Alvar, Paris, France) with a click stimulus of 100 μs duration,

a repetition rate of 19.1 Hz, and intensity of 70 dB. The electrodes were placed on the forehead (positive), the ipsilateral mastoid (negative), and chin (ground). The results were presented as a waveform graph and also in a tabular form where the latencies of particular waves and interpeak latencies were presented. Waves I, III and V were identified in 49 (97 ears), 47 (92 ears) and 57 patients (114 ears) respectively. Interpeak latencies I-III, I-V and III-V were assessed in 45 (90 ears), 49 (97 ears) and 47 subjects (92 ears) respectively. For comparisons between 2 or 3 groups, data from all ears were taken, whereas for linear correlation analysis between ABR latencies and different variables, mean values for each wave and interpeak latency in particular patients were used.

The blood lipids were assessed using an Architect c8000 analyser (Abbott Laboratories, Irving, TX, USA) at the Medical Diagnostic Center "Medicor", Rzeszow, Poland.

Glycated hemoglobin (HbA_{1c}) was measured from capillary blood using a DCA 2000®+ analyzer (Siemens, Elkhart, IN, USA) with the monoclonal antibody method. Also microalbuminuria, determined by the albumin concentration and albumin/creatinine ratio from a morning sample of urine, was assessed using the same analyzer.

Blood pressure was measured using an automatic Omron 705 IT blood pressure monitor (Omron Healthcare Europe BV, Hoofddorp, The Netherlands). Hypertension was diagnosed if measured values were ≥140/90 mm Hg or if the patient was using anti-hypertensive medications.

Body weight and height were measured using the legalized electronic medical scales WPT 150.0 (Radwag, Radom, Poland), and then the BMI was calculated.

To assess the presence of retinopathy in all but four subjects, eye fundus examination by an ophthalmologist was performed within a three-months window from the ABR evaluations.

Statistical analysis of the data was performed using SigmaPlot for Windows version 12.5 (Systat Software Inc., San Jose, CA, USA). If not mentioned otherwise, the data were expressed as mean and SD (standard deviation). The data comparing two groups of patients were analyzed using a two-tail Student's t-test for independent variables or a Mann-Whitney rank sum test where appropriate. The data comparing three groups of patients were analyzed using one way ANOVA or Kruskal-Wallis ANOVA on ranks where appropriate. The linear correlations between ABR latencies and HbA_{1c} level, blood pressure values, lipid parameters or BMI due to its non-parametric distribution, were analyzed using a Spearman rank order correlation test. A P value <0.05 was considered statistically significant.

Results

HbA_{1c}

HbA_{1c} level ≤7.0% (53.0 mmol/mol) is recommended by Polish Diabetes Association (PTD) as a general treatment target in diabetes.[15] Such value was measured in 28 patients. No significant differences in the ABR latencies between this group and subjects with HbA_{1c} >7.0 % was found. Also no linear correlations between HbA_{1c} and ABR latencies were revealed.

Serum lipids

Due to a large disproportion between number of patients fulfilling and not-fulfilling blood lipids concentration criteria recommended by the Polish Diabetes Association [23] (e.g. only 14 patients had trigliceride levels exceeding 150 mg/dl), we decided to divide patients into groups below and above median values of each lipid parameter.

Median total cholesterol concentration was 192 mg/dL (5.0 mmol/L). Surprisingly, patients with higher cholesterol level had shorter interpeak I-III latency. No other significant differences were revealed (Table 2).

Median LDL-cholesterol concentration was 110.1 mg/dL (2.85 mmol/L). No significant differences in ABR latencies between groups below and above median were found (Table 2).

Median HDL-cholesterol concentration was 49.5 mg/dL (1.3 mmol/L). Patients with lower HDL-cholesterol values had a delayed wave V and also delayed interpeak I-V latency compared to the group with higher HDL-cholesterol level (Table 2).

Median triglycerides concentration was 89 mg/dL (1.0 mmol/L). Higher triglycerides level was associated with significantly longer wave I and wave V latencies compared to the remaining group (Table 2).

Positive linear correlation between triglycerides level and latencies of waves I and III was found (coefficient R=0.442, p=0.003, and R=0.306, p=0.046 respectively) (Figure 1). For other blood lipids no linear correlations were revealed.

Blood pressure

Among the study participants 28 patients had diagnosed hypertension. In comparison with the remaining 30 subjects, patients with hypertension demonstrated significantly delayed wave I and wave III latencies (Table 2). Also patients with systolic and diastolic blood pressure above median had significantly longer wave III latency (Table 2). Moreover, linear association between SBP and wave III latency has been found (coefficient R=0.308, p=0.036) (Figure 2).

Body mass index (BMI)

Among study participants 27 subjects had normal weight (BMI <25 kg/m^2), 17 were overweighted (BMI

Table 2. Impact of analyzed variables on ABR latencies (significant differences in bold)

Parameter		*Latency (ms) (mean ± SD)*					
		Wave I	*Wave III*	*Wave V*	*Interpeak I-III*	*Interpeak III-V*	*Interpeak I-V*
HbA_{1c} (%)	≤7	1.76±0.13	3.93±0.21	5.85±0.25	2.17±0.16	1.90±0.21	4.08±0.20
	>7	1.76±0.13	3.93±0.19	5.78±0.26	2.17±0.16	1.83±0.15	4.01±0.19
Total cholesterol (mg/dL)	<192	1.75±0.13	3.95±0.21	5.83±0.28	**2.21±0.14**	1.86±0.16	4.06±0.21
	≥192	1.77±0.13	3.91±0.19	5.80±0.25	**2.11±0.17**†	1.87±0.21	4.02±0.20
LDL-cholesterol (mg/dL)	≤110	1.75±0.13	3.94±0.22	5.83±0.27	2.19±0.15	1.86±0.16	4.06±0.20
	>110	1.77±0.14	3.92±0.19	5.80±0.26	2.13±0.18	1.87±0.20	4.02±0.21
HDL-cholesterol (mg/dL)	≥50	1.76±0.13	3.92±0.20	**5.77±0.27**	2.15±0.16	1.88±0.19	**4.01±0.21**
	<50	**1.76±0.14**	**3.94±0.21**	**5.87±0.25***	2.18±0.17	1.90±0.20	**4.09±0.18***
Triglycerides (mg/dL)	<89	**1.72±0.12**	3.89±0.19	**5.77±0.25**	2.17±0.16	1.85±0.17	4.04±0.21
	≥89	**1.81±0.13**†	3.97±0.22	**5.87±0.27***	2.15±0.17	1.88±0.20	4.05±0.20
Hypertension	No	**1.74±0.13**	**3.89±0.19**	5.82±0.29	2.16±0.16	1.87±0.18	4.05±0.22
	Yes	**1.79±0.12***	**3.96±0.20***	5.82±0.22	2.17±0.17	1.86±0.19	4.04±0.17
SBP (mm Hg)	≤135	1.74±0.13	**3.87±0.18**	5.81±0.28	2.13±0.15	1.88±0.20	4.03±0.21
	>135	1.78±0.12	**3.97±0.20**†	5.83±0.24	2.19±0.17	1.86±0.17	4.05±0.18
DBP (mm Hg)	≤78	1.74±0.11	**3.88±0.18**	5.80±0.27	2.15±0.16	1.87±0.19	4.04±0.21
	>78	1.78±0.14	**3.97±0.22***	5.84±0.25	2.18±0.17	1.86±0.18	4.05±0.18
BMI (kg/m^2)	<25	1.74±0.12	3.90±0.20	5.80±0.26	2.17±0.16	1.87±0.15	4.06±0.21
	25-29.9	1.78±0.14	3.93±0.18	5.79±0.24	2.17±0.14	1.85±0.18	4.01±0.19
	≥30	1.80±0.12	3.99±0.22	5.88±0.27	2.16±0.20	1.86±0.25	4.04±0.19

SD – standard deviation; *p<0.05, †p<0.01

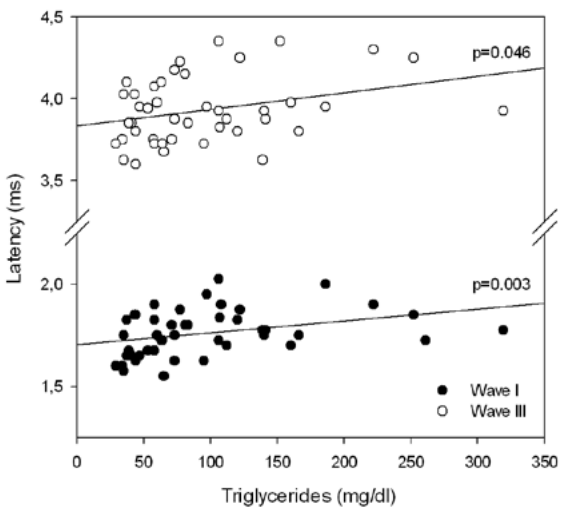

Figure 1. Linear correlation between triglycerides and waves I and III latencies (scatter plot and regression line)

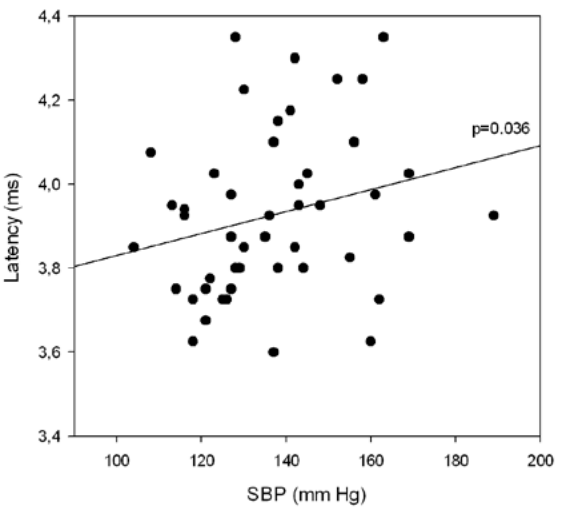

Figure 2. Linear correlation between systolic blood pressure and wave III latency (scatter plot and regression line)

≥25 kg/m^2 and <30 kg/m^2) and 14 were obese (BMI ≥30 kg/m^2). No significant differences in the ABR latencies between the three groups of patients were revealed (Table 2). Also no linear correlations between BMI and wave or interpeak latencies in ABR were noted.

Discussion

our study demonstrated that, apart from the known risk factors of hearing loss, several other mediators may influence the auditory organ function in diabetic patients.

The most of evidence indicate deleterious impact of poor metabolic control on auditory pathway function presented as ABR abnormalities.[16-21] However, in our study HbA_{1c} level was not associated with ABR disturbances.

The association between hyperlipidemia and ABR abnormalities has been evaluated in only two studies. Ben-David et al. revealed that hyperlipidemia (type non-specified) was associated with significantly longer all interpeak latencies in ABR.[22] In contrary, Bhattacharjee et al. did not find any significant differences in ABR audiometry between patients with cholesterol level above vs. below or equal to 200 mg/dl (5.2 mmol/L).[23] Unexpectedly, in our study total cholesterol level above median was associated with shorter interpeak I-III latency, while no relationship between

ABR latencies and LDL-cholesterol concentration was revealed. HDL-cholesterol level appeared to influence the ABR results and patients with lower HDL-cholesterol concentration had a significantly delayed wave V and interpeak I-V latencies. Also triglycerides level was associated with abnormal ABR results. Patients with higher triglycerides values had significantly delayed wave I and wave V latencies, and linear correlation between triglycerides concentration and wave I and wave III latencies was revealed. Because such relationship has not been analyzed previously, it requires further larger studies to be confirmed or excluded. However, some data regarding peripheral or autonomic nerves function support our findings. Triglycerides level above 300 mg/dl (3.39 mmol/L) affected conduction parameters in peripheral nerves.[24] Elevated triglycerides were also associated with progression of peripheral neuropathy in diabetes.[25] In type 1 diabetic patients triglycerides concentration exceeding 0.94 mmol/L (83.2 mg/dl) were related to higher prevalence of cardiac autonomic neuropathy (CAN) compared to the referent group with triglycerides level lower or equal to 0.71 mmol/L (62.8 mg/dl).[26] In this study HDL-cholesterol concentration was inversely associated with CAN prevalence, while total and LDL-cholesterol did not affect the risk of CAN. In the study by Voulgari et al., patients with both type 1 and type 2 diabetes and CAN appeared to have higher triglycerides, total and LDL-cholesterol and also lower HDL-cholesterol level compared to patients without CAN.[27] Thus, such an effect may be also seen in the cranial nerves, and this, at least in part, explains the altered function of a retrocochlear part of the auditory pathway revealed in our study.

Only few studies analyzed the relationship between hypertension and ABR abnormalities. In the first study in the field Tandon et al. revealed relationship between severity of hypertension and prolongation of wave I, II and V, as well as interpeak III-V latencies in subjects with grade III hypertension.[28] Also Goyal et al. observed relationship between severity of hypertension and ABR abnormalities (delayed latencies of wave I, V and interpeak III-V).[29] Similar results were obtained by Khullar et al. In this study delayed latencies of wave I, II and interpeak III-V were observed.[30] Bhattacharjee et al. demonstrated significantly prolonged wave I, II and V, and interpeak III-V latencies in patients with elevated both SBP and DBP. Among patients with both hypertension and hyperlipidemia almost all latencies were affected.[23]

In our study hypertension appeared to affect wave I and wave III latencies in ABR (wave II was not analyzed). Also linear correlation between both SBP and DBP level and wave III latency was revealed. Potential mechanisms of these findings remain unclear. In the mentioned earlier study by Voulgari et al. hypertension and SBP (together with other modifiable risk factors) appeared to be associated with the risk of cardiac autonomic neuropathy in both type 1 and type 2 diabetes.[27]

In two large population-based studies, and in one original study higher BMI appeared to correlate with a hearing impairment.[10,11,31] To date, the impact of BMI on ABR has not been studied yet. In our study we did not find significant differences in ABR results between patients with normal weight, overweight, and obese. Also no linear correlation between BMI and ABR latencies was noted.

The most important limitation of our study, frequently seen also in a vast majority of other original studies, is relatively small group of analyzed patients. Thus, random effect of our findings cannot be excluded. Also some trends observed in our study appeared to be insignificant, likely due to small study group. On the other hand, the strength of our study is a wide range of analyzed variables, which allowed us to find some relationships between these variables and auditory pathway function.

Relationship between blood lipids, blood pressure and ABR disturbances revealed in our and also in other studies, together with association of poor metabolic control with ABR abnormalities found by other researchers, can be, at least in part, explained by the fact, that both hyperglycemia, dyslipidemia and hypertension have a deleterious effect on the structure and function of both the macro- as well as the microvasculature. This may lead to accelerated atherosclerosis of arteries supplying auditory organ, and to development of microangiopathy of the cochlea and acoustic nerve nutritive vessels.[32-34] Moreover, hyperglycemia directly impairs function of a nervous tissue. Also elevated triglycerides and low HDL-cholesterol level seem to play an important role in the metabolism of nervous tissue. As a result an altered acoustic nerve function and delayed acoustic stimulus conduction through peripheral part of the auditory pathway may develop.

It is worth to note that both our study, as well as other original studies were conducted in a relatively small groups of patients. Moreover, in different studies frequently different methodology has been used. This can explain discrepancies in the obtained results, and it is obvious that further observations, involving a larger groups of patients and control subjects are required to confirm the existence of a relationship between these modifiable variables and hearing organ function in diabetic patients.

If these findings are confirmed, a vast area of possible interventions for the preservation of the auditory function in diabetic population will open. In the Fremantle Diabetes Study treatment with fibrates was associated with a lower prevalence of peripheral neuropathy

in type 2 diabetic subjects. Longitudinal observation showed also a lower neuropathy incidence among patients using statins and fibrates.[35] Thus, various hypolipemic and anti-hypertensive drugs, may be potentially useful in prevention of hearing deterioration in diabetes. However, this requires prospective, interventional studies to determine the value of such a treatment methods.

Disclosure

The authors declare no conflict of interest on the area covered by this paper.

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