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Apelin hormone level and its role in the etiology of sudden hearing loss

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Abstract

Sudden hearing loss (SHL) is a significant problem requiring emergency intervention; however, consensus on its diagnosis and treatment remains to be determined. Although several factors could cause SHL, its cause can only be determined in 10% of patients. Several approaches have been described for its treatment. The primary aim of treatment is to prevent cochlear hypoxia by increasing the partial O2 pressure in the perilymph. Apelin is an oxidative stress mediator. If apelin level changes are associated with SHL etiology, the protective and therapeutic effects of apelin can be beneficial. This study aimed to investigate the extent of influence of apelin hormone level changes in the SHL etiology. A total of 27 patients diagnosed with SHL and 26 healthy volunteers were evaluated as the patient and control groups, respectively. Apelin levels, biochemical parameters, and hemoglobin levels were measured. No difference was found between the patient and control groups in respect of apelin and other parameters. Although the study results did not show a statistically significant difference, the degree of hearing loss increased with decreased apelin levels in patients with SHL. Although not statistically significant, Apelin level was lower as the level of hearing loss increased in patients presenting with SHL. According to studies, it can be thought that patients with low apelin levels can be assumed to be less likely protected against inflammatory diseases related to oxidative stress. Therefore, further comprehensive and extensive clinical studies to examine apelin effect mechanisms should be performed. According to studies, the Apelin hormone shows a protective effect against inflammatory diseases caused by oxidative stress. In our study, there was no significant difference when Apelin hormone levels were compared with the patients with sudden hearing loss in the control group. However, due to the low number of patients to investigate the mechanisms of action of Apelin, more extensive and larger studies are needed.

Keywords: Apelin, etiology, oxidative stress, sudden hearing loss

Introduction

Sudden hearing loss (SHL) is a significant problem requiring emergency intervention in the Ear, Nose, and Throat clinics; however, consensus on its diagnosis and treatment remains to be determined. SHL is diagnosed when the hearing loss of >30 dB at 3 consecutive frequencies emerged for <3 days. The incidence has been reported to be 5-20/100,000 usually occurring at 40–60 years of age. It constitutes 1% of all sensorineural hearing losses. Although several factors could cause SHL, its cause can only be determined in 10% of patients [1].

Apelin is a hormone typically expressed in the vascular endothelium and adipose tissues. It was discovered as a gene consisting of 380 amino acids, with sequencing identical to the angiotensin II type I APJ (Apelin Junction Receptor), and Tatemato et al. isolated the apelin molecule as an endogenous ligand in 1998 [3]. APJ belongs receptor gene, by O'Dowd et al. in 1993 [2]. This gene was named to the G-protein-coupled receptor family formed from seven transmembrane regions. Apelin is located on chromosome Xq25–26.1 and encodes 77 amino acid preproapelin and forms fragments with a varying number of amino acids (such as apelin-10, apelin-11, apelin-12, apelin-13, apelin-15, apelin-17, apelin-19, and apelin-36) on fragmentation.

Apelin-13 is the primary active isoform that specifically binds to APJ [4]. Apelin aids in the vasoconstriction of damaged vessels, thereby functioning as an indicator of the severity of coronary artery stenosis [5]. Assuming that the functional mechanism of apelin abundantly found in the vascular endothelium is similar to that observed in the cardiovascular system during oxidative stress, then establishing an association between apelin level changes and the SHL etiology will help apply its protective and therapeutic effects to derive benefits.

Several approaches have been described for the treatment of SHL, such as anti-inflammatory treatment, vasodilators, diuretics, antiviral agents, volume expanders, and calcium antagonists. Most studies on SHL have not been controlled and double-blinded. The

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treatment for SHL primarily aims to prevent cochlear hypoxia by increasing the partial O2 pressure in the perilymph. However, its etiology remains unclear, and rates of spontaneous and placebo recovery are high (47-63%). Among the treatment drugs used, corticosteroids are the only drugs considered universally effective [6]. Further studies are required to investigate new factors on the etiology and develop different treatment options. If apelin level changes are associated with the SHL etiology, its protective and therapeutic effects can be applied to derive benefits.

This study aimed to investigate the extent of influence of apelin hormone level changes on the SHL etiology, considering its abundance in the vascular endothelium.

Materils and Methods

The study was approved by the Clinical Research Ethics Committee of Antalya Training and Research Hospital. Informed consent was obtained from all study participants. The study included patients aged >18 years diagnosed with SHL, defined as having hearing loss of >30 dB at 3 consecutive frequencies for <3 days. None of the participants in the patient or control group had any known diabetes, dyslipidemia, or cardiovascular disease. Apelin, fasting glucose, blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), aspartate transaminase (AST), Glycated hemoglobin (HbA1c), cholesterol, low-density lipoprotein (LDL), triglyceride (TG), high-density lipoprotein (HDL), and hemoglobin (Hb) levels were measured. The biochemical analyzer used was a Beckman Coulter au5800 device, and a Beckman Coulter LH780 device was used to measure Hb levels.

To evaluate the hearing levels, pure tone audiometry was used at frequencies of 250-8000 Hertz (Hz) using an Interacoustics AC40 clinical audiometer (Denmark).

Patients who did not meet the SHL criteria on the audiogram and those aged <18 years were excluded from the study. The study group of 27 patients diagnosed with SHL and a control group of 26 healthy volunteers were investigated. A 10-cc venous blood sample was obtained from all participants, immediately centrifuged at 4000 rpm for 20 min, and then stored at -80°C until assayed with a fully automatic Micro ELISA device (Triturus/Grifols, Spain) and human AP 13 ELISA kits (Sunred Biotechnology, Shanghai, China).

Statistical Analysis

Data obtained in the study were analyzed using SPSS 23.0 software. Descriptive statistics were presented as a number, percentage, mean, standard deviation, median, minimum, and maximum values. The Pearson Chi-square test was used to analyze categorical data. Conformity to normal distribution was assessed with the Shapiro-Wilk test. To analyze the difference between the numerical data of two groups, independent sample t-test was performed on normally distributed data, and Mann–Whitney U-test on non-normally distributed data. A value of $p < 0.05$ was accepted as statistically significant.

Results

The study included 27 patients diagnosed with SHL with a mean age of 46.22 ± 15.98 years and a control group of 26 healthy volunteers with a mean age of 39.96 ± 10.67 years. No statistically significant intergroup difference was observed on age, sex, or apelin values ($p > 0.05$). In the control group, age was not found to create a difference in the apelin values. However, apelin values in men were found to be lower than that in women in the patient group ($p = 0.017$) (Table 1).

No difference was observed between the patient and control groups regarding age, sex, apelin, BUN, creatinine, ALT, AST, HbA1c, cholesterol, LDL, TG, and Hb values. HDL values were low and glucose values were high in the patient group. The TG value was higher in the patient group than that in the control group, but the difference was not statistically significant (Table 2).

Despite the study results not showing a statistically significant difference, patients who complained of SHL were noted to have a low apelin level with increased the degree of hearing loss. There was no statistically significant correlation between the PTA values of the patients and the values of the apelin ($r = -0,208$; $p = 0.299$) (Figure 1). The median apelin value of the group with mild hearing loss was found to be 27 U/ml (23.8-120), 25.95 U/ml (14.7-120) for the moderate-level, 27.65 U/ml (15.7-33.3) for the severe and profound loss and there was no statistically significant difference between apelin values ($p = 0.412$) (Figure 2).

Discussion

Viral infections, vascular disorders of the labyrinth, intracochlear membrane tears, and inner ear immune diseases are considered as etiological factors of idiopathic SHL. Inner ear blood circulation is easily affected by vascular pathologies in the terminal vessels without collaterals. SHL may occur due to circulation disorders, such as thrombosis, vasospasm, emboli, hemorrhage, hypercoagulation, and high viscosity [7]. However, its causative agent is often not found in most SHL patients.

Table 1. Apelin values in control and patient groups

		Females			Males			p	Test
		n	Mean±SD	Median (Min-max)	n	Mean±SD	Median (Min-max		
Control	Age(yrs)	14	37.31±9.19	39(18-53)	12	42.75±13.38	41(21-72)	0.213	t
	Apelin U/ML	13	32.6±15.5	25.1(18.9-63.1)	12	22.94±5.52	21.5(16.9-35.4)	0.068	MWU
Patient	Age(yrs)	13	39.69±12.98	35(23-70)	14	50.29±16.28	52(19-75)	0.075	t
	Apelin U/ML	12	31.1±20.47	26.35(16.6-95)	12	25.28±6.17	26.5(14.7-34.1)	0.017	MWU

a Pearson Chi-square Test, b Independent Paired Samples t-test, c Mann-Whitney U Test (ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood Urea Nitrogen; TG: Triglycerides; PTA: Pure Tone Average; Hb: Hemoglobin; Hb A1c: Hemoglobin A1c)

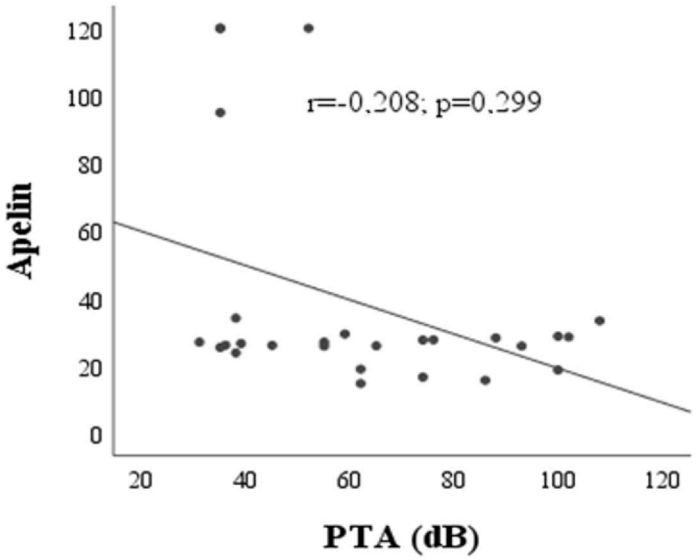

Figure 1: Correlation analysis between PTA and apelin

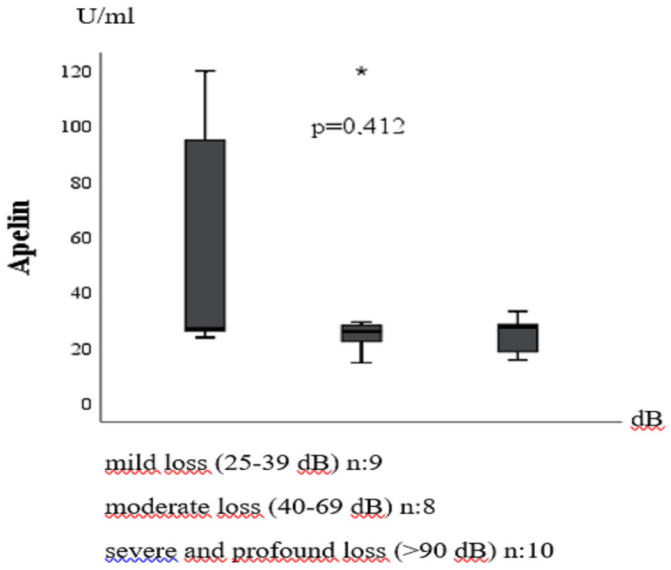

Figure 2. Apelin levels according to the degree of hearing (U/ml)

Table 2. Patient and control groups in respect of age gender, apelin, BUN, Creatinin, ALT, AST, Hb A1c, cholesterol, LDL, TG, and Hb values

	CONTROL			PATIENT			p
	n	Mean±SD	Median (Min-max)	n	Mean±SD	Median (Min-max	
Gender F/M(%F)[a]		16/10 (61.5%)			13/14 (51.9%)		0.328
Age [b]	26	39.96±10.67	40(18-72)	27	46.22±15.98	43(19-75)	0.099
Apelin (U/ML)[c]	23	28.57±12.95	24.5(16.9-63.1)	24	28.19±15.08	26.35(14.7-95)	0.463
PTA dB HL[c]	26	8.64±2.27	8.7(5-12.5)	27	62.15±24.84	59(31-108)	<0.001
Fasting glucose (mmol/L)[c]	26	92.58±8.76	89.5(83-118)	22	120.77±64.55	105(70-372)	0.019
BUN (mg/dL)[c]	26	12.42±3.94	11(8-23)	22	13.68±4.59	13(6-28)	0.18
Creatinin (mg/dL)[c]	26	0.91±0.14	0.88(0.73-1.29)	22	0.92±0.17	0.9(0.59-1.24)	0.756
ALT (U/L)[c]	26	19.5±13.81	15(8-65)	22	21.59±15.06	16(8-75)	0.59
AST (U/L)[c]	26	19.31±4.99	18(12-35)	23	20.22±6.24	20(8-36)	0.344
HbA1c(mg/dL)[b]	26	5.35±0.27	5.4(4.8-5.9)	22	5.88±1.73	5.4(3.2-10.7)	0.172
Cholesterol (mg/dL)[b]	26	193.15±20.45	199.5(154-233)	22	182.23±35.98	180.5(110-254)	0.216
HDL (mg/dL)[c]	26	56.81±13.48	55(30-91)	22	49.95±10.31	49(36-83)	0.016
LDL (mg/dL)[c]	26	121.62±26.48	112.5(80-200)	22	113.86±28.04	107.5(69-177)	0.156
TG (mg/dL)[c]	26	98.23±46.37	90(34-262)	22	128.27±88.72	110.5(67-486)	0.053
Hb (g/dL) [c]	26	13.93±1.35	13.5(12.1-17.4)	22	13.41±2.11	13.7(8.2-17.5)	0.671
Apelin U/ML	13	32.6±15.5	25.1(18.9-63.1)	12	22.94±5.52	21.5(16.9-35.4)	0.068
Age(yrs)	13	39.69±12.98	35(23-70)	14	50.29±16.28	52(19-75)	0.075
Apelin U/ML	12	31.1±20.47	26.35(16.6-95)	12	25.28±6.17	26.5(14.7-34.1)	0.017

[a] Pearson Chi-square Test, [b] Independent Paired Samples t-test, [c] Mann-Whitney U Test%"(ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood Urea Nitrogen; TG: Triglycerides; PTA: Pure Tone Average; Hb: Hemoglobin; Hb A1c: Hemoglobin A1c)

Notably, the effects of Apelin differ according to its forms. Apelin-13 is the primary active isoform that specifically binds to APJ [4]. Because of N-terminal pyroglutamate residues in Apelin-13, its biological activity is higher than that in other Apelin forms. Therefore, researchers have most often focused on Apelin-13 because of its higher level of biological activity [8]. Remarkably, the plasma peptide level in humans is 89.8 ± 5.3 pg/ml, and its half-life in the circulation is approximately 8 h [9,10]. Kawamata et al. reported that the Apelin concentration was extremely low in the plasma compared with other tissues. This finding suggests that besides functioning as an endocrine factor in the circulation, Apelin could exhibit a paracrine effect as a neurotransmitter [8].

The bioactive peptide Apelin is a specific endogenous ligand of G-protein-coupled receptor APJ and causes various biological effects in the body. In the healthy endothelium, the primary function of Apelin/Apelin receptor signalization is vasodilatation, but vasoconstriction in a damaged vascular endothelium [11]. The APJ system is an oxidative stress mediator in the vascular tissue [12]. Tatemato et al. reported that Apelin increases the production

of nitric oxide (NO) by regulating the NO synthesis enzyme [13]. Apelin is a proven efficacious vasodilator and aids cardiovascular hemodynamics to provide positive inotropic effects on the heart [14-16]. Yanga et al. determined that both Apelin-13 and Apelin-36 exhibited neuroprotective effects and inhibited damage originating from inflammation in cerebral ischemia-reperfusion [17]. Furthermore, the Apelin/APJ system can regulate insulin sensitivity and gastrointestinal functions and immune functions by supporting angiogenesis, cell migration, and proliferation [18].

Reducing the Apelin level is considered as an etiological factor, and then applying its protective and therapeutic effects can be proven beneficial. Therefore, Apelin-13, the most active form, was compared between the patient and control groups in this study. Although the study results did not show a statistically significant difference, the Apelin level in patients who complained of SHL was noted to decrease, which increased the degree of hearing loss (Figure 2). According to studies, it is stated that patients with low Apelin levels provide less protection against inflammatory diseases due to oxidative stress. In this study, we cannot say this result due to the low number of patients and insufficient statistical data. More patient-numbered studies are needed to understand the effect of Apelin on hearing physiology.

No statistically significant difference was found between the patient and control groups regarding age, sex, Apelin, BUN, creatinine, ALT, AST, HbA1c, cholesterol, LDL, TG, and Hb values. Patients included in the study were in the low-risk group concerning cardiovascular disease. TG values in the patient group were determined to be higher than those in the control group, albeit not statistically significant. Notably, Apelin reduces the serum TG level by regulating lipolysis [18]. Therefore, low Apelin values determined in the patient group compared with the control group could have been related to high TG levels.

Apelin/APJ system could be a new therapeutic target in inflammatory diseases, particularly those that suppress oxidative stress and apoptosis in vitro and in vivo [12,17,19-21]. Oxidative stress plays an important role in the activation of cochlear cell death pathways in the inflammatory pathogenesis of auditory disorders [20]. Yin et al. showed in their study that Apelin significantly reduced cisplatin-induced cell damage in inner hair cells. Apelin may have an otoprotective effect against cisplatin-induced ototoxicity by inhibiting the apoptotic pathway in the inner ear [21]. Apelin has protective roles in several diseases such as ischemia-reperfusion injury, neurodegenerative diseases, and metabolic disorders [22]. Mounting evidence shows that Apelin has anti-oxidative and anti-apoptotic roles in different cell types, but the role of Apelin in the cells of the inner ear has only been reported in vitro studies. Although we could not find meaningful results, to the best of our knowledge, this is the first reported documenting an association between idiopathic SHL and Apelin hormone. These results may be due to the low number of patients.

Conclusion

In this study, we did not find a significant relationship between oxidative stress-related idiopathic SHL and Apelin levels. Nonetheless, further comprehensive and extensive clinical studies are required to examine Apelin/APJ effect mechanisms and their role in oxidative stress and antioxidant effects in inflammatory diseases and the inner ear in vivo and in vitro.

Conflict of interests

The authors have no conflicts of interest to declare.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Approval was obtained from University of Health Sciences Antalya Training and Research Hospital Clinical Research Ethics Committee. no: 2015-158

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