Biological Trace Element Research (2021) 199:2844–2850
https://doi.org/10.1007/s12011-020-02420-4

The Role of Manganese, Cadmium, Chromium and Selenium on Subjective Tinnitus

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Received: 4 August 2020 / Accepted: 30 September 2020 / Published online: 9 October 2020
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Abstract

Elevated levels of heavy metals like cadmium (Cd) and manganese (Mn) are known to lead to oxidative damage-related oto-toxicity and decreased levels of chromium (Cr) and selenium (Se) are known to lead to oto-toxicity due to reduced anti-oxidant activity. The aim of the present study was to evaluate serum levels of Cd, Mn, Cr, and Se and their relationship with tinnitus. A total of 48 patients with tinnitus (Group 1) and 40 healthy controls (Group 2) were included in the study. All participants were applied audiology tests. Severity of tinnitus was measured with Tinnitus Severity Index Questionnaire (TSIQ) in group 1. Serum Mn, Cd, Cr, and Se measurements were done by using The Agilent ICP-MS system consisted of a 7700 coupled plasma mass spectrometry (ICP-MS). Serum Cd, Mn, and Cr levels were higher in group 1 and Se level was lower in group 1 than that of group 2. We may conclude that Cd, Mn, Cr, and Se levels could play an important role in etio-pathogenesis of tinnitus, and thereby supplementation or reduction of these elements could be considered as novel therapeutic goals.

Keywords Tinnitus · Trace elements · ICP-MS · Serum

Introduction

Tinnitus is being aware of the voices coming from an external origin in the ear or in the head. Tinnitus is a symptom, not a disease. Symptoms of tinnitus are usually defined as ringing bells, buzzing, or whistling [1, 2]. It is defined as "objective tinnitus" if the voice can be heard also by the others and "subjective tinnitus" if only the patient can hear it. Subjective tinnitus is a voice perception resulting from an abnormal neuronal activity. Tinnitus is usually subjective and defined as "chronic tinnitus" if lasts longer than 6 months [1–3]. Prevalence of tinnitus is 10–15% in adult population [4, 5]. Prevalence was reported as 32.9% in a study conducted in Kayseri from Turkey [6]. Tinnitus prevalence tends to increase with age and more common in the age groups of 40–49 years (23.9%) and 50–59 years (25.6%) [7].

Etiology of tinnitus includes otology disorders, neurologic problems (multiple sclerosis, vestibular schwannoma, head trauma etc.), medications (salicylic acid, aminoglycosides, antibiotics, some diuretics), metabolic disorders (thyroid dysfunction, hyperlipidemia, vitamin B12 deficiency), acoustic trauma, Meniere's disease, or psychogenic factors. However, these are not seen in about 50% of the cases [8]. Serum and tissue zinc, copper, and lead levels were analyzed and these levels were proposed to be associated with tinnitus etiopathogenesis in a study conducted in 2017 [9]. In a study conducted by Berkiten et al., serum zinc levels were reported to be low in tinnitus patients [10], and benefits of zinc supplementation were reported in other studies [7, 11].

Zinc and the other trace elements play a role in oxidative reactions [12]. The imbalance between formation of reactive oxygen /nitrogen species (ROS/RNS) and protective anti-oxidant system is defined as "oxidative stress." Oxidative

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stress and ROS production play a role in patho-physiology of various chronic diseases [13]. Endothelium is under great risk for free radical-induced lesions, and this damage is most evident in micro-circulation, particularly inner ear, retina, kidneys and brain [13–15]. Recent studies are available reporting that ROS plays a role in inner ear pathology through influencing micro-circulation [13, 16–18] and potentially related with idiopathic tinnitus [19]. Anti-oxidant treatment is recommended for reducing oxidative stress which harms inner ear structures in patients with idiopathic subjective tinnitus [20].

Various anti-oxidant systems are present in the body for preventing ROS-induced cellular damage and eliminating oxidant substances. Seleno-proteins act as anti-oxidant, protect the cell from harmful effects of oxidation of cellular proteins, eliminate free radical precursors, and play a role in preventing lipid peroxidation [21, 22]. Glutathione peroxidase (GPx), a seleno-protein, detoxifies H_2O_2 and lipid peroxidation and thereby eliminates toxic H_2O_2 which induces ciliary dysfunction and apoptosis of hairy cells of inner ear. Therefore H_2O_2 level and oxidative stress increase in selenium (Se) deficiency; this condition hinders cell proliferation and repairs [23]. Chromium (Cr) is another trace element; it was shown to reduce oxidative stress in isolated human mononuclear cells and monocyte cell cultures [24]. So Cr deficiency leads to oxidative stress and cell damage.

Heavy metals like Cadmium (Cd) and plumb (Pb) induce free radical production. Cadmium is a non-essential oto-toxic heavy metal and among the hazardous air pollutants in urban areas. Cadmium enters the body with dirty food, water, air, and inhalation of smoke [24–26]. Cadmium was reported to damage external hair cells and/or stria vascularis through accumulating in cochlea and consequently lead to a reduction in oto-acoustic emission and hearing loss [27]. Another heavy metal, manganese (Mn), is among the trace elements in the body. High Mn levels were reported to harm hair cells and spiral ganglion neurons (SGN) and thereby lead to hearing loss in a study conducted with postnatal cochlear organo-typical cultures [28].

Etiology of tinnitus is still not clear despite all developments in modern medicine. An ample amount of studies were conducted to enlighten physio-pathology of tinnitus which impairs quality of life and leads to sleep disturbances; different methods and medications were tried for treatment. As mentioned above, while studies are available reporting that elevated levels of heavy metals like Cd and Mn lead to oto-toxicity by specifically accumulating in inner ear, some others report that decreased Se and Cr values lead to oto-toxicity through increasing oxidative stress [22–24, 27, 28]. Some metals were reported to be able to lead to tinnitus due to toxic side effects when used as implant material [29]. However no studies could be encountered which concurrently analyze serum levels of these four elements in subjects with tinnitus. Based on these scientific data, the present study was conducted with the aim of investigating whether serum Mn, Cd, Cr, and Se levels are an important factor in etiology of tinnitus.

Materials and Methods

Study Population

Ethics committee for this case control study approval was obtained from Erzurum Region Research and Training Hospital (2017/14–93). Forty-eight tinnitus patients (Group 1) and 40 healthy volunteers (Group 2) who were admitted to Ear-Nose-Throat (ENT) Outpatient Clinic of Palandöken State Hospital (Erzurum) between December 2017 and November 2019 were included in the study.

A complete oto-rhino-laryngology examination was done for all participants, and age and gender were recorded. All subjects were performed speech discrimination score (SDS), speech reception threshold (SRT), and pure tone audiometry (PTA).

The subjects who had sensory-neural, conduction and mixed type hearing loss (>20 db) according to audiogram test, objective tinnitus, presbiacusia, noise exposure, Meniere's disease and other vertigo types, vestibular schwannoma, glomus tumors, oto-sclerosis, chronic otitis media, pregnancy, neurologic disorders, sudden hearing loss, psychotropic drug use, metabolic diseases (thyroid dysfunction, hyper-lipidemia, vitamin B12 deficiency), and industry workers were excluded from the study. The patients who had bilateral idiopathic subjective tinnitus for longer than 6 months were included in group 1. Healthy volunteers who were admitted to ENT Outpatient Clinic for getting a health report or other reasons; however no ENT disorder was detected which were included in group 2. Written informed consent was obtained from all participants prior to the study.

Assessment of Tinnitus Severity

Tinnitus severity was evaluated by using Tinnitus Severity Index Questionnaire (TSIQ), a questionnaire composed of 12 questions, in group 1. Scores of 13–24 were evaluated as "mild," 25–36 as "moderate," 37–48 as "severe," tinnitus and 49–60 as "very severe" tinnitus [30].

Hearing Threshold Test

All participants were performed audiologic tests including speech discrimination score (SDS), speech reception threshold (SRT), and pure tone audiometry (PTA). Audiometry assessment was done in a dead AC 40 audiometric cabinet which was calibrated in accordance with ISO 9001 standards. Hearing threshold levels were tested for air and bone conduction in frequencies between 125 and 8000 Hz.

Table 1 Tinnitus Severity Index distribution in Group 1

		n	%
Severity index	Mild	7	14.6
	Moderate	20	41.7
	Severe	12	25.0
	Very severe	9	18.7
Total		48	100

Assessment of Serum Manganese, Cadmium, Chromium, and Selenium Levels

Blood samples were obtained from ante-cubital vein to standard biochemistry tube (yellow top, with separation gel) following 8–10 h of fasting (Samples were collected from the patients at 8:30–10:00 am). The biochemistry tubes were centrifuged at 3500 rpm for 10 min to separate serum, and the serum samples were stored at −80 °C until the day of analysis. Serum samples removed from −80 on working day were included in the study after they reached room temperature. Concentrations of the trace elements were measured with coupled plasma mass spectrometry (ICPMS).

Biochemistry Analyses

Sample Preparation

A volume of 100 ml was taken from serum samples. H_2O_2/HNO_3 in a ratio of 1:4 mixture was added to serum samples. The mixture was subjected to digestion in microwave up to 200 °C. The volume of digested samples was adjusted to 10 ml by adding ultrapure water.

ICP-MS Analysis

The Agilent ICP-MS system consists of an 7700 Series (Agilent Technologies, Courtaboeuf, France). System equipped with a third-generation octopole reaction system (ORS3) using He gas. The samples were injected from the tubes arranged in a CETAC ASX-500 Series auto-sampler (CETAC Technologies, Omaha, NE, USA) with a peristaltic pump. The ion lenses, torch position, gas output, resolution axis, and background were optimized daily using tune solution (1 mg L^{-1}) to carry out stability test of the instrument.

Statistical Analysis

Statistical analyses were done by using SPSS 15.0 package program. Normality distribution was tested with Kolmogorov-Smirnov/Shapiro-Wilk tests. Gender distribution of case and control groups was evaluated with chi-square test. Comparison of the groups with regard to the other variables was done with Mann-Whitney U test. A p level of < 0.05 was accepted as statistically significant.

Results

Mean age of the participants was 50.89 ± 16.3 in group 1 and 50.5 ± 15.2 in group 2 and similar between groups ($p = 0.90$). In group 1, 24 patients were male and 24 were female; in Group 2, 21 of the volunteers were male and 19 were female. Female/male ratio was similar between groups ($p = 0.82$). Results of the study are summarized in Tables 1, 2, and 3 and in Fig. 1. Serum levels of Cd, Mn, and Cr were statistically significantly higher in group 1 compared with group 2; serum Se level was found to be statistically significantly lower in group 1 (Table 2). No correlation was found between tinnitus severity and serum Cd, Mn, Cr, and Se levels (Table 3).

Discussion

Tinnitus etiology is multi-factorial and complex. Studies are available reporting that oxidative stress and free oxygen radicals may be effective in tinnitus etiology. Oxidative stress may be considered as one of the factors in cell and tissue damage in many diseases [31–33]. Free radicals are very reactive oxidative products which can directly harm the tissues through influencing intra-cellular field, cell membrane,

Table 2 Comparison of serum Cd, Mn, Cr, and Se levels in group 1 and group 2 [microgram/Liter (mcg/L)]

	Group 1 ($n = 48$)		Group 2 ($n = 40$)		*p*
	Mean ± SD	(Min-Max)	Mean ± SD	(Min-Max)	
Cr (mcg//L)	0.17 ± 0.05	0.02–0.32	0.14 ± 0.03	0.09–0.26	0.005
Mn (mcg//L)	1.62 ± 1.65	0.64–11.8	0.93 ± 0.43	0.36–2.22	< 0.001
Se (mcg//L)	95.97 ± 32.09	17.87–138.29	154.96 ± 24.12	103.73–205.96	< 0.001
Cd (mcg//L)	2,30 ± 1.02	0.99–5.02	1.45 ± 0.55	0.37–3.59	< 0.001

Table 3 Distribution of serum Cd, Mn, Cr, and Se levels according to tinnitus severity in group 1

	Mild ($n = 7$) Mean (Min-Max)	Moderate ($n = 20$) Mean (Min-Max)	Severe ($n = 12$) Mean (Min-Max)	Very severe ($n = 9$) Mean (Min-Max)
Cr (mcg/L)	0.14 (0.11–0.18)	0.19 (0.20–0.32)	0.16 (0.12–0.21)	0.17 (0.12–0.32)
Mn(mcg/L)	0.19 (0.64–1.82)	1.70 (0.89–3.57)	1.34 (0.77–2.92)	2.29 (0.88–11.8)
Se (mcg/L)	118.10 (99.8–138.3)	90.59 (24.2–126.2)	92.92 (17.8–122.3)	94.79 (23.3–115.5)
Cd(mcg/L)	1.69 (0.99–4.47)	2.37 (1.08–5.02)	2.58 (1.35–4.48)	2.26 (1.25–3.98)

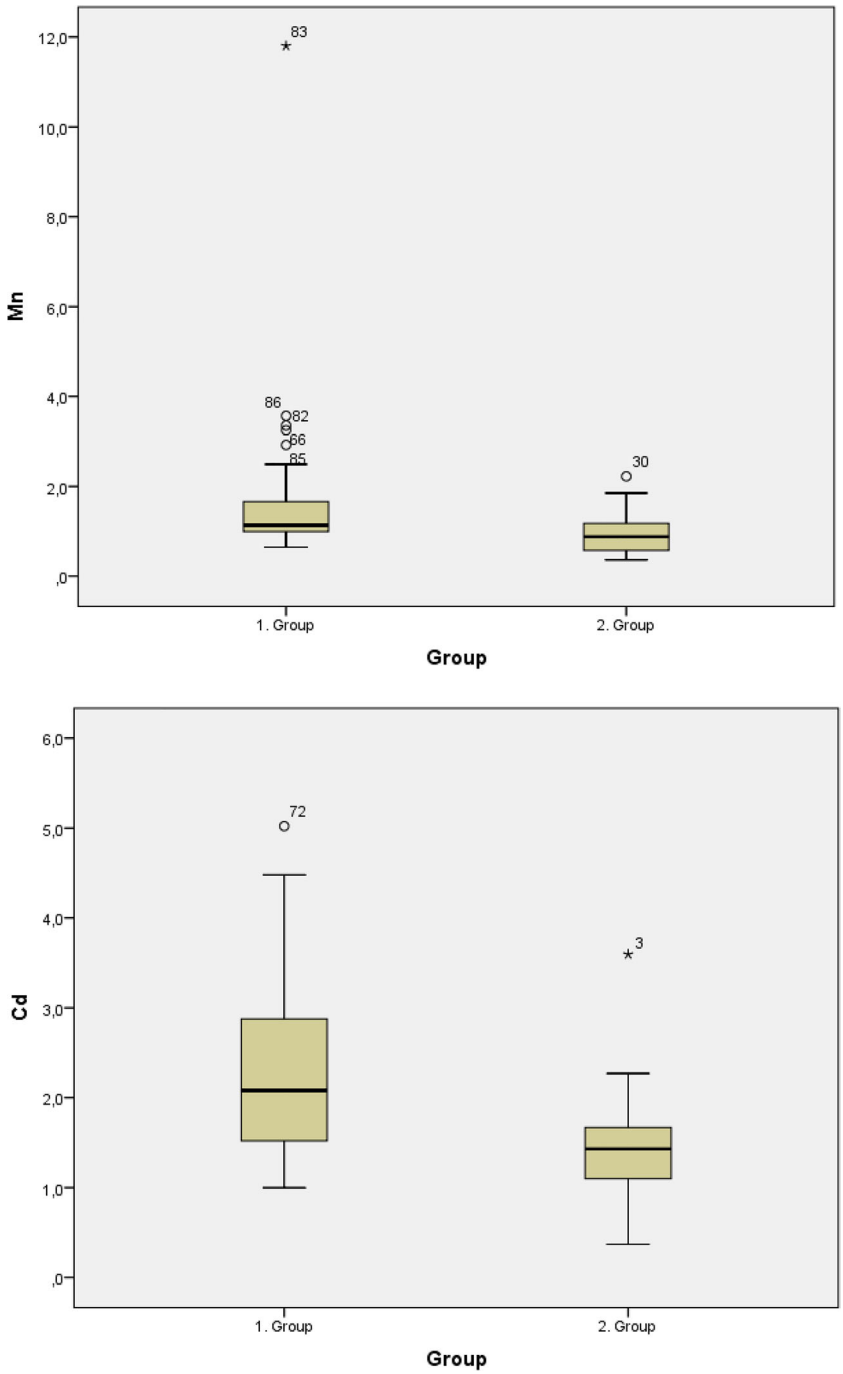

Fig. 1 Box-plot distribution of serum Cd, Mn, Cr, and Se levels in group 1 and group 2

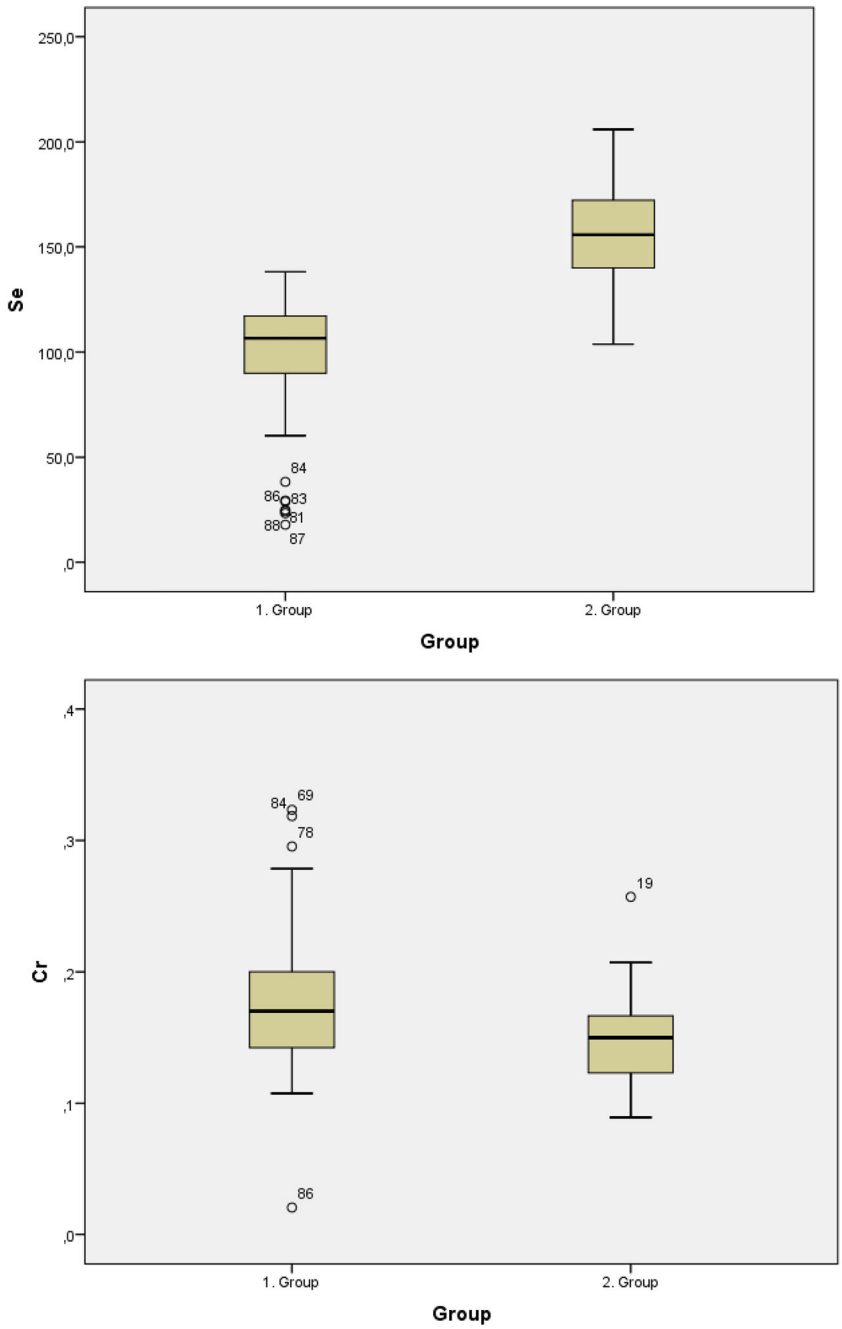

Fig. 1 (continued)

protein synthesis, and cell nucleus. No doubt that endothelium is the most sensitive and selective target of cytotoxic effects of free radicals. Endothelial damage mainly impairs microcirculation in inner ear, renal glomerulus, and retina [31–33].

Studies are available reporting that oxidative stress could lead to oxidative damage in acoustic-vestibular system [34]. The harmful effects of oxidative damage are well known in some inner ear diseases like Meniere's disease, drug oto-toxicity, and labyrinthitis. Sensory-neural cells in cochlea are more susceptible to the harmful effects of oxidative stress more than the other tissues of the body [34]. Experimentally induced oxidative stress is known to lead to labyrinthitis, elevated free radical levels in acoustic and vestibular canals, lipid peroxidation in phospho-lipid membranes, and thereby apoptosis in acoustic neurons and ciliary cells [35].

Heavy metals (like Cd) may exhibit their oto-toxic effects by leading to oxidative stress, reducing glutathione, protein-bonded sulphydril groups, blood circulation, and lipid peroxidation in cochlea [27]. Cadmium was shown to lead to ROS formation, matrix metallo-proteinase loss, cytochrome C

release, caspase, ERK (extra-cellular signaling regulating kinase) activation, and apoptotic cell death. The final effect is the reduction in energy production needed for maintenance of cellular function, increased ROS production, and induction of apoptosis by increased oxidative stress [36, 37]. Cadmium was reported to be able to cause hearing loss by accumulating in cochlea [37, 38]. In a study of Ozcaglar et al. conducted by using post-natal cochlear organo-typical cultures, Cd-related damage was shown in hair cells, acoustic nerve (AN) fibers, and SGN depending on the dose and duration [27]. The same study has reported loss in inner hair cells (IHC) and external hair cells (EHC) in low Cd concentrations, loss in a large proportion of hair in the whole cochlea besides AN, and SGN in high concentrations. Hair cell loss was reported to progress from the cochlear base to the top of cochlea proportionally with the increasing dose and exposure time, similarly with oto-toxic drugs and toxic reactives [27]. Based on these data, it is possible that increased serum Cd levels could lead to hearing loss and/or tinnitus by showing oto-toxic effect. However in another study, smoking status and tinnitus risk factors were evaluated in adolescents and a significant difference was not reported in serum Cd levels in subjects with tinnitus [39]. The results of our study indicate that serum Cd level could be associated with tinnitus.

Mn is a trace element required for growing, development, and cellular homeostasis. It acts as a cofactor for many enzymes [40]. Recent studies showed that high Mn concentrations could lead to harmful effects on central and peripheral nervous system including acoustic system [41]. Animal studies showed that manganese could accumulate in inner ear of rats (Ma et al. 2008) indicating the likelihood of harmful effects on hair cells in cochlea, neurons, or supportive cells [40]. In another study, the workers who were exposed to inorganic Mn in a factory which produces manganese oxide and salt for a long time (mean 7.1 years) were found to experience tinnitus in higher rates [42]. Based on these findings, it may be stated that high serum Mn levels may lead to hearing loss and/or tinnitus in humans and test animals through causing oto-toxicity. The present study indicates that high serum Mn levels could lead to tinnitus through oto-toxic effect in subjects with tinnitus, consistently with the abovementioned studies.

Chromium was reported to reduce oxidative stress in the studies conducted with isolated human mononuclear cell and monocyte cell cultures [28]. This condition was associated with the inhibiting effect of Cr in protein glycolyzation, lipid peroxidation, and pro-inflammatory cytokine release [43]. Free radicals directly harm neuron membranes by causing lipid peroxidation [44]. Serum Cr level was reported to be significantly low in patients with tinnitus and low Cr levels was reported to be able to cause tinnitus due to reduced inhibiting effect on lipid peroxidation [40]. On the contrary to literature, Cr level was found to be significantly high in patients with tinnitus in our study.

GPx is a sulphydril-containing tri-peptide found in all cells. It is essential for inhibiting oxidative stress and preserving intra-cellular redox potential. Selenium acts as redox center for GPx synthesis and plays an important role in anti-oxidant defense [21]. Selenium treatment was reported to be effective in treatment of sudden hearing loss [45]. Besides, Se supplementation is used as an alternative treatment in Se deficiency [22]. Serum Se level was found to be low in patients with tinnitus in our study, and it is considered that Se deficiency could lead to oxidative damage-related tinnitus by causing reduced GPx synthesis, thereby reducing anti-oxidant activity.

Limitations

This study showed the relationship between serum trace element levels and tinnitus in a relatively small number of patients. Future clinical studies are required to determine the relationship between the trace elements and tinnitus in larger samples, thus contributing in both diagnosis and treatment options of tinnitus patients in ear-nose-throat clinics.

Conclusion

The results of the present study indicated that elevated serum levels of Cd, Mn, and Cr and decreased serum levels of Se were associated with tinnitus. Definition of this association showed that serum Cd, Mn, Cr, and Se levels could be another factor in etiology of tinnitus ad also it is considered to contribute in both diagnosis and treatment options for tinnitus.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest.

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