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Original Article

Is Hypozincemia Related to Tinnitus?: A Population Study Using Data From the Korea National Health and Nutrition Examination Survey

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Objectives. The aim of present study was to determine the relationship between serum zinc level and tinnitus using data from the Korea National Health and Nutrition Examination Survey (KNHANES).

Methods. The present study examined the relationship between serum zinc level and tinnitus using data from the KNHANES. A total of 2,225 KNHANES participants responded to the tinnitus questionnaire and provided blood samples to measure serum zinc concentration. Based on questionnaire responses, participants were categorized into control, mild tinnitus, moderate tinnitus, and severe tinnitus subgroups.

Results. There were no significant differences between groups in serum zinc level after adjustment for sex, age, and hearing loss.

Conclusion. It was concluded that hypozincemia is not related to tinnitus in a large population.

Keywords. *Tinnitus; Serum Zinc; Zinc Deficiency; Hearing Loss*

INTRODUCTION

Tinnitus is the perception of sound without external sound [1]. Recent research has revealed promising treatments for tinnitus, but no cure is currently available. Various medications and supplements have been proposed for treating tinnitus, but none are U.S. Food and Drug Administration-approved. However, zinc supplementation has been considered as a treatment option for tinnitus [2,3]. Zinc is a trace element found in the auditory pathway of both the peripheral and central nervous systems. Zinc is found in auditory synapses [4] and in the stria vascularis of the dorsal cochlear nucleus of the brainstem [5]. Zinc is also a component of Cu-Zn superoxide dismutase that protects against reactive oxygen species [6], and Cu-Zn superoxide dismutase knockout mice had more severe auditory hair cell damage [7]. These findings suggest zinc might have a role in tinnitus generation. This is supported by clinical studies suggesting zinc deficiency might be related to tinnitus etiology. For example, zinc deficiency occurred more frequently in tinnitus patients [8-10]. Some studies have reported the effect of zinc treatment for tinnitus [8,11]. Patients taking zinc showed reduced subjective tinnitus symptoms [11]. However, in two well-controlled studies on zinc treatment, Paaske et al. [12] reported that hypozincemia was found in only one patient and that, compared to a placebo, zinc treatment was not effective in treating tinnitus, and Coelho et al. [13] reported that zinc treatment was not effective in elderly tinnitus patients, with a careful focus on individual results. The conclusion from these studies was that zinc supplementation was not effective for reducing tinnitus. There has not been a large population study examining the relationship between zinc deficiency and tinnitus. The etiology of tinnitus might be hetero-

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geneous, and tinnitus is related with known and unknown factors such as aging and hearing loss; therefore, a large population-based study is needed to investigate the relation between tinnitus and zinc. The Korea National Health and Nutrition Examination Survey (KNHANES) is a large population study that surveyed most aspects of health and nutritional status of a South Korean population. This survey included a tinnitus questionnaire, a pure tone audio test, and a serum zinc level test. Most large population studies usually lack more objective data from tests such as pure tone audiometry. However, KNHANES included studies about serum zinc level, pure tone audiometry, and a tinnitus questionnaire. The present study was expected to determine the relationship between serum zinc level and tinnitus using KNHANES data.

MATERIALS AND METHODS

The KNHANES was conducted in 2010 and included 8,958 participants. Of these, 2,225 had their serum zinc levels measured and completed the tinnitus questionnaire. These subjects were included in the analysis.

The tinnitus-related question in KNHANES was "Have you experienced tinnitus within the past year?" If the subject answered yes, he or she was required to answer the question "Does your tinnitus annoy you?" If this answer was yes, the subject would mark one of the following: (1) My tinnitus is not annoying. (2) My tinnitus is annoying and makes me nervous. (3) My tinnitus is so annoying that I can hardly sleep at night.

Based on the respondents' answers to the questionnaire, we categorized them into four subgroups: control, mild tinnitus, moderate tinnitus, and severe tinnitus. Participants who marked "My tinnitus is not annoying" were included in the mild tinnitus subgroup, those who marked "My tinnitus is annoying and makes me nervous" were included in the moderate tinnitus subgroup, those who marked "My tinnitus is so annoying that I can hardly sleep at night" were included in the severe tinnitus subgroup, and those who responded "no" to the question "Have you experienced tinnitus within the past year?" were included in the control group.

Serum zinc level

The original purpose of measuring serum zinc concentration was to determine mean serum zinc concentration in the general South Korean population. For this purpose, venous blood was collected. Serum zinc concentration was measured using inductively coupled plasma mass spectrometry.

Pure tone hearing test

The pure tone hearing test was performed by an ENT (ear, nose, and throat) physician in a sound-proof booth. Test frequencies were 0.5, 1, 2, 3, 4, and 6 kHz. The average threshold for each frequency was used for evaluation. Hearing loss was defined as a pure tone average ([0.5+1+2+3+4+6 kHz]/6) greater than 25 dB hearing level.

Statistics

All data were analyzed using survey sample weights assigned to represent the Korean population.

The mean and standard error for serum zinc levels were calculated by gender, age group, hearing loss, and tinnitus severity. The proportion and standard error for the ratio of the hearing loss population were also calculated.

The mean and standard error of serum zinc levels were estimated after adjusting for age, gender, and hearing loss. Differences among groups for continuous variables were tested using one-way analysis of variance. Categorical variables were analyzed using the chi-square test.

Sex, age, and hearing loss were considered confounder for evaluating relation between serum zinc level and tinnitus severity. For adjustment of age, gender and hearing loss, analysis of covariance was used to compare mean serum zinc level by tinnitus severity. Statistical analyses were performed using the survey procedure in SAS ver. 9.3 (SAS Institute Inc., Cary, NC, USA). *P*-values <0.05 were considered statistically significant.

RESULTS

The study population included 2,225 total participants. Of these, there were 1,765 in the control group, 322 in the mild tinnitus group, 120 in the moderate tinnitus group, and 18 in the severe tinnitus group. Mean age was 40.66 ± 16.74 years for the control group, 40.20 ± 17.66 years for the mild tinnitus group, 48.53 ± 17.01 years for the moderate tinnitus group, and 60.61 ± 13.23 years for the severe tinnitus group (Table 1). The ratio of men to women and the ratio of hearing loss were similar among groups, except for the severe tinnitus group, which had older subjects and more subjects with hearing loss. The mean serum zinc level was 136.17 μg/dL for the control group, 135.49 μg/dL for the mild tinnitus group, 130.62 μg/dL for the moderate tinnitus group, and 118.98 μg/dL for the severe tinnitus group (Table 1). There was no significant difference in serum zinc level among groups, except for a difference between the control group and the severe tinnitus group ($P=0.026$) (Fig. 1).

DISCUSSION

Previous studies have examined the relationship between zinc deficiency and tinnitus. The prevalence of hypozincemia in tinnitus patients has been reported to range from 2% to 69% [8-9,11-12,14]. The discrepancy in results might be due to the small numbers of subjects and different criteria for defining hy-

Table 1. Basic characteristics of study groups

Characteristic	Mild tinnitus (n=322)	Moderate tinnitus (n=120)	Severe tinnitus (n=18)	Control group (n=1,765)	Total (n=2,225)	*P*-value*
Age (year), mean±SD (range)	40.20±17.66 (12–80)	48.53±17.01 (12–83)	60.61±13.23 (27–82)	40.66±16.74 (12–77)	41.18±17.04 (12–83)	<0.001
Sex						
Female	178	58	12	877	1,125	0.137
Male	144	62	6	888	1,100	
Ratio of population with hearing loss (%)	14.48±2.9	34.72±6.67	74.03±12.4	10±1.02	12.8±1.06	<0.001
Pure tone average right (dB HL)						
0.5+1+2+4 kHz/4	15.64±1.17	24.66±3.28	39.77±5.26	14.55±0.53	15.56±0.50	<0.001
0.5+1+2+3+4+6 kHz/6	18.18±1.36	28.49±3.66	43.63±5.54	16.99±0.55	18.13±0.52	<0.001
Pure tone average left (dB HL)						
0.5+1+2+4 kHz/4	15.4±1.20	26.7±2.83	43.97±5.62	14.29±0.49	15.53±0.50	<0.001
0.5+1+2+3+4+6 kHz/6	17.93±1.40	30.91±2.94	49.85±5.54	17.03±0.53	18.35±0.54	<0.001

Values are presented as mean±standard deviation.
HL, hearing level.
*Analysis of variance was used for comparison of each group. Age, gender and hearing loss was not adjusted.

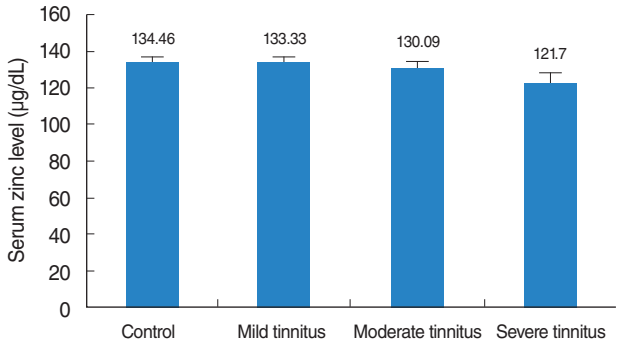

Fig. 1. The distribution of serum zinc concentration of participant by tinnitus severity group. Analysis of covariance was used to compare mean serum zinc level of groups and *P*-values <0.05 were considered statistically significant.

pozincemia and tinnitus. Serum zinc levels vary by sex, age, and systemic conditions such as infection or trauma [15,16]. Previous studies have been inconclusive regarding the relationship between hypozincemia and tinnitus and the effect of zinc treatment for tinnitus. Gersdorff et al. [14] reported that 68.7% of 115 tinnitus patients had lower serum zinc concentrations than that of control group. Ochi et al. [9] reported that tinnitus patients had significantly lower serum zinc levels than a control group and that zinc treatment was effective in improving the subjective severity of tinnitus. On the other hand, Paaske et al. [12] reported in a double-blind placebo-controlled study that only 1 of 48 patients had a low zinc level and that zinc was not more effective than placebo in treating tinnitus, and Coelho et al. [13] concluded that zinc treatment was not effective in elderly people in a randomized placebo-controlled crossover study.

In addition to serum zinc concentration, the prevalence of tinnitus is influenced by age and sex [17,18]. The prevalence of tinnitus generally ranges from 7% to 20% in the general population [18]. Tinnitus and hearing loss increase with aging [17-21]. Sindhusake et al. [21] reported hearing loss was a significant risk factor for tinnitus; however, age and sex did not show statistically significant association with tinnitus. Therefore, aging and sex could be considered as confounding factors. In the current study, we adjusted sex, age, and hearing loss for a more exact analysis.

The present results showed no significant difference in serum zinc concentration between a tinnitus population and a control population after adjustment for age, sex, and hearing loss. The most severe tinnitus group showed significantly lower serum zinc concentrations than the control group. However, there were only 18 subjects with severe tinnitus; thus, it is difficult to interpret the true relationship between zinc and tinnitus. Plasma zinc concentration may not be an accurate indicator of whole-body zinc levels, as most zinc in the human body is intracellular [22]. Only an extremely low zinc diet can cause hypozincemia; this is because there is an exchangeable pool of zinc acting as a buffer for zinc deficiency [23]. It is possible that zinc deficiency is one causative factor in some tinnitus populations.

The population of tinnitus might be heterogeneous as indicated in a study showing there are at least four tinnitus subgroups [24]. This is consistent with the present study, which also suggests various tinnitus subgroups; thus, zinc deficiency could be associated with tinnitus in a subpopulation. However, our study suggests that zinc deficiency is not related to tinnitus in a large portion of the tinnitus population. In the present study, the most severe tinnitus group had a lower zinc concentration than the other groups. However, there was no significant difference of serum zinc concentrations between other groups. This is the first large population study regarding serum zinc level and tinnitus. The present study has limitations. First the questions about tinnitus which used in KHANES were simple and brief. It did not include sufficient information about their tinnitus such as duration, loudness, site of tinnitus. Second severe tinnitus group in-

cluded only 18 subjects, it is too small to draw a conclusion.

In conclusion, hypozincemia was not related to tinnitus in this large population study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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