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Original Article

Serum Trace Elements and Heavy Metal Levels in Patients Diagnosed with Chronic Otitis Media and Their Association with Surgical Treatment Outcomes

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OBJECTIVE: To determine the serum iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), magnesium (Mg), cobalt (Co), and lead (Pb) levels in patients with chronic otitis media (COM) and to evaluate the association of the serum levels of these elements with treatment outcomes.

MATERIALS and METHODS: Thirty-one healthy volunteers and 31 patients with COM were prospectively included in this study. Serum levels of Fe, Zn, Mn, Mg, Cu, Co, and Pb were determined by an atomic absorption UNICAM-929 spectrophotometer.

RESULTS: Serum Co, Pb, and Fe levels were significantly increased ($p<0.001$) and serum Cu, Zn, Mg, and Mn levels were significantly reduced in patients with COM compared with controls ($p<0.001$). Serum Co and Mn levels were significantly decreased ($p<0.001$ and $p<0.005$, respectively) and serum Cu levels were significantly increased after surgery ($p<0.005$). The other evaluated blood chemicals and heavy metals did not exhibit significant differences ($p>0.05$).

CONCLUSION: Significant alterations in the serum chemical composition of patients with COM were observed. Moreover, with surgical treatment, serum levels of some of these chemicals were significantly altered. Further prospective studies are warranted to elucidate the exact association of these alterations in the etiopathogenesis of COM.

KEYWORDS: Chronic otitis media, trace elements, heavy metals

INTRODUCTION

Chronic otitis media (COM) is a common disease with some severe complications that result from long-standing damage to the middle ear by inflammation or infection [1]. Although the etiopathogenesis of COM has not been fully elucidated to date, genetic, inflammatory, autoimmune, and infectious factors, including cytokines, endotoxins, and oxidative stress, have been implicated [2].

Blood chemicals and trace elements play important roles in the establishment of vital chemical responses [3]. However, some immunological and inflammatory responses may alter the distribution of these chemicals in the body. In contrast, the status of blood chemicals may influence lymphocyte and granulocyte function as well as the immune response [4]. Moreover, trace elements play various vital roles as important constituents of vitamins, enzymes, and other proteins.

Some data in the literature support the immunological function of various blood chemicals. Serum iron (Fe) and zinc (Zn) levels are reduced during infection and inflammation [5]. Manganese (Mn) is an important cofactor for several enzymes that maintain DNA integrity. In addition, Mn is an important antioxidant. Cobalt (Co) is a critical fragment of vitamin B_{12} that is crucial in foliate and fatty acid metabolism[6]. Lead (Pb) down-regulates nitric oxide production and induces oxidative stress and inflammation. Copper (Cu), magnesium (Mg), Zn, and Fe have been previously studied in some acute and chronic infections, including tuberculosis, *Helicobacter pylori* (*H. pylori*) infection, sepsis, and viral hepatitis [7-9].

Preliminary results of this study were presented as a oral presentation in 15th International Meeting of The Mediterranean Society of Otology and Audiology Congress, 28-30 April 2016, Nevşehir, Turkey.

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However, data regarding alterations of blood chemicals in patients with COM are limited. In this study, we aimed to determine the serum Fe, Zn, Mn, Cu, Mg, Co, and Pb levels in patients with COM and to evaluate the associations of the serum levels of these elements with treatment outcomes.

MATERIALS and METHODS

Study Design

The local institutional review board approved the study, and informed consent was obtained from all participants. In this prospective study, 31 patients with COM and 31 healthy volunteers were evaluated.

Patients were diagnosed based on their medical histories and routine otomicroscopic evaluations. Patients with a history of diabetes mellitus, hypertension, rheumatoid arthritis, liver disease, renal disease, and coronary artery disease as well as those who received immunosuppressive treatments were excluded from the study. However, all participants in the control group were asymptomatic nonsmokers with normal physical examination and otomicroscopic evaluations. None of the participants were taking antioxidant vitamin supplements.

Outcome Parameters

Prior to treatment, blood samples were obtained and stored at 4°C. Serum was isolated by centrifugation (3,000 rpm, 10 min) and stored at -80°C. The Fe, Zn, Mn, Mg, Cu, Co, and Pb levels were determined using a UNICAM-929 atomic absorption spectrophotometer (Unicam Ltd, York Street, Cambridge, UK).

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences version 11 (SPSS Inc.; Chicago, IL, USA). Qualitative variables were assessed using the Chi-square test. To compare patients and healthy controls, Student's *t*-test was used. To compare values before and after treatment, a paired t-test was used. A p value of 0.05 or less was considered significant.

RESULTS

The study group included 31 patients (16 females and 15 males) with a mean age of 41±6 years, and the control group included 31 volunteers (14 females, 17 males) with a mean age of 39±7 years (Table 1). No significant differences regarding age or gender were noted between groups.

Compared with the healthy controls, serum Co, Pb, and Fe levels were significantly increased in the COM group (p<0.001), whereas serum Cu, Zn, Mg, and Mn levels were significantly reduced (p<0.001; Table 2, Figure 1).

After surgery, serum Co and Mn levels decreased significantly (p<0.001 and p<0.005, respectively), whereas serum Cu levels increased significantly (p<0.005). Other serum chemicals did not exhibit any significant alterations after surgery (Table 3, Figure 2).

DISCUSSION

In this study, we aimed to determine the levels of serum chemicals and heavy metals in patients with COM before and after surgery and compare the results with healthy volunteers. To the best of our knowledge, this is one of the foremost studies regarding blood chemicals in patients with COM. We determined that patients with COM exhibit increased serum Zn, Mn, Mg, and Cu levels and reduced Co, Pb, and Fe levels compared with healthy subjects. Moreover, after surgery, serum Co and Mn levels decreased, whereas serum Cu levels significantly increased.

Table 1. Demographic characteristics of the two groups in this study

Parameters	Controls (n=31)	COM (n=31)	p
Age (years)	39±7	41±6	0.237
Sex (female/male)	14/17	16/15	0.611

COM: chronic otitis media; SD: standard deviation
Values are the mean±SD

Table 2. Serum chemicals and heavy metal levels

Parameters	Controls (n=31)	COM (n=31)	p
Fe (µg/dL)	0.23±0.03	0.66±0.14	p<0.001
Mg (µg/dL)	26.62±2.89	12.56±2.35	p<0.001
Mn (µg/dL)	0.31±0.10	0.13±0.02	p<0.001
Zn (µg/dL)	2.30±0.27	0.85±0.08	p<0.001
Pb (µg/dL)	0.31±0.06	0.16±0.22	p<0.001
Co (µg/dL)	0.19±0.06	0.79±0.01	p<0.001
Cu (µg/dL)	5.05±1.22	3.92±1.17	p<0.001

Fe: iron; Mn: manganese; Mg: magnesium; Zn: zinc; Pb: lead; Co: cobalt; Cu: copper; COM: chronic otitis media; SD: standard deviation
Values are the mean±SD

Table 3. Serum trace and heavy metal levels before and after treatment

Parameters	Controls (n=31)	COM (n=31)
Fe (µg/dL)	0.66±0.14	0.64±0.06
Mg (µg/dL)	12.56±2.35	12.70±1.41
Mn (µg/dL)	0.13±0.02	0.11±0.01[a]
Zn (µg/dL)	0.85±0.08	0.84±0.06
Pb (µg/dL)	0.16±0.22	0.10±0.01
Co (µg/dL)	0.79±0.01	0.57±0.08[b]
Cu (µg/dL)	3.92±1.17	4.34±1.12[a]

Fe: iron; Mn: manganese; Mg: magnesium; Zn: zinc; Pb: lead; Co: cobalt; Cu: copper
Values are the mean±SD
[a]p<0.005 compared with before surgical treatment
[b]p<0.001 compared with before surgical treatment

Considering that blood chemicals and trace elements are essential for immune system function via the integration into regulatory pathways or control of oxidative stress, their deficiencies may result in infectious diseases [10]. Data regarding blood chemicals in COM are limited. Elemraid et al. [11] investigated the nutritional factors associated with chronic suppurative otitis media in children and reported that children with this disease were more undernourished compared with controls, with lower mean serum Zn, selenium (Se), and calcium (Ca) concentrations.

Previous studies have revealed that trace elements, such as Zn, Fe, Cu, and Mg, may play a role in infectious diseases, such as tuberculosis, *H. pylori* infection, sepsis, and viral hepatitis [7-9]. Zn is an important micronutrient in the body with numerous functions, including growth, nerve impulse transmission, hormone release, and activation of immune-enhancing T-cells [12]. In an experimental study, Prasad et al. [13] stated that a significant decrease in Zn concentrations was associated with a decrease in interferon-gamma and interleukin (IL)-2 production as well as the nat-

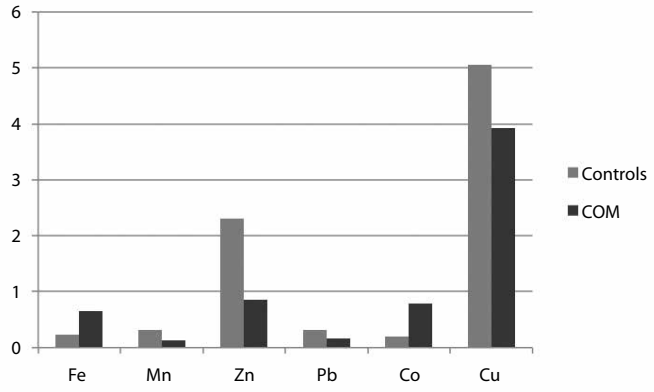

Figure 1. Distribution of various blood chemicals among study participants

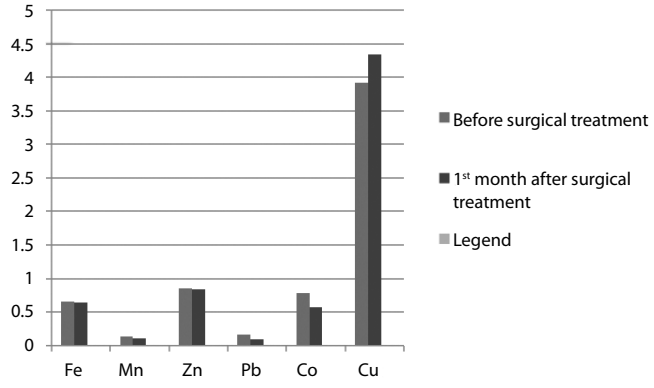

Figure 2. Serum levels of various chemicals before and after surgery.

ural killer cell lytic activity, resulting in susceptibility to infectious agents. Mertens et al. [9] demonstrated that patients with sepsis had significantly lower plasma Zn concentrations compared to control subjects. Consistent with our results, Elemraid et al. [11] also reported significantly reduced serum Zn levels in patients with chronic suppurative otitis media. Aydogan et al. [14] also reported reduced serum Zn concentrations in children with otitis media with effusion compared with patients who underwent adenoidectomy alone. In a recent review, the role of Zn supplements in the prevention of otitis media in adults and children of different ages was investigated. Although the data are controversial, limited evidence exists on the benefits in children treated for severe malnutrition [15]. Interestingly, in another study, 2 subcutaneous injections of a multimineral preparation containing Zn, Mn, Se, and Cu increased neutrophil function [16]. In the present study, we revealed that serum Zn concentrations were significantly reduced in patients with COM compared with control subjects. During the first month after surgical treatment, serum Zn levels did not exhibit a significant alteration. The reduced Zn levels observed in this study may cause a defect in the immunologic response, preventing the appropriate reaction to otitis media.

Zn and Cu are required to maintain a proper immune response and antioxidant protection in the body as they are the cofactors of metalloenzymes [17, 18]. Superoxide dismutase, one of the most important enzymatic antioxidants, also contains Zn and Cu [19]. Serum Cu levels are increased in some infections and inflammatory processes, as previously noted [7,20]. Recently, the serum Cu/Zn ratio was defined as an important inflammatory marker [21]. However, in the present study, we revealed that serum Cu levels were reduced in COM patients compared with control subjects. In patients with COM, serum Cu levels were significantly increased after the surgical treatment. The lower serum Cu and Zn levels determined in this study may be associated with defects in the immune response and antioxidant mechanisms.

Mn is a trace element that is related to the transport and absorption of Fe, and the levels of these two elements exhibit a positive correlation [22]. Mn also plays a significant role in the immune system, interacting with neutrophils and macrophages and protecting the body against oxidative stress [23]. To the best of our knowledge, no studies have evaluated serum Mn levels in COM patients. In the present study, we found that serum Mn levels were reduced in COM patients compared with controls. Interestingly, after surgical treatment, serum Mn levels were significantly further reduced. The role of Mn in the etiopathogenesis and treatment of COM warrants further studies.

Mg is a vital element for the function of numerous enzymes that are involved in DNA and RNA synthesis [24]. Some antibacterial effects of Mg have also been previously reported [25, 26]. Yue et al. [27] reported higher Mg levels in the middle ear fluids of patients with otitis media. In the present study, we revealed that serum Mg levels were significantly reduced in COM patients compared with controls. This finding may be attributed to the utilization of Mg in this inflammatory response. After surgical treatment, serum Mg levels were not altered in patients.

Fe is crucial for cell growth and numerous metabolic processes, and Fe deficiency is associated with several diseases and oxidative DNA damage [28]. Based on its function in cell proliferation and bactericidal activity, low levels of Fe can also result in an impaired immune response. Moreover, Fe is essential for the growth and virulence of numerous microbial pathogens [29]. In the present study, serum Fe levels were significantly increased in COM patients compared with control subjects. Increased serum Fe levels may cause susceptibility to infections by providing an appropriate media for microorganisms. After surgical treatment, serum Fe levels were not altered in patients.

Heavy metals, such as Pb and Co, may accumulate in different organs of the body and inhibit vital enzymes. Pb affects endothelial function and alters the inflammatory response [30]. In a recent study, increased serum Pb and cadmium (Cd) levels were associated with the development of COM [31]. In the present study, we demonstrated that serum Pb levels were significantly increased in COM patients compared with control subjects. Co is an essential part of vitamin B12, which is crucial for foliate metabolism. Co harvests reactive radicals and may facilitate free radical production [32]. In our study, we found that serum Co levels were significantly increased in COM patients compared with control subjects. After surgical treatment, serum Co levels in patients with COM were significantly reduced, but serum Pb levels were not altered.

Although this is the first study in the literature evaluating blood chemicals in patients with COM, it has some limitations that should be mentioned. First, due to the cross-sectional design of this study, we cannot address causal relationships. Second, we assessed serum levels of blood chemicals, and these values may not always correlate with definite functions at the tissue level.

In conclusion, we determined that there were significant alterations in serum chemicals in COM patients. Moreover, upon surgical treatment, the serum levels of some of these chemicals were also significantly altered. Further prospective studies are warranted to elucidate the exact association of these alterations in the etiopathogenesis of COM.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yüzüncü Yıl University School of Medicine (Decision No: 05/18.04.2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.B., M.E.D.; Design - N.B., A.F.K.; Supervision - E.G.; Materials - N.B., H.D., A.Y., C.D., A.A., H.Ö., P.K.; Data Collection and/or Processing - H.D., A.Y., M.T., P.K.; Analysis and/or Interpretation - H.D., A.F.K.; Literature Search -E.G., C.D., A.A., M.T., H.O.; Writing Manuscript - N.B., M.E.D; Critical Review - A.F.K.

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REFERENCES

1. Garça MF, Aslan M, Tuna B, Kozan A, Cankaya H. Serum myeloperoxidase activity, total antioxidant capacity and nitric oxide levels in patients with chronic otitis media. J Membr Biol 2013; 246: 519-24. [CrossRef]
2. Yilmaz T, Koçan EG, Besler HT, Yilmaz G, Gürsel B. The role of oxidants and antioxidants in otitis media with effusion in children. Otolaryngol Head Neck Surg 2004; 131: 797-803. [CrossRef]
3. Ozturk P, Belge Kurutas E, Ataseven A. Copper/zinc and copper/ selenium ratios, and oxidative stress as biochemical markers in recurrent aphthous stomatitis. J Trace Elem Med Biol 2013; 27: 312-6. [CrossRef]
4. Elemraid MA, Mackenzie IJ, Fraser WD, Brabin BJ. Nutritional factors in the pathogenesis of ear disease in children: a systematic review. Ann Trop Paediatr 2009; 29: 85-99. [CrossRef]
5. Saaka M, Oosthuizen J, Beatty S. Effect of joint iron and zinc supplementation on malarial infection and anaemia. East Afr J Public Health 2009; 6: 55-62. [CrossRef]
6. Chen PC, Guo CH, Tseng CJ, Wang KC, Liu PJ. Blood trace minerals concentrations and oxidative stress in patients with obstructive sleep apnea. J Nutr Health Aging 2013; 17: 639-44. [CrossRef]
7. Choi R, Kim HT, Lim Y, Kim MJ, Kwon OJ, Jeon K, et al. Serum concentrations of trace elements in patients with tuberculosis and its association with treatment outcome. Nutrients 2015; 7: 5969-81. [CrossRef]
8. Öztürk N, Kurt N, Özgeriş FB, Baygutalp NK, Tosun MS, Bakan N, et al. Serum zinc, copper, magnesium and selenium levels in children with helicobacter pylori infection. Eurasian J Med 2015; 47: 126-9. [CrossRef]
9. Mertens K, Lowes DA, Webster NR, Talib J, Hall L, Davies MJ, et al. Low zinc and selenium concentrations in sepsis are associated with oxidative damage and inflammation. Br J Anaesth 2015; 114: 990-9. [CrossRef]
10. Yang CY, Wu ML, Chou YY, Li SY, Deng JF, Yang WC, et al. Essential trace element status and clinical outcomes in long-term dialysis patients: a two-year prospective observational cohort study. Clin Nutr 2012; 31: 630-6. [CrossRef]
11. Elemraid MA, Mackenzie IJ, Fraser WD, Harper G, Faragher B, Atef Z, et al. A case-control study of nutritional factors associated with chronic suppurative otitis media in Yemeni children. Eur J Clin Nutr 2011; 65: 895-902. [CrossRef]
12. Raqib R, Roy SK, Rahman MJ, Azim T, Ameer SS, Chisti J, et al. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. Am J Clin Nutr 2004; 79: 444-50.
13. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. J Infect Dis 2000; 182: S62-8. [CrossRef]
14. Aydogan F, Aydin E, Tastan E, Arslan N, Senes M, Unlu I, et al. Is there a relationship between serum levels of vitamin a, vitamin e, copper and zinc and otitis media with effusion in children? Indian J Otolaryngol Head Neck Surg 2013 ;65: 594-7. [CrossRef]
15. Gulani A, Sachdev HS. Zinc supplements for preventing otitis media. Cochrane Database Syst Rev 2014; (6): CD006639. [CrossRef]
16. Teixeira AG, Lima FS, Bicalho ML, Kussler A, Lima SF, Felippe MJ, et al. Effect of an injectable trace mineral supplement containing selenium, copper, zinc, and manganese on immunity, health, and growth of dairy calves. J Dairy Sci 2014; 97: 4216-26. [CrossRef]
17. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr Med Chem 2005; 12: 1161-208. [CrossRef]
18. Honkanen VEA, Lamberg-Allardt CH, Vestermen MK, Lehto JH, Westermark TW, Metsa-Ketala TK, et al. Plasma zinc and copper concentration in rheumatoid arthritis: influence of dietary factors and disease activity. Am J Clin Nutr 1991; 54: 1082-6.
19. Aladag I, Guven M, Eyibilen A, Sahin S, Köseoglu D. Efficacy of vitamin A in experimentally induced acute otitis media. Int J Pediatr Otorhinolaryngol 2007; 71: 623-8. [CrossRef]
20. Dizdar OS, Baspınar O, Kocer D, Dursun ZB, Avcı D, Karakükcü C, et al. Nutritional risk, micronutrient status and clinical outcomes: A prospective observational study in an infectious disease clinic. Nutrient. 2016; 8: 124. [CrossRef]
21. Malavolta M, Giacconi R, Piacenza F, Santarelli L, Cipriano C, Costarelli L, et al. Plasma copper/zinc ratio: An inflammatory/nutritional biomarker as predictor of all-cause mortality in elderly population. Biogerontology 2010; 11: 309-19. [CrossRef]
22. Finley JW, Davis CD. Manganese deficiency and toxicity: are high or low dietary amounts of manganese cause for concern? Biofactors 1999; 10: 15-24. [CrossRef]
23. Yesilkaya H, Kadioglu A, Gingles N, Alexander JE, Mitchell TJ, Andrew PW. Role of manganese-containing superoxide dismutase in oxidative stress and virulence of Streptococcus pneumoniae. Infect Immun 2000; 68: 2819-26. [CrossRef]
24. Li Y, Liu G, Zhai Z, Liu L, Li H, Yang K, et al. Antibacterial properties of magnesium in vitro and in an in vivo model of implant-associated methicillin-resistant Staphylococcus aureus infection. Antimicrob Agents Chemother 2014; 58: 7586-91. [CrossRef]
25. Romani AM. Magnesium in health and disease. Met Ions Life Sci 2013; 13: 49-79. [CrossRef]
26. Chaigne-Delalande B, Li FY, O'Connor GM, Lukacs MJ, Jiang P, Zheng L, et al. Mg2+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science 2013; 341: 186-91. [CrossRef]
27. Yue WL, Xu ZH, Fu YL, Ye QZ, Luo JY. Magnesium levels in middle ear fluids and sera in otitis media with effusion. Eur Arch Otorhinolaryngol 1992; 249: 209-10. [CrossRef]
28. Dayani PN, Bishop MC, Black K, Zeltzer PM. Desferoxamine (DFO)-mediated iron chelation: rationale for a novel approach to therapy for brain cancer. J Neurooncol 2004; 67: 367-77. [CrossRef]
29. Cherayil BJ. The role of iron in the immune response to bacterial infection. Immunol Res 2011; 50: 1-9. [CrossRef]
30. Farkhondeh T, Boskabady MH, Koohi MK, Sadeghi-Hashjin G, Moin M. The effect of lead exposure on selected blood inflammatory biomarkers in guinea pigs. Cardiovasc Hematol Disord Drug Targets 2013; 13: 45-9. [CrossRef]
31. Park M, Lee JS, Lee JH, Oh SH, Park MK. Prevalence and risk factors of chronic otitis media: the Korean National Health and Nutrition Examination Survey 2010-2012. PLoS One 2015; 10: e0125905. [CrossRef]
32. Scharf B, Clement CC, Zolla V, Perino G, Yan B, Elci SG, et al. Molecular analysis of chromium and cobalt-related toxicity. Sci Rep 2014; 4: 5729.[CrossRef]