The relationship of serum selenium, zinc, and copper levels with seborrheic dermatitis: a case-control study

Zohreh Hajheydari [1*]
Majid Saeedi [2]
Mohammad Hosseinzadeh [2]

1. Department of Dermatology, Faculty of Medicine, Mazandaran University of Medical sciences, Sari, Iran
2. Department of Pharmacology, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

Corresponding Author:
Zohreh Hajheydari, MD
Department of Dermatology, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari, Mazandaran, Iran
Tel & Fax: +98 11 33344506
Email: zhajheydari@yahoo.com

Received: 20 October 2018
Accepted: 9 December 2018

Background: Seborrheic dermatitis is a common chronic relapsing inflammatory skin disease with unknown etiology. Using zinc and selenium supplements have shown some relieving effects on the symptoms of the disease. The present study was conducted to determine the relationship between serum selenium, zinc, and copper levels with seborrheic dermatitis.

Methods: A prospective case-control study was performed on 30 patients with seborrheic dermatitis and 30 age and sex-matched healthy volunteers as a control group. Trace elements were measured by atomic absorption spectrophotometer in both groups.

Results: The mean serum selenium, zinc, and copper levels were 98.90 ± 27.61 µg/dL, 91.27 ± 10.84 µg/dL, and 100.9 ± 20.06 µg/dL in case groups, respectively. In the control group, the mean serum selenium, zinc, and copper levels were 91.61 ± 15.74 µg/dL, 94.03 ± 11.11 µg/dL, and 96.5 ± 15.82 µg/dL, respectively. There was no significant difference between the mean serum selenium, zinc, and copper levels in case and control groups (P>0.05).

Conclusions: Although no statistically significant relationship was observed in serum selenium, zinc, and copper levels between the cases and controls, the serum selenium level among patients in case group was higher than that in the healthy subjects.

Keywords: seborrheic dermatitis, selenium, zinc, copper

Iran J Dermatol 2019; 22: 7-12

INTRODUCTION

Seborrheic dermatitis (SD) is a common chronic relapsing inflammatory papulosquamous disease that inflicts about 3-5% of the adult population with more prevalence in men. The disease has two incidence peaks; the first peak is at the first three months of life and the second occurs in adults of around 30-60 years of age [1-4].

Although the pathogenesis of the disease remains controversial and the cause of the disease is unknown and thought to be a multifactorial disease, the yeast of Malassezia (*Pityrosporum ovale*) is considered to be the causative organism. There is evidence suggesting that *Pityrosporum ovale* as a lipophilic yeast naturally lives on human skin and plays a role in the pathogenesis of this disease. There are two reasons that *Pityrosporum ovale* can contribute to the pathogenesis of seborrheic dermatitis: a) the yeast exists abundantly in sebaceous areas of skin and in dandruff of seborrheic individuals and 2) seborrheic dermatitis is responded to a variety of treatment that inhibits the growth of Pityrosporum ovale [2].

Several predisposing factors have shown an effect on seborrhoeic dermatitis included human immunodeficiency virus, neurological conditions such as Parkinson's disease, neuronal damage such as facial nerve palsy, spinal injury, ischemic heart disease, and alcoholic pancreatitis. Genetic and environmental factors may also predispose specific population to the development of the disease [1-3].

Some topical therapeutic options are corticosteroids, antifungal agents, mild keratolytic agents, and calcineurin inhibitors [4].

Trace elements have also been investigated as nutrient mediators in seborrheic dermatitis. Small amounts of trace elements such as iron, iodine, fluoride, copper, zinc, chromium, selenium, manganese and molybdenum are essential and vital for maintaining human health [5-8].

Iron, zinc, and copper are the most abundant trace elements in the human body. Copper, as an essential trace element in humans, is involved in different metabolic processes such as electron transport activity, oxidative metabolism, and cellular respiration. It is required for neurotransmitter regulation, collagen synthesis, wound healing, and nutrients metabolism, especially for iron uptake. Copper is also active against free radicals. Zinc is essential for anabolic pathways. Zinc deficiency causes a delay in wound healing. In this regard, chronic inflammation also leads to zinc deficiency. Zinc has antioxidant and anti-inflammatory effects and increases immunity against pathogens. Selenium is essential for the natural immune system and thyroid functions [9,10].

Given that the etiology of seborrheic dermatitis is unknown and the cutaneous inflammatory lesions seem to be reduced and controlled following the use of trace element, this study was conducted to determine the relationship between the serum selenium, zinc, and copper levels with seborrheic dermatitis.

MATERIALS & METHODS

This prospective case-control study was approved by the ethical committee of Research and Technology vice Chancellor of Mazandaran University of Medical Sciences. Before starting this research, informed consent was taken from all participants.

A total of 30 patients were diagnosed with seborrheic dermatitis and underwent no systemic therapy while a set of 30 age and sex-matched healthy volunteers were considered as a control group. The sample size was calculated by the following formula:

$$n_1 = \left(\frac{1+\varphi}{\varphi}\right)\frac{(z_{1-\frac{\alpha}{2}} + z_{1-\alpha})^2}{\Delta^2} + \frac{z^2{}_{1-\frac{\alpha}{2}}}{2(1+\varphi)}$$

$$\Delta = \frac{\mu_2 - \mu_1}{\sigma}\ ; \varphi = \frac{n_2}{n_1}$$

All participants were selected from the outpatient dermatology clinic of Bou Ali Sina Hospital, Sari, Iran during 2014-2015. Patients with allergic diseases, hypersensitive reactions, inflammatory bowel disease, asthma, infectious disease, previous surgery or invasive procedures within last month, atopy, acne vulgaris, vasculitis, lupus, immunodeficiency, and those who had been taking zinc and selenium elements at least in the last 6 months before the study were excluded. The cases were comprised of patients with seborrheic dermatitis who were examined by a dermatologist. The control group comprised of patients with other unrelated non-significant complaints.

Measuring serum levels of selenium, zinc, and copper, a 5 ml blood sample was taken from all participants in case and control groups under complete aseptic precautions. Blood sampling was done from the antecubital vein by a laboratory coworker. Then, blood samples were centrifuged at 3000 rpm for 10 minutes. The separated sera were transferred to 3 separated vials for each of the trace elements and were immediately stored at -20°C until analysis.

Selected trace elements were measured using Atomic Absorption Spectrophotometer Perkin Elmer AA100 manufactured by the USA at the faculty of pharmacy. For measuring selenium, zinc, and copper serum levels, the standard serial solutions of the three elements by 5 concentrations including 100 ppm, 10 ppm, 1 ppm, 0.1 ppm, and 0.01 ppm were prepared separately. The deionized water sample was also used as a blank sample (0 ppm). At first, for each element, absorption of standard samples was read by atomic absorption spectrometry. Then, the serum samples obtained from all participants in case and control groups were injected into the spectrophotometer. To determine the exact serum level of each element, the number obtained from the standard samples related to each trace element was put into Excel software to obtain a statistical formula for measuring serum level of selected trace elements.

Data were analyzed using SPSS v.16 (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for the data in the form of mean and standard deviation for quantitative data. Qualitative data

were presented as number and percentage. Student t-test was used to compare the mean of the two groups. Inter-group comparison of qualitative data was performed using the Chi-square test and Fisher exact test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of total 30 patients in the case group, 17 (56.7%) were female and 13 (43.3%) were male. In the control group, 10 (33.3%) were female and 20 (66.7%) were male. Fisher exact test showed no significant difference between the two groups (P=0.119). The mean age of participants in case and control group was 28.14 ± 9.3 and 23.5 ± 2.5, respectively. As shown in Table 1, the mean serum selenium levels were different between the case and control group, but the difference was not statistically significant (P=0.215).

The mean serum zinc level was statistically lower in the case group compared to the control group, but the difference was not significant (P=0.333).

The mean serum copper level in the case group was higher than the control group but the difference was also not significant (P=0.350).

The comparison of the normal and abnormal serum selenium, zinc and copper levels between the case and control groups is shown in Table 2.

As shown in Table 2, there was a significant difference in abnormal serum selenium level between the case and control groups (P=0.038).

No significant difference was observed between normal and abnormal serum zinc level in case and control groups (P=0.549).

The normal and abnormal serum copper level in the case group compared to the control group showed no statistically significant difference (P=0.549). From 3 (10%) patients with abnormal serum copper level in the case group, 2 (6.7%) were in the lower normal range and 1 (3.3%) was higher than normal range of reference. In the control group, 3 (10%) with abnormal serum copper level had serum copper level less than normal range of reference.

The correlation between the mean serum selenium, zinc and copper levels and positive history of seborrheic dermatitis is shown in Table 3. Four patients (13.3%) in the case group had a previous history of seborrheic dermatitis. The relationship between the mean serum selenium level and a positive history of seborrheic dermatitis between cases and controls was significantly different (P=0.037). There was no significant relationship between the mean serum zinc and copper with a positive history of seborrheic dermatitis in cases and controls.

There was no significant statistical difference

Table 1. The mean ± SD serum levels of selenium, zinc, and copper in case and control groups

Trace elements	Case group Mean serum level ± SD (µg/l)	Control group Mean serum level ± SD (µg/l)	*P*
Selenium	98.90±27.61	91.61±15.74	0.215
Zinc	91.27±10.84	94.03±11.11	0.333
Copper	100.9±20.06	96.5±15.82	0.350

Table 2. Normal and abnormal serum levels of selenium, zinc and copper in case and control groups

Trace elements	Case group		Control group		*P*
	Normal (No.%)	Abnormal (No.%)	Normal (No.%)	Abnormal (No.%)	
Selenium	26 (86.7%)	4 (13.3%)	30 (100%)	-	0.038
Zinc	28 (93.3%)	2 (6.7%)	29 (96.7%)	1 (3.3%)	0.554
Copper	27 (90%)	3 (10%)	27 (90%)	3 (10%)	0.549

Table 3. Mean serum selenium, zinc, and copper levels and positive history of seborrheic dermatitis in the case and control groups

Trace elements	Case group (Past history of seborrheic dermatitis) Mean±SD (µg/l)		Control group Mean±SD (µg/l) (N=30)	*P*
	Positive (N=4)	Negative (N=26)		
Selenium	73±8.12	100.83±26.78	91.61±15.74	0.037
Zinc	83.25±10.24	92.04±10.2	94.03±11.11	0.171
Copper	96.25±5.5	101.67±21.98	96.53±15.82	0.575

Table 4. Mean serum selenium, zinc, and copper levels and positive family history of seborrheic dermatitis in the case and control groups

Trace elements	Case group (Family history) (µg/l) Mean±SD		Control group Mean±SD (µg/l) (N=30)	*P*
	Positive (N=8)	Negative (N=20)		
Selenium	89.65±20.88	99.74±28.75	91.61±15.74	0.361
Zinc	91.38±11.69	90.55±23	96.53±15.82	0.522
Copper	108.13±19.65	10.28±20.54	94.03±11.11	0.276

between the mean serum selenium, zinc and copper levels and family history of seborrheic dermatitis in case and control groups (Table 4).

DISCUSSION

Seborrheic dermatitis is a chronic relapsing inflammatory skin disease that involves the areas with a high concentration of sebaceous glands [2]. Although the etiology of the disease remains unknown, several factors such as Malassezia yeasts, sex hormones, sebum level in the skin, immune response, neurological conditions such as Parkinson's disease, seasonal changes (more relapse in winter), and psychological stress, can play an important role in pathogenesis of the disease [11].

Trace elements such as zinc and selenium are the most common elements used in different forms of skin care products and therapeutic purposes in dermatology and play an important role in the physiological function of the body [7,12]. The normal serum levels of the copper, zinc, and selenium are 1.6-2.4 µmol/L or 10-15µg/dL, 70 - 120 µg/dL, and 70-150 ng/mL, respectively [13-15].

In our study, 56.7% of patients in the case group were women and the mean age of the patients in cases was 28.14 years. In line with our results, previous studies also estimated the peak incidence of the disease in the third and fourth decades among the adult population [1,11].

We found that the mean serum selenium level in case group was higher than that in the healthy control group. The dissimilar result was reported by Akinboro et al.. They investigated the effect of selenium on skin disorders and found that the serum selenium level in patients with dermatologic problems was significantly lower than healthy individuals [12]. In another case-control study by Javanbakht et al., the serum selenium, zinc, and copper levels were evaluated in early diagnosed Pemphigus Vulgaris patients. They showed that the serum selenium level in pemphigus patients was obviously lower than the healthy control group [16]. Our study revealed that the serum selenium level in cases was significantly higher than controls. It seems that the diet of the people in this region plays a role in their serum selenium level.

Koohkan et al., in a case-control study, evaluated the selenium level in serum and whole blood of children with atopic dermatitis. They compared 46 pediatric patients as a case group with 46 healthy children as controls. Their result showed that the mean serum selenium level in the case group (72.58 ng/ml) was significantly lower than that of the control (84.8 ng/ml) [17].

Serum selenium level has been recognized as an important component in selenoproteins such that about 60% of selenium in plasma is included in selenoprotein P. Selenium also plays an important role in innate immunity against inflammatory reaction caused by luminal bacteria, stimulation of immunoglobulin production, increasing body resistance to the diseases, regulating thyroid hormone on metabolism of the body, and a protective effect against cancer. Moreover, selenium can enhance the antioxidant activity of vitamin E [18-22].

Although zinc level in seborrheic dermatitis patients was low, no significant differences were seen in normal and abnormal serum zinc levels between the case and control groups. We concluded that this difference was due to the small sample size. This result was similar to the result of a study by Kreft et al. in Germany [22]. Different results were reported by others, however [23-25].

El-Kholy et al., in Egypt, measured the serum levels of zinc and copper in children with asthma and atopic dermatitis. They showed that low zinc level was more significant in atopic dermatitis patients than the healthy individuals in the control group [26]. Kaymak et al. studied the serum zinc level in patients with Acne Vulgaris. They measured the serum level of zinc in 47 patients in the case group and 40 healthy volunteers as controls [27]. Their results showed that the serum levels of zinc

were lower in the acne vulgaris patients than in controls. Mashaly et al. (2014) stated that the serum level of zinc in the pemphigus vulgaris patients is considerably lower than the controls [28].

Zinc plays an important role in protein synthesis, gene expression, and transcription and is also an essential trace element component in more than 250 metalloenzymes. Zinc deficiency causes failure to thrive, immune deficiency, anorexia, dermatitis, diarrhea, and allergic dermatitis [27,29,30].

It has been stated that a seborrheic dermatitis-like rash can be produced by zinc deficiency in patients with acrodermatitis enteropathica and acrodermatitis-like conditions [31].

In addition, Zinc plays an important role in normal function of skin and hair and there is a correlation between serum level of zinc and presence of diseases like acne vulgaris, wound healing, and pustular psoriasis [32].

Brocard et al stated that zinc is a cofactor of many metalloenzymes, indicating its crucial role in cell proliferation and regulation of the immune system. Their results also showed that zinc can play a critical role not only in the regulation of adaptative immunity but also in innate immunity, which plays a crucial role in the skin. They found that zinc has an important role in the inflammatory process of inflammatory diseases such as inflammatory acne, acrodermatitis enteropathica, hidradenitis suppurativa, and folliculitis decalvans [33].

Copper was another trace element in the present study. This study revealed that the serum copper levels were not different among patients in the case group with controls. El-Kholy et al. in Egypt showed that the serum copper levels were significantly higher in patients with dermatitis than in controls ($P<0.001$) [26]. However, Mashaly et al. (2014) stated that the serum copper levels in cases were significantly lower than controls [25]. Copper is transported in plasma in two forms. Copper competes with zinc for the binding site on albumin in plasma, leading to some changes in the amount of these trace elements and affecting plasma levels of both of them. Ceruloplasmin does not play a role in transporting copper into the tissue such that its transport occurs mainly by albumin.

CONCLUSION

It can be concluded, although there is no significant difference in the serum levels of Selenium, zinc, and copper in seborrheic dermatitis between cases and controls, the abnormal serum selenium level in cases was higher than that in the controls. In addition, patients with prolonged atopic dermatitis involvement showed lower serum selenium level. However, further investigation is recommended.

Acknowledgment

This paper was extracted from the dissertation of Dr. Mohammad Hosseinzadeh (registration number: 1845), which was approved by the ethics committee of research and technology, Vice Chancellor of Mazandaran University of Medical Sciences. The authors offer their special thanks to all participants and all staffs in the clinical setting.

Conflict of Interest: None declared.

REFERENCES

1. Sampaio AL, Mameri AC, Vargas TJ, et al. An Bras Dermatol. 2011; 86(6):1061-71; quiz 1072-4.
2. Stefanaki I, Katsambas A. Therapeutic update on seborrheic dermatitis. Skin Therapy Lett. 2010; 15(5):1-4.
3. Turlier V, Viode C, Durbise E, et al. Clinical and biochemical assessment of maintenance treatment in chronic recurrent seborrheic dermatitis: randomized controlled study. Dermatol Ther (Heidelb) 2014; 4(1):43-59.
4. Gary G. Optimizing treatment approaches in seborrheic dermatitis. J Clin Aesthet Dermatol. 2013; 6(2):44-9.
5. Gupta M, Mahajan VK, Mehta KS, et al. Zinc therapy in dermatology: a review. Dermatol Res Pract. 2014;2014:709152.
6. Klevay LM. Diets deficient in copper and zinc? Medical hypotheses. 1979; 5(12): 1323–1326.
7. Rayman MP. The importance of selenium to human health. Lancet. 2000; 356(9225):233-41.
8. Brenner S, Horwitz C. Possible nutrient mediators in psoriasis and seborrheic dermatitis. II. Nutrient mediators: essential fatty acids; vitamins A, E and D; vitamins B1, B2, B6, niacin and biotin; vitamin C selenium; zinc; iron. World Rev Nutr Diet. 1988;55:165-82.
9. Horn D, Barrientos A. Mitochondrial copper metabolism and delivery to cytochrome c oxidase. IUBMB Life. 2008; 60(7):421-9.
10. Schlecht U, Suresh S, Xu W, et al. A functional screen for copper homeostasis genes identifies a pharmacologically tractable cellular system. BMC Genomics. 2014; 15: 263.

11. Bukvic MZ, Kralj M, Basta-Juzbasic A, et al. Seborrheic dermatitis: an update. Acta Dermatovenerolog Croatia. 2012; 20: 98-104.
12. Akinboro AO1, Mejiuni DA, Onayemi O, et al. Serum selenium and skin diseases among Nigerians with human immunodeficiency virus/acquired immune deficiency syndrome. HIV AIDS (Auckl). 2013; 5: 215–221.
13. Brewer GJ. Wilson's disease.In: Longo B, Fauci AS, Kasper DL, et al (Eds). Harrison's principles of internal medicine. New York: McGraw-Hill; 2012. 3188-90.
14. Mashhadi M A, Bakhshipour A, Zakeri Z, et al. Reference range for zinc level in young healthy population in southeast of Iran. Health Scope. 2017; 6(1):e18181.
15. https://www.mayomedicallaboratories.com/test-catalog/.
16. Javanbakht M, Daneshpazhooh M, Chams-Davatchi C, et al. Serum selenium, zinc, and copper in early diagnosed patients with pemphigus vulgaris. Iran J Public Health. 2012; 41(5): 105–109.
17. Koohkan a., Pourpak Z., Safaralizadeh r., et al. Assessment of serum selenium level and whole blood selenium level in children with atopic dermatitis: A case-control study. Iran J Dermatol 2006; 9(2):143 -149.
18. Cheng J. Diet and asthma. Second National Conference on Asthma, Qing Dao, China, 4-7 Apr, 1997.
19. Cheng J. Role of lipid in diet and lipid metabolism disorder in pathogenesis of atopic diseases. Academic Journal Guangdong College of Pharmacy. 1998; 14(4): 295-299.
20. Devereux G. and Seaton A. Diet as a risk factor for atopy and asthma, J. Allergy Clin Immunol.2005; 115(6): 1109-1117.
21. Brown KM, Arthur JR. Selenium, selenoproteins and human health: a review. Public Health Nutr. 2001; 4(2B):593-9.
22. Kreft B, Wohlrab J, Fischer M, et al. Analysis of serum zinc level in patients with atopic dermatitis, psoriasis vulgaris and in probands with healthy skin. Hautarzt. 2000; 51(12): 931-4.
23. Mrinal G, Vikram KM, Karaninder SM, et al. Zinc therapy in dermatology: a review. Dermatol Res Pract. 2014; 1-11.
24. Toyran M, Kaymak M, Vezir E, et al. Trace element levels in children with atopic dermatitis. J Investig Allergol Clin Immunol. 2012; 22: 341-344.
25. Hon KL, Wang SS, Hung EC, et al. Serum levels of heavy metals in childhood eczema and skin diseases: friends or foes. Pediatr Allergy Immunol. 2010; 21: 831-836.
26. el-Kholy MS, Gas Allah MA, el-Shimi S, et al. Zinc and copper status in children with bronchial asthma and atopic dermatitis. J Egypt Public Health Assoc. 1990; 65(5-6): 657-68.
27. Kaymak Y, Adisen e, Erhan M, et al. Zinc levels in patients with acne vulgaris. J Turk Acad Dermatol. 2007; 1(3): 71302a.
28. Mashaly HM, Sayed KS, Mohammad FN., et al. Estimation of serum zinc and copper in Egyptian patients with pemphigus vulgaris. J Egypt Women Dermatol Soc. 2014; 11(1): 32-5.
29. Hardy G, Menendez AM, Manzanares W. Trace element supplementation in parenteral nutrition: pharmacy, posology, and monitoring guidance. Nutrition. 2009; 25(11-12):1073-84.
30. Papet I, Meunier N, Béchereau F, et al. Effect of zinc supplementation on protein metabolism in late-middle-aged men: the Zenith study. Nutrition. 2008; 24(2): 155-61.
31. Goldsmith LA, Katz SI, Gilchrest BA,et al (Eds). Fitzpatrick's dermatology in general medicine. New York: McGraw- Hill; 2012.
32. Sehgal VN, Srivastava G. Traditional/Ayurvedic pharmacotherapy for skin diseases. Skinmed. 2010; 8(5):282-4.
33. Brocard A, Dréno B. Innate immunity: a crucial target for zinc in the treatment of inflammatory dermatosis. J Eur Acad Dermatol Venereol. 2011; 25(10):1146-52.

