Ann Dermatol Vol. 25, No. 4, 2013 http://dx.doi.org/10.5021/ad.2013.25.4.405

ORIGINAL ARTICLE

Analysis of Serum Zinc and Copper Concentrations in Hair Loss

Min Seong Kil, Chul Woo Kim, Sang Seok Kim

Department of Dermatology, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea

Background: It is well known that some trace elements such as zinc and copper play a significant role in many forms of hair loss. However, the effect of zinc and copper in the pathogenesis of hair loss is still unknown. **Objective:** The purpose of this study is to evaluate the zinc and copper status in each of four types of hair loss. **Methods:** A study was carried out with 30 health controls and 312 patients who were diagnosed with alopecia areata (AA), male pattern hair loss, female pattern hair loss and telogen effluvium (TE) (2008 to 2011; Hallym University Kangdong Sacred Heart Hospital). Zinc and copper serum concentrations were evaluated between controls and each of four types of hair loss patients. **Results:** In all of the hair loss patients, the mean serum zinc was 84.33 ± 22.88, significantly lower than the control group (97.94 ± 21.05 μg/dl) ($p=0.002$), whereas the serum copper was 96.44 ± 22.62, which was not significantly different ($p=0.975$). The analysis of each group showed that all groups of hair loss had statistically lower zinc concentration, but not copper concentrations. However, the ratio of the patients with serum zinc concentration lower than 70 μg/dl was significantly high in only the AA group (odds ratio, OR 4.02; confidence interval, CI 1.13 to 14.31) and the TE group (OR 1.12; CI 1.12 to 17.68). **Conclusion:** The data led to the hypothesis of zinc metabolism disturbances playing a key role in hair loss, especially AA and TE, whereas the effect of copper on hair growth and shedding cycles still needs more study. **(Ann Dermatol 25(4) 405~409, 2013)**

-Keywords-
Alopecia, Copper, Zinc

INTRODUCTION

Zinc and copper are essential micronutrients that play an important role in the metalloenzyme process of the body. Zinc is involved in protein and nucleic acid synthesis, and plays a role in various metabolic pathways and cellular functions, whereas copper is involved in thyrosinase and lysyl oxidase, playing a part in melanin synthesis and collagen cross-liking[1]. With regard to hair loss, zinc is a potent inhibitor of hair follicle regression, and accelerates hair follicle recovery[2]. More specifically, transient zinc deficiency is a major pathogenesis in acrodermatitis enteropathica, resulting in hair loss[3]. Arguments that zinc deficiency can be a disturbing factor for the growth of hair have been emerging since the 1990s[4,5]. There is also a contradicting argument that there exists no relationship between zinc and hair loss[6]. Even though a few studies have reported that zinc deficiency has correlations with alopecia areata (AA) and telogen effluvium (TE), no studies have mentioned the relation between zinc and androgenic alopecia so far[7]. Additionally, not many studies have been conducted on the relationship between copper and hair loss. Most studies have reported that a decreased concentration of copper was not observed in AA, although the relationship between copper and other types of hair loss was not studied at all[5]. Therefore, in this study, an attempt is made to investigate the deficiency of zinc and copper by hair loss type, and their relationship is examined.

Received June 11, 2012, Revised July 23, 2012, Accepted for publication August 19, 2012

Corresponding author: Sang Seok Kim, Department of Dermatology, Hallym University Kangdong Sacred Heart Hospital, 150 Seongan-ro, Gangdong-gu, Seoul 134-701, Korea. Tel: 82-2-2224-2285, Fax: 82-2-474-7913, E-mail: kimss@hallym.or.kr

MATERIALS AND METHODS

Patients and controls

The study was carried out with outpatients visiting Hallym University Kangdong Sacred Heart Hospital (Seoul, Korea) for hair loss as their main complaint from 2008 to 2011. A total of 312 hair loss patients were enrolled in this study, and 32 normal people without any underlying disease or alopecia were selected as a control group. Those who have taken supplements containing zinc or copper for the past 6 months and those who have had treatment from other hospitals for hair loss as their main complaints were excluded from the patient and control groups. In order to find the serum zinc and copper concentration for different hair loss types, the patient group was divided into 4 groups: the AA group (group 1) was defined as a patient group with exclamation-point- hairs and circular hair loss patch, with no evidence of infection. The male pattern hair loss group (MPHL; group 2) was defined as a patient group with Hamilton-Norwood classification[8] grade 2 and above. The female pattern hair loss group (FPHL; group 3) was defined as a patient group with Ludwig[9] grade 1 and above. The TE group (group 4) was defined as a patient group who had mental or physical stress for the past 2 to 4 months and was positive in hair pull tests. The classification of patients was made by two dermatologists, and 10 patients who did not meet the criteria or who met two definitions simultaneously were excluded. Finally, the past medical history and present illnesses were recorded in detail for the 302 hair loss patients and 32 people in the normal control group. The study was approved by the Ethics Committee of Hallym University Kangdong Sacred Heart Hospital (KDIRB No.12-1-006).

Biochemical analysis

Venous blood was sampled before meals. The serum zinc and copper concentrations were determined using inductively coupled plasma mass spectrometry (ICP-MS, Elan DRC-e; PerkinElmer Inc., Waltham, MA, USA).

Statistical analysis

The results were expressed as means±standard deviations. In order to compare the serum zinc and copper concentration of the 4 hair loss patient groups with those of the control group, the statistical significance among the groups was investigated by comparing the means using the Student's t-test. In addition, each group was divided into patients with normal blood concentration and patients with lower concentration than normal, and then compared with the control group. The ratios were examined for the statistical significance using Fisher's exact test. Furthermore, to identify the confounding variables, the correlation between zinc and copper concentration, and that between zinc, copper, and age were checked using Pearson's correlation. A p-value of <0.05 was considered statistically significant (IBM SPSS Statistics 19.0; IBM Co., Armonk, NY, USA).

RESULTS

Ninety-four patients with AA (group 1) and 84 patients with MPHL (group 2) were identified, and 77 patients were diagnosed with FPHL (group 3) and 47 patients were diagnosed with TE (group 4). The mean ages of the patient group and control group were 36.61±13.81 and 33.50±10.50, respectively, and other demographic data are described in Table 1. In the normal control group, the mean serum zinc was 97.94±21.05 μg/dl, and the mean serum copper was 96.29±28.84 μg/dl. In all the hair loss patients, the mean serum zinc was 84.33±22.88, which was significantly lower than that of the control group ($p=0.002$), whereas the serum copper was 96.44±22.62, which was not significantly different ($p=0.975$). The hair loss patient groups and the control were individually compared. In each hair loss group, the serum zinc concentration was significantly lower than that of the control, but the serum copper concentration was not significantly different (Table 2). The hair loss patients were divided based on the lower normal limit of 70 μg/dl of

Table 1. The demographic data of 302 hair loss patients and 32 control groups

Variable	Hair loss patient group					Control group
	Group 1 (AA)	Group 2 (MPHL)	Group 3 (FPHL)	Group 4 (TE)	Total	
Patient	94 (31.1)	84 (27.8)	77 (25.5)	47 (15.6)	302 (100.0)	32
Age (yr)	37.13±14.86	33.23±9.68	37.70±13.51	39.85±17.24	36.61±13.81	33.50±10.50
Total (male/female)	94 (44/50)	84 (84/0)	77 (0/77)	47 (11/36)	302 (139/163)	32 (14/18)

Values are presented as number (%) or mean±standard deviation or number (number). AA: alopecia areata, MPHL: male pattern hair loss, FPHL: female pattern hair loss, TE: telogen effluvium.

Table 2. Comparison of serum zinc and copper concentration in hair loss patients and control groups

Variable	Hair loss patient group								Control group
	Group 1 (AA)	*p*-value*	Group 2 (MPHL)	*p*-value	Group 3 (FPHL)	*p*-value	Group 4 (TE)	*p*-value	
Zinc	84.96±24.25	0.01	87.74±21.20	0.03	79.61±19.39	0.01	84.65±27.23	0.03	97.94±21.05
Copper	98.11±20.17	0.74	86.75±13.57	0.09	104.07±26.68	0.21	99.61±27.67	0.67	96.29±28.84

Values are presented as mean±standard deviation. AA: alopecia areata, MPHL: male pattern hair loss, FPHL: female pattern hair loss, TE: telogen effluvium. *Student's t-test.

Table 3. Statistic analysis of zinc for patient proportion of control and hair loss patients

Variable	Hair loss patient group							
	Group 1 (AA)		Group 2 (MPHL)		Group 3 (FPHL)		Group 4 (TE)	
	OR (CI)	*p*-value*	OR (CI)	*p*-value	OR (CI)	*p*-value	OR (CI)	*p*-value
Zinc	4.02 (1.13～14.31)	0.03	2.32 (0.63～8.56)	0.27	3.44 (0.94～12.54)	0.07	4.65 (1.22～17.68)	0.03

AA: alopecia areata, MPHL: male pattern hair loss, FPHL: female pattern hair loss, TE: telogen effluvium, OR: odds ratio, CI: confidence interval. *Fisher's exact test.

zinc, and their ratios were compared with those of the control group. The analysis of each group showed that the ratio of the patients with serum zinc concentration lower than 70 μg/dl was significantly high in only the AA group (odds ratio [OR] 4.02; confidence interval [CI] 1.13 to 14.31) and TE group (OR 4.65; CI 1.12 to 17.68) (Table 3). The correlation analysis of zinc, copper, and age for all subjects showed that there was no correlation between zinc and copper ($p=0.325$), and the correlations between zinc and age and between copper and age were not statistically significant (zinc: $p=0.083$, copper: $p=0.104$).

DISCUSSION

As a cofactor of metalloenzyme, zinc is involved in almost every metabolism occurring in the body, and affects hair growth. It also plays an important functional role in hair follicle cycling[2]. A recent study revealed that copper plays a crucial role in the differentiation and proliferation of dermal papilla cells, which are specialized fibroblasts that play an important role in the development of hair follicles[10]. Even though zinc and copper are theoretically considered to play certain roles in the pathogenesis of hair loss, clinical research has shown opposing views on the relationship. In a recent study, AA patients whose serum zinc was lower than 70 μg/dl were administered zinc gluconate 50 mg every day for 12 weeks. The findings showed that the serum zinc concentration was elevated by 27.6 μg/dl on average, and 60% of the patients administered zinc showed a clinically therapeutic effect[11]. Another study examined the blood and urine samples of children with alopecia, and found that the zinc concentrations in blood and urine were lower than in the normal group[12]. However, another study found that even though there was a difference in serum zinc and copper concentrations between hair loss patients and normal individuals, there was no statistical significance. A similar study also found that there was no difference in zinc and copper, but the concentration of serum magnesium was quite higher[13,14]. Although it is likely that there is a close theoretical relationship between serum copper and hair loss, as with zinc, more studies have shown contradictory results. In a study conducted on Koreans consisting of a control group of 10 normal people and a group of 30 AA patients, the serum zinc concentration was significantly low in the patients group, but the serum copper concentration was a little higher in the patients group without any statistical significance[5]. In a study conducted in Indonesia that measured serum zinc, copper, and magnesium for 50 AA patients and 50 people in a normal control group, copper and magnesium levels did not show any significant differences, in contrast to the zinc levels[4]. However, there was a study that indicated the serum copper concentration in alopecia universalis was lower in the patient group[13].

The findings of this study indicate that the serum zinc concentration of the hair loss patients group was generally lower than that of the control group, and the serum copper concentration was not significantly different from that of the control group. The mean serum zinc concentration of the hair loss patients group was 84.33 μg/dl, which was lower than the normal group by 13 μg/dl,

indicating a statistical difference from the control group. However, this value is within the range of the reference value of the measuring equipment (70 to 130 μg/dl), and is higher than the concentration of 70 μg/dl, at which zinc supplementation begins. The patients group was therefore divided into a group with low zinc concentration and a group with normal zinc concentration based on the lower normal limit of 70 μg/dl within each hair loss group. The ratios with the control group were then compared. From this comparison, it was statistically confirmed that there were more patients with low serum zinc in the AA group and TE group than in the normal group. This finding is similar to those of the studies mentioned earlier, where the zinc concentration was low in the AA groups[6].

Zinc and copper are absorbed in the small intestine by the specialized ZnT (zinc transporter) channel, as well as by a common divalent cationic transporter[1,15,16]. Therefore, it can be assumed that if the levels of either of the two are excessive, they can affect the serum concentration by competing with each other, which can lead to erroneous results. Accordingly, the correlation between serum copper and zinc was tested using Pearson's correlation, but no significant correlation was found. The correlation of zinc and copper with age was also tested, considering that the concentration of zinc and copper varies by age, but a statistical significance was not found, confirming that the variables are not confounding variables.

The exact mechanism of how zinc affects hair loss has not been found so far, although zinc-related metalloenzymes may have the potential to regulate hair growth. Zinc is a component of zinc finger motifs for many transcription factors, which regulate hair growth through hedgehog signaling, and is a catagen inhibitor via its inhibitory action on apoptosis-related endonucleases[17-19]. Paus et al.[20] reported that zinc is a potent dose-dependent immunomodulator of hair follicles. It is also a potent inhibitor of hair follicle regression and accelerates hair follicle recovery[2]. Therefore, zinc metalloenzymes may be necessary for hair growth rather than the components of hair itself. Many other studies have also verified the correlation between serum zinc concentration and hair loss[4,11-14].

Of the hair loss groups, the ratio of the patients with low serum zinc concentration was significantly lower in the AA and TE groups than in the control group. It seems that the serum zinc concentration of the two groups affected the pathogenesis characteristic of hair loss, which has a fast onset. In the FPHL and MPHL groups, the serum zinc concentration was lower than in the control group, but it was in the normal serum zinc range. In addition, the ratio of the patients with low serum zinc concentration was not statistically significant. This result can be attributed to the fact that the abrupt zinc deficiency in the AA and TE, where the onset is acute, affected the pathogenesis, in contrast to the pattern hair loss, which slowly develops by hormonal changes such as the aging process. Since the serum copper concentration did not show any significant difference in the value and the patient ratio with the control group in all 4 groups, it is considered that there is no direct relationship between serum copper concentration and hair loss, which is consistent with other studies. Further studies are needed[4,6,11-14].

The findings of this study are different from other studies, in that the hair loss types were divided into AA, MPHL, FPHL, and TE, and the serum zinc and copper concentrations of each type were compared with those of the control, rather than focusing on the entire hair loss group or a specific patient group. A literature review shows that no studies, excluding the ones with general hair loss or AA, have been conducted on the relationship of serum zinc and copper concentration with other types of hair loss, other than TE[7,19].

The issue of hair loss is an important part of the dermatology field, and it is gradually expanding its scope. Based on this research, it is recommended that the zinc concentration, rather than copper concentration, be measured, and that zinc be supplied if the concentration of zinc is low. Even though the present study did not attempt to measure the zinc and copper concentration in the hair itself, large-scale of studies on the zinc concentration of both serum and hair are needed for zinc supplementation in the future.

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