Studying the relationship between serum Zinc and Copper levels in Alopecia Areata patients with Controls in India

[1]KRISHNA CHAITANYA PALETI, [2]Dr.SHREYANSH TIWARI, [3]Dr.PAYASVI SACHDEVA

[1] PhD Scholar in Medical Biochemistry, Department of Biochemistry, LNMC &J. K Hospital, LNCT University, Bhopal, India,
[2]Senior Resident, Department of Dermatology, LNMC &J. K Hospital, LNCT University, Bhopal, India,
[3] Associate Professor, Department of Biochemistry, LNMC &J. K Hospital, LNCT University, Bhopal, India

***Abstract*— Introduction: Background As co-factors of metalloenzymes, zinc (Zn) and copper (Cu) have a significant impact on practically every metabolic process that occurs in bodily organs, including the metabolism of the skin.**

OBJECTIVE: This study looked at the levels of zinc and copper in people with alopecia areata.

METHODS Using atomic absorption spectrometry, we examined the zinc and copper levels in the serum of 150 alopecia areata patients and 150 healthy people. We also looked into the relevance of the difference in serum levels of the two metals.

RESULTS When compared to healthy controls, alopecia areata patients had considerably reduced serum zinc levels. In comparison to healthy controls, alopecia areata patients had somewhat lower serum copper levels. Cu and Zn values were marginally less in alopecia areata patients than in unaffected controls. Their variations, however, were highly statistically significant.

CONCLUSION
We suggest that serum Cu & Zn assay should be included in the chemical assessment of patients with alopecia areata.

***Index Terms*—Copper, Zinc, Fully automated Analyzer, Alopecia Areata , p-value** *(key words)*

I. INTRODUCTION (HEADING 1)

Alopecia refers to any form of hair loss, thinning, or baldness in any area of the body with hair. Hair loss is a natural part of the hair-growth cycle. It is not a life-threatening illness, but for the majority of people, it has psychological impacts.
The two types of alopecia are localized and diffuse [22]. There are two types of focal alopecia: those that leave scars and those that don't. Alopecia areata is an example of hair loss that doesn't leave scars. The loss of hair might appear as a single oval patch or as several patches. Scarring alopecia is an uncommon condition that is typically brought on by discoid lupus erythematosus. The three types of diffuse alopecia are telogen effluvium, female pattern, and male pattern[2]. Androgenic alopecia, which affects both men and women, results from an abnormal metabolism of androgen.[3]

Hair density loss and thinning over the crown and frontal areas are characteristics of female pattern alopecia. 4. Trace elements play significant functional roles in hair follicles and are necessary cofactors for numerous enzymes. The trace elements like as zinc ($Zn2+$) and copper ($Cu2+$) have a significantly important role in the growth and development of hair5 and they perform various catalytic, structural, and regulatory roles of human body.[18]

An vital trace element with numerous functions in human nutrition is zinc (Zn2+). Zn2+ aids in hair follicle healing and is necessary for functional hair follicle activity. It keeps the oil-secreting glands that are connected to the hair follicles, which retain sebum and stop hair from drying out7,8. In fact, a Zn2+ deficit causes the protein structure of the hair follicle to deteriorate. This follicle weakening results in hair loss and shedding. Zn2+ deficiency affects the creation of DNA and RNA, which is necessary for regular hair follicle cell division and the developmental stage of hair growth [9].

Numerous biological and physiological processes involve copper (Cu2+). Copper expands hair follicles and results in thicker hair. Additionally, Cu2+ inhibits the 5-Alpha Reductase enzyme, which is crucial for turning testosterone into dihydrotestosterone (DHT). DHT is produced in excess when Cu2+ is deficient. Male pattern alopecia is primarily caused by dihydrotestosterone [10,11]. At the molecular level, trace elements are active at any very low concentration.

Thus, a trace element shortage of a modest amount may result in alopecia. Serum Zn2+ and Cu2+ levels in patients with hair loss were studied by many researchers and organizations from various nations. Since there aren't many published studies on this subject in India, it's unclear how serious this problem is among the populace there. The goal of the current study is to evaluate serum Zn2+ and Cu2+ levels and determine whether they are correlated with alopecia. [25]

Materials & Methods:

Between November 2019 and November 2020, the Department of Dermatology in Bhopal, India, worked with Biochemistry, LN Medical College and Research Center, and JK Hospital to perform this observational study. The LNCT University's Research Review and Ethical Committee gave the protocol their okay. The study comprised 150 participants with both localised and diffuse hair loss, ranging in age from 18 to 45 years, and 150 age-matched healthy participants served as the control group. Patients were chosen from the dermatology department in cooperation with the biochemistry department, LN Medical College and Research Center, and JK Hospital, Bhopal. Patients with active Alopecia as well as those with chronic illnesses were not allowed to be chosen as subjects.

Following subject selection, each participant received a thorough explanation of the study's nature, purpose, and advantages before providing their written consent. A thorough family and medical history was taken before testing the blood pressure. The subjects were anthropometrically measured. A data schedule contained all the information. 5ml of venous blood were drawn from the ante-cubital vein using a disposable 10cc test tube under aseptic conditions. The blood was then allowed to clot for 30 minutes in the tilted position before being centrifuged for 15 minutes at a speed of 3000 rpm. The separated supernatant serum was then aliquoted, collected in a labelled Eppendorf tube, and kept at -20°C until analysis. Using a fully automated analyzer, the levels of serum zinc and copper were estimated.

Statistics used:

The **statistical package SPSS (Statistical Package for Social Sciences)** Version 20 was used to conduct the statistical analysis. The mean and standard deviation (mean and SD) were used to represent the results. Both the Chi-square test and the unpaired Student's t test were conducted as necessary.

Results:

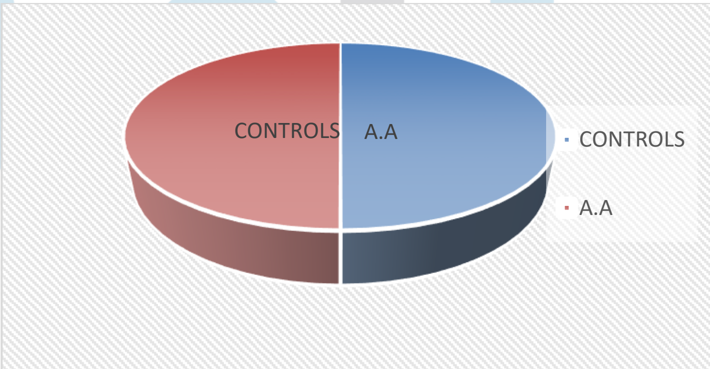
II. A total of 300(150 cases of AA +150 controls were included Copper with mean± SD are given in the Table no.1. The two groups were comparable (P<0.0001), (P<0.0001).

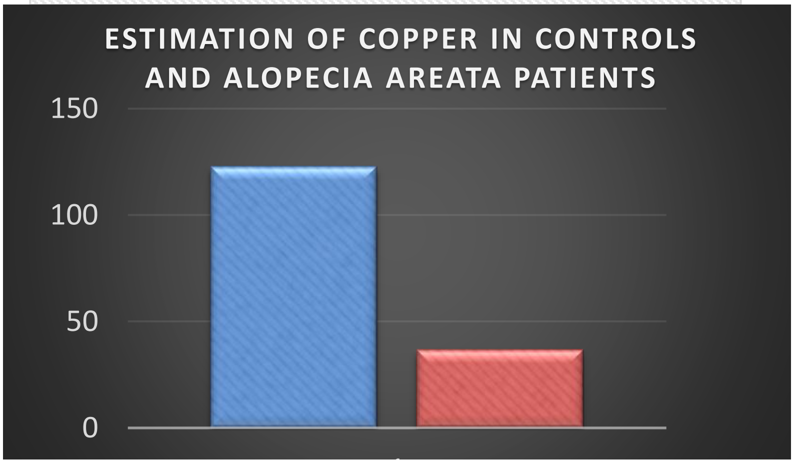
III. Copper levels in controls is 122.75+22.64 µg/dl

IV. Copper levels in AA is 36.65 ± 15.00 µg/dl

V. The difference in the values Serum Copper parameter in respect of these groups was highly statistically significant (P<0.0001*)

PARAMETERS	CONTROLS	ALOPECIA AREATA PATIENTS
	MEAN ± SD	MEAN ± SD
Copper(µg/dl)	122.75 + 22.64	36.65 + 15.00
Zinc(µg/dl)	108.66 + 26.31	31.007 + 12.745





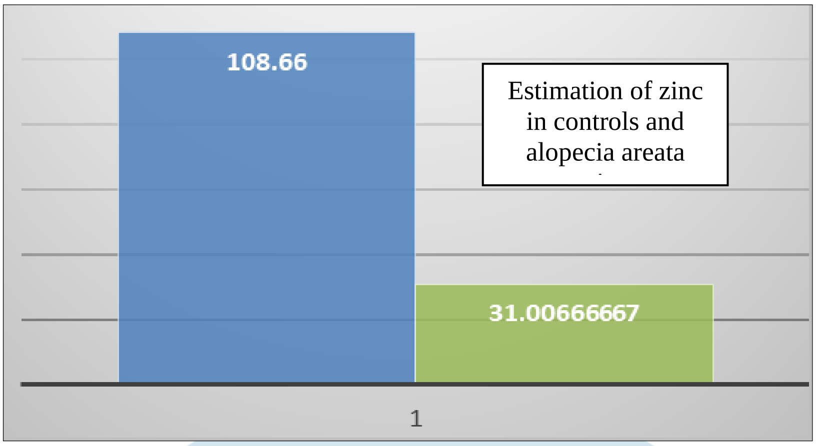


Table-2: This table shows the Critical Value, T-value and P-Value

DISCUSSION

In the current study, alopecia patients' mean blood zinc and copper levels were lower than those of controls. Again, alopecia patients' blood Zn2+ and Cu2+ levels were found to be considerably lower than those of controls' male and female counterparts. Similar outcomes may be seen in [6, 7], and [10.] Zn2+ and Cu2+ levels in a group of healthy people are reported to be **108.66 + 26.31** and **122.75 + 22.64 µg/dl** respectively. However, in this study, Zn2+ and Cu2+ concentrations were lower in alopecia, with respective values of **31.007 + 12.745** and **36.65 + 15.00 µg/dl**, which are attributable to dietary deficiencies and environmental pollution.

According to a literature study, zinc functions as a coenzyme during the four cell cycle phases of G1, S, G2, and mitosis. RNA and protein synthesis take place in the G1 stage, and cell size rises. In the S stage, DNA is created. Cell division and nuclear division both take place at the G2 stage of mitosis. Zinc serves as a cofactor in each of these metabolic processes. Due to zinc deficiency, hair follicle cell division is arrested, which results in hair loss, as DNA and RNA are required for hair follicle cell division and optimum hair development during the anagen stage of the hair growth cycle.

Due to excessive DHT production and suppression of dermal fibroblast growth, copper ion deficiency causes hair loss. The 5-alpha reductase enzyme converts testosterone into DHT. Strong inhibitors of this 5-alpha reductase enzyme, copper ions prevent the production of DHT. DHT is produced in excess in copper ion shortage and binds to androgen receptors on hair follicles to create a hormone receptor complex. The anagen and telogen phases of the follicle are gradually lengthened and the androgen dependent gene transcription is promoted by this complex. The end effect is a reduction in the size of the hair follicle during the anagen phase, which causes the hair to thin down as it grows. Vascular endothelial growth factor is produced by dermal fibroblasts (VEGF).

This cutaneous fibroblast is stimulated by copper ions, which helps new capillary development. This multiplication does not happen when there is a copper shortage. As a result, the development of hair follicles and reduced blood flow result in insufficient hair production. 3,11, 12

Conclusion:

According to the study's findings, alopecia may be linked to reduced blood zinc and copper levels regardless of gender. These minerals may be involved in the pathophysiology of AA based on their roles in anti-oxidant defence and nucleotide synthesis. There are currently few research on serum levels and supplementation in AA patients, therefore it is impossible to draw any conclusions about their function in the onset, progression, and management of AA.

Parameter	**Critical Value**	**t-value**	**P-value**	**Statistically**
Copper(µg/dl)	**1.968**	**38.8145**	**P<0.0001***	**extremely statistically significant**
Zinc(µg/dl)	1.972	32.5237	P<0.0001*	extremely statistically significant

Therefore, assessment of serum Zn2+ and Cu2+ levels may be useful for effective alopecia care.

References:

1) Roem NR, Tarib F, NN, Wasodo, Patellongi I, Bukhair A, Nafie NL.Hair's zinc level onandrogenic alopecia. Am J of Clin and Exp Med 2016;4(5):129- 33.
2) Dinh QQ and Sinclair R. Female pattern hair loss: Current treatmentconcepts. Clin Interv in Ag 2007;2(2):189-99.

3) Dastgheib L, Mostafavi-Pour Z, Abdoraazagh AA, Khoshdel Z, SadatiMS,Ahrari I, AhrariS, GhavipishehM.Comparison of Zn, Cu and Fecontent in hair and serum in alopeciaareata patients withnormal group. Dermatol Res and pract 2014; 2014: 1-5.
4) El- Ashmawy AA andKhedr AM. Some trace elements level in alopeciaareata. Egypt Dermatol Online J 2013;9(1): 1-11.
5) Hamad WAM, Said AF, El Hamid AAA.Role of some trace elements inthepathogenesisoftelogen 24 J Bangladesh Soc Physiol. 2019, June; 14(1): 21-25 Zn & Cu in Alopecia Rahman & Akhter 25 effluvium in Egyptian female. Egypt Women Dermatol Soc 2010; 7: 44-48.
6) Kil MS, Kim CW, Kim SS. Analysis of serum zinc and copper concentrations in hair loss. Ann Dermatol 2013; 25 (4): 405-09.
7) Falchuk KH, Fawcett DW, Vallee BL. Role of zinc in cell division of Euglena Gracilis. J Cell Sci 1975; 17: 57-78.
8) Lee SY, Nam KS, Seo YW, Lee SJ, Chung H. Analysis of serum zinc and copper levels in alopecia areata. Ann of Dermatol 1997; 9(4): 239-41.
9) PickartL. Improving hair growth with skin remodeling copper peptides. Dermatol 2004;3(6).
10) Pyo HK, Yoo HG, Won CH, Lee SH, Kang YJ, Eun HC, Cho KH, Kim KH. The effect of Tripeptidecopper complex on human hair growth in vitro. Arch Pharm Res 2007; 30(7):834-39.
11) Kasumagić-Halilović E. Thyroid autoimmunity in patients with alopecia areata. Acta Dermatovenerol Croat. 2008;16(3):123–5.
12) Baars MP, Greebe RJ, Pop VJ. High prevalence of thyroid peroxidase antibodies in patients with alopecia areata. J Eur Acad Dermatol Venereol. 2013; 27(1): e137-9.
13) Rahnama Z, Farajzadeh S, Mohamamdi S, et al. Prevalence of thyroid disorders in patients with alopecia areata. JPAD. 2016;24(2):246-50.
14) Dilas LT, Icin T, Paro JN, et al. Autoimmune thyroid disease and other non-endocrine autoimmune diseases. Med Pregl. 2011;64(3-4):183–7.
15) Alkhalifah A, Alsantali A, Wang E, et al. Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. J Am Acad Dermatol. 2010;62(2):177–88.
16) Guo H, Cheng Y, Shapiro J, et al. The role of lymphocytes in the development and treatment of alopecia areata. Expert Rev Clin Immunol. 2015;11(12):1335-51.
17) Gilhar A, Etzioni A, Paus R. Alopecia areata. N Engl J Med. 2012;366(16):1515–25.
18) Huang KP, Mullangi S, Guo Y, et al. Autoimmune, atopic, and mental health comorbid conditions associated with alopecia areata in the United States. JAMA Dermatol. 2013;149(7):789–94.
19) Abdel Fattah NS, Atef MM, Al-Qaradaghi SM. Evaluation of serum zinc level in patients with newly diagnosed and resistant alopecia areata. Int J Dermatol. 2016;55(1):24-9.
20) Ogawa Y, Kinoshita M, Shimada S, et al. Zinc and skin diisorders. Nutrients. 2018;10(2). pii: E199. 11. Jin W, Zheng H, Shan B, et al. Changes of serum trace elements level in patients with alopecia areata: A metaanalysis. J Dermatol. 2017;4
21) Van Etten E, Decallonne B, Verlinden L, et al. Analogs of 1alpha, 25-dihydroxyvitamin D3 as pluripotent immunomodulators. J Cell Biochem. 2003;88(2):223-6.
22) Hansen KE, Johnson MG. An update on vitamin D for clinicians. Curr Opin Endocrinol Diabetes Obes. 2016;23(6):440-4.
23) Erpolat S, Sarifakioglu E, Ayyildiz A. 25-hydroxyvitamin D status in patients with alopecia areata. Postepy Dermatol Alergol. 2017;34:248-52.
24) Gade VKV, Mony A, Munisamy M, et al. An investigation of vitamin D status in alopecia areata. Clin Exp Med. 2018 Nov;18(4):577-584.
25) Bakry OA, El Farargy SM, El Shafiee MK, et al. Serum vitamin D in patients with alopecia areata. Indian Dermatol Online J. 2016;7(5):371-7.
26) Omidian M, Salehi AR, Ahmadi M. Serum zinc levels in patients with alopecia areata: a case-control study. Iran J Dermatol. 2006;35(9): 64-5.
27) Amirnia M, Sinafar S, Sinafar H, et al. Assessment of zinc and copper contents in the hair and serum and also superoxide dismutase, glutathion peroxidase and malondi aldehyde in serum in androgenetic alopecia and alopecia areata. Life Sci J. 2013;10:204-9.
28) Nassiri S, Saffarian Z, Younespour S. Association of vitamin D level with alopecia areata. Iran J Dermatol. 2013;16(1):1-5. 20. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81.
29) Aiempanakit K, Chiratikarnwong K, Chuaprapaisilp T, et al. A study of plasma zinc levels in Thais with alopecia areata. J Med Assoc Thai. 2016;99(7):823-7.
30) Bhat YJ, Manzoor S, Khan AR, et al. Trace element levels in alopecia areata. Indian J Dermatol Venereol Leprol. 2009;75(1):29-31.
31) Dastgheib L, Mostafavi-Pour Z, Abdorazagh AA, et al. Comparison of zn, cu, and fe content in hair and serum in alopecia areata patients with normal group. Dermatol Res Pract. 2014;2014: 784863.
32) Mussalo-Rauhamaa H, Lakomaa EL, Kianto U, et al. Element concentrations in serum, erythrocytes, hair and urine of alopecia patients. Acta Dermato-Venereologica. 1986;66(2):103–9.
33) Bhat YJ, Latif I, Malik R, et al. Vitamin D level in alopecia areata. Indian J Dermatol. 2017;62(4):407-10.
34) Ghafoor R, Anwar MI. Vitamin D deficiency in alopecia areata. J Coll Physicians Surg Pak. 2017;27 :200-2.
35) Aksu Cerman A, Sarikaya Solak S, Kivanc Altunay I. Vitamin D deficiency in alopecia areata. Br J Dermatol. 2014;170(6):1299-304