ROLE OF SERUM ZINC AND COPPER AND ZINC/ COPPER RATIO IN ALOPECIA AREATA

Ashwaq Najjem Elldin Al- Jaff

Department of clinical pharmacy

College of pharmacy, university of Baghdad, Baghdad, Iraq

Received: 02.03.2002 **Accepted: 23.10.2002**

ABSTRACT:

Alopecia areata is considered as a major health problem, its importance is attributed to its recent increased incidence in our population. Till now, there is no exact cause for alopecia areata although researchers thought it's an autoimmune disease.

This clinical study was designed to evaluate the role of trace elements (zinc and copper) in patients with alopecia areata. Twenty patients were diagnosed as having alopecia areata with an age range (10-40 years) were involved in this study. Normal subjects of the same age group were also evaluated as control. The level of serum Zn and Cu were measured by flame atomic absorption spectrophotometry in both control and patient group. And the ratio of Zn/Cu was also estimated.

The results of patients group revealed that serum Zn level was significantly lower than those of control ($p<0.001$), while serum Cu was significantly higher than that of control group ($p=0.002$). Furthermore, Zn/Cu ratio of patients group was significantly lower than that of control subjects ($p<0.001$). These results suggest the possible role of Zn and Cu level in alopecia areata. In addition to that the utility of measuring Zn/ Cu ratios for the diagnosis of the disease over that of determining the serum level of Zn or Cu alone since this ratio clearly reflects the severity of the progress.

الخلاصة :

يعتبر مرض داء الصلع من المشاكل الصحية الكبرى، وتأتي أهميته من خلال سرعة انتشار حدوثه مؤخرا في مجتمعنا. إلى وقتنا هذا لا يوجد سبب حقيقي مثبت لمرض داء الصلع بالرغم من إن معظم الباحثين يعزون السبب إلى الجهاز المناعي للجسم. إن هذه الدراسة السريرية صممت لتقييم دور العناصر النادرة (الزنك والنحاس) في مصل الدم في مرضى المصابين بداء الصلع. عشرين مريضا شخصوا بإصابتهم بداء الصلع وتتراوح أعمارهم من (١٠-٤٠ عاما). وأشخاص من الأصحاء المقاربين لأعمار المرضى شملوا في هذه الدراسة وقد مثلوا العينة الضابطة. تم قياس مستوى العناصر النادرة (الزنك والنحاس) في مصل الدم في كل من المرضى والأصحاء، بالإضافة إلى تحديد نسبة عنصر الزنك إلى النحاس. أظهرت نتائج هذه الدراسة انخفاض ملحوظ في مستوى الزنك لمرضى المصابين بداء الصلع مقارنة بالأصحاء، بينما مستوى النحاس أعلى بصورة ملحوظة منهُ في الأصحاء. بالإضافة لذلك أن نسبة الزنك للنحاس اقل لمرضى داء الصلع مقارنة بالأصحاء، تبعاً لذلك يمكن الاعتماد على هذه النسبة في تشخيص المرض بدلاً من الاعتماد على نسبة كل من الزنك أو النحاس كلُ على حدة حيث إن هذه النسبة تعكس حدة المرض. وتبين هذه النتائج احتمالية دور العناصر النادرة في داء الصلع.

INTRODUCTION

****

Alopecia areata (A.A) simply is sudden patchy hair loss [1]. The exact cause of AA is unknown, however researchers believe it is an autoimmune condition [l, 2,3,4]. Recently, Al-Jaff et al [5], reported a significant increase in basal malondialdehyde (MDA) level, as a strong biomarker of lipid peroxidation, and a significant decrease in glutathione (GSH) level, as a major antioxidant, in erythrocytes of alopecic patients compared to their normal control, suggesting the role of oxidative stress in the pathogenesis of alopecia areata.

Zinc (Zn), an essential trace element, is important in numerous critical biochemical processes since it's a cofactor in about 200 metalloenzymes including Cu/Zn-superoxide dismutase, a critical cytoplasmic antioxidant enzyme[6].

Zinc may stimulate the immune system, possibly through its antioxidant properties and protect sulfhydryl groups (-SH) from oxidation [6]. Also, Zinc maybe important in stimulation of NADPH oxidase since it's a cofactor for phospholipase A_2 and phospholipase C**,** as well as in the stabilization of arachidonic acid against iron-catalyzed oxidation, among others [7], including ATPase, which is important in cell membrane fluidity[8,9].

Since Zn is an essential component of Cu**,** Zn-SOD, the deficiency of Zn could induce an increase in tissue oxidative damage. Zn deficiency is associated with an increase of Cu and Fe due to the antagonistic relationships between these metals [10]. Also, Zn deficiency resulting from a failure in absorption gives rise to alopecia areata and Cutaneous changes in acrodermatitis enteropathica[6].

Copper (Cu) could be a potential inducer of LDL oxidation**.** On one hand, Cu has the ability to oxidize LDL in vitro [11]. On the other hand, it is a constituent of Cu, Zn-SOD which is involved in preventing oxidative injury. In addition, caeruloplasmin, a multifunctional protein which contains most of the Cu in blood, is thought to possess antioxidant functions, which could be beneficial in resisting disease. In contrast, high caeruloplasmin levels have been speculated to be a risk factor for atherosclerosis, based on its pro-oxidant properties [12].

Therefore, the present study was designed to investigate the extent to which Zn and Cu levels were attributed in serum of alopecic patients.

SUBJECTS AND METHODS

****

1- Subjects

A-Patients: twenty patients aged 10-40 years (9 females**,** 11 males) with alopecia areata were included in this study. Some patients were selected from various specialty dermatological centers and others from dermatology private clinics in Baghdad.

B-Study group: comprised of total of 40 subjects, 20 normal controls and 20 cases with alopecia areata. Patients involved in this study were under dermatologist supervision who determined the severity of the disease according to number of the patches they have and according to progression of disease [2] they were non-smokers, non-alcoholics and free from apparent other diseases. The duration of disease ranged from (20 day- 18 year).

C-Samples: venous blood samples were collected from alopecic patients as well as from controls using plastic disposable syringes with 22*1 1/4 G, hypodermic needles. Serum samples were stored at -20 C° until the analysis was performed.

2-METHODS

Serum Zn and Cu were measured by flame atomic absorption spectrophotometry (F.A.A.S) Shimadzu AA-670/ GU-7. Dilution of the serum was made by deionized water according to the sensitivity of the (F.A.A.S) and as mentioned in the manual instruction of the manufacturer in order to avoid the viscosity and to decrease the interference of the protein [13].

The statistical significance of the difference in mean was tested by Student t test.

RESULTS

****

The serum zinc and copper concentrations of alopecic patients and control subjects were presented in (Table 1). The mean zinc concentration was significantly lower in patients with alopecia areata as compared to the control group ($p < 0.001$). However, the serum copper concentration in alopecic patients was significantly higher than that of controls ($p=0.002$) (Table 1). The serum zinc to copper ratio of alopecic patients was significantly higher than that of controls ($p<0.001$), (Table l). In this regard, further analysis of the data revealed that Zn/Cu ratio was lowest in those patients with severe progression (i.e., with more than 10 patches) compared to control and to those with mild severity of the disease (Table 2).

Table 1: Case- control differences in mean of certain outcome variables.

	Control N=20	**Cases N=20**	**P value**
Zinc concentration (mcg/dl)	94.20±1.92	58 .40 ±4.30	< 0.001
Copper concentration (mcg/dl)	75.60±3.14	96.10 ±4.79	< 0.002
Zn/Cu ratio	1.30 ±0.50	0.61 ±0.40	< 0.001

Values are represented as mean ± SE

Table 2: Zn/Cu ratio in control subjects and patients with alopecia areata with variable severities

		Alopecic patients (Severity)		
	Control N=20	**Mild N=7**	**Moderate N=7**	**Severe N=6**
Number of patches	No patches	1-2	3-5	>6
Zn/Cu ratio	1.3 ±0.09	0.73 ± 0.027*	0.59 ±0.09*	0.54 ±0.08* #

Values are represented as mean ± SE.

*** Significantly different from control ($p< 0.001$).**

 # Significantly different from alopecia areata patients with mild severity ($p<0.05$).

Note: Severity of disease was performed by a dermalogist on the basis of the number of patches, and of progression of disease [2].

DISCUSSION

****

The present study showed a significant decline in serum Zn level in Alopecic patients (Table 1), a fact that agree with that of Tasaki et al [14] who, in addition to alopecia areata, reported comparable decreases in Zn levels in serum of patients with other skin diseases (e.g. bullous pemphigoid and decubitus ulcer). Factors responsible for this decline in Zn levels are unknown**.** However, decreases in plasma Zn content has been attributed to reductions in intake or absorption in small intestine, or to increases in urinary loss, or to redistribution from plasma to tissue [l5]. Furthermore, tissues with high cellular turnover (e.g. skin**)** are characteristically affected by Zn deficiency calling the attention to the possibility that some dermatological manifestations, such as alopecia areata, may be attributed to Zn deficiency [15].

Zn plays an important role in achieving proper function of the immune system in the body. Also, it is required for the enzyme activities necessary for cell division, cell growth; and wound healing. Immunologic defects of T-cell function are typical in Zn deficiency [14]. Experimentally, suboptimal intake of Zn has rapid adverse effects on the immune system of humans [6], including T cell mediated responses critical for host protection against parasitic infection. Beck et al [16] concluded that mild zinc deficiency lead to an imbalance between TH1 and TH2 lymphocytes, decreases the recruitment of T native cells, and decreases the percentage of T cytolytic cells.

Therefore, the presence of a significant reduction in Zn level of alopecic patients (Table 1) may lead to impaired immune function of those patients. Further study may be required to evaluate the role of Zn supplementation in alopecic patients. Oral Zn supplementation has been reported to stimulate both T and B-cell activity [17-18] and improves the immune system in elderly people [19].

Patients of the present study also showed an increase in serum Cu levels. This finding dose not agree with that of Tasaki et al(15) who failed to observe an elevation in Cu concentrations in patients with alopecia areata. Increases in serum Cu content occur in various inflammatory and connective tissue disorders (15, 20). Accordingly, the present finding may, therefore, suggest the presence of an inflammatory condition in patients with alopecia areata.

It is possible that the observed changes in Zn and Cu plasma levels reflect the presence of an imbalance in these trace metals metabolism in alopecia areata. The consequences of this imbalance are unknown at present. These changes, however, are reflected in the Zn/Cu ratio, which was decreased in patients with alopecia areata compared with controls. Furthermore, the fact that this ratio was lowest in patients with severe manifestations (e.g. those with more than 10 patches) compared with those patients with mild severity (i.e., those with less than 3 patches) is suggestive of the presence of a possible correlation with the severity of the disease. This fact further supports the hypothesis of Tasaki et al [14] who demonstrated that Cu/Zn ratio clearly reflects the severity of the progression of skin diseases. Further studies, using large number of patients, are required to test this hypothesis and to investigate whether or not it may also be useful in assessing the effects of various therapies against alopecia areata.

REFERENCES

****

1- Bennett-J C; Plum-F, Eds; Cecil "Text Book of Medicine" 20th edition;W.B.Saundres Company London; 1996; p 2215-2217.

2- Champio-RH; Burton-JL, Bums-DA; Breathanach, Eds Rook "Text Book of Dermatology " 6th edition. Blackwell science. England 1998; 1: p 2903-2938.

3- Fauci-AS. Braunwald-E, Isselbacher-KJ, Eds Harrisons "Principles of Internal Medicine" 14th edition. Me Graw-Hill, New York; 1998; P 312-314

4- Peter-J; Lynch-M.D, "Dermatology" 3rd edition, Williams & Wilkins Awaverly Company; 1994; chapter 17: p 358-366.

5- Ashwaq AL-Jaff et al The role of oxidative stress in alopecia areata. Iraqi journal of pharmacy.2001vol 1, No 1:34-45.

6- Knight J. A Ed; "Free radicals, antioxidants, aging and disease" 1st edition; American association for clinical chemistry; 1999;chapter.l0, p 274.

7- Chandra RK. Nutrition and the immune system: an introduction. Am J Clin Nutr 1997; 66:460S-463S.

8- Lesomed BM. Nutrition and immunity in the elderly: modification of immune responses with nutritional treatment. Am J Clin Nutr 1997; 66:478S-484S.

9- Cunningham-Rundles S. Bockam RS, Lin Act al. Physiological and pharmacological effects of zinc on immune response. Ann NY Acad Sci 1990, 587:113-122,

10- Disilvestro RA & Blostein-Fujii A. Moderate zinc deficiency in rats enhances lipoprotein oxidation in vitro. Free radicals in biology and medicine.1997r; 22:739-742.

11- Ziouzenkova 0. Sevanian A, Abuja PM Ramos P & Esterbauer H Copper can promote oxidation of LDL by markedly different mechanisms. Free radical biology and medicine. 1998, 24:607-623

12- Fox PL, Mukhopadhyay C & Ehrewald E. structure oxidant activity and cardiovascular mechanisms of human ceruloplasmin. Life sciences. 1995; 56:1749-1758.

13- Burtis-A.C; and Ashwood-R.E, Eds; Tietz "Text Book of Clinical Chemistry" 3rd edition W, B Sannders Company; London, 1999, p482-484.

14- Tasaki-M; Hanada-K; Hashimoto-I. Analysis of serum copper and zinc levels and copper/zinc ratios in skin j-dermatol. 1993; 20(1): 21-4.

15- Falchuk KH Disturbances in trace metal metabolism In: Hamson's principles of internal medicine. Isselbacher KJ et al (ed.). 13th ed. Me Graw Hill Inc. 1994: pp 481-483.

16- Beck FWJ. prasad AS Kaplan J et ndal changes in cytokine production and cell subpopulations in experimentally induced Zinc-deficient humans. Am J Physiol. 1997; 272:E1002-E 1007

17- Keen CL, Gershwin ME. Zinc deficiency and immune function Annu Rev Nutr-.1990; 10:415-431.

18- Mitchell G FT cell dependent effects in parasite infection and disease- Prog Immunol. 1980; 4:794-808.

19- Roebothan.B VChandra.R.K.Relationship between nutritional status and immune function of elderly people. Age Ageing. 1994, 23:49-57

20- Gowenlock AH. Varleys practical clinical biochemistry. (ed). Heinemann professional publishing: 1988; pp 633.