SERUM COPPER, CERULOPLASMIN, IRON, TRANSFERRIN LEVEL IN PATIENTS WITH PSORIASIS AND THEIR RELATIONSHIP WITH SEVERITY OF THE DISEASE

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Abstract

Psoriasis is a common, chronic, immune mediated inflammatory disease that involves the innate immunological system (keratinocyte, dendritic cell, histiocytes, mast cells and endothelial cells) and acquired immunological system (T lymphocytes). Essential trace elements like iron (Fe), copper (Cu) undergo redox cycling and have physiological significance in inflammatory process. This study is aimed at measuring the level of copper, ceruloplasmin, iron and transferrin in psoriasis patient and to assess its relationship with the severity of the disease.

This is an observational cross sectional study. It was conducted at the department of Dermatology and Venereology, BSMMU, Dhaka. Age range of the patient was 18 to 65 years. The mean age of the patients was 39.1±13.54 years, 57.9% patients were male and 42.1% were female. Male: female ratio was 1.4:1. Male patients were predominant. Mean duration of disease 5.36±4.05 years with range from 1.0 to 14 years. Most of the (76.3%) patients had mild disease followed by 23.7% had moderate to severe disease. Serum level of trace elements was compared between mild and moderate to severe group of psoriasis patients but difference were not statistically significant (p>0.05). Weak negative correlation was found between PASI score and serum levels of copper (r = "0.134, P = 0.423), iron (r = –0.080, p = 0.632), transferrin (r = –0.079, p = 0.638) and weak positive correlation was found with ceruloplasmin (r = 0.228, p = 0.168).

The results of the present research provide valuable information and correlation between the measured biomarkers and severity of psoriasis. Serum Ceruloplasmin, copper, iron and serum transferrin could serve as a biomarker of psoriasis but not as a marker of psoriasis severity.

Keywords: *Copper, Ceruloplasmin, Iron, Psoriasis, Transferrin level*

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Introduction

Psoriasis is a common, chronic, noncontagious inflammatory dermatosis with a global prevalence of 2-3%.[1] It is characterized by recurrent episodes of red and scaly skin plaques that are sharply demarcated from adjacent normal skin. A number of risk factors have been recognized in the etiology and pathogenesis of psoriasis, including family history and environmental risk factors, such as diet, obesity, smoking, stress, and alcohol consumption.[2] Psoriasis is a T-cell mediated autoimmune disease. Genetic, environmental, immune defect, and hormonal factors take part in autoimmune pathogenesis of diseases.[3] An environmental factor stimulates cytokines secretion by T-cells that lead to keratinocytes proliferation; in dermal blood vessels, it will also lead to antigenic adhesion molecules production.[4] Psoriasis was first described as a disease that primarily affects epidermal keratinocytes proliferation and secondary cutaneous inflammatory infiltration.[5] In the last decade it has been evident that psoriasis is a systemic, immune mediated, inflammatory disease primarily involving Th1 cells. Cytokines of the Th1 pathway (interferon-Gamma, interleukin 2, interleukin 12, and TNF-alpha) predominate in psoriatic plaques. It is widely accepted that an unknown stimulus activates dendritic antigen presenting cells. The activated antigen presenting cells then activate helper T cells which lead to the subsequent release of a cascade of inflammatory cytokines. This cascade results in recruitment and activation of other cells types such as endothelial cells and neutrophils, and production of chemokines and growth factors. Eventually that leads to hyperproliferation of keratinocytes. A chronic inflammatory state the ensures and leads to formation of psoriatic skin lesions.[5,6] Recently, interleukin-17-secreting helper T (Th17) cells have been identified to play a very impotrant role in the pathogenesis of psoriasis.

Trace elements are involved in immunological and inflammatory reactions. Worsening of psoriasis due to oxidative stress and the involvement of trace metals have been reported. Effects of altered trace metal homeostasis in psoriasis have also been studied.[7,8] However, limited studies have focused on the involvement of metal binding proteins in psoriasis.[9–11] The only study on trace elements in Iranian psoriatic patients measured zinc (Zn) and copper (Cu).[12] The serum redistribution of essential trace elements Cu and iron (Fe), together with the increase in synthesis of acute-phase proteins [such as ceruloplasmin (Cp)], during the course of inflammations is well established.[9] These changes are induced by cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-á), and interleukin-6 (IL-6).[10,11] These cytokines are liberated in a dose-dependent mode, mostly by activated macrophages, in response to several stimuli, including trauma, stress, or infection and are implicated in psoriasis pathogenesis.[12]

Increased iron concentrations were found in psoriatic epidermis. Heme oxygenase (HO) is the rate-limiting enzyme in heme catabolism, which leads to the generation of biliverdin, iron, and carbon monoxide. HO-1 is a stress-responsive protein whose expression is induced by various oxidative agents, and is known for its cytoprotective, antioxidant, and anti-inflammatory properties.[13] Transferrin plays a vital and central role in iron metabolism. It is a true carrier molecule in that it is conserved for many cycles of iron transport in its interaction with target tissues and because Cp is an acute phase reactant. It has been reported that transferrin may also play a role in Zn transport.[14]

Trace elements and their compounds have been used since ancient times for their therapeutic as well as cosmetic effects on the skin.[15] The unique process of keratinization and melanin formation is enzyme-dependent and therefore could be influenced by trace element deficiencies or excesses as trace elements are involved in enzymatic activities and immunologic reactions.[16] Studies have also shown that essential trace elements like iron (Fe), copper (Cu), chromium (Cr), and vanadium (V) undergo redox cycling and have physiological significance, while nonessential toxic elements like cadmium (Cd), mercury (Hg), nickel (Ni) and lead (Pb), deplete glutathione and protein-bound sulfhydryl groups, resulting in the production

of reactive oxygen species (ROS) like superoxide ion, hydrogen peroxide, and hydroxyl.[17] There is a limited data on importance of trace elements in the etiopathogenesis and treatment of psoriasis.[18] All these limited studies centered on changes in single element in psoriasis. There is no comprehensive study on the levels of different micro and macro elements and their inter element relationships in psoriasis. It is becoming increasingly clear that the levels of dietary Cu and Zn uptake may be marginal for patients with particular diseases or for entire population groups. Additionally, pharmacological doses of these nutrients have been reported to have therapeutic properties for specific diseases.[19] In fact, congenital and acquired Zn deficiencies manifest as a variety of skin manifestations, such as psoriasis-like eruptions, blisters, blisters, loss of hair, and onychopathy.[20] Wilson's disease and Menkes kinky hair disease, which are caused by abnormal Cu metabolism, elicit hyper-pigmentation and morphological changes of the hair,[21] respectively. These various symptoms suggest the possibility that the abnormal metabolism of both metals may also exist in other diseases with similar skin lesions. Many researchers have initiated research to illuminate the possible role of trace metals in the pathogenesis and treatment of psoriasis. This approach appears reasonable because Cu and Zn are known to be among the constituents of the skin and to play essential roles in the maintenance of its function in association with the enzyme systems activated by trace metals.[22] Serum Zn and Cu have been reported to be associated with the immune response, inflammation, and oxidative stress in the human bod.[23]

The Cu/Zn ratio is also considered a useful marker of malnutrition in addition to other classic anthropometric and biological nutritional parameters.[23,24] Approximately 20 % of the total Zn in the body is located in the skin. Zn has been reported to play a role in protein and nucleic acid synthesis and the function of T-lymphocytes.[25] Therefore, Zn deficiency, which is prevalent in Iran, leads to thymus atrophy and the impairment of cell and antibody-mediated immunity.[26] Cu is also an important constituent of metalloenzymes, and its role in oxidation-reduction systems and against free radicals has been demonstrated. Cu deficiency leads to a decrease in antibodies, thymus weight, and T-lymphocytes as well as increased oxidative injury.[27] Unlike Zn, the results of studies concerning Cu in autoimmune diseases (asthma and diabetes mellitus) have indicated higher levels of this trace element in patients.[28]

Cu, Zn and Fe are important co-factors and modulators of many critical biologic functions in the states of health and diseases.[29,30] There has been an increased awareness that the levels of dietary intake of copper, zinc and iron may be marginal for patients with particular diseases or for entire population groups.[20]

The total amount of iron in an adult body is 3-5 gm. About 70% of this occurs in the body as a constituent of haemoglobin. European food and safety authority (EFSA) has confirmed that iron helps in normal function of RBC and haemoglobin, immune systems and normal cell division.[31] So sufficient iron is critical to several immune functions, including the development and division of WBC and the generation of free radicals, which are used for killing infectious agents (eg. bacteria). So decreased serum iron level is reported in psoriasis by many investigators[8] may be because of accelerated loss of nutrients from the hyperproliferation and desquamation of epidermal layer of skin in psoriasis.

Different world wide studies suggested that level of serum copper, iron, ceruloplasmin, transferrin level have influence in the pathogenesis of psoriasis by modulating immune cell function, regulating keratinocytes and T-cell proliferation. The influence of these chemicals on the severity of Psoriasis is studied widely. No such study has been conducted in Bangladeshi population till date to evaluate level of these chemicals in psoriatic patients. Hence this study will serve as a reference for future studies.

Objectives

The general objective of the study was to find out the relationship between the severity of psoriasis and serum level of iron, ceruloplasmin,

copper and transferrin. The specific objectives are to measure the serum level of iron, ceruloplasmin, copper and transferrin in psoriasis patient and to find out their correlation with the severity of the disease. Another objective is to assess the severity of the disease by PASI score and to correlate the PASI score with severity.

Materials and Methods

This observational cross sectional study was done at the department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University, Dhaka, and Armed Forces Institute of Pathology (AFIP), Dhaka, Bangladesh. The study was conducted from September 2017 to August 2019. Psoriasis patients attending in the department of Dermatology and Venereology and the department of Rheumatology, BSMMU. We selected our participants by non-probable purposive sampling.

Selection criteria

All patients who are diagnosed as psoriasis either by dermatologist or by histopathology report with age between 18 and 65 years were included in this study. We excluded the pregnant patient and lactating mothers, patient taking systemic corticosteroid, calcium supplementation, patients of chronic kidney disease, chronic liver disease, Malabsorption syndrome., Hypoparathyroidism, presence of other autoimmune diseases (RA, Inflammatory bowel disease, IDDM ,Lupus erythematosus). Patients who received topical or UVB therapy within previous 2 weeks, PUVA (Psoralen - ultraviolate A) therapy in 4 weeks, Laser phototherapy within previous 4 weeks and Other systemic or biological therapy within previous 12 weeks had been excluded from our study.

Study procedure:

Patients was informed about the objectives of this study. After proper understanding of whole process, if they are willingly like to take part in my study then they were included preliminarily for history taking, physical examination and necessary laboratory tests. Then 38 patients with psoriasis were enrolled finally for this study according to the aforementioned inclusion & exclusion criteria. Then informed written consent was obtained from each participant. Height, weight, body mass index (BMI), waist circumference of all participants were measured. Duration of disease was measured in year, positive family history; smoking and alcohol intake was noted. Disease severity of each and every patient was measured by Psoriasis Area Severity Index (PASI). The score of PASI usually varies between 0 and 72. PASI score of less than or equal to 10 is classified as mild disease, whilst a score of greater than 10 is considered to be moderate to severe.

Extent of involvement was defined according to the classification suggested by Molin et al., where < 5% involvement of total body surface area (TBSA) was regarded as mild , moderate was (5–30%) involvement of TBSA), severe was > 30% involvement of TBSA.

Disease activity was defined according to the classification of Haftek *et al.* mild (stationary skin lesions for the previous month), moderate (peripherally spreading plaque lesions with occasional small papules), and severe (rapidly developing new lesions from the periphery of plaques or normal skin or newly developing pustules).

Blood samples of the patients were taken from at their first visits at BSMMU. Serum was separated and carried to armed forces institute of pathology (AFIP), Dhaka. Serum concentrations of copper, ceruloplasmin, iron, transferrin was measured and data were collected for analysis.

Data Analysis

Statistical analysis was carried out by using the Statistical Package for the Social Sciences (SPSS) software version 23.0 for windows (SPSS Inc, Chicago, Illinois, USA). Continuous data are expressed as the mean ± standard deviation (SD) and categorical variables are expressed as percentages. Spearman's rank correlation coefficient test was used to correlate between mean serum copper, ceruloplasmin, iron, transferrin with continuous variable. Association of PASI and duration of psoriasis with serum copper, ceruloplasmin, iron, and

transferrin was analyzed by using adjusted logistic regression model. Multivariate regression analysis was used to study the effect of independent (predictor) variables on dependent variables. For all statistical tests, P-value is less than 0.05 was considered as statistically significant.

Ethical consideration

Ethical clearance for the study was taken from the Institutional Review Board and concerned authority, BSMMU. Permission for the study was taken from the concerned department from where we collected out study subjects.

Operational definitions

Psoriasis:

Psoriasis is a common, chronic and recurrent inflammatory papulosqamous disease of the skin characterized by circumscribed, erythematous, dry, scaling plaques of various sizes. The lesions are usually covered by silvery white lamellar scales. The lesions have a predilection for the scalp, nails, and extensor surfaces of the limbs, umbilical region and sacrum. The eruption is usually symmetrical (James & Elston, 2016).

Most common clinical variant of psoriasis is psoriasis vulgaris. Other varients includes guttate psoriasis, pustular psoriasis, small plaque psoriasis, inverse psoriasis, erythrodermc psoriasis etc[32] Psoriasis is a clinical diagnosis. Histopathology confirms the diagnosis.

Presence of psoriasis was ascertained by the question 'Have you ever been told by a doctor or other health care professional that you had psoriasis?' The degree of psoriasis was assessed using the question 'Do you currently have (i) little or no psoriasis, (ii) only a few patches (that could be covered by one or two palms of your hand), (iii) scattered patches (that could be covered between 3 and 10 palms of your hand), (iv) extensive psoriasis (covering large areas of the body that would be more than ten palms of your hand).

Psoriasis Area Severity Index (PASI):

A PASI score is a tool used to measure the severity and extent of psoriasis. According to PASI score, the body is divided into four sections head (H) (10% of a person's skin); arms (A) (20%); trunk (T) (30%); legs (L) (40%). Each of these areas is scored by itself, and then the four scores are combined into the final PASI. For each section, the percent of area involved is estimated and then transformed into a grade from 0 to 6.

- 0% of involved area, grade: 0
- <10% of involved area, grade:1
- 10-29% of involved area,grade:2
- 30-49% of involved area,grade:3
- 50-69% of involved area,grade:4
- 70-89% of involved area,grade:5
- 90-100% of involved area,grade:6

Within each area, the severity is estimated by three clinical signs: erythema (redness), indurations (thickness) and desquamation (scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum. The sum of all three severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs). The score is given as a number from 0 (not affected) to 72 (severely affected). A PASI score of less than or equal to 10 is classed as mild disease, whilst a score of greater than 10 is considered to be moderate to severe (Mrowietz et al., 2011).

Serum copper, ceruloplasmin, iron, transferrin levels:

Following box shows levels of the chemicals in blood:

Name	Sample	Normal range (SI unit)
Iron	Blood	Male: 14-32 micromoml/L
		Female: 10-28 micromol/L
Copper	Blood	Free serum Cu: 1.6-2.4 micromoml/L
		Total serum Cu:10-22 micromoml/L
Ceruloplasmin	Blood	0.16- 0.47 gram/L
Transferrin	Blood	2.0- 4.0 gram/L

Results

A total of 38 patients with psoriasis age between 18-65 years of both sexes were included. Age range of the patient was 18 to 65 years. The mean age of the patients was 39.1±13.54 years. Maximum 55.3% patients below 40 years followed by 44.7% patient's age above 40 years (Table:I). Among the participants 57.9% patients were male and 42.1% were female. Male: female ratio was 1.4:1.

Table 1

Distribution of the study patients by age (n=38)

Age in years	Number of patients	Percentage
≤ 40	21	55.3
> 40	17	44.7
Total	38	100.0
Mean±SD	39.1±13.54	
Range	(18-65) years	

Distribution of the patients according to their BMI showed that most patients were overweight (50%) followed by normal weight (39.5%).

We have found that 22 (57.9%) suffered from psoriasis vulgaris, 9(23.7%) from pastular psoriasis, 4(10.5%) from erythrodermic psoriasis and 3 (7.9%) from psoriasis vulgaris with psoriatic arthritis. The mean duration of disease is 5.36±4.05 years with range from 1.0 to 14 years. Mean age of onset of psoriasis is 30.95±13.74 years with range from 18.0 to 50 years.

Among the clinical features all patient had of scaling, erythema, itching with symmetrical distribution of lesions in 92.1% and 84.2% had extensor surface of limb involvement, 78.9% had scalp involvement. Auspitz sign was positive in 73.3% patients and 68.4% patients had indurations (Table II).

We have measured the severity of psoriasis by PASI severity scale. Most (76.3%) patients had mild disease followed by 23.7% had moderate to severe disease. Comparison of serum levels of trace elements were done between mild and moderate to severe group of psoriasis patients and difference were not statistically significant (p>0.05) Table III)

Table-II

Distribution of the study participants by evaluation of psoriasis (n=38)

Evaluation of psoriasis	Number of patients	Percentage
Scaling	38	100.0
Erythema	38	100.0
Itching	38	100.0
Symmetrical distribution lesion	35	92.1
Extensor surface of limb involvement	32	84.2
Scalp involvement	30	78.9
Auspitz sign	29	76.3
Indurations	28	73.7
Umbilical region involvement	26	68.4
Sacrum Involvement	24	63.2
Pitting	22	57.9
Subungual hyperkeratosis	20	52.6
Noycholoysis	17	44.7
Oil spot	17	44.7

Table III

Summary of serum Copper, Ceruloplasmin, Iron and Transferrin levels (n=38)

Serum levels	Severity of psoriasis		p-value
	Mild(n=29) Mean±SD	Moderate(n=9) Mean±SD	
Serum Copper (mg/dl)	85.41±24.28	75.89±15.17	0.276^{ns}
Serum Ceruloplasmin (mg/dl)	26.81±4.42	26.70±5.54	0.951^{ns}
Serum Iron (mgm/dl)	80.45±39.72	75.67±29.40	0.741^{ns}
Serum Transferrin (%)	124.50±110.13	68.67±73.92	0.165^{ns}

Pearson correlation of PASI with the Serum Copper (mg/dl), Ceruloplasmin (mg/dl), Iron (mgm/dl), Transferrin (%) levels revealed weak negative correlation between PASI score and serum levels of copper (r = "0.134, P = 0.423), iron (r = –0.080, p = 0.632), transferrin (r = –0.079, p = 0.638) and weak positive correlation with ceruloplasmin (r = 0.228, p = 0.168) (Table 4) (Figure 1).

Table IV

Correlation of PASI with Serum Copper (mg/dl), Serum Ceruloplasmin (mg/dl), Serum Iron (mgm/dl) and Serum Transferrin (%) (n=38)

PASI	r value	P value
Serum Copper (mg/dl)	– 0.134	0.423^{ns}
Serum Ceruloplasmin (mg/dl)	+ 0.228	0.168 ^{ns}
Serum Iron (mgm/dl)	– 0.080	0.632 ^{ns}
Serum Transferrin (%)	– 0.079	0.638 ^{ns}

ns= not significant

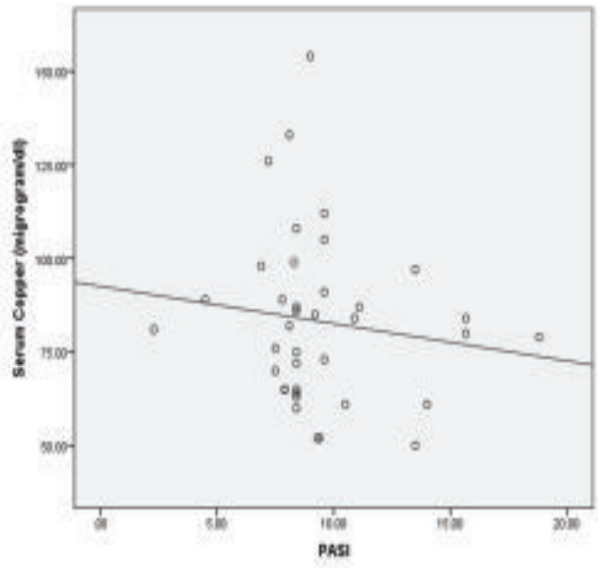

Figure 1: *Correlation of serum Copper (mg/dl) with PASI*

[Scatter diagram showed that statistically insignificant weak negative correlation of PASI with serum copper (r= - 0.134, p=0.423)].

Discussion

Psoriasis is a chronic skin disease of multifactorial etiology. The exact pathogenesis of psoriasis has remained unclear, but some factors are known to trigger, participate or aggravate the disease process.[33,34] The stages of psoriasis as mild, moderate and severe are based on the PASI score. The PASI is a useful tool in monitoring response to treatment.[35]

Normal trace (minerals) elements in the blood are important for maintenance of skin health, abnormality of trace elements can lead to many.[36] There are some studies that have investigated the levels of trace elements in psoriasis, whereas only few studied metal binding proteins.[8,14]

In this study age range of the patient was 18 to 65 years. The mean age of the patients was 39.1±13.54 years. Maximum 55.3% patients below 40 years followed by 44.7% patient's age above 40 years. In accordance Hasan et al. (2016) noted mean age 36.0±17.4 years.[37] Elhaddad et al. (2017) reported the mean age of patients 42.1±21.26 years.[38] Asian studies by Kawada et al. (2001) and Ding et al. (2012) showed dual peaks located in the 20s and 40s, correlated with our study.[39,40] Additionally, early-onset (<40 years) psoriasis accounted for

more than 75% of patients in western studies (Henseler, 1995) and 67.6% of patients in the Chinese study (Ding et al., 2012) and 55.3% in our study, have similar with others.[40,41]

In present series 57.9% patients were male and 42.1% were female. Male : female ratio was 1.4:1. Male patients were predominant. Similarly Elhaddad et al. (2017) reported males comprised 67% and females were 33%.[38]

In present study the psoriasis patients graded by PASI severity scale, maximum (76.3%) patients had mild disease followed by 23.7% had moderate to severe disease. Elahaddad et al. (2017) reported their study according to the PASI score, 6(10.0%) patients were with mild psoriasis (PASI <7.0), 52(86.7%) patients were with moderate psoriasis (PASI 7.0-12.0), and 2(3.3%) patient with severe psoriasis (PASI >12.0).[38]

PASI score has been used for the assessment of severity of psoriasis and as a tool to monitor response to treatment. The use of markers in combination with clinical measures like PASI will help in better understanding the disease as well as to develop treatment strategies and monitor responses. Serum markers like cytokines have been instrumental in understanding the pathology of skin diseases like psoriasis. The presence of excess Fe has been demonstrated in many skin diseases involving an inflammatory response including psoriasis.[42,43] In present study, weak negative correlation of serum transferrin with disease severity. In psoriasis, low serum Fe levels have been reported.[8] There are a few studies describing the role of transferring and transferrin receptors in psoriasis.[7] Reshmi et al. (2012) noted increased Fe concentration and high ferritin levels in psoriatic epidermis and serum levels of Fe were decreased in patients, which is correlate present study[42].

The increased inflammatory activity in psoriasis results in increased neutrophil activation resulting in degranulation and generation of superoxide radicals that result in development of oxidative stress in psoriasis.[44] Serum ceruloplasmin level may be a complementary factor associated with inflammatory conditions and its levels are raised in psoriasis. However, raised levels of ceruloplasmin show only weak correlation with severity of psoriasis (r=0.228, p=0.168). The findings of present study correlate well with findings of previous studies.[7,45]

In this study it was found that the serum copper was insignificant weak negative correlation with PASI. Khan et al. (2018) found mean copper level of severe group was significantly increased when compared with controls which were above than normal levels.[46] Similar results were reported by Alwasiti and colleagues.[47] The elevation of serum Cu level in psoriasis may be ascribed to an increase in both fractions, especially an increase in ceruloplasmin, a Cu-binding protein, in response to inflammation. Another study by Sheikh et al. (2015) demonstrated that serum copper and ceruloplasmin levels were significantly increased in psoriasis.[48] It is still unknown, that whether psoriasis accelerate the release of synthesized protein (ceruloplasmin) into the blood serum or whether the synthesizing capacity is enhanced, or both.

Shahid-Dadras et al. (2017) demonstrated higher Cu level in psoriasis patients and suggested Cu chelating agents such as penicilamine for treatment.[49] A positive correlation between serum Cu levels and severity of psoriasis is reported. Weak negative correlation between Cu levels and psoriasis severity was detected in our study.

Mezzetti et al. (1998) found a strict relationship between copper/zinc ratio and systemic oxidative stress.[50] These inconsistent results may arise from different study designs. Overall, it seems that Cu/Zn is a more effective parameter rather than either Zn or Cu level alone, although it had no correlation with the severity of psoriasis in our study.

Increase of serum ceruloplasmin levels occurs under certain conditions such as physical stress, inflammation, or disease. Since over 90% of serum copper is carried in ceruloplasmin, which is increased in many inflammatory conditions, elevated Cu serum may simply be a marker of inflammation[51,52] Basavaraj et al. (2009) analyzed Cu levels in mild and severe psoriasis. Elevated Cu serum levels have been reported in both groups. The results of our study

show insignificant negative correlation with disease severity of psoriasis.[8] This is in accordance with the studies conducted by Sheikh et al. (2015) and Rashimi et al. (2010) where elevated Cu levels have been reported in psoriasis.[42,48] In contrast, reduced Cu levels in active and remissive phases of psoriasis have been reported by Bhatnagar et al. (1994).[53]

This study showed a weak correlation between ceruloplasmin, copper, iron and serum transferrin levels and PASI but it did not differ significantly suggesting that serum ceruloplamin, copper, iron and serum transferrin level has no prognostic significance for the worsening of psoriasis.

Limitations of the study

The study population was selected from single tertiary centre in Dhaka city, so that the results of the study may not reflect the exact picture of the country. Sample size of our study was small. Finally, dietary factors which might contribute to the serum trace elements were not considered.

Conclusion

The results of the present research provide valuable information and correlation between the measured biomarkers and severity of psoriasis. Weak negative correlation was found between PASI score and serum levels of copper (r = "0.134, P = 0.423), iron (r = –0.080, p = 0.632), transferrin (r = –0.079, p = 0.638) and weak positive correlation with ceruloplasmin (r = 0.228, p = 0.168). In conclusion, ceruloplasmin, copper, iron and serum transferrin could serve as a biomarker of psoriasis but not as a marker of psoriasis severity.

References

1. National guidelines for diagnosis and management of Psoriasis. National psoriasis Foundation. 2015;
2. Huerta C, RivZero E, Rodriguez LA. Incidence and risk factors for psoriasis in the general population. Arch Dermatol. 2007;143(12):1559–1565.
3. Ozawa M, Aiba S. Immunopathogenesis of psoriasis. Current Drug Targets: Inflammation & Allergy. 2004;3(2):137–144.
4. Wisnieski JJ. Urticarial Vasculitis. Current Opinion in Rheumatilogy. 2000;12(1):24–31.
5. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263–271.
6. Schon MP, Boehncke WH. Psoriasis. The New England Journal of Medicine. 2005;352(18):1899–1912.
7. Rocha Pereira P, Santos Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. The inflammatory response in mild and in severe psoriasis. British Journal of Dermatology. 2004;150(5):917–28.
8. Basavaraj KH, Darshan MS, Shanmugavelu P, Rashmi R, Mhatre AY, Dhanabal SP, et al. Study on the levels of trace elements in mild and severe psoriasis. Clinica Chimica Acta. 2009;405(1–2):66–70.
9. Grigorian VA, Karagezian KG, Babaian KR, Simonian MA, Badalian MA, Obeian GA. Blood metalloproteins of prooxidant and antioxidant action in psoriasis. Ukr Biokhim. 1998;70:149–52.
10. Lal S, Rajagopal G, Subrahmanyam K. Serum caeruloplasmin in psoriasis. Indian J Dermatol. 1971 Jul;16(7):103–4.
11. Stratigos J, Kasimatis B, Panas E, Capetanakis J. [The biochemistry of psoriasis. Serum copper and ceruloplasmin in psoriasis patients]. Ann Dermatol Syphiligr (Paris). 1976;103(5–6):584–7.
12. Ala S, Shokrzadeh M, Golpour M, Salehifar E, Alami M, Ahmadi A. Zinc and copper levels in Iranian patients with psoriasis: a case control study. Biological trace element research. 2013;153(1–3):22–27.
13. Pelc AW, Marcinkiewicz J. What is a role of haeme oxygenase 1 in psoriasis? Current concepts of pathogenesis. Int J Exp. 2007;88:95–102.
14. Sargent PJ, Farnaud S, Evans RW. Structure/function overview of proteins involved in iron storage and transport. Curr Med Chem. 2005;12(23):2683–93.
15. Afridi HI, Kazi TG, Jamali MK, Kazi GH, Shar GQ. The status of trace and toxic elements in biological samples (scalp hair) of skin-disease patients and normal subjects. Turkish Journal of Medical Sciences. 2006;36(4):223–230.
16. Bock M, Schmidt A, Bruckner T, Diepgen TL. Occupational skin disease in the construction industry. 2003.
17. Stohs SJ, Bagchi D. Oxidative mechanisms in the toxicity of metal ions. Free Radical Biology & Medicine. 1995;18:321–6.
18. Greaves NM, Boyde TRC. Plasma zinc concentrations in patients with psoriasis, other dermatoses, and venous leg ulceration. Lancet. 1967;2:1019–22.
19. Cousins RJ. Absorption, transport, and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. Physiol Rev. 1985;65:238–309.
20. Prasad AS. Clinical manifestations of zinc deficiency. Annu Rev Nutr. 1985;5:341–363.
21. Tasaki M, Hanada K, Hashimoto I. Analyses of serum copper and zinc levels and copper/zinc ratios in skin diseases. J Dermatol. 1993;20:21–24.

22. Michaelsson G, Edqvist LE. Erythrocyte glutathione peroxidase activity in acne vulgaris and the effect of selenium and vitamin E treatment. Acta Derm Venereol. 1984;64:9–14.

23. Belbraouet S, Biaudet H, Tebi A, Chau N, Gray-Donald K, Debry G. Serum zinc and copper status in hospitalized vs. healthy elderly subjects. 2007;26:650–4.

24. Peng LN, Liang CK, Chou MY, Lin MH, Lai HY, Hwang SJ, et al. Association between serum copper, zinc and hospital admissions among care home residents. Arch Gerontol Geriatr,vol. 2010;51:24–27.

25. Jen MSK, Yan AC. Cutaneous changes in nutritional disease. In WGL, K K, S.I., editors. New York: McGraw Hill; 2007. 1201–1218 p.

26. Allen B. Skin, hair and nails. In: M LOE, J D, editors. Clinical nutrition. Blackwell, Oxford; 2005. p. 731–744.

27. Turnlund JR, Jacob RA, Keen CL, Strain JJ, Kelley DS, Domek JM, et al. Long-term high copper intake: effects on indexes of copper status, antioxidant status, and immune function in young men. Am J Clin Nutr. 2004 Jun;79(6):1037–44.

28. Ermis B, Armutcu F, Gurel A, Kart L, Demircan N, Altin R, et al. Trace elements status in children with bronchial asthma. Eur J Gen Med. 2004;1:4–8.

29. Halsted JA, Smith JC. Plasma-zinc in health and disease. Lancet. 1970 Feb 14;1(7642):322–4.

30. Bouzayan M, G F. Iron/ : an essential cofactor for the conversion of 1- Aminocyclopropane-1-carboxylic to ethylene. Springer Link. 1991;184:244–7.

31. Fairbanks VF, Fahey JL, Buetler E. Clinical Disorders of Iron Metabolism. 2nd ed. New York: Grunard Stratton, Pub. N.Y; 1971.

32. Fitzpatrick's dermatology in general medicine. New York: McGraw-Hill medical; 2012.

33. Sabat R, Philipp S, Höflich C, Kreutzer S, Wallace E, Asadullah K. Immunopathogenesis of psoriasis. Exp Dermatol. 2007;16:779–98.

34. Guenther L, Gulliver W. Psoriasis comorbidities. J Cutan Med Surg. 2009;13:S77-87.

35. Kerkhof PCM V. On the limitation of the psoriasis area and severity index (PASI) (letter. Br J Dermatol. 1992;126:205.

36. Siva ME, Subramanian KN. Kinetic models of trace element and mineral metabolism during development. Boca Raton: CRC; 1995. 159–70 p.

37. Hasan NS, Alwahad HSA, Jawad RF. Evaluation of trace elements zinc & copper in Iraqi Patients with psoriasis & extent of the disease. International Journal of Research in Pharmacy and Chemistry. 2016;6(1):9–14.

38. Elhaddad H, Morsy R, Mourad B, Elnimr T. A comprehensive study on the content of serum trace elements in psoriasis. Journal of Elementology. 2017;22(1):31–42.

39. Kawada A, Tezuka T, Nakamizo Y, Kimura H, Nakagawa H, Ohkido M. A survey of psoriasis patients in Japan from 1982 to 2001. J Dermatol Sci. 2003;31:59–64.

40. Ding X, Wang T, Shen Y, Wang X, Zhou C. Prevalence of psoriasis in China: a population-based study in six cities'. Eur J Dermatol. 2012;22(5):663–7.

41. Henseler T, Christophers E. Disease concomitance in psoriasis. Journal of the American Academy of Dermatology. 1995;32(6):982–986.

42. Rashmi R, Yuti AM, Basavaraj KH. Relevance of copper and ceruloplasmin in psoriasis. Clinica chimica acta; international journal of clinical chemistry. 2010;411(17–18).

43. Leveque N, Robin S, Muret P, Mac-Mary S, Makki S, Berthelot A. In vivo assessment of iron and ascorbic acid in psoriatic dermis. Acta Derm Venereol. 2004;84:2–5.

44. Keerthana BL, Kumar TA. Serum biomarkers for diagnosis and assessment of severity in psoriasis. International Journal of Biomedical and Advance Research. 2016;7(1):17–21.

45. Manjula VD, Sreekiran S, Saril PS, Sreekanth MP. A study of psoriasis and quality of life in a tertiary care teaching hospital of Kottayam, Kerala. Indian Journal of Dermatology. 2011 Jul 1;56(4):403.

46. Khan F, Naeem SM, Ahmad Z, Zuberi NA. Association of serum levels of zinc and copper with degree of severity in patients with psoriasis. Journal of Saidu Medical College. 2018;7(2).

47. Alwasiti EARK, TAI_Rubayee W, Al-Tammimy SM. Serum copper, zinc and oxidative stress in patients with psoriasis. Iraqi J Med Sci. 2011;9:137–142.

48. Sheikh G, Masood Q, Majeed S, Hassan I. Comparison of levels of serum copper, zinc, albumin, globulin and alkaline phosphatase in psoriatic patients and controls: A hospital based casecontrol study. Indian dermatology online journal. 2015;6(2):81.

49. Shahidi-Dadras M, Namazi N, Younespour S. Comparative analysis of serum copper, iron, ceruloplasmin, and transferrin levels in mild and severe psoriasis vulgaris in iranian patients. Indian dermatology online journal. 2017;8(4):250.

50. Mezzetti A, Pierdomenico SD, Costantini F, Romano F, De Cesare D, Cuccurullo F, et al. Copper/zinc ratio and systemic oxidant load: effect of aging and aging-related degenerative diseases. Free Radic Biol Med. 1998 Oct;25(6):676–81.

51. Afridi HI, Kazi TG, Kazi N, Kandhro GA, Baig JA, Shah AQ. Evaluation of cadmium, chromium, nickel, and zinc in biological samples of psoriasis patients living in Pakistani cement factory area. Biological trace element research. 2011;142(3):284–301.

52. Wacewicz M, Socha K, Soroczyñska J, Niczyporuk M, Aleksiejczuk P, Ostrowska J, et al. Concentration of selenium, zinc, copper, Cu/Zn ratio, total antioxidant status and c-reactive protein in the serum of patients with psoriasis treated by narrow-band ultraviolet B phototherapy: A case-control study. J Trace Elem Med Biol. 2017 Dec;44:109–14.

53. Bhatnagar M, Bapna A, Khare AK. Serum proteins, trace metals and phosphatases in psoriasis. Indian Journal of Dermatology, Venereology, and Leprology. 1994;60(1):18.