

Comparative Analysis of Serum Copper, Iron, Ceruloplasmin, and Transferrin Levels in Mild and Severe Psoriasis Vulgaris in Iranian Patients

Abstract

Background: There is a great body of evidence indicating that some inflammatory skin diseases, such as psoriasis, are mediated by oxidative stress. Trace metals have been shown to be involved in oxidative stress response. Altered trace metal homeostasis in psoriasis has been studied. However, limited number of studies has focused on the involvement of metal binding proteins in psoriasis. **Materials and Methods:** In a case control-study, serum levels of Iron (Fe), Copper (Cu), Transferrin (Trf), and Ceruloplasmin (Cp) were measured in 40 psoriasis patients and matched healthy controls. The severity of the disease was measured using psoriasis area and severity index (PASI), and the association of severity based on PASI score and measured elements and proteins was investigated. **Results:** Forty patients with psoriasis (mild: 14 and moderate to severe: 26) and 40 healthy controls were included in this study. The serum Fe, Trf, and Cu/Cp levels of the patients with psoriasis were statistically lower compared with those of the controls; serum levels of Cp was elevated in patients with psoriasis compared to controls ($P = 0.02$). No significant difference was observed between the two groups regarding serum levels of Cu ($P = 0.07$). **Conclusion:** Cu/Cp ratio of the patients with psoriasis was statistically lower compared with those of the controls.

Keywords: Ceruloplasmin, copper, psoriasis, trace element

Introduction

Psoriasis is a chronic, inflammatory, hyperproliferative cutaneous disorder that affects approximately 2% of the population and poses a lifelong burden for those affected.^[1] 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.^[2,3] However, limited studies have focused on the involvement of metal binding proteins in psoriasis.^[4-6] The only study on trace elements in Iranian psoriatic patients measured zinc (Zn) and copper (Cu).^[7] 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.^[4] These changes are induced by cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6).^[5,6] 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.^[7]

Increased Fe concentrations were found in psoriatic epidermis. Heme oxygenase (HO) is the rate-limiting enzyme in heme catabolism, which leads to the generation of biliverdin, Fe, 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.^[8]

Transferrin plays a vital and central role in Fe metabolism. It is a true carrier molecule in that it is conserved for many cycles of Fe 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.^[9]

We conducted a study to determine the serum level of Fe, Cu, Transferrin (Trf), and Cp in Iranian patients with psoriasis.

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Material and Methods

We designed a case-control study to determine the serum levels of Fe, Cu, Cp, and Trf and the association between these elements and the severity of psoriasis in patients attending dermatology clinic of Shohada-Tajrish Hospital, Tehran, Iran (December 2013 to March 2015). We also recruited a group of age and sex-matched healthy participants as controls. The study protocol was designed in accordance to Helsinki declaration, and conducted after receiving approval from the ethics board of Shahid Beheshti University of Medical Sciences.

The cases were clinically and pathologically diagnosed as plaque psoriasis; eligible patients did not receive topical or systemic treatment during the last 3 months.

Psoriasis was graded according to the psoriasis area severity index (PASI), presenting at the time of blood collection; equal or more than 10 and less than 10 were graded as severe and mild, respectively.

Participants with following conditions were excluded from study: women during pregnancy/lactation, receiving any medication that might change serum level of trace elements (i.e., diuretics, psychologic drugs, antiarrhythmic medications, or mineral supplements), diabetes mellitus, hypertension, metabolic disorders, and malignancy. Patients were included after written informed consent was obtained.

Blood samples were collected without any anticoagulant under aseptic condition. The collected blood was centrifuged at 3000 rpm for 5 min. Then, the plasma was frozen and stored at -80°C until analyzed. The levels of serum trace elements were measured by direct method using inductively coupled plasma mass spectrometer (ICP-MS) (model 8500, Shimadzu, Tokyo, Japan), Cp and Trf levels were analyzed by immunoturbidimetry assays and iron using Ferene, using ABX Pentra from Horiba ABX reagents.

Statistical analysis

Patients were classified into mild and severe psoriasis groups according to their PASI score. The normality assumption of continuous variables was assessed using the Shapiro–Wilk’s test. Independent-sample *t*-test was applied to compare the means of continuous variables. When the normality assumption was not satisfied, the logarithmic transformation was applied to the data, or the nonparametric Mann–Whitney-U-test was used, wherever appropriate. Pearson and Spearman correlation tests were used to detect the linear relationships between two variables. Statistical analysis was performed using the statistical software SPSS 16.0.0. (SPSS Inc. Chicago, IL, USA). *P*-value equal or less than 0.05 considered significant.

Sample size determination

According to previous studies, mean [standard deviation (SD)] serum levels of Cu and Fe were

0.014 (0.003) $\mu\text{mol/l}$ and 0.023 (0.004) $\mu\text{mol/l}$, respectively. With a sample size of 40 per group, a power of 87 to 91% is achieved to detect a difference of $\geq 15\%$ in mean serum levels of elements between the two groups, using a two-sample *t*-test and assuming a two-sided α of 0.05.

Results

This study comprised 40 patients with psoriasis and 40 healthy controls. Baseline demographics and clinical characteristics of patients and controls is described in Table 1. There was no statistical difference between the groups with regard to demographic variables. Moreover, the duration of disease was not different between patients with mild and severe psoriasis ($P = 0.11$, *t*-test).

Table 2 shows the mean serum concentrations of Cu, Fe, Trf, Cp, and Cu/Cp in study groups. The serum Fe, Trf, and Cu/Cp levels of the patients with psoriasis were lower compared with controls ($P < 0.01$). Significantly elevated level of serum Cp in patients with psoriasis compared with the controls was observed ($P = 0.02$). No significant difference was detected between case and controls in serum levels of Cu ($P = 0.10$).

There was no statistically significant difference between patients with mild and severe psoriasis in the evaluated serum levels ($P = 0.28$). No significant correlation was found between PASI score and serum levels of Cu ($r = -0.02$, $P = 0.93$), Fe ($r = 0.12$, $P = 0.47$), Trf ($r = 0.12$, $P = 0.47$), Cp ($r = 0.20$, $P = 0.22$) and Cu/Cp ratio ($r = -0.17$, $P = 0.29$). Also, there was no association between duration of disease and serum levels of Cu ($r = -0.23$, $P = 0.15$), Fe ($r = -0.30$, $P = 0.06$), Trf ($r = -0.30$, $P = 0.06$), Cp ($r = 0.18$, $P = 0.27$) and Cu/Cp ratio ($r = -0.27$, $P = 0.09$).

Discussion

Psoriasis may exacerbate due to oxidative stresses, and trace elements are involved in production of radical oxygen species (ROS). Thus, they might be involved in the pathogenesis of psoriasis.^[3] There are some studies that have investigated the levels of trace elements in psoriasis whereas only few studied metal binding proteins.^[3,9,10]

Basavaraj *et al.* reported low levels of Fe in both mild and severe psoriasis patients.^[3] Our study also conforms to their results. We could not link Fe levels to psoriasis severity. Cell loss from exfoliation and high rate of epithelial cells turnover may lead to Fe deficiency.^[10] It has been shown that the levels of Fe-linking proteins including lactoferrin, Cp, and Trf, are higher in active psoriasis; this can lead to reduction of antioxidant defence, which is one of the mechanisms involved in pathogenesis of psoriasis.^[2] In our study, decrease in Trf levels in patients might be associated with the simultaneous loss of proteins and Fe through skin exfoliation. While increased Fe concentration

Table 1: Baseline demographics and clinical characteristics of patients with psoriasis and healthy controls

Characteristics	Healthy controls (n=40)	Patients with psoriasis		
		Mild (n=14)	Severe (n=26)	Total (n=40)
Age, years				
Mean±SD	36.25±14.50	34.79±15.58	37.65±14.65	36.65±14.84
Median (range)	33.0 (10-66)	31.0 (8-66)	35.5 (12-61)	33.5 (8-66)
Gender, no. (%)				
Female	16 (40.0%)	7 (50.0%)	11 (42.3%)	18 (45.0%)
BMI	24.4±3.8	25±4.9	25±3.2	25±3.9
PASI ^a				
Mean±SD	-	5.84±2.41	17.83±8.76	13.64±9.20
Median (range)	-	6.0 (2.4-9.6)	16.0 (10.8-54.0)	12.05 (2.4-54.0)
Duration of disease (years)				
Mean±SD	-	7.50±6.45	11.56±8.89	10.14±8.27
Median (range)	-	6.0 (0.08-20)	10.0 (0.5-42.0)	9.0 (0.08-42.0)

Values are mean±SD (standard deviation) unless otherwise noted. ^aPASI: Psoriasis area and severity index score ranges from 0 to 72, with 0 indicating no psoriasis and 72 indicating severe disease, BMI: Body mass index

Table 2: Summary of serum Cu, Fe, Trf, Cp, and Cu/Cp levels by groups of study

	Healthy controls (n=40)	Patients with psoriasis		
		Mild (n=14)	Severe (n=26)	Total (n=40)
Cu (µmol/L)	18.78±1.05	19.49±2.61	19.45±1.34	19.47±1.85
Fe (µmol/L)	21.84±4.01	19.43±6.33	19.37±4.92	19.39±5.37
Trf (g/L)	3.66±0.68	3.26±1.06	3.24±0.83	3.25±0.90
Cp (mg/L)	3.02±0.69	3.72±0.80	3.44±0.76	3.54±0.77
Cu/Cp	6.50±1.40	5.43±1.24	5.86±1.10	5.71±1.15

Values are expressed as mean±SD (standard deviation). Cu: Copper, Fe: Iron, Trf: Transferrin, Cp: Ceruloplasmin

and high ferritin levels in psoriatic epidermis has been reported, serum levels of Fe were decreased in our patients. Decreased Trf can be an additive mechanism for lowered Fe serum level.

Elevated and decreased Cu levels have been reported in psoriasis.^[3,11-14] Cu levels in patients and controls were not different in our study. Only one study in Iranian patients demonstrated higher Cu level in psoriasis patients and suggested Cu chelating agents such as penicillamine for treatment;^[7] however, this population study was selected from northern Iran with different demographic, geographic, and nutrition patterns compared with the patients living in the capital. A positive correlation between serum Cu levels and severity of psoriasis is reported.^[11] No correlation between Cu levels and psoriasis severity was detected in our study.

More than 70–80% of plasma Cu is associated with Cp.^[15] The association of Cp levels with psoriasis has been investigated previously.^[11,16] Although Cp was increased significantly in our study, there was no association between Cp levels and severity of disease; this increase in Cp levels might be due to increased inflammation in the active phase of the disease. Increased serum Cp can be a confounding factor associated with elevated Cu level in other studies that did not measure this protein.

We also measured Cu/Cp ratio which is supposed to be a more reliable index of Cu status rather than Cu levels because it does not need gender-derived or age-derived reference intervals.^[17] The ratio was significantly lower in patients of our study.

None of the elements were related to psoriasis chronicity. Interestingly, elevated Cp level and decreased Trf and Fe levels in serum of patients with systemic lupus erythematosus (SLE) has been shown in a study, which is similar to our finding.^[18] Although SLE is different in many features, it may show that inflammatory disorders share some common metabolic abnormalities. The mechanisms by which these alterations occur in certain inflammatory conditions need to be elucidated.

The increased or decreased levels of measured trace elements and proteins may participate in pathogenesis of psoriasis via ameliorating inflammation, producing ROS or removing inhibition on immune system. It has been reported that serum Cp may be an important risk factor predicting myocardial infarction and cardiovascular disease,^[19] and hence, increased Cp level could be a laboratory marker for cardiovascular disease in psoriasis patients. This study had some limitations. We enrolled patients without treatment during the last few months; it led to limitation of eligible patients and a small sample size. Future studies must assess larger population with the aim of measuring these elements not only in serum but also in urine, lesional skin, and normal skin of affected individual.

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Conflicts of interest

There are no conflicts of interest.

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