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Enhanced ferritin/iron ratio in psoriasis

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***Background & objectives*: Psoriasis is a chronic, recurrent skin disorder, with a poorly understood pathogenesis. Studies at molecular/genetic levels continue to explore various biomolecules as potential markers of the disease. In the present study, we sought to evaluate the possible roles of ferritin and iron in psoriasis.**

***Methods*: Patients with psoriasis (n=81) and healthy controls (n=45) were included. Patients were graded as mild, moderate and severe based on the Psoriasis Area Severity Index (PASI). Serum ferritin and iron levels were measured by electro chemiluminescence and inductively coupled plasma - atomic emission spectrometry (ICP-AES), respectively.**

***Results*: The ferritin levels in psoriasis patients were not significantly different from that of controls. There was no significant difference in ferritin concentrations between psoriasis groups of severity. Fe was found to be significantly reduced ($P<0.05$) in the psoriasis patients when compared to controls. The ferritin to Fe ratio was significantly higher ($P<0.05$) in the psoriasis groups when compared to the control group.**

***Interpretation & conclusions*: Our results indicate a possible role of ferritin and iron in psoriasis. Further studies with large samples need to be done to confirm findings.**

Key words Ferritin - ferritin iron ratio - iron - psoriasis - Psoriasis Area Severity Index

Psoriasis is a chronic and recurrent skin disorder characterized by marked inflammatory changes in the epidermis and dermis[1]. The pathogenesis of this complex, multifactorial disease is incompletely understood. The genetic susceptibility and involvement of the innate immune system in psoriasis have been reported[2,3]. The involvement of proinflammatory cytokines, such as interleukins (ILs), tumour necrosis factor (TNF), and interferon-γ (IFN-γ), has been identified in psoriasis[4,5]. The worsening of psoriasis has been linked with oxidative stress[1]. Disorders in the antioxidant defense mechanisms are known to be involved in the pathogenesis of psoriasis[6,7]. The Psoriasis Area Severity Index (PASI)[8] is a useful tool in monitoring the response of psoriasis to any therapeutic regimen. Besides the use of clinical measures like PASI, attempts have been made to establish markers for psoriasis at both tissue[9] and serum levels[10,11].

There is some evidence regarding the roles of various metals and metal binding proteins in psoriasis and possibilities of evaluating these as potential markers of the disease would provide better targets for effective control of the disease. The involvement of trace metals[12-14] and altered trace metal homeostasis[15] in psoriasis has been reported. However, very limited

studies have focused on the involvement of metal binding proteins in psoriasis[1,16-18]. The metalloproteins are known to ameliorate the deleterious effects of the reactive oxygen species (ROS) by binding to the redox active metals like copper (Cu) and iron (Fe), thus minimizing their capacity to catalyze ROS production via the Fenton reaction[19]. Ferritin is an iron storage protein, the levels of which is known to increase as a result of oxidative stress[20] and inflammation[21]. The role of ferritin in patients with rosacea[22] and alopecia[23] has been reported. The present study was undertaken to investigate the role of ferritin and iron in psoriasis.

Material & Methods

A total of 81 consecutive patients consulting the Department of Dermatology, JSS Medical College Hospital, Mysore, India, during November 2007 and July 2009 were included in the study. Psoriasis was graded according to the PASI, presenting at the time of blood collection. The patients were divided into three groups based on the severity of the disease as mild (PASI <3), moderate (PASI 3.1-10) and severe (PASI >10). Among the patients, 15 were mild cases, 37 moderate and 29 were severe cases. The age ranged between 9 and 70 yr in the cases. The male : female ratios in the three psoriasis groups were 10 :5, 26 : 11 and 23 :6. Controls were volunteers with no significant illness. The duration of psoriasis varied from 5 days to 15 yr. Persons with history of diabetes, hypertension, psychiatric disorders, cardiac problems and other chronic skin disorders (other than psoriasis) were excluded. The control group consisted of healthy volunteers (n=45) having no significant medical illness (34 men and 11 women). The study protocol was approved by the Research Ethical Committee of J.S.S. Medical College Hospital, Mysore, India. A written consent was obtained from the patients/guardians prior to the collection of blood samples.

Blood (10 ml) was collected under aseptic condition from the cubital fossa using IV cannula with injection port. Blood was allowed to clot at room temperature for about 15 min and centrifuged at 3000 rpm for 20 min to separate the serum. The serum was frozen at -80 °C for subsequent analyses. Serum ferritin was measured by electro chemiluminescence method using automated analyzer (Elecsys 2010). A reference range of 30-340 ng/ml for men and 13-150 ng/mL for women was used. Analysis of serum Fe was carried out using an inductively coupled plasma- atomic emission spectrometry (ICP- AES) model Jobin Yvon 38 sequential analyzer. All dilutions were made with ultra pure milliQ water.

Comparisons between groups of severity were done using one way analysis of variance (ANOVA). Comparisons between the psoriasis and the control groups were done by t test. All statistical analyses were performed using SPSS software for Windows (Version 16.0).

Results & Discussion

The ferritin level in the mild group (50.4 ± 46.24 µg/l) was found to be lower than the control group (77.42 ± 12.42 µg/l). Ferritin level in moderate psoriasis group was found to be slightly higher than the control group (Table). No significant difference was observed between male and female subjects and controls.

When compared with the control group, Fe levels in the psoriasis groups were lower. This decrease was significant in the mild and severe groups (P<0.05). The moderate group showed an insignificant reduction in Fe levels when compared to the controls. The variation in the Fe levels did not present a particular trend in the psoriasis groups of severity. No significant difference was seen in the Fe levels between psoriasis groups. When Fe levels of all the psoriasis patients (1.1 ± 0.04 µg/ml) was compared with the controls, a significant difference (P<0.05) was observed (Table).

In order to address disequilibrium between ferritin and Fe in psoriasis, the ratio of ferritin to Fe was

Table. Ferritin and iron (Fe) levels in psoriasis patients and controls

	Psoriasis (n=81)	Mild (n=15)	Moderate (n=37)	Severe (n=29)	Controls (n=45)
Ferritin (µg/l)	73.93 ± 9.27	50.4 ± 46.24	83.23 ± 16	74.25 ± 14.64	77.42 ± 12.42
Fe (µg/l)	1.1 ± 0.04*	1.03 ± 0.1*	1.19 ± 0.07	1.06 ± 0.07*	1.47 ± 0.12
Ferritin/Fe	0.07 ± 0.01*	0.05 ± 0.007*	0.07 ± 0.017*	0.08 ± 0.022*	0.02 ± 0.04

Values are expressed as mean ± standard error
*P<0.05 compared to control

computed and compared. The ferritin : Fe ratios in the mild, moderate and severe groups were 0.05 ± 0.007, 0.07 ± 0.017 and 0.08 ± 0.022, respectively. Though the ratio appeared to increase with groups of severity, the increase was not significant. When compared to the control group (0.02 ± 0.04), the psoriasis groups exhibited significantly (P<0.05) higher values of the ratio (Table).

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[24,25]. In psoriasis, low serum Fe levels have been reported[15]. There are a few studies describing the role of transferrin and transferrin receptors in psoriasis[1,26].

Ferritin is known to be a proven marker of iron status[27,28]. Blood ferritin concentration is a biomarker of iron storage[29]. Ferritin and iron homeostasis is implicated in the pathogenesis of many disorders, including diseases involved in iron acquisition, transport and storage as well as in atherosclerosis, Parkinson's disease, Alzheimer disease and restless leg syndrome[30]. Serum ferritin protein is an acute phase reactant and apoferritin is known to be raised in conditions such as inflammation[21] and infection[31]. During acute phase response, IL-1β and TNF-α have been shown to influence the expression of ferritin[21].

Accelerated loss of nutrients from the hyperproliferation and desquamation of the epidermal layer of skin in psoriasis has been reported[32]. It can be speculated that Fe may be lost due to desquamation resulting in reduced ferritin levels in psoriasis. Fe is an important requirement of cell division. Increased utilization of Fe by the proliferating cells may also result in reduced levels of ferritin in psoriasis. Our results are in contradiction with other studies reporting an increased ferritin expression due to inflammation[21,33]. It is established that severe psoriasis may lead to nutrient depletion as reflected by the decreased haematocrit[32]. Our study reveals a significant reduction in the Fe levels in the serum of psoriasis patients. However, we have not evaluated tissue levels of Fe. A higher Fe level has been reported in the dermis of psoriasis patients when compared to controls[24]. Psoriatic arthritis cases were not included in our study. Further, we analysed the total Fe (bound and unbound) in the serum samples. These could be the reasons for difference in findings. However, our data on ferritin in psoriasis patients remained insignificant. Studies engaging larger patient groups may provide a better picture of whether or not ferritin has a role to play in the disease pathogenesis. It would be interesting to study the variations of both ferritin and Fe at tissue and serum levels and their correlation.

In order to understand the effect of ferritin on psoriasis severity, we calculated the ratio of ferritin to Fe in all psoriasis patients. We observed a significant increase in the Ferritin-Fe ratio in the psoriasis groups compared to controls. Further, an increasing trend in the ratio was seen between groups of severity though our results were not significant. Despite the diminished systemic Fe levels the ferritin levels were not reduced because inflammation induces a ferritin response in active psoriasis. This inflammation-related ferritin induction might increase with psoriasis disease severity leading to a tendency in increasing ferritin/Fe ratio. The ratio describes the effect of non-ferritin iron in psoriasis and probably this would distinguish subjects as mild, moderate or severe. However, in the representative population of 81 psoriasis patients, this finding was not significant.

We have not measured markers of inflammation such as proinflammatory cytokines like TNF-α and their possible effects on the expression of ferritin. Interpreting ferritin along with inflammatory markers in psoriasis may explain its role in psoriasis better. Although the importance of measurement of metals and metal binding proteins in psoriasis is evident from our results, the levels of Fe and ferritin did not prove to be useful in assessing severity of psoriasis. The ratio of ferritin to Fe may be useful in assessing psoriasis severity. However, larger study groups are needed to validate the appropriateness of these findings. Further studies correlating both tissue and serum levels of ferritin are needed to understand at what level ferritin may be involved in the pathogenesis of psoriasis. Our results suggest that larger prospective studies are required to evaluate the role of serum ferritin in psoriasis.

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