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Hepcidin expression in psoriasis patients

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Abstract

Background: Iron is an essential nutrient for mammals. Accelerated loss of nutrients through hyperproliferation and desquamation from the skin in psoriasis is known. Hepcidin is an important and recently discovered regulator of iron homeostasis. **Aims and Objectives:** The present study was undertaken to investigate the hepcidin expression in psoriasis patients. **Materials and Methods:** We examined peripheral blood cell counts, serum Fe, ferritin, interleukin-6 (IL-6) and hepcidin levels using respectively automated hematology analyzer, Iron assay on the AEROSET system, chemiluminescent microparticle immunoassay with automated analyzer, and enzyme-linked immunosorbent assay. **Results:** The independent comparison of Fe, ferritin, IL-6 and hepcidin levels in psoriasis patients and control group (healthy volunteers) revealed lower Fe and higher IL-6, hepcidin levels in psoriasis patients. No significant difference was seen in the ferritin level between the psoriasis and the control group. **Conclusions:** We think that studies on hepcidin expression in psoriatic plaques will contribute to our understanding the role of iron and hepcidin in the pathogenesis of psoriasis.

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Full Text

Introduction

Iron is an essential nutrient for mammals. Iron is a central component of heme groups, enzymes that are involved in respiration and deoxyribonucleic acid synthesis. [1] The largest iron pool in our body is heme, the metal is required for oxygen transport in hemoglobin. The second largest pool of iron is the non-heme form stored in ferritin. [2] However, the essential metal can be toxic to cells when present at high concentrations because of its ability to promote the formation of damaging oxidative radicals therefore, humans and animals have evolved highly efficient mechanisms for iron conservation. [3],[4] The daily losses of iron, 1-2 mg in adults, represent <0.1% of total iron in the human body, this loss occurs predominantly through desquamation of epithelial cells in the intestine and the skin, through minor bleeding and must be replaced from dietary sources to maintain iron balance. [5] Psoriasis is a

hyperproliferative skin disease with a markedly increased (5-6 times normal) rate of epidermal turnover. [6] Accelerated loss of nutrients in psoriasis through the hyperproliferation and desquamation of the epidermal layer of skin and decreased serum iron concentration has been reported. [7],[8]

Hepcidin is a recently discovered regulator of iron homeostasis. There is strong evidence that supports the important role of hepcidin in the etiology of the anemia of chronic disease. [9] We predicted that serum hepcidin levels in patients with psoriasis would differ from the healthy subjects with similar age and sex. Also, there is no study in the literature about the hepcidin in patients with psoriasis. The present study was undertaken to investigate the hepcidin expression in psoriasis patients.

Materials and Methods

A total of 46 psoriasis patients (21 females, 25 males, mean age 36.89 ± 6.76 years) consulting the Department of Dermatology, during September 2011 and February 2012 were included in the study. The control group consisted of healthy volunteers (n = 32, 15 females, 17 males, mean age 37.50 ± 7.11) having no significant medical illness. Persons with history of diabetes, hypertension, psychiatric disorders, cardiac problems, respiratory problems, endocrine diseases and other chronic skin disorders (other than psoriasis) were excluded. The duration of psoriasis varied from 4 years to 16 years. Psoriasis was graded according to the psoriasis area severity index (PASI), presenting at the time of blood collection. Patients who have the high PASI score were included study to investigate the relationship with hepcidin. Peripheral blood cell counts of patients and controls were studied using automated hematology analyzer (CELL-DYN Ruby-Abbott Diagnostics). Patients and control sera was stored at −20°C until analysis. Analysis of serum Fe was carried out using iron assay on the AEROSET System (Abbott Diagnostics). Serum ferritin was measured by chemiluminescent microparticle immunoassay method using automated analyzer (Abbott Diagnostics). Interleukin (IL-6) level in serum was measured by enzyme-linked immunosorbent assay (ELISA) test kit (eBioscience-Human IL-6 Platinum ELISA, Austria) according to the manufacturer's protocol. Serum hepcidin was measured using ELISA test kit (DRG Instruments GmbH, Germany). According to the manufacturer's protocol; 10 μL sample buffer added to each of 96-well plates, which were coated with a monoclonal antibody directed toward the antigenic site of the bioactive hepcidin 25 molecule. 20 μL of each standard, control and samples dispensed into appropriate wells and incubated for 30 min at room temperature on a plate shaker at ≈500 rpm. Following incubation, 150 μL assay buffer and 100 μL enzyme conjugate added to each of wells and incubated for 180 min at room temperature on a plate shaker at ≈500 rpm. Following incubation, wells rinsed for five times with distilled water (400 μL/well) and 100 μL enzyme complex dispensed into each well and incubated for 45 min at room temperature. After this incubation, wells rinsed for five times with distilled water again and 100 μL of substrate solution dispensed into each well and incubated for 30 min at room temperature, after incubation the enzymatic reaction stopped by adding 100 μL of stop solution and the absorbance (optical density) of each well determined at 450 ± 10 nm with a microtiter plate reader (Multiskan GO, Thermo Scientific) within 10 min. Standard curves of both ELISA tests were fitted using Titri ELISA software. The each fitted curve was then used to convert sample absorbance readings to concentrations. Comparisons between the psoriasis and the control group were carried out by independent t-test. All statistical analyses were performed using SPSS software for Windows (version 18.0).

Results

Mean PASI score of patients who participated in the study was high (mean score of PASI was 14.6 ± 2.7). When compared with the control group, Fe levels in the psoriasis groups were lower. This decrease was significant ($P < 0.05$). No significant difference was seen in the ferritin level between the psoriasis and the control group [Table 1]. Additionally, a gender-related statistically significant difference was not detected between the groups.

IL-6 and hepcidin levels (respectively 24.33 ± 0.87 pg/ml and 17.59 ± 0.33 ng/ml) in the psoriasis patients were found to be higher than the control group (10.59 ± 0.66 pg/ml and 12.97 ± 0.64 ng/ml) [Figure 1] and [Figure 2]. These differences were statistically significant ($P < 0.05$).{Figure 1}{Table 1} {Figure 2}

Discussion

Iron is essential for hemoglobin synthesis. Daily approximately 20-25 mg iron is needed for production about 200 billion erythrocytes. This requirement is mainly provided by macrophages recycling iron from senescent erythrocytes and in a small amount by intestinal iron absorption. [10] During critical illness anemia is results from two main factors: Inflammation and iron deficiency. [11] Iron deficiency anemia is the most common anemia worldwide. [10] Response to a variety of inflammatory stimuli can cause significant changes in iron metabolism. The most important of these are the redistribution of body iron out of the circulation and into reticuloendothelial macrophages. [12]

Recently, Lee and Beutler isolated a peptide from human urine and named it hepcidin (hepatic bactericidal protein). Hepcidin is encoded by the hepcidin antimicrobial peptide gene located on chromosome 19 (19q13) and humans have only a single copy of the hepcidin gene. [13],[14] Hepcidin is produced primarily in hepatocytes and transcriptionally regulated by IL-6 through the STAT-3 signaling pathway, enters the circulation and negatively regulates the export of iron in certain cell populations such as RE macrophages (important for iron storage) and duodenal enterocytes (iron absorption). [5],[12] In addition, hepcidin expression has been reported in polymorphonuclear neutrophils, macrophages and peripheral blood mononuclear cells. [15] Hepcidin is synthesized as a preprohepcidin; the signal peptide is cleaved leading to prohepcidin, which is further processed causing the 25 amino acids hepcidin. The predominant form is the 25 amino acid peptide, although shorter peptides with 20 and 22 amino acids are also detectable in human urine. [13] Hepcidin is a negative regulator of intestinal iron absorption and iron recycling by macrophages. [11] While the iron store and inflammatory regulation activate hepcidin transcription in the hepatocytes, hypoxia, anemia, excessive iron burden and increased erythropoiesis all negatively regulate hepcidin expression. The interplay between positive and negative stimulus is critical in determining the net hepcidin levels. [14],[16]

Reactive oxygen species (ROS) are involved in the pathogenesis of psoriasis. Iron and ROS are closely related and during the inflammation process, free iron is released from storage proteins such as ferritin. There is a relationship between ROS formation and iron, iron promotes the ROS formation responsible for frequent oxidative damage. [17] Psoriasis is considered a T helper-1 (Th1) disease, because of significantly high levels of Th1 cytokines (IL-1 interferon-γ, tumor necrosis factor-alpha [TNF-α]) have been reported in serum. [18] In a study, pro-inflammatory cytokines (IL-1 and TNF-α) injected mice developed hypoferraemia and anemia. [19] IL-6 is a small glycoprotein and produced in a broad spectrum of cells including immune cells (macrophages, dendritic cells and mast cells, B cells, T cells) and a variety of non-leukocytes cells (endothelial cells, fibroblasts, astrocytes, epithelial cells). [20] IL-6 has a wide variety of functions, acts not only on B cells but also on T cells and hepatocytes. [21] As in our study, increased blood levels of IL-6 has been shown in both the circulation and in lesional skin compared with controls in psoriasis patients. [22],[23] This high level of IL-6 may contribute to the height level of hepcidin.

PASI score has been used for the assessment of severity of psoriasis and as a tool to compare with serum markers like iron, ferritin, IL-6 and hepcidin in our study. Patients who have only high PASI score enrolled the study for determining the accuracy of our hypothesis; therefore, comparisons were not made with PASI score. Considering the increased IL-6 level, Th1-mediated pathogenesis and accelerated loss of nutrients from the hyperproliferation and desquamation of the epidermal layer of skin in psoriasis, it can be speculated that hepcidin may play a role in regulation of iron and consequently in the pathogenesis of psoriasis so the results of our study supports this claim. [7]

As in our female patients, anemia is a common condition in women of reproductive age, but in our study, more than half of patients (58.7%) were 36 years old and over so that we think that this situation did not affect our results in the statistical size. [24]

It is known that a mild to moderate normocytic normochromic anemia is characterized by decreased serum iron and transferrin and increased iron stores in the form of ferritin in chronic inflammatory diseases. [25] In a study, hepcidin was already found to be higher in 23 patients who have the anemia of chronic disease than in controls. [16] Considering the results of our study (No significant difference in the ferritin level, lower Fe levels, higher IL-6 and hepcidin levels), similar situation may have occurred in our patients who have a high-pass score.

References

1 Nairz M, Schroll A, Sonnweber T, Weiss G. The struggle for iron-A metal at the host-pathogen interface. Cell Microbiol 2010;12:1691-702.
2 Johnson EE, Wessling-Resnick M. Iron metabolism and the innate immune response to infection. Microbes Infect 2012;14:207-16.
3 Cherayil BJ. The role of iron in the immune response to bacterial infection. Immunol Res 2011;50:1-9.
4 Andrews NC. Disorders of iron metabolism. N Engl J Med 1999;341:1986-95.
5 Ganz T, Nemeth E. Hepcidin and disorders of iron metabolism. Annu Rev Med 2011;62:347-60.
6 Joshi R. Immunopathogenesis of psoriasis. Indian J Dermatol Venereol Leprol 2004;70:10-2.
7 Rashmi R, Yuti AM, Basavaraj KH. Enhanced ferritin/iron ratio in psoriasis. Indian J Med Res 2012;135:662-5.
8 Marks J, Shuster S. Iron metabolism in skin disease. Arch Dermatol 1968;98:469-75.
9 Hugman A. Hepcidin: An important new regulator of iron homeostasis. Clin Lab Haematol 2006;28:75-83.
10 Camaschella C, Pagani A. Iron and erythropoiesis: A dual relationship. Int J Hematol 2011;93:21-6.
11 Lasocki S, Baron G, Driss F, Westerman M, Puy H, Boutron I, *et al*. Diagnostic accuracy of serum hepcidin for iron deficiency in critically ill patients with anemia. Intensive Care Med 2010;36:1044-8.
12 Fleming RE. Iron and inflammation: Cross-talk between pathways regulating hepcidin. J Mol Med (Berl) 2008;86:491-4.
13 Atanasiu V, Manolescu B, Stoian I. Hepcidin - Central regulator of iron metabolism. Eur J Haematol 2007;78:1-10.
14 Lee PL, Beutler E. Regulation of hepcidin and iron-overload disease. Annu Rev Pathol 2009;4:489-515.
15 Pinto JP, Dias V, Zoller H, Porto G, Carmo H, Carvalho F, *et al*. Hepcidin messenger RNA expression in human lymphocytes. Immunology 2010;130:217-30.
16 Cheng PP, Jiao XY, Wang XH, Lin JH, Cai YM. Hepcidin expression in anemia of chronic disease and concomitant iron-deficiency anemia. Clin Exp Med 2011;11:33-42.
17 Leveque N, Robin S, Muret P, Mac-Mary S, Makki S, Berthelot A, *et al*. *In vivo* assessment of iron and ascorbic acid in psoriatic dermis. Acta Derm Venereol 2004;84:2-5.
18 Coimbra S, Figueiredo A, Castro E, Rocha-Pereira P, Santos-Silva A. The roles of cells and cytokines in the pathogenesis of psoriasis. Int J Dermatol 2012;51:389-95.
19 Cullis JO. Diagnosis and management of anaemia of chronic disease: Current status. Br J Haematol 2011;154:289-300.
20 Rincon M. Interleukin-6: From an inflammatory marker to a target for inflammatory diseases. Trends Immunol 2012;33:571-7.
21 Tanaka T, Narazaki M, Kishimoto T. Therapeutic targeting of the interleukin-6 receptor. Annu Rev Pharmacol Toxicol 2012;52:199-21.
22 Pietrzak AT, Zalewska A, Chodorowska G, Krasowska D, Michalak-Stoma A, Nockowski P, *et al*. Cytokines and anticytokines in psoriasis. Clin Chim Acta 2008;394:7-21.
23 Nakajima H, Nakajima K, Tarutani M, Morishige R, Sano S. Kinetics of circulating Th17 cytokines and adipokines in psoriasis patients. Arch Dermatol Res 2011;303:451-5.
24 Murray-Kolb LE, Beard JL. Iron deficiency and child and maternal health. Am J Clin Nutr 2009;89:946S-50.
25 Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med 2010;267:543-60.