ORIGINAL ARTICLE

Deranged iron status in psoriasis: the impact of low body mass

Malgorzata Ponikowska[1]*, Malgorzata Tupikowska[1], Monika Kasztura[2,3], Ewa A. Jankowska[2,3] & Jacek C. Szepietowski[1]

[1]Department of Dermatology, Venereology, and Allergology, Wroclaw Medical University, Wroclaw, Poland; [2]Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wrocław Medical University, Wrocław, Poland; [3]Cardiology Department, Centre for Heart Diseases, Military Hospital, Wrocław, Poland

Abstract

Background   Iron deficiency (ID) frequently complicates inflammatory-mediated chronic disorders, irrespective of anaemia. Psoriasis is a chronic, immune-mediated skin disease with systemic pro-inflammatory activation; thus, these patients may be prone to develop ID. ID adversely affects immune cells function, which can further contribute to disease progression. This study investigates iron status in psoriasis.

Methods   Serum concentrations of ferritin, transferrin saturation (Tsat), soluble transferrin receptor (sTfR), and hepcidin were assessed as the biomarkers of iron status in 39 patients with psoriasis (17 men, age: 47 ± 10 years) and 44 healthy subjects (30 men, age: 53 ± 6 years).

Results   Compared with healthy controls, patients with psoriasis demonstrated similar haematologic status but deranged iron status as evidenced by decreased Tsat and elevated sTfR (negative tissue iron balance) and low levels of hepcidin (depleted iron stores) (all $P < 0.05$ vs. controls). In patients, the levels of interleukin-6 (level of pro-inflammatory activation) significantly correlated with hepcidin ($R = 0.54$), but not with ferritin, Tsat, and sTfR. Biomarkers reflecting ID were not associated with the severity of the disease (assessed with the Psoriasis Area and Severity Index) but significantly correlated low body mass index (BMI). Patients with $BMI < 24 \, kg/m^2$ compared with those with $BMI \geq 24 \, kg/m^2$ demonstrated lower levels of ferritin (40 ± 30 vs. 186 ± 128 ng/mL, $P < 0.001$) and hepcidin (4.9 ± 2.3 vs. 10.7 ± 6.7 ng/mL, $P = 0.03$).

Conclusion   Psoriasis is associated with deranged iron status characterized by depleted iron stores with concomitant unmet cellular iron requirements. The magnitude of these abnormalities is particularly strong in patients with low body mass index. Whether iron deficiency may become a therapeutic target in psoriasis needs to be investigated.

Keywords   Psoriasis; Iron deficiency; Hepcidin; Inflammation; Lean patients

Psoriasis is one of the most common chronic diseases of the skin affecting up to 2% of the general population.[1,2] Psoriasis is a complex condition, with not yet fully understood pathophysiology, recently viewed as extending far beyond the skin-deep with numerous generalized abnormalities among which autoimmune mechanisms and pro-inflammatory activation seem to play a crucial role.[1–4] Clinical picture of the disease is a consequence of inadequate immune response directed against autoantigens with concomitant inflammatory reactions and changes affecting not only the skin but also numerous body organs and tissues.[1,4,5]

In recent years, there is growing interest in the role of iron status as a fundamental factor modifying the functioning of immune cells involved in innate immune response.[6,7] This immune mechanism (along with a modulating role of iron) is considered as an important pathophysiological element of chronic inflammatory diseases (e.g. chronic kidney disease and rheumatoid arthritis). On the other hand, chronic inflammatory diseases are often associated with deranged iron status reflecting iron deficiency (ID).[8,9] The major underlying mechanism here is linked with overexpression of hepcidin due to pro-inflammatory cytokines with subsequent development of functional ID (reflecting

inadequate iron supply to meet the demand despite normal body iron stores, because iron is trapped inside cells of the reticuloendothelial system and is unavailable for cellular metabolism).[10,11]

All these premises seem to place iron metabolism in the centre of the pathophysiological relationships underlying psoriasis. Surprisingly, iron status has never been comprehensively investigated in these patients. There are only few small observational studies,[12–15] which in fact have not investigated iron status itself, but rather anaemia in the context of potentially concomitant iron deficiency.[14,15] Moreover, the authors have used standard biomarkers of iron status (iron, ferritin, and transferrin saturation),[14] which although used in clinical practice, have several significant limitations in their interpretation when diagnosing iron status in the presence of inflammation.

Therefore, we aimed to investigate iron status among patients with psoriasis using both standard and novel biomarkers of iron status (hepcidin and soluble transferrin receptor) and relate these measures with the severity of the disease, the magnitude of pro-inflammatory activation, and the presence of extra-cutaneous complications (including psoriatic arthritis and low body weight), in comparison with healthy controls.

Material and methods

Study cohort

Thirty-nine patients with plaque-type psoriasis (17 men, age: 47 ± 10 years) were recruited for the study at the Department of Dermatology, Venereology, and Allergology, Wroclaw Medical University, Poland. Exclusion criteria included: (i) any acute or chronic illness that might influence iron metabolism (including known malignancy, infection, severe chronic kidney disease requiring dialysis, chronic cardiovascular diseases, and haematological diseases) and (ii) any treatment for anaemia or ID in the previous 12 months. All patients received standard management for psoriasis; severity of the disease was assessed with Psoriasis Area and Severity Index (PASI).[2,3] Psoriatic arthritis was diagnosed according to the standard criteria.[2,16] Low body weight was defined as body mass index (BMI) below 24 kg/m^2. Clinical characteristics of patients recruited for the study are presented in *Table* 1.

Forty-four healthy subjects (30 men, age: 53 ± 6 years) were recruited among volunteers, relatives, and colleagues of the staff or patients at the Centre for Heart Diseases, Military Hospital, Wrocław, Poland. The criteria for healthy subjects to be included in the study were the following: age ≥18 years, normal cardiovascular status, absence of any acute (during the previous 6 months) or chronic (at any time in the past) illness, and related therapy.

Table 1 Baseline characteristics of patients with psoriasis and healthy subjects

	Patients with psoriasis (n = 39)	Healthy subjects (n = 44)
Gender, men %	44	68
Age, years	47 ± 10	54 ± 6
Weight, kg	80 ± 17	80 ± 16
Height, m	1.70 ± 0.08	1.72 ± 0.09
BMI, kg/m^2	28.0 ± 5.7	26.7 ± 3.9
PASI,	9.3 ± 4.4	
Systemic treatment, %	38	
Psoriatic arthritis, %	28	

Data are presented as mean ± standard deviation or percentage. BMI, body mass index; PASI, Psoriasis Area and Severity Index.

The study protocol was approved by the local ethics committee, and all subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Haematological parameters, indices of iron status, and other laboratory measurements assessed in peripheral blood

In all patients and control subjects, venous blood samples were taken in the morning following an overnight fast and after at least 15 min of supine rest. Haematological measurements were made in fresh venous blood with EDTA and clotted blood. After centrifuging, the plasma and serum were collected and frozen at −70°C until further laboratory analyses.

The following haematinics were measured using an automatic system ADVIA 120 (Siemens, Healthcare Diagnostics, Deerfield, IL, USA): haemoglobin concentration (g/dL), haematocrit (%), red blood cells (T/L), mean corpuscular volume (fL), mean corpuscular haemoglobin (pg), and mean corpuscular haemoglobin concentration (g/L). Anaemia was defined as haemoglobin level <12 g/dL in women and <13 g/dL in men.[17]

The following standard blood biomarkers reflecting iron metabolism were measured directly: serum concentrations of ferritin (μg/L), iron (μg/dL), and total iron binding capacity (TIBC, μg/dL). Transferrin saturation (Tsat) was calculated as the ratio of serum iron (μg/dL) and TIBC (μg/dL) multiplied by 100 and expressed as a percentage. Serum ferritin was measured using an immunoassay based on electrochemiluminescence with the Elecsys 2010 System (Roche Diagnostics GmbH, Mannheim, Germany). Serum iron and TIBC were assessed using a substrate method with Feren S (Thermo Fisher Scientific, Waltham, MA, USA). Circulating iron bound to transferrin (expressed as Tsat) reflects the amount of iron available to metabolizing cells.[9,18,19] The interpretation of circulating ferritin levels

should always take into account its dual physiological role as the major iron storage molecule and as the acute phase protein, which expression is increased in response to inflammatory stimuli, regardless of the amount of stored iron.[9,18,19]

Serum soluble transferrin receptor (sTfR, mg/L) was measured using immunonephelometry (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois, USA). Increased circulating sTfR (originating from all cells metabolizing iron) is a sensitive indicator of ID and quantitatively reflects tissue iron demand along with the erythroid proliferation rate, but not body iron stores.[20,21]

Serum hepcidin (ng/mL) was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) (BACHEM). This ELISA method was validated with a gold standard for hepcidin assessment, namely liquid chromatography mass spectrometry developed at King's College London, confirming a strong correlation between the measurements performed using the liquid chromatography mass spectrometry and the BACHEM assay in patients with chronic kidney diseases and healthy subjects.[22] Increased serum hepcidin may be due to either inflammation or/and excessive iron stores[12,13]; low-circulating hepcidin reflects specifically depleted body iron stores with or without concomitant anaemia; the lower the hepcidin, the more profoundly depleted iron stores in patients with chronic diseases.[23,24]

In this study, we also used the definition of ID applied in previous studies in patients with chronic diseases[8,23,24] based on serum ferritin and Tsat (serum ferritin < 100 mg/L, or serum ferritin 100–299 mg/L with Tsat $< 20\%$) in additional analyses.

Serum level of interleukin 6 (IL-6, pg/mL) was measured using a commercially available ELISA (R&D Systems, Minneapolis, Minnesota, USA). Estimated glomerular filtration rate (mL/min/1.73 m^2) was calculated using the Modification of Diet in Renal Disease equation.[25]

Statistical analysis

The normality of the distributions of continuous variables was tested using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution were expressed as means with standard deviations. The remaining continuous variables with a skewed distribution were expressed as medians with upper and lower quartiles. For further analyses, these variables were log-transformed in order to normalize their distribution. The categorical variables were expressed as numbers with percentages. The statistical significance of differences between the groups was tested using Student's *t*-test, Mann–Whitney U test, or the χ^2 test, where appropriate. The associations between variables were assessed using the Spearman rank correlatory coefficients. All statistical analyses were performed with Statistica 10 (Statsoft, Tulsa, OK, USA). A value of $P < 0.05$ was considered statistically significant.

Results

Baseline clinical characteristics of patients with psoriasis and control subjects are shown in *Table* 1. Patients were younger than controls (mean: 47 vs. 54 years). Clinical severity of the disease was evaluated with the PASI, with baseline ranging from 2.1 to 19.8 (mean: 9.3 ± 4.4); 11 (28%) patients had psoriatic arthritis, and 15 (38%) received systemic treatment of the disease.

Iron status in patients with psoriasis and healthy controls

Compared with healthy controls, patients with psoriasis had similar haematinics (haemoglobin and haematocrit), slightly bigger mean corpuscular volume, and trends towards lower red blood count and mean corpuscular haemoglobin concentration (*Table* 2). Only two (5%) patients had mild anaemia (haemoglobin levels 9.9 and 11.9 g/dL, respectively).

There was no difference in the ferritin levels between groups, but patients demonstrated significantly lower Tsat ($P < 0.001$), elevated TIBC ($P < 0.001$) and sTfR levels (p = 0.01), and markedly decreased hepcidin levels ($P < 0.0001$) (*Table* 2).

Applying the definition of ID used in the previous studies in chronic diseases (based on serum ferritin and Tsat—see the Material and Methods section), 20 (51%) patients with psoriasis fulfilled this definition.

None of the iron-related biomarkers correlated with the severity of the disease assessed with PASI ($P > 0.1$ for all correlatory coefficients). Also, patients receiving systemic treatment for psoriasis did not differ from not-treated patients in iron-related biomarkers ($P > 0.1$ in all comparisons).

Patients with psoriasis presented only slightly elevated levels of IL-6: mean 4.1 ± 6.2 pg/mL, range 0–19 pg/mL. Among iron-related biomarkers, hepcidin ($R = 0.54$, $P < 0.001$) and ferritin ($R = 0.44$, $P = 0.001$) significantly correlated with levels of IL-6.

Eleven (28%) patients had psoriatic arthritis complicating the natural course of the disease, and they demonstrated elevated levels of IL-6 (6.3 ± 5.6 vs. 2.4 ± 5.4 pg/mL, patients with vs. without psoriatic arthritis, respectively, $P < 0.05$). Neither haematologic parameters nor iron-related biomarkers were different between patients with and without psoriatic arthritis ($P > 0.2$ in all comparisons).

Iron status in patients with low body mass index

Body mass index significantly correlated with ferritin ($R = 0.61$, $P < 0.001$) and hepcidin ($R = 0.51$, $P = 0.005$) levels. Eleven (28%) patients had low BMI (i.e. BMI < 24 kg/m^2). Compared with patients with BMI ≥ 24 kg/m^2, lean patients demonstrated

Table 2 Comparison of haematological parameters, iron status biomarkers, and other laboratory parameters between healthy subjects and patients with psoriasis

	Healthy subjects ($n = 44$)	Patients with psoriasis ($n = 39$)	P
Haematological parameters			
Haemoglobin, g/dL	14.4 ± 1.2	14.1 ± 1.2	0.27
Haematocrit, %	42.5 ± 3.3	42.5 ± 3.0	0.50
RBC count, T/L	4.8 ± 0.4	4.7 ± 0.4	0.07
MCV, fL	88.2 ± 3.2	90.2 ± 5.0	0.04
MCH, pg	29.9 ± 1.3	30.3 ± 1.9	0.21
MCHC, g/dL	33.9 ± 1.1	33.5 ± 1.1	0.06
Iron status biomarkers			
Ferritin, ng/mL	138 (82; 218)	133 (52; 231)	0.45
Iron, μg/dL	124 ± 35	119 ± 50	0.29
TIBC, μg/dL	293 ± 44	365 ± 38	<0.001
Tsat, %	43 ± 11	33 ± 14	<0.001
sTfR, mg/L	1.04 (0.94; 1.16)	1.18 (1.01; 1.42)	0.01
Hepcidin, ng/mL	36.1 (27.6; 50.1)	7.1 (3.5; 14.3)	<0.001
Other laboratory parameters			
IL-6, pg/mL	—	4.1 ± 6.2	
Creatinine, μg/dL	0.9 ± 0.2	0.9 ± 0.1	0.96
eGFR, mL/min/1.73 m^2	91.7 ± 20.8	88.2 ± 18.5	0.45

Data are presented as mean ± standard deviation or median with lower and upper quartiles were appropriate; P values for between-group comparison using Mann–Whitney U test were presented.
eGFR, estimated glomerular filtration rate; IL-6, interleukin 6; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration TIBC, total iron binding capacity; MCV, mean corpuscular volume; RBC, red blood cells; sTfR, soluble transferrin receptor; Tsat, transferrin saturation;

markedly deranged iron status reflecting iron deficiency—it was evidenced by the following: low levels of ferritin ($P < 0.001$) and hepcidin ($P = 0.03$) and strong trend towards low Tsat ($P = 0.06$) and elevated sTfR ($P = 0.06$) (Table 3).

Applying definition of ID based on serum ferritin and Tsat (see the Material and Methods section), 9 (82%) patients with low BMI had ID vs. 11 (39%) with BMI ≥ 24 kg/m^2 ($P = 0.02$) (Figure 1).

Discussion

The major novel findings of this study are the following: (i) patients with psoriasis demonstrated deranged iron status, which can be characterized by decreased transferrin saturation and elevated sTfR (both reflecting negative tissue iron balance) and low levels of hepcidin (reflecting depleted iron

Figure 1 Prevalence of iron deficiency defined as serum ferritin <100 mg/L, or serum ferritin 100–299 mg/L with Tsat <20% in the whole group of patients with psoriasis and comparison between patients with body mass index (BMI) <24 vs. ≥24 kg/m^2.
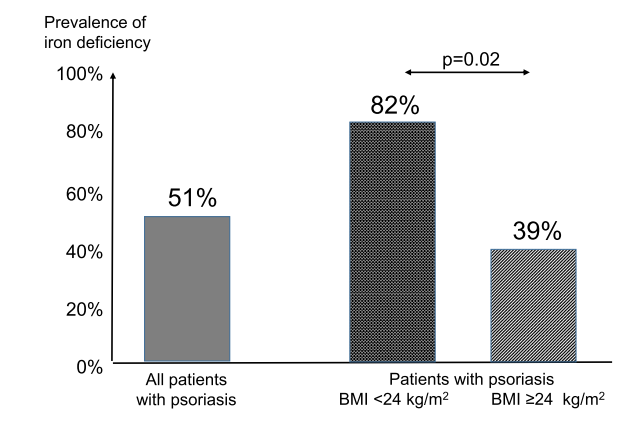
Table 3 Comparison of iron status biomarkers between psoriatic patients with body mass index < 24 and ≥24.0 kg/m^2

	Patients with BMI < 24 kg/m^2 ($n = 11$)	Patients with BMI ≥ 24 kg/m^2 ($n = 28$)	P
Ferritin, ng/mL	40 (13; 52)	160 (75; 263)	<0.001
Iron, μg/dL	100 ± 45	128 ± 55	0.09
TIBC, μg/dL	371 ± 32	357 ± 42	0.30
Tsat, %	27 ± 12	36 ± 15	0.06
sTfR, mg/L	1.45 (1.11; 1.79)	1.15 (0.95; 1.31)	0.06
Hepcidin, ng/mL	6.0 (3.0; 6.4)	10.7 (5.1; 16.4)	0.03

Data are presented as mean ± standard deviation or median with lower and upper quartiles where appropriate; P values for between-group comparison using Mann–Whitney U test were presented.
TIBC, total iron binding capacity; Tsat, transferrin saturation; sTfR, soluble transferrin receptor.

stores), and such composition of iron-related biomarkers are typical for iron deficiency; and (ii) iron deficiency in psoriatic patients was not related to severity of the disease, but predominantly determined by patients low body mass index. This point is interesting, because no treatment is currently available for cachexia, that is, involuntary weight loss or *a-priori*-low body weight,[26,27] but also, nutrition and rehabilitation offer only few advances at this stage.[28,29] Nevertheless, there are some promising new developments,[30,31] and many new experimental therapies are in development.[32]

Psoriasis represents an autoimmune disease where primary abnormalities are seen within the skin. However, there is increasing evidence that skin lesions constitute an element of a complex syndrome, and concomitant extra-cutaneous pathologies are crucial (if not critical) for disease progression, quality of life, and prognosis of these patients.[1,2,4,5] Impaired immune response is accompanied by marked inflammatory reaction with concomitant systemic pro-inflammatory milieu observed in patients with psoriasis.[1,4]

Only recently, there is growing interest in iron status in chronic, immune-mediated disorders. However, in contrast to previous reports focusing mainly on potentially deleterious effects of iron overload and linking pathophysiology of several chronic diseases to iron excess,[33,34] there is now mounting evidence placing iron deficiency with subsequent clinical consequences as the key abnormality of such diseases.[8,9,23,24] It has been demonstrated that deranged iron status is a fundamental element underlying dysfunction of immune cells involved in innate immune response (monocytes and derivates).[6,7] Interestingly, both innate immune response and processes of iron metabolism (as well as an interplay between them) belong to evolutionary conservative mechanisms, which as they tackle critically important for survival processes, have remained virtually unchanged during the phylogenesis. Additionally, patients with chronic diseases are prone to become iron deficient as a consequence of a depletion of iron stores but more frequently as a result of impaired iron metabolism in the course of underlying inflammatory processes.[8,9,11]

We have hypothesized that taking into consideration underlying systemic pathophysiological processes in psoriasis this chronic entity may be characterized by markedly deranged iron status. To test this, we investigated a group of patients presenting with fairly broad clinical spectrum of the disease (including disease severity and medical management) and applied novel biomarkers of iron status (hepcidin and soluble transferrin receptors). Surprisingly, complex evaluation of iron status has never been performed is patients with psoriasis.

We observed that psoriatic patients frequently presented the picture of iron deficiency. Once we applied a previous definition of ID based on low ferritin levels and Tsat,[8,24] it appeared that half of our population tended to have ID. However, we are aware that the approach may well not be optimal. Serum ferritin reflects body iron stores, but either inflammation or oxidative stress (both present in psoriasis) may artificially increase its concentrations, regardless of actual iron status.[18,19] Importantly, high circulating ferritin provides no insight about the amount of intracellular iron available for metabolic (including energetic) needs. Tsat is a direct measure of the circulating iron pool, but it is unclear if this reflects the amount in peripheral tissues.[18,19] Thus, we used other biomarkers—hepcidin and soluble transferrin receptor—that we believe can better characterize iron status in psoriasis.

Hepcidin is acknowledged as the key regulator of iron metabolism. Hepcidin, upon binding to the only known cellular iron export protein, ferroportin, results in a ferroportin degradation and the blockage of cellular iron egress with a decrease of duodenal iron absorption and retention of iron in the reticuloendothelial system.[10,11] As a consequence, circulating iron concentrations and iron availability to target tissues are significantly reduced.[10,11] Inflammatory stimuli (among which IL-6 is the most potent) are able to induce the hepatic expression of hepcidin, which seems to be the mechanism underlying the development of functional ID and anaemia in patients with chronic inflammatory diseases.[8,10,11] Interestingly, in our study, patients with psoriasis had markedly low levels of hepcidin. At the same time, they demonstrated correlation between IL-6 and hepcidin levels, which indirectly confirms intact regulatory mechanisms mentioned before and forms the background to believe that low hepcidin levels reflecting depleted iron stores (absolute ID) in patients is not related to pro-inflammatory status.

It is worthy of noting that patients with psoriasis with low hepcidin did not demonstrate significantly impaired haematopoiesis as assessed based on haemoglobin level and red cell indices, which suggests that in psoriasis, depleted iron stores occur in patients without concomitant anaemia. Circulating hepcidin levels were very low, indicating severely depleted iron stores.

At the same time, psoriatic patients demonstrated elevated levels of sTfR that did not correlate with the presence of anaemia nor with pro-inflammatory activation. It strongly suggests that the major source of transferrin receptors shed into circulation is not the erythron (as psoriatic patients had normal haematinics), but it reflects the extra-haematopoietic origin of circulating sTfR and unmet iron needs within non-haematopoietic cells. We have previously reported a similar pattern of ID is patients with heart failure that carried ominous clinical consequences.[23,35]

Interestingly, deranged iron status was not related to disease severity evaluated with PASI score, and also once patients receiving systemic treatment and/or those who developed psoriatic arthritis were analysed separately. The magnitude of changes reflecting iron deficiency was particularly strong in psoriatic patients with low BMI. We did not study cachexia in the strictest sense, which is frequent in

many chronic diseases[36,37] and associated with high costs,[38] but we observed that lean patients with psoriasis demonstrated features of depleted iron stores (low circulating hepcidin and ferritin) at the same time having unmet needs for iron at the periphery (elevated levels of sTfR). Additionally, the vast majority of them (>80%) had ID defined according to the criteria used in the previous studies.[23,24] This pattern was related neither to pro-inflammatory activation (no significant difference in IL-6 between patients with BMI <24 and ≥24 kg/m^2—data not shown) nor to any other clinical variable we have analysed. Taking into consideration the important role iron plays in numerous processes engaged into pathophysiology of psoriasis, it may well be hypothesized that profound ID seen in these patients may further deteriorate clinical status, leading to disease progression. We are not aware of any previous report linking iron status to low body mass index in patients with chronic disorders. Whereas there are studies showing that obese patients develop functional ID associated with inflammatory response,[39,40] the high prevalence of absolute ID in psoriatic patients is a novel and intriguing finding. Its origin remains unclear. It may be a consequence of generalized malnourishment, but other unclear pathomechanisms may contribute here, and their elucidation seems to be of a particular importance.

Our study was not designed to investigate the mechanisms that may underlie iron deficiency in psoriasis. Naturally, one can speculate that as in the other chronic diseases, pro-inflammatory activation may be the leading cause. Our data seem to contradict such relationship. Some previous studies reported accelerated loss of nutrients from the hyperproliferation and desquamation of the epidermal layer of skin in psoriatic patients, which may lead to ID.[41] As mentioned before, malnutrition may be involved in patients with low BMI. Further studies are needed to confirm iron deficiency in psoriasis and reveal underlying mechanisms.

In conclusion, psoriasis is associated with deranged iron status characterized by depleted iron stores with concomitant unmet cellular iron requirements. The magnitude of these abnormalities is particularly evident in patients with low body mass index. The deranged pattern of iron status seen in psoriatic patients reflects mainly absolute ID associated with very low circulating hepcidin and is not accompanied by augmented inflammation. Whether ID may become a therapeutic target in psoriasis needs to be investigated.

Acknowledgement

References

1. Boehncke WH, Schön MP. Psoriasis. *Lancet* 2015. pii: S0140-6736(14)61909-7. doi: 10.1016/S0140-6736(14)61909-7.

2. Lubrano E, Cantini F, Costanzo A, Girolomoni G, Prignano F, Olivieri I, *et al.* Measuring psoriatic disease in clinical practice. An expert opinion position paper. *Autoimmun Rev* 2015. pii: S1568-9972(15)00118-4. doi: 10.1016/j.autrev.2015.05.010.

3. Gulliver W, Lynde C, Dutz JP, Vender RB, Yeung J, Bourcier M, *et al.* Think beyond the skin: 2014 Canadian expert opinion paper on treating to target in plaque psoriasis. *J Cutan Med Surg* 2015; **19**: 22–27.

4. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. *Cytokine* 2015;**73**: 342–350.

5. Mosca S, Gargiulo P, Balato N, Di Costanzo L, Parente A, Paolillo S, *et al.* Ischemic cardiovascular involvement in psoriasis: a systematic review. *Int J Cardiol* 2015; **178**: 191–199.

6. Nairz M, Haschka D, Demetz E, Weiss G. Iron at the interface of immunity and infection. *Front Pharmacol* 2014 Jul 16; **5**: 152.

7. Dutra FF, Bozza MT. Heme on innate immunity and inflammation. *Front Pharmacol* 2014; **5**: 115.

8. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2013; **34**: 816–826.

9. Besarab A, Hörl WH, Silverberg D. Iron metabolism, iron deficiency, thrombocytosis, and the cardiorenal anemia syndrome. *Oncologist* 2009; **14**: 22–33.

10. Hentze MW, Muckenthaler MU, Galy B, Camaschella C. Two to tango: regulation of mammalian iron metabolism. *Cell* 2010; **142**: 24–38.

11. Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Haematol* 2009; **122**: 78–86.

12. Molin L, Reizenstein P. Hematological changes in psoriasis. Secondary anemia, XVIII. *Acta Derm Venereol* 1974; **54**: 465–469.

13. 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. *Clin Chim Acta* 2009; **405**: 66–70.

14. Rashmi R, Yuti AM, Basavaraj KH. Enhanced ferritin/iron ratio in psoriasis. *Indian J Med Res* 2012; **135**: 662–665.

15. Dilek N, Dilek AR, Sahin K, Kaklıkkaya N, Saral Y. Hepcidin expression in psoriasis patients. *Indian J Dermatol* 2014; **59**: 630.

16. Huynh D, Kavanaugh A. Psoriatic arthritis: current therapy and future approaches. *Rheumatology (Oxford)* 2015; **54**: 20–28.

17. Blanc B, Finch CA, Hallberg L. Nutritional anaemias. Report of a WHO scientific group. *WHO Tech Rep Ser* 1968; **405**: 1–40.

18. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol* 2006; **1**: S4–S8.

19. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010; **116**: 4754–4761.

20. Speeckaert MM, Speeckaert R, Delanghe JR. Biological and clinical aspects of soluble transferrin receptor. *Crit Rev Clin Lab Sci* 2010; **47**: 213–228.

21. Koulaouzidis A, Said E, Cottier R, Saeed AA. Soluble transferrin receptors and iron deficiency, a step beyond ferritin. A systematic review. *J Gastrointestin Liver Dis* 2009; **18**: 345–352.

22. Rumjon A, Bansal SS, Malyszko J, Macdougall IC. Intra-individual variability of hepcidin in haemodialysis patients using mass spectrometry and ELISA. *J Amer Soc Nephrol* 2011; **22**: 481A–482A.

23. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von Haehling S, *et al.* Iron status in patients with chronic heart failure. *Eur Heart J* 2013; **34**: 827–834.

24. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, *et al.* FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–2448.

25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–470.

26. Morley JE, von Haehling S, Anker SD. Are we closer to having drugs to treat muscle wasting disease? *J Cachexia Sarcopenia Muscle* 2014; **5**: 83–87.

27. Ebner N, Steinbeck L, Doehner W, Anker SD, von Haehling S. Highlights from the 7th Cachexia Conference: muscle wasting pathophysiological detection and novel treatment strategies. *J Cachexia Sarcopenia Muscle*– 2014; **5**: 27–34.

28. Wakabayashi H, Sakuma K. Rehabilitation nutrition for sarcopenia with disability: a combination of both rehabilitation and nutrition care management. *J Cachexia Sarcopenia Muscle* 2014; **5**: 269–277.

29. de Campos-Ferraz PL, Andrade I, das Neves W, Hangai I, Alves CR, Lancha AH Jr. An overview of amines as nutritional supplements to counteract cancer cachexia. *J Cachexia Sarcopenia Muscle* 2014; **5**: 105–110.

30. Pietra C, Takeda Y, Tazawa-Ogata N, Minami M, Yuanfeng X, Duus EM, *et al.* Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. *J Cachexia Sarcopenia Muscle* 2014; **5**: 329–337.

31. Pötsch MS, Tschirner A, Palus S, von Haehling S, Doehner W, Beadle J, *et al.* The anabolic catabolic transforming agent (ACTA) espindolol increases muscle mass and decreases fat mass in old rats. *J Cachexia Sarcopenia Muscle* 2014; **5**: 149–158.

32. Palus S, von Haehling S, Springer J. Muscle wasting: an overview of recent developments in basic research. *J Cachexia Sarcopenia Muscle* 2014; **5**: 193–198.

33. Meroño T, Gómez L, Sorroche P, Boero L, Arbelbide J, Brites F. High risk of cardiovascular disease in iron overload patients. *Eur J Clin Invest* 2011 May; **41**: 479–486.

34. Arija V, Fernández-Cao JC, Basora J, Bulló M, Aranda N, Estruch R, *et al.* Excess body iron and the risk of type 2 diabetes mellitus: a nested case-control in the PREDIMED (PREvention with MEDiterranean Diet) study. *Br J Nutr* 2014; **112**: 1896–1904.

35. Jankowska EA, Kasztura M, Sokolski M, Bronisz M, Nawrocka S, Oleśkowska-Florek W, *et al.* Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure. *Eur Heart J* 2014; **35**: 2468–2476.

36. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. *J Cachexia Sarcopenia Muscle* 2014; **5**: 253–259.

37. von Haehling S, Anker SD. Prevalence, incidence and clinical impact of cachexia: facts and numbers-update 2014. *J Cachexia Sarcopenia Muscle* 2014; **5**: 261–263.

38. Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. *J Cachexia Sarcopenia Muscle* 2013; **4**: 173–178.

39. Aigner E, Feldman A, Datz C. Obesity as an emerging risk factor for iron deficiency. *Nutrients* 2014; **6**: 3587–3600.

40. Nikonorov AA, Skalnaya MG, Tinkov AA, Skalny AV. Mutual interaction between iron homeostasis and obesity pathogenesis. *J Trace Elem Med Biol* 2015; **30**: 207–214.

41. Prystowsky JH, Orologa A, Taylor S. Update on nutrition and psoriasis. *Int J Dermatol* 1993; **32**: 582–586.