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Review

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Is iron deficiency involved in the pathogenesis of chronic inflammatory skin disorders?

Czy niedobór żelaza ma udział w patogenezie przewlekłych chorób zapalnych skóry?

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Summary

Iron is an essential microelement in the human body due to its role in hematopoiesis, involvement in energetic processes, synthesis and decomposition of lipids, proteins and nuclear acids. Iron deficiency (ID) is common in healthy populations and also frequently coincides with natural course of chronic diseases. The former is typically present when the overall iron body storages are exhausted (absolute ID), most often due to insufficient iron supply, malabsorption or increased blood loss and coincides with anemia. The latter is a result of defected iron metabolism and reflects a condition, when despite adequate iron stores in the body, iron itself is trapped in the reticuloendothelial system, becoming unavailable for the metabolic processes. It typically occurs in the presence proinflammtory activation in chronic conditions such as chronic kidney disease, inflammatory bowel disorders, malignancies and heart failure.

To date there are very few publications concerning the potential role of ID in chronic dermatological disorders. We have recently found that patients with psoriasis demonstrate pattern of ID which can be characterized by negative tissue iron balance with depleted iron stores in the body. Interestingly, presence of ID was not related to the severity of psoriasis, but rather determined by patients low body mass index. We are currently investigating the hypothesis that derangements in iron metabolism resulting in ID can be also present in hidradenitis suppurativa – the other chronic dermatologic disease associated with inflammatory and autoimmune activation.

Keywords: **iron deficiency • inflammation • dermatology • psoriasis • hidradenitis suppurativa • skin diseases**

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Abbreviations: **ID** – iron deficiency, **DMT1** – divalent metal transporter 1, **TfR** – transferrin receptor, **IL-6** – interleukin-6, **Tsat** – transferrin saturation, **HS** – hidradenitis suppurativa

IRON METABOLISM

Iron is an essential microelement in human body due to its role in hematopoiesis, involvement in metabolic pathways of oxidative metabolism, synthesis and decomposition of lipids, proteins and nuclear acids. It is also the component of oxidizing and reducing enzymes and iron-containing proteins such as hemoglobin, myoglobin and various cytochromes [3, 7].

The total amount of body iron is estimated at 3–4 g, vast majority of which (~75%) is in the hemoglobin of red blood cells, muscles myoglobin and other tissues. The remaining pool is stored in hepatocytes and macrophages of the reticuloendothelial system [10].

In humans dietary uptake of iron is approximately 1-2 mg daily, all of which is absorbed in duodenum. It remains in balance with iron loss, mainly through skin desquamation and, to a lesser extent, blood loss. Due to various retrieval kidney mechanisms, urinary iron excretion seems to be vestigial [12]. Dietary iron is mostly nonorganic in oxidized form (Fe^{3+}) and must be reduced to Fe^{2+} to become bioavailable for intestinal absorption. This process is carried out by ferrireductases facilitated by vitamin C as a coenzyme. Reduced iron is subsequently transported by divalent metal transporter 1 into enterocyte and, depending on current iron status, can either remain inside bind to iron storage protein – ferritin or – if tissue iron demand is high – is transported to the circulation [1, 26, 39]. This transport across basolateral membrane requires iron export protein – ferroportin. Then, iron is oxidized to Fe^{3+} by hephaestin and ones in bloodstream, binds to plasma transporter transferrin and is available for redistribution. The amount of circulating iron is relatively small (~3–4 mg) but extremely dynamic and corresponds to tissue and erythropoietic needs as required in given state [11].

There are two major pools of iron in the body – utilized and stored – which interacts under tight regulatory mechanisms. The pool of iron utilized by the body comprises circulating iron bound to transferrin and intracellular iron, which is used by haematopoietic and non-haematopoietic cells for the metabolic processes. Iron bound to transferrin is delivered to the peripheral tissues and enters the cells [27]. The crucial agent in sustaining this process is transferrin receptor, a carrier protein involved in iron import into target cells in the specific receptor-mediated endocytosis as a response to individual intracellular iron needs. In humans two types of TfRs have been characterized – TfR1 (considered to be the major element of iron cellular intake, dependent of its concentration inside target cell) and TfR2 (independent of cellular iron concentration) [11]. In the endosomes, ferric iron (Fe^{3+}) is reduced into ferrous iron (Fe^{2+}) and transported into cytoplasma forming labile iron pool readily used in the mitochondrial energetic processes, incorporated into enzymes or stored [5]. The majority of the stored iron comes from the recycling processes which are essential in maintaining its homeostasis – senescent erythrocytes are degraded by macrophages in the mononuclear phagocyte system mainly in the spleen and lymph nodes. Then, iron can be stored in the non-toxic form in the ferritin shells mainly in the liver, bone marrow and spleen. Thus, serum ferritin reflects body iron storages, but is also an acute-phase protein that is produced by the liver when inflammation occurs [10].

Iron homeostasis in the body is tightly orchestrated by complex, interrelated mechanisms, in which hepcidin-related pathways and intracellular iron-regulatory proteins play a pivotal role. Hepcidin – a liver-synthesized peptide hormone – is considered to be the key regulator (negative regulation) of dietary iron absorption in enterocytes, iron recycling from macrophages and its mobilization and usage from body storages, mainly hepatocytes of the liver [34]. Bound to ferroportin, hepcidin inhibits iron flux to blood plasma, and therefore its availability for the tissues. Ferroportin is the only iron exporter discovered so far and its activity is inhibited by hepcidin. Hepcidin production is affected by various processes reflecting general body iron status and erythropoietic needs. When iron levels are high, the production of hepcidin is enhanced, which results in limited iron absorption and its release from the body storages. Analogically, in the case of iron deficiency, hepcidin production is suppressed. Importantly, hypoxia and non-effective erythropoiesis inhibit hepcidin production, whereas inflammation increases it [35].

IRON DEFICIENCY IN CHRONIC DISEASES

There are two types of iron deficiency – absolute and functional. The former is defined as a condition in which the overall iron body storages are exhausted, most often due to insufficient iron supply, malabsorption (e.g. due to gastric/gut resection, celiac disease, chronic use of protein pump inhibitors) or increased blood loss (e.g. due to chronic use of aspirin/nonsteroidal anti-inflammatory drugs, gastrointestinal malignancies). The latter is a result of a defected iron metabolism and reflects in a condition where, despite adequate iron stores in the body, iron itself is trapped within the reticuloendothelial system, becoming unavailable for metabolic processes. This typically occurs in the presence of inflammation and a crucial role in this process is attributed mainly to interleukin-6 and also to the other proinflammatory cytokines, such as interleukins -1, and -22 and tumor necrosis factor-alpha, which cause an increase of hepatic hepcidin synthesis and release, leading to a decrease in iron recycling [37]. Iron is being accumulated in the reticuloendothelial system unavailable for tissue use and unable to meet current metabolic needs [35]. As discussed above, hepcidin also downregulates ferroportin expression, leading to the inhibition of dietary iron absorption. Proinflammatory stimulation with subsequent cytokines synthesis correlate with the decreased amount of erythoid progenitors, which consequently disrupts the entire process of

erythropoiesis, therefore resulting in so-called anaemia of chronic illnesses, which is often an typical element of ID in various chronic conditions such as chronic kidney disease, inflammatory bowel disorders, malignancies and heart failure [4, 9].

IRON DEFICIENCY COMPLICATING CHRONIC DERMATOLOGIC DISORDERS

To date there are very few publications concerning the potential role of ID in chronic dermatological disorders in which pathogenesis is related to inflammation.

In our recent study, we investigated iron status in psoriatic patients [31]. Also, we reported our preliminary results of deranged iron status in patients with hidradenitis suppurativa [30]. Previously, there were few small observational studies linking anaemia with ID; however, they all yielded inconclusive results [6, 24, 33]. Psoriasis is a complex chronic dermatologic condition which is now viewed as extending far beyond the skin with numerous generalized abnormalities, among which auto-immune mechanisms and proinflammatory activation play an important pathophysiological role [2, 22]. Importantly, preserved iron status is a fundamental factor modifying the functioning of immune cells involved in innate immune response [8, 28]. Additionally, patients with chronic diseases are prone to develop ID as a consequence of proinflammatory-driven derangements of iron utilization and absorption [15, 18, 29]. All these premises form a strong background to link deranged iron metabolism with the pathophysiology of psoriasis.

To test this hypothesis, we investigated patients presenting broad clinical spectrum of psoriasis and applied comprehensive assessment of iron status using blood biomarkers [31]. Our major novel findings were as follows: a. patients with psoriasis demonstrated deranged iron status, which can be characterized by decreased transferrin saturation and elevated soluble transferrin receptor (both reflecting negative tissue iron balance) and low levels of hepcidin (reflecting depleted iron stores); such composition of iron-related biomarkers are typical for ID; b. the presence of ID was not related to the severity of psoriasis, but was rather determined by patients with low body mass index.

Applying a widely accepted definition for the evaluation of ID in chronic disorders based on low ferritin levels and low transferrin saturation (serum ferritin <100 mg/L, or serum ferritin 100–299 mg/L with Tsat <20%), we qualified half of our psoriatic patients as having ID. A similar prevalence of ID was reported in the other chronic disorders, such as heart failure or chronic kidney disease [17, 18].

For better characterization of iron status, we also used other biomarkers – hepcidin and a soluble transferrin receptor. Interestingly, patients with psoriasis demonstrated markedly low levels of hepcidin, which was rather in contrast to expected elevated levels, if ID would be pro-inflammatory. We believe this reflects depleted iron stores (absolute ID) in psoriatic patients. As the patients had normal indices of haematopoiesis, in psoriasis ID does not coincide with anaemia. The other interesting finding was significantly elevated levels of soluble transferrin receptor in psoriatic patients. We can speculate that the major source of transferrin receptors shed into circulation is not the erythron (as psoriatic patients had normal hematinics) but it rather reflects extra-haematopoietic origin and unmet iron needs within non-haematopoietic cells. A similar pattern of hepcidin and soluble transferrin receptor in the circulation was previously described in patients with acute heart failure, where it predicted poor clinical outcomes [16].

Interestingly, deranged iron status was not related to disease severity assessed with Psoriasis Area and Severity Index (PASI) or whether patients received systemic treatment, but was of particular magnitude in those with low body mass index. The origin of the relationship remains unclear [13, 22].

Although our study was not designed to investigate the ID underlying mechanisms, we believe that the results rather contradict the thesis that, like in the other chronic diseases, it is proinflammatory driven. 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 [32]. Further studies are needed to investigate the prevalence and underlying mechanisms of ID in psoriasis.

Hidradenitis suppurativa is the other chronic, dermatologic disease, where derangements in iron metabolism seem to be present and play a pathophysiological role [30]. HS is a chronic, debilitating disease of a relapsing nature predominantly involving apocrine gland-bearing areas of the skin [40]. The etiology is complex and multifactorial, associated with genetics, hormonal imbalance, bacterial infection and numerous coexisting comorbidities [14]. Current understanding of the underlying pathophysiology of HS links the disease with proinflammatory activation and auto-immune processes [20]. It is further supported by the more frequent association of inflammatory and autoimmune comorbidities with HS, the presence of innate and adaptive immune cells in lesional and perilesional skin before clinical manifestations of the disease and high effectiveness of biologic therapies [19, 21, 40].

We and others have demonstrated a pro-inflammatory pattern of several cytokines in patients with HS [23, 36]. In the context of potential impairment of iron metabolism in HS, recent findings suggesting that serum levels of inteleukin-6 are elevated and predicting poor response to infliximab treatment are of particular relevance [25, 38]. IL-6 is pro-inflammatory cytokine that is a major stimulus for systemic hepcidin production and is therefore considered to be involved in the pathophysiology of functional ID in chronic diseases (see above).

Taking into consideration all above premises, we hypothesize that in HS there are derangements in iron metabolism resulting in iron deficiency. It is not only associated with HS pathophysiology but may potentially deteriorate already existing auto-immune processes and unfavorably impact the effects of biological therapies. We are currently studying this intriguing hypothesis in a group of patients with HS [30].

CONCLUSION

In summary, iron is an essential microelement in the human body due to its role in hematopoiesis, involvement in energetic processes, synthesis and decomposition of lipids, proteins and nuclear acids. ID frequently occurs in healthy populations and complicates natural course of chronic diseases. The former scenario is associated with absolute ID when the overall iron body storages are exhausted and coincides with anaemia. The latter referred to as functional ID reflects adequate iron stores in the body with iron becoming unavailable for metabolic processes, typically occurring in the presence proinflammtory activation in chronic conditions such as chronic kidney disease, inflammatory bowel disorders, malignancies and heart failure. To date there are very few publications concerning the potential role of ID in chronic dermatological disorders. We have recently found that patients with psoriasis demonstrate pattern of ID which can be characterized by negative tissue iron balance with depleted iron stores in the body. Interestingly, presence of ID was not related to the severity of psoriasis, but rather determined by patients low body mass index. Our preliminary results strongly indicate that derangements in iron metabolism resulting in ID can be also present in hidradenitis suppurativa – another chronic dermatologic disease associated with inflammatory and autoimmune activation. We are currently investigating this hypothesis. According to our results it would be particularly interesting to explore iron status in another chronic skin disorder – atopic dermatitis in which inflammatory drive plays crucial role.

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