

## LETTER TO THE EDITOR

### Iron Deficiency

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Iron deficiency, in its various clinical forms, is the most common nutritional disorder worldwide. People at increased risk include young children, especially in developing countries, young women of childbearing age, and pregnant women. Iron deficiency is the most common cause of anemia, and women suffer from it much more frequently. The limited ability of the intestinal epithelium to absorb iron from food and the inhibitory control mechanism of hepcidin on human iron homeostasis can lead to a negative iron balance in the body, particularly in the context of reduced iron intake or blood loss [1]. Iron deficiency has a significant impact on human iron homeostasis. Adaptive mechanisms are induced, particularly via the hepcidin-ferroportin axis. Suppression of hepcidin synthesis during iron deficiency leads to an increased iron absorption in the duodenal enterocytes and, at the same time, to an increased iron release from the cells of the reticulohistiocytic system (RHS) [2]. Basically, two forms of iron deficiency must be distinguished: a) absolute iron deficiency and b) functional iron deficiency [3]. Absolute iron deficiency occurs when iron stores are empty or depleted. In functional iron deficiency, there is sufficient or increased stored iron, but it is not bioavailable. This leads to an inadequate supply of iron to the bone marrow. Absolute and functional iron deficiency can also occur in a combined form [3].

#### Causes of iron deficiency

There are a variety of physiological and pathological factors that can lead to iron deficiency. The etiology differs between different patients and age groups (children, women, elderly people) and geographical conditions (developing countries, industrialized countries) [4]. Se-

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vere iron deficiency with or without anemia can occur, for example, when iron requirements are increased due to physical growth in children, during pregnancy (especially in the second and third trimesters), during breastfeeding, in athletes, or during treatment with erythropoiesis-stimulating agents [1]. Other causes can be not getting enough iron if you are vegetarian or vegan, or not absorbing iron well in your gut after stomach surgery, because of a *Helicobacter pylori* infection, chronic inflammatory bowel disease, or celiac disease [1]. The most common cause of absolute iron deficiency (approximately 80% of cases) is iron loss due to heavy menstrual bleeding in women, bleeding from the digestive tract (erosive gastritis, ulcers, chronic inflammatory bowel disease, carcinomas, esophageal variceal bleeding, hemorrhoids), surgical or traumatic bleeding, blood donation, or excessive blood sampling from the patient [5].

### Clinical presentation of iron deficiency

Iron deficiency can manifest itself through a variety of different symptoms. The severity of the clinical symptoms depends on the speed at which they develop, the severity of the anemia, age, and comorbidities. Iron deficiency particularly affects cells (e.g., skin and mucous membrane epithelial cells) with rapid turnover. This can lead to skin and mucous membrane symptoms such as diffuse hair loss, brittle nails, ridges on the nails, hollow nails (koilonychia), dry and rough skin, mucous membrane atrophy of the tongue, or rhagades at the corners of the mouth [3,4]. In addition, nonspecific neurological symptoms such as headaches, dizziness, syncope, concentration problems, restless legs, or abnormal cravings for chalk and soil may occur [4]. The first signs of anemia can include pale skin, exertional dyspnea, tachycardia, and poor physical performance [4].

### Stages of iron deficiency

From a clinical perspective, it makes sense to classify iron deficiency into different stages according to its severity. Depending on the severity, three stages are distinguished: a) Latent iron deficiency (iron storage deficiency), b) manifest iron deficiency (iron-deficient erythropoiesis), and c) iron deficiency anemia [6]. In the stage of iron deficiency, iron stores are reduced due to a negative iron balance. Laboratory diagnostics show that this stage is characterized by reduced serum ferritin levels. Since there is still sufficient functional iron available for erythropoiesis in the bone marrow, anemia does not occur. In the second stage, the manifest iron deficiency, the erythropoietic precursor cells are no longer adequately supplied with iron. This is accompanied by an increase of the soluble transferrin receptor (sTfR) and a decrease of the reticulocyte hemoglobin (RetHb). In the stage of iron deficiency anemia, when iron stores are depleted and functional iron is significantly reduced, an adequate supply of iron for erythropoiesis can no longer be guaranteed for normal hemoglobin (Hb) synthesis. This results in anemia.

### Diagnosis of iron deficiency

Clinical signs and symptoms of iron deficiency are often nonspecific and frequently overlooked. This makes accurate laboratory diagnosis important [2]. A ferritin level  $\leq 30 \mu\text{g/L}$  is considered the accepted threshold for iron deficiency [2,4,7]. However, the significance of this parameter is limited due to its characteristic as an acute phase protein. Acute and chronic inflammation or malignant tumors can lead to an increase in ferritin and thus mask an existing iron deficiency. In this case, a cutoff value of  $\leq 100 \mu\text{g/L}$  ferritin should be used to define iron deficiency [4,7]. The sTfR is an inflammation-independent indicator of functional iron deficiency (iron-deficient erythropoiesis). The sTfR/log ferritin index provides information about the iron supply for erythropoiesis [2]. This index is particularly helpful for the differential diagnosis of iron deficiency in cases of anemia associated with chronic diseases [6]. An elevated index indicates iron deficiency. If the sTfR/log ferritin index is low, the cause of anemia is primarily attributable to the underlying chronic disease [3,6]. RetHb is also a laboratory parameter that is independent of inflammation. This parameter is an early indicator of the iron requirements for erythropoiesis [2]. A RetHb  $< 28 \text{ pg}$  means that there has been an iron deficiency for approximately 3 - 5 days and that the erythrocytes have a reduced Hb content [3]. The diagnostic combination of RetHb with the sTfR/log ferritin index (= iron plot according to Lothar Thomas) allows for adequate classification of iron deficiency according to the stages of iron supply in erythropoiesis and enables differential diagnosis between iron deficiency anemia and anemia in chronic diseases.

### Declaration of Interest:

None to declare.

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