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Iron deficiency – diagnosis, classification and its association with heart failure**

Niedobór żelaza- diagnostyka, klasyfikacja oraz jego powiązanie z niewydolnością serca

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Słowa kluczowe
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Summary

Iron is a key element in the cell metabolism and is critical for the maintenance of homoeostasis. Because of the unique ability of electron exchange under aerobic conditions, iron plays a crucial role in oxygen transport, enzymatic reactions and DNA synthesis. However, due to its toxicity, iron levels in the human body must be strictly controlled. Iron participates in the Fenton reaction to form the most reactive oxygen species – hydroxyl radical (•OH) by reaction with hydrogen peroxide. Iron deficiency is the most common nutritional disorder, affecting one third of the general population all over the world. Heart failure affects approximately 1-2% of the adult population in developed countries, and its prevalence rises to 10% among people over 70 years old. In patients with heart failure, iron deficiency is common and independently relates to poor quality of life, more severe depression symptoms, exercise intolerance and increased risk of hospitalisation and death, while iron supplementation in HF patients improves exercise capacity, left ventricular ejection fraction and quality of life.

Streszczenie

Żelazo jest mikroelementem kluczowym dla metabolizmu komórkowego, niezbędnym do utrzymania homeostazy organizmu. Dzięki wyjątkowej zdolności wymiany elektronów w warunkach tlenowych żelazo bierze udział w istotnych procesach biologicznych: transporcie tlenu, reakcjach enzymatycznych, czy syntezie DNA. Jednak żelazo ze względu na swoją toksyczność musi podlegać ścisłej kontroli w organizmie człowieka. Żelazo uczestniczy w reakcji Fentona, w wyniku której w reakcji z nadtlenkiem wodoru powstaje najbardziej reaktywna forma tlenu- rodnik hydroksylowy (•OH). Niedobór żelaza jest najczęstszym niedoborem żywieniowym, występuje u 1/3 populacji świata. Podział na czynnościowy oraz bezwzględny niedobór żelaza narzuca, by diagnostyka rozróżniała obie te formy, w celu doboru odpowiedniej metody leczenia. Niewydolność serca występuje u 1-2% osób dorosłych w populacji krajów rozwiniętych, a u osób powyżej 70 roku życia zachorowalność rośnie powyżej 10%. Niedobór żelaza występuje często u chorych z niewydolnością serca i jest skorelowany z gorszą jakością życia, częstszym występowaniem objawów depresyjnych, pogorszeniem tolerancji wysiłku fizycznego oraz zwiększonym ryzykiem hospitalizacji i zgonu. Natomiast suplementacja żelaza, korzystnie wpływa u pacjentów z niewydolnością serca na wydolność fizyczną, frakcję wyrzutową lewej komory oraz jakość życia.

Conflict of interest
Konflikt interesów
None
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PHYSIOLOGICAL ROLE OF IRON

Iron is a mineral necessary for normal functioning of most living organisms. Due to its functions, it is considered a crucial microelement in human metabolism (1).

Iron is a component of many proteins and enzymes participating in many important biological processes. As an element of various proteins, it is responsible for oxygen transport (in haemoglobin), oxygen storage (in myoglobin), metabolism in cardiac and skeletal muscles (in oxidative enzymes and respiratory chain proteins), synthesis and degradation of proteins, lipids, and nucleic acids (in enzymes) as well as the functioning of mitochondria (2).

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A unique biochemical feature of iron, allowing it to participate in many chemical reactions, is its capacity to exchange electrons in aerobic conditions. It the human body, this element is present in two oxidation states: as ferric ion (Fe^{3+}) and ferrous ion (Fe^{2+}), so it can act as both acceptor and donor of ions (3, 4).

IRON METABOLISM

On average, there is 3.5-4.5 g of iron in the organism of an adult human, with differences between females and males. It is estimated that the average content of iron in a healthy male should be 4-4.5 g, while in a healthy female, it should be 3.5 g. Most iron (2-2. g – over 60% of total iron) is found in red blood cells in the form of haemoglobin. More than 20% of iron is stored, in the form of ferritin and haemosiderin, mainly in the liver, spleen and bone marrow, while 5-6% is found in the cells of skeletal muscles in the form of myoglobin and less than 1% is iron bound with transferrin (5).

In physiological conditions, small amounts of iron are absorbed in the digestive tract and minor amounts are excreted (fig. 1). The human body cannot remove large amounts of iron (5). The daily loss of iron of only 1-2 mg occurs due to exfoliation of epidermis and intestinal enterocytes, while in women iron is additionally lost due to menstrual bleeding. However, a person consumes an average of 10-15 mg of iron with diet, of which about 10% is absorbed to blood (22% of haem iron and 2-5% of non-haem iron), which is completely sufficient considering the daily loss of this element. However, in circumstances of increased iron demand, e.g. due to haemolysis or haemorrhage, intestinal absorption of this element may increase tenfold (6). Every day, 20-30 mg of iron is released in the process of phagocytosis of old and used red cells, and this amount is used mainly in erythropoiesis, while a small proportion is stored in cellular storage depots (7).

IRON ABSORPTION

Iron is absorbed from food in the duodenum and proximal jejunum, due to the action of specialised cells

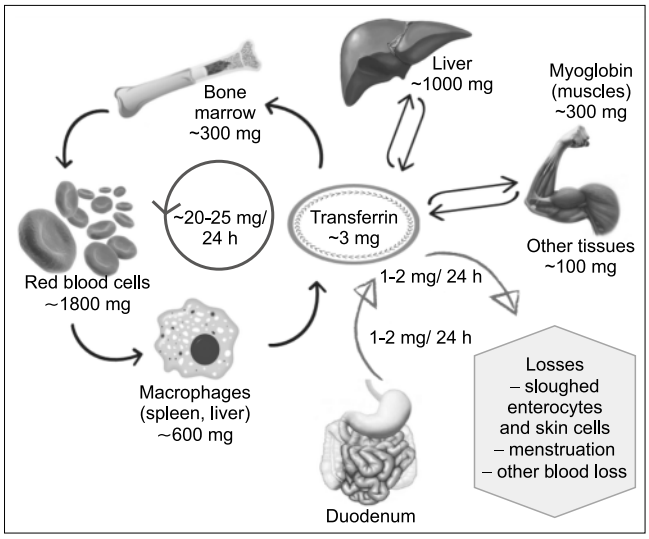

Fig. 1. Schematic representation of the systemic iron homeostasis

in the small intestine, called enterocytes. The small intestine contains numerous folds which protrude into its lumen and are covered with finger-like intestinal villi that increase the absorption area of the intestine. On the apical membrane (directed toward the intestinal lumen), every epithelial cell covering the villi has numerous cytoplasmic protrusions called microvilli, which join with microvilli of the neighbouring enterocytes to form the brush border. Enterocytes are polarised cells, specialised in transporting iron ions from the small intestine to blood, as they contain proteins responsible for importing and releasing iron ions (6).

In the diet of humans, iron is present in divalent and trivalent forms. Trivalent iron, which forms non-absorbable, non-soluble complexes in alkaline environment, must be reduced to divalent iron in the acidic environment of the stomach (8). The reaction is catalysed by ferroreductase – duodenal cytochrome B – present on the surface of the brush border. Only the obtained divalent iron can be a substrate for divalent metal transporter 1 (DMT1), whose role is to transport iron ions through membranes to the interior of an enterocyte (7). Inside epithelial cells, a part of iron is stored or used by the cell, while the rest is exported from the enterocyte to blood by ferroportin (Fnp), which occurs in the basal section of the epithelium. Next, protein hephaestin (Heph) oxidizes Fe^{2+} to Fe^{3+}, which means that it transforms iron into the form that enables binding with apotransferrin circulating in blood to form transferrin (Tf). Transferrin is a transport protein that can bind two ions at the same time to deliver them to all live cells in the organism (6). Transferrin is captured by specific cell surface receptors (transferrin receptor 1 – TfR1), so that the receptor–transferrin complex is absorbed inside the cell and iron is released. Next, the complex returns to the surface of cell membrane and apotransferrin is separated from the complex at physiological pH and is circulated in blood again to transport more iron ions. Reticulocytes, i.e. immature erythrocytes present in the bone marrow, are characterised by the greatest TfR1 expression. In cytoplasm of cells, iron ions are stored in the form of ferritin and haemosiderin. However ferritin-bound iron is released more easily than haemosiderin-bound iron. An apotransferrin molecule can bind up to 4,500 iron ions (8).

THE OTHER FACE OF IRON – TOXICITY

Human organism has developed a precise mechanism for controlling iron concentration because of its toxic and oxidative properties (4, 9). Iron participates in the Fenton's reaction (fig. 2), where it acts as a catalyser in the formation of hydroxyl radical, considered one of the most reactive forms of oxygen. Oxidative stress is defined as a condition in which there is increased production of free radicals in proportion to antioxidants. A free radical, in turn, is a cell containing an unpaired electron and presenting highly reactive properties (10).

A small amount of superoxide anion ($O_2^{\bullet-}$) radical is produced as a by-product of cellular respiration.

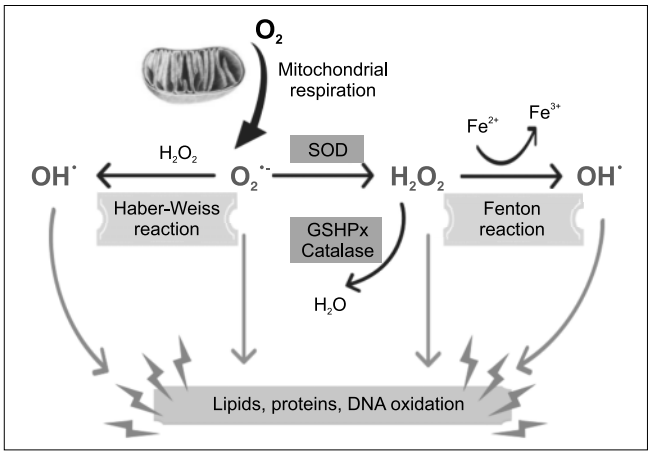

Fig. 2. Production of reactive oxygen species

In physiological conditions, superoxide anion radical is transformed by superoxide dismutase (SOD) into hydrogen superoxide (H_2O_2), which is in turn reduced to water due to catalase and glutathione peroxidase (GSHPx). In pathological conditions, H_2O_2 can be a substrate in the production of highly reactive hydroxyl radical ($OH^{\bullet}$) in the Haber-Weiss reaction with $O_2^{\bullet-}$ or in the Fenton's reaction in the presence of iron (11).

In the human organism, iron is mostly present in complexes with proteins, like ferritin or transferrin, as mentioned above. However, a small amount of iron (3-5%) circulates in the body in free form, which is called the labile iron pool (LIP). LIP is defined as a pool of low-molecular, poorly chelated, available iron that easily passes through cells. LIP is composed of two forms of iron (Fe^{2+} and Fe^{3+}) bound with different ligands with low affinity to iron ions (12). LIP is the main source of iron participating in the production of hydroxyl radical in the Fenton's reaction, and therefore its concentration is maintained at the lowest possible level. Hydroxyl radical, a particle with high oxidative potential, can react with every cell in its proximity, which eventually leads to damage to proteins, lipids, and DNA (4).

IRON DEFICIENCY AND ITS CLASSIFICATION

Iron deficiency (ID) is the most common nutritional disorder. It is estimated to occur in 1/3 of the global population. Iron deficiency is most probable in pregnant and breastfeeding women, and in adolescents due to increased demand for this element (13). Iron deficiency is related to anaemia, disturbances in immune and coagulation system function as well as abnormal cell functioning, which requires major energy expenditure and can eventually lead to premature death (1).

There are two types of iron deficiency: absolute and functional. Absolute iron deficiency means a significant reduction of iron storage in the body, most often caused by limited iron supply from diet, haemorrhage or disturbed absorption of iron in the digestive system. Functional iron deficiency is a state in which iron storage is full, but the body cannot use it, as iron is locked inside the reticuloendothelial system, while iron supply from diet is not sufficient to meet the demand for this element. Such functional deficiency occurs mainly in inflammation, when there is increased production of hepcidin, a factor reducing iron availability (14, 15).

DIAGNOSIS OF IRON DEFICIENCY

Bone marrow biopsy with quantitative sideroblast evaluation is the gold standard in iron deficiency diagnosis. Unfortunately, as this method is invasive and costly, it is not useful in routine diagnosis of this deficiency (2). Therefore, daily evaluation of iron balance is based on the following peripheral blood parameters: concentration of iron, ferritin, transferrin and soluble transferrin receptor (sTfR) as well as transferrin saturation (TSAT), total iron binding capacity (TIBC), and unsaturated iron binding capacity (UIBC). Integrated indices, which combine several parameters, seem very reliable (16).

Assessment of iron concentration in blood, although performed very often, is not the best method of evaluating iron balance due to numerous limitations. Iron concentration changes depending on age, gender, diet and time of the day (morning results may be even 20% higher). Additionally, too low serum iron concentration indicates significant iron deficiency – blood iron concentration is decreased only once the storage of this element has been exhausted, which makes the diagnosis of early deficiency difficult. Normal concentration of this element is 60-160 μg/dL in women and 6-180 μg/dL in men. The concentration of transferrin, the only protein binding and transporting iron in blood, is more stabilised, although it is also dependent on many factors, e.g. inflammation, liver diseases or pregnancy. The norm for transferrin is 200-400 mg/dL. Values of transferrin above the norm indicate advanced iron deficiency. The transferrin concentration, which indicates the size of transport iron pool, has been replaced with the TSAT value. Saturation of transferrin with iron is calculated using the formula: iron concentration x 100% / TIBC. The normal value of TSAT is 15-45%. Since it informs about the maximum amount of iron needed for complete saturation of transferrin, the TIBC parameter allows an indirect assessment of blood transferrin concentration. Normal TIBC values are 40-80 μmol/L for women and 45-75 μmol/L for men. Increased TIBC values indicate iron deficiency. UIBC is a parameter reflecting the number of free transferrin able to bind iron. UIBC is the difference between TIBC and iron concentration in blood. Normal UIBC is 27-60 μmol/L and increases in iron deficiency. Ferritin, an iron-storage protein, can also be used in iron deficiency diagnosis. There is a small fraction of ferritin in blood, i.e. the circulating L-ferritin, which reflects the state of iron in cellular storage depots. Normal ferritin values are 10-200 μg/L for women and 15-400 μg/L for men but, when interpreting test results, one must remember that ferritin is an acute phase protein, so its value can increase in cases of inflammation (17-19).

New, more reliable biomarkers allowing an evaluation of iron balance are still being searched for, however. One of the best-described and best-studied markers are hepcidin concentration, sTfR, and integrated markers based on a combination of several parameters, like the sTfR/F index. sTfR is a soluble form of transferrin receptor, present in blood. The number of circulating sTfR corresponds to the number of receptors on cell surface, which means that it reflects the functional iron pool. This parameter does not belong to the acute phase proteins, so it is particularly useful for iron deficiency evaluation in patients with inflammation. The normal value is 2.2-5 mg/L for men and 1.9-4.4 mg/L for pre-menopausal women. In consequence of iron deficiency, blood sTfR concentration increases due to increased synthesis of membrane receptors (15). The ratio of sTfR to the logarithm of ferritin concentration in serum is considered an index of iron content in the body that is more reliable than ferritin concentration. Despite the fact that this integrated index reflects iron storage and iron absorption during supplementation, it is not used often (20). Hepcidin is a protein produced mainly in hepatocytes. It regulates iron concentration in the body by inhibiting ferroportin. Hepcidin leads to ferroportin degradation by attaching to it, and then to phosphorylation of its tyrosine residues. In consequence, intestinal absorption of iron is inhibited and this element is released from reticuloendothelial system macrophages. Hepcidin is an acute phase protein, so its increased concentration indicates inflammation, while low levels of hepcidin reflect iron deficit (14, 21).

Diagnostic methods should allow the differentiation between functional and absolute iron deficiency to enable the selection of appropriate treatment. Treatment of absolute iron deficiency is based on oral or intravenous supply of iron. However, this form of treatment is not efficient in the case of functional deficiency. Currently, absolute iron deficiency is diagnosed when concentration of ferritin is lower than 30 μg/dL. However, this classification applies only to healthy persons (15). In accordance with the European Society of Cardiology (ESC) guidelines from 2012, absolute iron deficiency is diagnosed in chronically ill patients (with heart failure, chronic kidney failure) when ferritin level is lower than 100 μg/dL. This is related to inflammation, which causes a significant increase in ferritin level (since it is an acute phase protein). Functional deficiency, in turn, is diagnosed in chronically ill persons when ferritin concentration is within the normal range (100-300 μg/dL), but TSAT values are below 20% (22).

IRON DEFICIENCY IN HEART FAILURE

Heart failure (HF) is a clinical syndrome, in which abnormal structure and function of the heart prevents the delivery of appropriate amounts of oxygenated blood to tissues. This condition is characterised by typical symptoms: dyspnoea, swollen ankles and fatigue, possibly accompanied by e.g. increased jugular vein pressure, peripheral oedema or pulmonary oedema. The most common causes of heart failure are coronary artery disease (including myocardial infarction), hypertension, valve disorders and cardiomyopathies.

Heart failure occurs in 1-2% of adults in the population of developed countries, which means there are about 26 million people with this pathology. Heart failure incidence increases with age with estimated incidence of 10% among persons over 70 years old (23). The latest document of the ESC about heart failure indicates that 17-45% of patients admitted to hospitals due to HF die within one year and a large majority die within 5 years from admission (24).

Currently, there are no data on the iron deficiency prevalence in the world. All analyses of the prevalence of this deficit are based on data relating to iron deficiency anaemia. Thus, indirectly, it is estimated that iron deficiency occurs in developed countries in the highest risk patients (i.e. pregnant women and children) with a 30-40% incidence (25).

Iron deficiency is common in patients with HF regardless of anaemia (26). It is estimated that iron deficiency occurs in 30-50% of patients with chronic heart failure, both with co-morbid anaemia and with normal haemoglobin values. In most studies, conducted to determine the prevalence of iron deficiency in heart failure, the study groups were patients aged 50-77 years, with a numerical predominance of men. According to data published by the World Health Organization (WHO) anaemia in developed countries occurs in 10% of women aged 15–59 years, 4% of men aged 15-59 years and in 12% of people above 60 years of age (25). However, according to Klip et al. (27) iron-deficiency anaemia is present in up to more than 30% of heart failure patients (age 64 ± 13 years).

In their study on 955 HF patients, De Silva et al. (28) noted iron deficiency in 43% of anaemic patients and in 15% patients without anaemia. By contrast, in a study on 546 patients with chronic systolic heart failure, iron deficiency was noted in 37% of patients, including 32% of anaemic patients and 57% of non-anaemic patients (29). Functional iron deficiency (defined as TSAT < 20%) was noted in 43% of 157 chronic HF patients participating in the study (30). Data obtained in an international study indicate that iron deficiency occurs in a half of chronic HF patients, among whom 61% are anaemic and 46% are not anaemic (27). Cohen-Solal et al. (31) conducted studies taking into account gender and type of iron deficiency including patients with acute HF. They concluded that this element is deficient in 75% of women (among whom 79% do not have co-morbid anaemia) and 69% of men (among whom 57% do not have co-morbid anaemia) and that absolute iron deficiency is the most common (41% in men, 48% in women). Moreover, in the latest study, iron deficiency was found in 51% of 324 patients with chronic heart failure (32).

An analysis of patients with chronic HF indicates that there are 4 independent risk factors for iron deficiency: female gender, higher NYHA class (related

to aggravation of HF symptoms), higher serum NT-proBNP concentration (a peptide indicating the level of neurohormonal activation), and higher hsCRP concentration (marker of inflammation) (29). In addition, it was found that iron deficiency in patients with heart failure correlates with exercise intolerance, more severe depression symptoms, poor quality of life, increased risk of hospitalisation and death (tab. 1).

Tab. 1. Adverse effects of iron deficiency in heart failure – suggested causes

The role of iron	Iron deficiency	Consequence
Iron as a component of myoglobin	improper oxygen storage	Deterioration in exercise tolerance
	deterioration in energy efficiency	
Iron present in the active site of enzymes and proteins	impairment of the activity of enzymes involved in mitochondrial ATP production	Mitochondrial dysfunction, Impairment of cardiomyocyte function, especially sensitive to ATP deficiencies, because of considerable ATP consumption -> cardiac dysfunction, Impairment of myocytes -> lower exercise tolerance
	impairment of oxidative enzymes and proteins of the respiratory chain	Impaired oxidative metabolism of cardiac and skeletal muscles
	impairment of other enzymatic functions	Impaired synthesis and degradation of proteins, lipids, nucleic acids
Iron as a component of haemoglobin	reduced oxygen transport to cells of the body, including cardiomyocytes	Cardiomyocyte dysfunction, Structural disorder – myocardial hypertrophy (LV hypertrophy and dilatation in a rat model)
Iron participating in haematopoiesis	disorders of haemoglobin synthesis	Microcytic, hypochromic anaemia
	abnormal differentiation and maturation of all blood cell types	Anaemia, Coagulation disorders, Disorders of the immune system

IRON SUPPLEMENTATION IN PATIENTS WITH HEART FAILURE

ESC recommendations from 2012 include guidelines to consider iron supplementation in patients with chronic heart failure and iron deficiency. These guidelines were formed based on results of clinical studies that confirmed beneficial effects of iron supplementation in HF patients. The first such study was performed by Bolger et al. (33) on 16 HF patients with co-morbid anaemia due to iron deficiency, NYHA class II-III. Intravenous administration of iron (in the form of an iron hydroxide and sucrose complex) for 5-17 days was well-tolerated and caused an increase in haemoglobin level as well as improved physical performance and health (evaluated using NYHA functional class). Tobili et al. (34) investigated 40 HF patients, NYHA class II–IV, with ejection fraction below 35%, anaemia, iron deficiency and mild renal failure. The study confirmed that intravenous administration of iron caused an increase in the haemoglobin level, reduction of CRP and NT-proBNP as well as improvement of physical performance and quality of life. In the FERRIC-HF study (35), 16-week-long iron supplementation in HF patients (NYHA class II–III) with iron deficiency was well-tolerated, improved exercise tolerance and alleviated HF symptoms. The FAIR-HF multicentre, randomised clinical trial (36) including 459 NYHA class II-III patients with iron deficiency (with or without co-morbid anaemia) confirms the efficacy of using iron in HF patients. For 24 weeks, patients were administered intravenously a complex of iron hydroxide with carboxymaltose or placebo. During 6 months of follow-up, increase in the haemoglobin level and ferritin concentration was noted in patients receiving iron, which led to improved general health (evaluated by patients and based on the NYHA class). In addition, improved exercise tolerance (longer distance in the 6-minute walk test) and improved quality of life were observed. Beneficial effects of iron supplementation were observed in patients with and without co-morbid anaemia.

CONCLUSIONS

Iron deficiency often accompanies heart failure, even in persons without anaemia. Although iron deficiency is considered an independent factor of poor prognosis in HF patients, it is still underdiagnosed. Patients with chronic heart failure should undergo routine assessment of ferritin and TSAT concentrations. Study results indicate that, in HF patients, iron deficiency aggravates symptoms of the disease, limits exercise tolerance, deteriorates quality of life and increases the risk of death. Iron supplementation in HF, on the other hand, improves exercise capacity, NYHA class and quality of life, i.e. it alleviates symptoms of the disease. However, the effect of iron on hard endpoints and left ventricular remodelling parameters fundamental for prognosis is still unknown. The mechanism in which iron balance disturbances affect the pathogenesis and progression of heart failure has not been explained either. There are also no data regarding the effect of iron on the function of cardiomyocytes. Finding the answer to these burning questions might allow us to develop new methods of treating heart failure.

BIBLIOGRAPHY

1. Sciatti E, Lombardi C, Ravera A et al.: Nutritional Deficiency in Patients with Heart Failure. Nutrients 2016; 8: 442.
2. Jankowska EA, von Haehling S, Anker SD et al.: Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. European Heart Journal 2013; 34(11): 816-826.
3. Kell DB: Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. BMC Med Genomics 2009; 2: 2.
4. Emerit J, Beaumont C, Trivin F: Iron metabolism, free radicals, and oxidative injury. Biomed Pharmacother 2001; 55(6): 333-339.

5. Arytm J: Udział laktoferryny w gospodarce żelazem w organizmie. Część I. Wpływ laktoferryny na wchłanianie, transport i magazynowanie żelaza. Postepy Hig Med Dosw 2008; 42: 599-611.
6. Beaumont C, Delaby C: Recycling iron in normal and pathological states. Semin Hematol 2009; 46(4): 328-338.
7. Andrews NC: Disorders of iron metabolism. N Engl J Med 1999; 341(26): 1986-1995.
8. Andrews NC: Forging a field: the golden age of iron biology. Blood 2008; 112(2): 219-230.
9. Wang J, Pantopoulos K: Regulation of cellular iron metabolism. Biochem J 2011; 434(3): 365-381.
10. Bigarella CL, Liang R, Ghaffari S: Stem cells and the impact of ROS signaling. Development 2014; 141(22): 4206-4218.
11. Tsutsui H, Kinugawa S, Matsushima S: Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol 2011; 301(6): H2181-2190.
12. Kruszewski M: Labile iron pool: the main determinant of cellular response to oxidative stress. Mutat Res 2003; 531(1-2): 81-92.
13. Frewin R, Henson A, Provan D: ABC of clinical haematology. Iron deficiency anaemia. BMJ 1997; 314(7077): 360-363.
14. Hentze MW, Muckenthaler MU, Galy B et al.: Two to tango: regulation of Mammalian iron metabolism. Cell 2010; 142(1): 24-38.
15. Wish JB: Assessing iron status: beyond serum ferritin and transferrin saturation. Clin J Am Soc Nephrol 2006; 1 Suppl 1: S4-8.
16. Thomas C, Thomas L: Biochemical markers and hematologic indices in the diagnosis of functional iron deficiency. Clin Chem 2002; 48(7): 1066-1076.
17. Wu AC, Lesperance L, Bernstein H: Screening for iron deficiency. Pediatr Rev 2002; 23(5): 171-178.
18. Hellman A: Choroby układu krwiotwórczego. Szczeklik A, editor. Kraków: Medycyna Praktyczna 2006.
19. Beard JL, Finch CA: Iron Deficiency. Clydesdale FM, Wiemer KL, editors. Orlando: Academic Press 1985. 6-9.
20. Skikne BS: Serum transferrin receptor. Am J Hematol 2008; 83(11): 872-875.
21. Franchini M: Hepcidin: the main regulator of iron homeostasis. Clin Chem Lab Med 2011; 49(2): 165-166.
22. McMurray JJ, Adamopoulos S, Anker SD et al.: [ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012]. Turk Kardiyol Dern Ars 2012; 40 Suppl 3: 77-137.
23. Ponikowski P, Voors AA, Anker SD et al.: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18(8): 891-975.
24. Ponikowski P, Anker SD, AlHabib KF et al.: Heart failure: preventing disease and death worldwide. ESC Heart Failure 2014; 1(1): 4-25.
25. (WHO) WHO. Iron Deficiency Anaemia: Assessment, Prevention, and Control. A Guide for Program Managers. Geneva: World Health Organization 2001.
26. Cohen-Solal A, Leclercq C, Deray G, et al. Iron deficiency: an emerging therapeutic target in heart failure. Heart 2014; 100(18): 1414-1420.
27. Klip IT, Comin-Colet J, Voors AA et al.: Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 2013; 165(4): 575-582.e3.
28. de Silva R, Rigby AS, Witte KK et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol 2006; 98(3): 391-398.
29. Jankowska EA, Rozentryt P, Witkowska A et al.: Iron deficiency: an ominous sign in patients with systolic chronic heart failure. European Heart Journal 2010; 31(15): 1872-1880.
30. Okonko DO, Mandal AK, Missouris CG et a.: Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. J Am Coll Cardiol 2011; 58(12): 1241-1251.
31. Cohen-Solal A, Damy T, Terbah M et al.: High prevalence of iron deficiency in patients with acute decompensated heart failure. Eur J Heart Fail 2014; 16(9): 984-991.
32. Belmar Vega L, de Francisco A, Albines Fiestas Z et al.: Investigation of iron deficiency in patients with congestive heart failure: A medical practice that requires greater attention. Nefrologia 2016; 36(3): 249-254.
33. Bolger AP, Bartlett FR, Penston HS et al.: Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. J Am Coll Cardiol 2006; 48(6): 1225-1227.
34. Toblli JE, Lombraña A, Duarte P et al.: Intravenous iron reduces NT-pro--brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol 2007; 50(17): 1657-1665.
35. Okonko DO, Grzeslo A, Witkowski T et al.: Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008; 51(2): 103-112.
36. Anker SD, Colet JC, Filippatos G et al.: Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency. New England Journal of Medicine 2009; 361(25): 2436-2448.

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