EVALUATION OF HYPOPHEREMIA IN HEMODIALYSIS PATIENTS

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Aim: The aim of this study was to evaluate the type of iron deficiency in hemodialysis patients and compare their clinical, hematological and inflammatory parameters according to this type of deficiency. ***Material and methods:*** The study included 100 chronic hemodialysis patients with their demographic and clinical characteristics, and analyzed for their complete blood count, erythropoietin level, iron, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), iron saturation, transferrin, ferritin, C-reactive protein (CRP) and hepcidin. ***Results:*** Absolute iron deficiency was found in 10%, functional deficiency in 2% and reticuloendothelial blockade in 2% of patients, while 86% of them had no iron deficiency. Examining clinical, hematologic and inflammatory parameters in patients on hemodialysis in relation to the type of iron deficiency, it was found that patients with absolute iron deficiency had significantly shorter duration of hemodialysis, length of erythropoietin therapy, significantly lower iron, ferritin and significantly lower saturation index values compared to patients without iron deficiency. Erythropoietin levels were low in 15% and high in 29% of patients. The study showed that anemia was present in 96% of patients receiving therapy for anemia, 90% received iron supplements; all of 100 patients received folic acid, 80% of patients received erythropoietin. Patients on hemodialysis had elevated hepcidin values up to 72%, which is expected in hemodialysis population, given the reduced renal clearance and a quarter of patients with inflammation, and proven CRP and hepcidin positive correlation. ***Conclusion:*** Patients with absolute iron deficiency should initially receive iron supplements in therapy, compared to erythropoietin for a more adequate response and better correction of anemia. Patients with functional iron deficiency receive maintenance doses of iron preparations, while patients with inflammation may have lower ferritin values and falsely low iron depots until the inflammatory parameters are corrected.

Key words: absolute and functional iron deficiency, erythropoietin, ferritin, inflammation, hepcidin

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INTRODUCTION

Hypoproliferative, normocytic, normochromic anemia caused by excretory and endocrine renal dysfunction is often present in patients with chronic kidney disease (CKD). Patients with CKD have an increased loss of iron from the body, which contributes to the development of anemia. Iron deficiency can occur due to losses of blood from the digestive and genital systems and loss of iron and folic acid during hemodialysis (HD) procedure due to frequent blood clotting and poor flushing of dialyzers, hemodialysis filters and dialysis systems. Frequent bleeding can also occur due to platelet dysfunction in uremia, frequent blood sampling for medical analysis, blood loss during the HD procedure itself, i.e., bleeding during the prick or removal of needles from vascular access, blood clotting in the extracorporeal hemodialysis system or infiltration of vascular access to the hemodialysis blood. The underlying disease, along with associated infections, contributes to the development of chronic anemia.

Erythropoietin therapy will most often correct anemia and improve the quality of life of patients, and avoid possible complications of treatment with blood transfusions. Today, different types of erythropoietin are used, from short-acting (erythropoietin alpha, beta, delta, zeta) to long-acting (darbepoetin and continuous erythropoietin receptor activator (CERA)). In addition to erythropoietin therapy, iron (preferably intravenously) and folic acid should always be added to therapy for iron deficiency anemia (1-4).

Iron is important in many physiological functions of the body such as respiration, energy production in the form of adenosine triphosphate (ATP) in mitochondria, deoxyribonucleic acid (DNA) synthesis and cell proliferation (1,2,4). Due to the lack of iron, weakness and fatigue of the body occurs.

In iron deficiency anemia, the most sensitive and reliable test for detecting iron deficiency and iron reserves is ferritin, especially in the absence of chronic disease. Absolute iron deficiency is characterized by sideropenic anemia (SA), while functional iron deficiency is characteristic of anemia of chronic or inflammatory diseases. Absolute iron deficiency implies reduced levels of Fe and Fe/total iron binding capacity (TIBC), low levels of ferritin and hepcidin. Ferritin is usually below 15 μg/L (children and women). Ferritin <30 μg/L is a diagnostic indicator of absolute iron deficiency. Decreased iron levels and increased transferrin synthesis correlate with the degree of sideropenia. Red blood cell (RBC) parameters (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)) are reliable if there is no anemia in chronic disease or hemoglobinopathy (1,4).

Functional iron deficiency occurs due to inadequate delivery of iron to the bone marrow despite existing reserves (with normal or elevated ferritin values) in patients with chronic or inflammatory disease (e.g., autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, kidney disease, heart failure, malignancy). This anemia is most often normochromic and normocytic, mild to moderate. Ferritin is generally above 100 μg/L, often between 100 and 300 μg/L, rarely above 800 μg/L, and transferrin saturation is less than 20%.

An average of 10-20 mg of iron *per* day is ingested through the diet, and only 1-2 mg is absorbed (2). Iron intake may be reduced due to the loss of appetite for iron-rich foods or due to reduced protein intake. Decreased absorption of iron ingested with food has also been demonstrated, which is particularly present in HD patients (2). Iron consumption may be increased after the introduction of erythropoiesis-stimulating agents into therapy, resulting in reduction in body reserves and circulating iron (2,4). Absolute and functional iron deficiency may be observed in patients with CKD.

Hepcidin is a small cationic peptide which is produced in the liver and named liver-expressed antimicrobial peptide (LEAP-1) (3-5). The basic significance and role of hepcidin is in the regulation of iron metabolism and mediation in the body defense and inflammation (6-11). As hepcidin is considered the central regulator of iron metabolism, its role in the development of anemia in CKD has been investigated in several studies. Studies confirmed elevated levels of hepcidin in CKD (5,7,10). Serum hepcidin levels have been associated with anemia in patients on a chronic hemodialysis treatment program (7,9,11-15). Elevated hepcidin levels are thought to be caused by overproduction due to impaired iron metabolism and chronic inflammation (16-20), which can often be unrecognized, as well as decreased excretion due to reduced renal clearance (21-25).

The objective of this study was to evaluate the type of iron deficiency in hemodialysis patients and compare their clinical, hematologic and inflammatory parameters according to this type of deficiency.

MATERIAL AND METHODS

This cross-sectional, observational clinical study (Ethics Committee approval number 0302-30013/2018) was performed at the Hemodialysis Department, Sarajevo University Clinical Center, and included 100 patients older than 18 years on chronic hemodialysis treatment (more than 3 months). Exclusion criteria were age over 80 years, patients with blood-borne diseases (hepatitis, HIV), autoimmune diseases and malignant diseases. All patients signed informed consent to take blood tests and other data as part of the study.

During the study period of 10 months, demographic (age, gender, length of hemodialysis treatment) and clinical characteristics (underlying renal disease, erythropoietin level, type of erythropoietin, length of erythropoietin administration and type of response to erythropoietin therapy) were analyzed in these 100 patients. Besides that, laboratory data on complete blood count, serum iron, saturation index, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), ferritin, transferrin, C-reactive protein (CRP) and hepcidin were analyzed.

Blood was drawn immediately after starting hemodialysis treatment at the second HD treatment in the middle of the week. Erythropoietin and other drugs were administered at the end of the treatment and were administered intravenously in all patients. The erythropoietin resistance index (ERI) was determined for each subject.

Statistical calculations were performed with the SPSS 19 software (version 19.0, SPSS Inc., Chicago, Illinois, USA). All collected and obtained results were presented in tables and graphs. Descriptive methods were performed for all monitored parameters as measures of central tendency; mean values and mean numbers, standard error of arithmetic mean (SEM) and stan-

dard deviation (SD) were calculated. Numerical data were expressed as arithmetic means and standard deviations and medians. Comparisons were done by use of Student's t-test and Mann Whitney test. The Pearson, Spearman and Kendall correlation coefficients were used in correlation analysis. The level of statistical significance was set at $p \leq 0.05$.

RESULTS

Therapy for anemia was received by 96% of study patients; 90% of patients were taking iron preparations, while all of them were taking folic acid. Erythropoietin therapy was received by 80% of patients for median length of 2 years (95% confidence interval (95% CI): 1-5 years). The mean RBC value was $3.58 \pm 0.62 \times 10^{12}$/L, hemoglobin 106.9±18.3 g/L, hematocrit 32.5±5.7, TIBC 39.6 (33.3-44.7), UIBC 25.2 (20.1-31.3), and transferrin 1.8 (1.6-2.1) g/L, which was below the cut off value.

Most of the patients (39%) received darbepoetin at a mean dose of 29.5±12.2 μg, then epoetin beta at a mean dose of 5809.5±1661.9 IU/weekly and epoetin alfa at a mean dose of 5571.4±1785.2 IU/weekly. CERA was used in 6% of patients at a mean dose of 119.2±27.0 μg (Table 1).

Table 1. *Type and doses of erythropoietin in HD patients*

Type of erythropoietin	Epoetin alfa (n=14)	Epoetin beta (n=21)	Darbepoetin (n=39)	CERA (n=6)
Dose (weekly)	5571.4±1785.2 IU	5809.5±1661.9 IU	29.5±12.2 μg	
Dose (monthly)				119.2±27.0 μg
Therapy length (years)	1.0 (0.9-4.3)	1.0 (0.5-4.5)	2.0 (1.0-5.0)	5.0 (3.0-6.3)

Data are presented as median and interquartile range; CERA = continuous erythropoietin receptor activator

Examining the proportion of patients with low hemoglobin values, it was found that 40% of them had hemoglobin values below 100 g/L, while 35.0% of them had hemoglobin in the range of 100-120 g/L. Hemoglobin >130 g/L was found in 8 (8.0%) patients. Low hematocrit values were recorded in 40% of study patients.

Low UIBC values were recorded in 72.0% and low TIBC values in 58.0% of patients. Saturation index was low in 14% and high in 18% of patients, while the rest of them had values in normal ranges. Transferrin was low in 45% and only 2% of patients had elevated values.

Ferritin values <100 ng/mL were found in 22.2% and ferritin values in the range of 100-200 ng/mL in 32.3% of patients. Other ranges are shown in Figure 1.

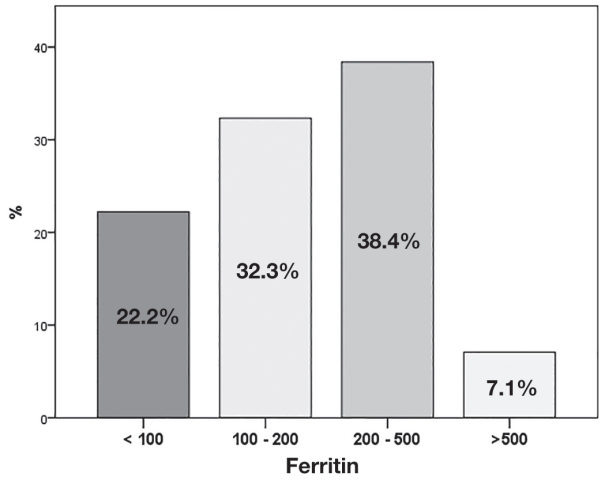

Figure 1. *Representation of hemodialysis patients with low, reference and high serum ferritin values*

Serum iron levels were in the normal range in 78% of hemodialysis patients, while only 22.0% had lower values.

Erythropoietin levels were low in 15.0% and high in 29.0% of patients, while 56% of patients had erythropoietin in normal ranges.

Absolute iron deficiency was found in 10% and functional deficiency in 2.0% of hemodialysis patients, while 86% of patients had no iron deficiency. Reticuloendothelial blockade was found in 2.0% of patients.

Examining clinical, hematologic and inflammatory parameters in patients on hemodialysis in relation to the type of iron deficiency, it was found that patients with absolute iron deficiency had a significantly shorter dialysis length, length of erythropoietin therapy, significantly lower iron, ferritin and hepcidin concentrations, and significantly lower iron saturation index values compared to patients without iron deficiency. Statistically significantly higher values of platelet count, TIBC and UIBC were found in patients with absolute iron deficiency compared to patients without iron deficiency. The mean CRP values were not statistically significantly different between patients with and without iron deficiency (Table 2).

Table 2. *Clinical, hematologic and inflammatory parameters in hemodialysis patients according to type of iron deficiency*

	Absolute iron deficiency	*Without deficiency*	*p*
Hemodialysis length	**7.0 (4.0-31.0)**	**35.0 (9.8-70.0)**	**0.02**
Length of erythropoietin therapy	**0.8 (0.5-1.0)**	**2.0 (1.0-5.5)**	**0.009**
Vascular access	9/1 (9/1%)	62/24 (72.1/27.9%)	0.4
Body mass index	28.1 (25.5-35.1)	25.5 (22.7-29.1)	0.06
Red blood cells	3.6±0.5	3.6±0.6	0.9
Sedimentation rate	43.5 (24.0-75.8)	41.5 (22.5-64.0)	0.5
Hemoglobin (g/L)	100.7±15.7	107.7±18.7	0.25
Hematocrit	30.6±5.0	32.8±5.7	0.26
Platelets	**264.0 (224.0-333.0)**	**184.0 (159.0-232.0)**	**<0.001**
Reticulocytes	89.0 (64.0-132.3)	78.0 (57.8-119.3)	0.6
Leukocytes	**7.9 (7.3-9.5)**	**6.1 (5.2-8.1)**	**0.005**
Iron	**8.9 (6.1-10.1)**	**13.1 (10.4-17.4)**	**<0.001**
TIBC	**49.8 (43.3-55.0)**	**39.0 (32.3-43.2)**	**0.002**
UIBC	**40.6 (35.4-46.9)**	**23.9 (20.0-29.1)**	**<0.001**
Saturation index	**18.1 (13.0-19.7)**	**33.7 (29.0-44.0)**	**<0.001**
Transferrin	1.95 (1.7-2.4)	1.8 (1.6-2.1)	0.13
Ferritin	**45.4 (19.0-75.0)**	**203.0 (137-300)**	**<0.001**
Erythropoietin	15.0 (6.2-44.9)	15.7 (7.0-36.6)	0.9
ERI	0.7 (0.5-1.0)	0.8 (0.5-1.1)	0.9
Hepcidin	**39.8 (14.6-67.2)**	**89.2 (59.0-184)**	**0.003**
C-reactive protein	5.6 (1.9-13.3)	4.0 (2.1-9.9)	0.62

Data with normal distribution are presented as mean and standard deviation, others are presented as median and interquartile range; p≤0.05. TIBC – total iron binding capacity, UIBC – unsaturated iron binding capacity, ERI – erythropoietin resistance index

The median serum hepcidin value in patients without iron deficiency was 89.2 (58.9-183.9) μg/L, and was significantly higher than in patients with absolute deficiency whose hepcidin median concentration was 39.8 (14.6-67.2) μg/L (p=0.003)

The median serum hepcidin value in patients with functional iron deficiency was 26.7 (14.74-26.7) μg/L, while in patients with reticuloendothelial blockade it was 87.8 (26.0-87.8) μg/L (Figure 2). There was also a significant positive correlation between CRP and serum hepcidin levels (Rho=0.22; p=0.028) (Figure 3), as well as between hepcidin and ferritin values (Rho=0.45; p<0.001) in hemodialysis patients (Figure 4).

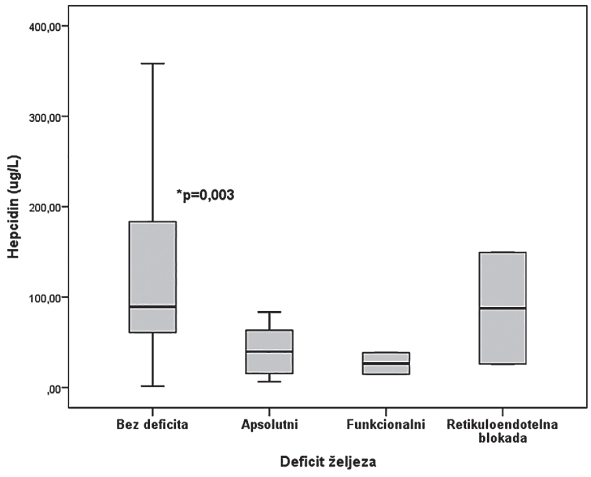

Figure 2. *Serum hepcidin concentration in hemodialysis patients according to the presence and type of iron deficiency. Data are presented as median and interquartile range.*

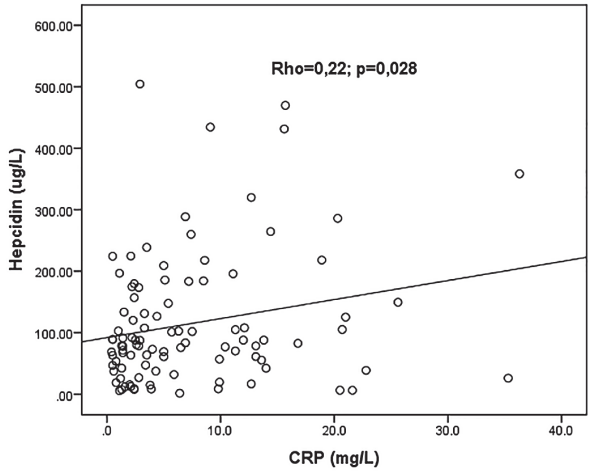

Figure 3. *Correlation between C-reactive protein and serum hepcidin levels.*

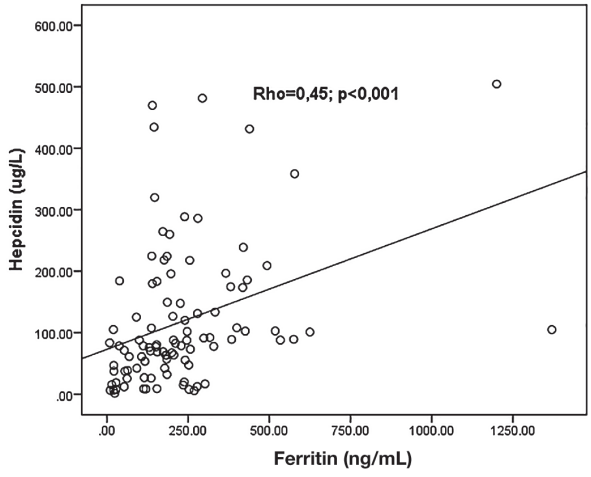

Figure 4. *Correlation between hepcidin and ferritin serum values.*

DISCUSSION

Anemia is a common complication of CKD, the incidence of which increases with disease progression, so that, according to data from studies and scientific literature (26-30), the fifth (terminal) stage of CKD is present in over 90% of patients on hemodialysis. Our study showed that anemia, according to the definition and guidelines of the KDIGO Guidelines for the Treatment of Renal Anemia (1), is present in 96% of patients receiving therapy for anemia. Ninety percent of patients were taking iron preparations, while all of them were taking folic acid. Analysis of RBC indices (MCV, MCH and MCHC) showed that normocytic-normochromic, hypoproliferative anemia was present, which is common in anemia within CKD (1). Analysis of the total number of leukocytes, reticulocytes and platelets revealed that they were within the physiological values in a very high percentage, which means that the hematopoietic ability of bone marrow was preserved in our patients. The incidence of anemia increases with CKD progression, so that it is present in almost all patients in the fifth stage of CKD (26-38).

In accordance with the recommendations (1), 35% of our patients were treated with short-acting erythropoietin, while 45% of patients received long-acting erythropoietin. The highest percentage of patients received darbepoetin (Aranesp) at a mean dose of 29.5 μg *per* week. Erythropoietin preparations were administered intravenously to all patients. We analyzed various parameters of serum iron metabolism. Iron levels were reduced in 22% of patients, 78% of patients had reference values, and none of the patients had high iron values; 38.4% of patients with ferritin values of 200-500 ng/mL had replenished iron reserves, 7.1% of patients had ferritin values above 500, and only two patients had ferritin values above 1000 ng/mL.

Ten patients had absolute iron deficiency with ferritin values below 100 ng/mL and transferrin saturation (TsAT) lower than 20%. Two patients had functional iron deficiency and reticuloendothelial blockade each. Examining clinical, hematologic and inflammatory parameters in hemodialysis patients according to the type of iron deficiency, it was found that patients with absolute iron deficiency had a significantly shorter duration of hemodialysis treatment, length of erythropoietin therapy, significantly lower serum iron, ferritin and hepcidin, as well as lower values of saturation index compared to patients without iron deficiency. The most important question that arises and is important for patients with anemia is which of these patient groups could benefit from therapy with iron supplements. Erythropoietin levels were low in 15% and high in 29% of patients. An adequate response to iron therapy would lead to better response to erythropoietin therapy, while avoiding the risks associated with iron over-substitution, which would be of great clinical and economic importance (35-39). Patients with absolute iron deficiency should first receive iron supplements, then erythropoietin for a more adequate response and correction of anemia in terms of the action of erythropoietin itself. Patients with functional deficits receive maintenance doses of iron supplements, while patients with inflammation may have lower ferritin values and falsely low iron depots until correction of inflammatory parameters (1,35,39-40).

Examining hepcidin in patients with iron deficiency and association with inflammation, the median value of hepcidin in patients without serum iron deficiency was significantly higher than in patients with absolute serum iron deficiency. Patients without iron deficiency were treated for a long time with hemodialysis and with saturated depots and higher serum ferritin values. Patients on a chronic HD program are expected to have elevated serum hepcidin levels compared to the healthy population due to decreased renal excretion of hepcidin and increased synthesis due to inflammation and increased body iron reserves (10,11,27). The mean value of hepcidin in the study group of hemodialysis patients was 83.5 ug/L (42.3-173.4). Hepcidin reference values were found in 28% of patients, while 72% of patients had high hepcidin values, and none of the patients had low hepcidin values. A positive correlation between hepcidin and CRP was demonstrated, as well as positive correlation between ferritin and CRP.

According to CRP values, 25% of our study patients were in a state of inflammation. Other studies found that the parameters of inflammation in HD patients were increased compared to the healthy population, and hepcidin and CRP positively correlated as in many other published studies (7-11,17,23,36).

CONCLUSION

Patients with absolute iron deficiency should initially receive iron supplements in therapy, compared to erythropoietin for a more adequate response and better correction of anemia. Patients with functional iron deficiency receive maintenance doses of iron preparations, while patients with inflammation may have lower ferritin values and falsely low iron depots until the inflammatory parameters are corrected. Adequate iron therapy will also lead to better response to erythropoietin therapy, while avoiding the risks associated with iron over-substitution, which would be of great clinical and economic importance (37-40). Patients on HD had elevated hepcidin values up to 72%, which is expected in HD population, given the reduced renal clearance and a quarter of patients with inflammation, and proven CRP and hepcidin positive correlation.

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S A Ž E T A K

EVALUACIJA HIPOFEREMIJE KOD PACIJENATA NA HEMODIJALIZI

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Cilj: Cilj ovog istraživanja bio je procijeniti vrstu nedostatka željeza u hemodijaliziranih pacijenata i usporediti njihove kliničke, hematološke i upalne parametre prema ovoj vrsti nedostatka. ***Ispitanici i metode:*** U studiju je bilo uključeno 100 pacijenata različite životne dobi, oba spola, različitog trajanja liječenja hemodijalizom, pacijenti s dobrim i lošijim odgovorom na terapiju eritropoetinom. Analizirali smo kompletnu krvnu sliku (KKS), eritropoetin, željezo, ukupni kapacitet vezanja željeza (TIBC), nezasićeni kapacitet vezanja željeza (UIBC), indeks zasićenja (IZ), transferin, feritin, C-reaktivni protein (CRP), hepcidin. ***Rezultati:*** Apsolutni nedostatak željeza nađen je u 10 %, funkcionalni nedostatak u 2 %, a retikuloendotelna blokada u 2 % bolesnika, dok 86 % nije imalo nedostatak željeza. Ispitivanjem kliničkih, hematoloških i upalnih parametara u bolesnika na hemodijalizi u odnosu na vrstu nedostatka željeza utvrđeno je da bolesnici s apsolutnim nedostatkom željeza imaju značajno kraće trajanje hemodijalize, duljinu terapije eritropoetinom, značajno niže željezo, feritin i značajno nižu saturaciju te vrijednosti indeksa u usporedbi s pacijentima bez nedostatka željeza. Razina eritropoetina bila je niska kod 15 % i visoka kod 29 % pacijenata. Studija je pokazala da je anemija bila prisutna kod 96 % pacijenata koji su primali terapiju za anemiju, 90 % je primalo dodatke željeza; svih 100 pacijenata je primalo folnu kiselinu, 80 % pacijenata je primalo eritropoetin. Pacijenti na hemodijalizi imali su povišene vrijednosti hepcidina do 72 %, što je i očekivano u populaciji na hemodijalizi s obzirom na smanjeni bubrežni klirens i četvrtinu bolesnika s upalom te dokazanu pozitivnu korelaciju CRP-a i hepcidina. ***Zaključak:*** Bolesnici s apsolutnim nedostatkom željeza trebali bi u početku primati nadomjestke željeza u terapiji, u usporedbi s eritropoetinom za adekvatniji odgovor i bolju korekciju anemije. Bolesnici s funkcionalnim nedostatkom željeza primaju doze održavanja pripravaka željeza, dok bolesnici s upalom mogu imati niže vrijednosti feritina i lažno niske depoe željeza dok se upalni parametri ne korigiraju.

Ključne riječi: apsolutni i funkcionalni nedostatak željeza, eritropoetin, feritin, upala, hepcidin