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Assessment of erythroferrone levels in children with chronic kidney disease on regular hemodialysis

Mahmoud Ahmed El-Hawy[1], Ahmed Adel Mahmoud Nowir[1], Shimaa Abdelsatar Refat Zaki[2], Mohamed Shokry El-Haruon[1]

[1]*Menoufia University, Menoufia, Egypt*
[2]*National Liver Institute, Menoufia University, Menoufia, Egypt*

Correspondence:
Mahmoud Ahmed El-Hawy,
Department of Pediatrics,
Faculty of Medicine, Menoufia University,
Shebin El Kom, Egypt
Address: Shebin El Kom,
32511 Menoufia, Egypt
E-mail: mahmodelhawy18@yahoo.com

Anemia is a common comorbidity in children with chronic kidney disease (CKD) and is associated with adverse outcomes. Erythroferrone (ERFE) is a hepcidin inhibitor whose synthesis is stimulated by erythropoietin, which increases iron absorption and mobilization. Aim of the study: to assess the levels of ERFE hormone in children with CKD on regular hemodialysis. This case–control study was carried out at Menoufia University Hospital and included 70 subjects: 38 healthy individuals (controls) and 32 children with CKD on regular dialysis (cases). The study was approved by the Faculty of Medicine Ethics Committee at Menoufia University. All children were subjected to full history taking, complete clinical examination, blood tests such as complete blood count, reticulocyte count, serum iron, ferritin, and total iron binding capacity, liver and renal function tests, and an immunoassay to measure human ERFE. There was a statistically significant difference in the levels of ERFE between the cases and controls ($p < 0.001$). There was a significant, strong correlation between the levels of hemoglobin and serum iron and the level of ERFE ($r = –0.655$, $p < 0.001$). There was no significant correlation between the administered dose of exogenous erythropoietin and the level of ERFE ($p = 0.460$). Serum ERFE levels in the children with CKD on regular hemodialysis were significantly higher than in the controls and were negatively correlated with hemoglobin and iron levels. There was no significant correlation between ERFE levels and both serum ferritin and total iron binding capacity levels.

Key words: *anemia, chronic kidney disease, erythroferrone, hemodialysis*

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Iron plays a crucial role in several fundamental biological processes such as oxygen transport, cellular respiration, and metabolic reactions [1]. A complex system of proteins and hormones controls iron metabolism, and hepcidin is a major regulator of this system [2].

Hepcidin reduces the intestinal absorption of dietary iron and the release of stored iron from hepatocytes and macrophages, a process involving the cellular iron exporter ferroportin. Iron and inflammation are both hepcidin enhancers, while hypoxia-inducible factors, the sex hormones estrogen and testosterone, downregulate hepcidin [2].

In 2014, a new iron metabolism regulating factor synthesized in erythroblasts in response to erythropoietin (EPO) – erythroferrone (ERFE) – was identified [3].

ERFE hormone is encoded by the *FAM132B* gene – now renamed *ERFE* gene – and coincides with a protein also expressed in the skeletal muscle, called myonectin (CTRP15) [4].

By suppressing hepcidin, ERFE increases the absorption and mobilization of iron to provide an adequate iron supply during stress erythropoiesis such as during rapid growth or blood loss [3].

Anemia is a hallmark of chronic kidney disease (CKD) [5] and EPO deficiency and reduced iron bioavailability by high hepcidin levels are fundamental factors underlying this condition in CKD [6].

ERFE production is stimulated by endogenous or exogenous EPO, thus serving to couple increased erythropoietic activity with decreased hepcidin, allowing for maintenance of plasma iron concentrations in the setting of increased erythropoiesis-associated iron demand [3].

As ERFE is a newly discovered hormone, there is a limited number of studies investigating ERFE levels. Our study aimed to assess the levels of ERFE hormone in children with CKD undergoing regular hemodialysis at Pediatric Nephrology Unit, Menoufia University Hospital.

MATERIALS AND METHODS

This study is a case–control study conducted at Menoufia University Hospital from July 2021 till January 2022 among children aged 3–18 years old with CKD undergoing regular hemodialysis and exogenous EPO treatment and healthy controls. The study was approved by the Faculty of Medicine Ethics Committee

at Menoufia University. Informed consent from the participants' parents was obtained verbally and the confidentiality of information was assured.

The study subjects were allocated into two groups. Group 1 (cases) consisted of 32 children with CKD undergoing regular hemodialysis who attended the Department of Pediatrics of Menoufia University Hospital. Group 2 (controls) consisted of 38 healthy children that were randomly selected from the Department of Pediatrics of Menoufia University Hospital. Patients under 3 years old or over 18 years old and those without parental consent were excluded from our study.

All the patients were subjected to full history taking (age, sex, the presence of parental consanguinity, age at diabetes onset, a family history, comorbidities, a medication history, the duration of hemodialysis. The duration of dialysis and dialysis doses (calculated by the number of dialysis sessions per week × dialysis hours; dialysis doses) were also assessed. The efficiency of hemodialysis was evaluated by measuring the urea reduction rate. We also collected data on the onset of anemia, the intake of iron supplements, a history of fatigue, poor activity, exertion, dyspnea, breathlessness at rest, blood transfusions in the past, diabetes mellitus (type – duration – treatment – controlled or not – presence of other diabetic complications), and hypertension (duration – controlled or not).

A complete clinical examination included the evaluation of general appearance, body measurements (weight and height), measurements of blood pressure and other vital signs such as temperature, heart rate, respiratory rate. We also performed chest, cardiovascular (CV), abdominal, and neurological examination.

Laboratory examinations included complete blood count, reticulocyte count, serum iron, ferritin and total iron binding capacity (TIBC), liver and renal function tests and human ERFE assay (a sandwich enzyme immunoassay).

Statistical analysis

Data analysis was performed using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. Student's t-test was performed to compare parametric quantitative variables between two groups. Qualitative variables were compared using chi-square test or Fisher's exact test when frequencies were < 5. Pearson's correlation coefficients were employed to assess the association between two normally distributed variables. When a variable was not normally distributed, a p-value < 0.05 was considered significant.

RESULTS

There was a significant difference in the level of ERFE between the cases and controls (p < 0.001) (*table 1*).

There was a significant strong correlation between the levels of hemoglobin and ERFE (r = –0.655, p < 0.001) (*table 2*).

There was a strong correlation between the levels of ERFE and serum iron (r = –0.906, p < 0.001) (*table 3*).

There was no significant correlation between the administered dose of exogenous EPO and the level of ERFE (p = 0.460) (*table 4*).

There was no significant impact of age, sex and body mass index (BMI) on the level of ERFE (p = 0.28, p = 0.71 and p = 0.235, respectively). The level of ERFE changed significantly by the change in the serum iron when adjusting the age, sex and the dose of the exogenous ERFE (p = < 0.001) (*table 5*).

DISCUSSION

Management guidelines for anemia in pediatric CKD patients have been developed from reported studies

Table 1
A comparison of the groups by the level of ERFE

Level of ERFE	Cases (n = 32)	Controls (n = 38)	p
Range	9.85 – 27.25	4.75 – 14.45	< 0.001*
Mean ± SD	17.37 ± 4.53	10.26 ± 2.05	

*Note. SD – standard deviation; p – p-value for the difference in the levels of ERFE between the two groups; * – statistically significant at p ≤ 0.05.*

Table 2
A correlation between the levels of ERFE and hemoglobin (g/dL)

Hemoglobin	Level of ERFE, ng/mL	
	r	p
Total sample	–0.655	< 0.001*
Cases	–0.019	< 0.042*
Controls	–0.909	< 0.001*

*Note. Here and in tables 3, 4: r – the Pearson coefficient; * – statistically significant at p ≤ 0.05.*

Table 3
A correlation between the level of ERFE and different parameters in the group of cases (n = 32)

Parameter	Level of ERFE (ng/mL)	
	r	p
Serum iron, mg/dL	–0.906	< 0.001*
Serum ferritin, ng/mL	–0.074	0.687
TIBC, mg/L	–0.288	0.110

Table 4
A correlation between the level of ERFE and the dose of exogenous EPO (IU/week) in the group of cases (n = 32)

Parameter	Level of ERFE (ng/mL)	
	r	p
Dose of exogenous EPO, IU/week	–0.135	0.460

Table 5
Univariate and multivariate linear regression analysis for the parameters affecting the level of ERFE (ng/mL) in the group of cases (n = 32)

Parameter	Univariate		Multivariate#	
	p	B (95% CI)	*p*	B (95% CI)
Sex	0.710	–0.629 (–4.058–2.799)		
Age, years	0.280	0.252 (–0.216–0.720)		
Complication: vomiting dehydration edema gastroenteritis polyuria enuresis	 0.067 0.024* 0.801 0.468 0.364 0.226	 3.746 (–0.282–7.773) 4.305 (0.614–7.995) 0.571 (–4.006–5.148) –1.520 (–5.745–2.704) –2.039 (–6.558–2.479) –3.367 (–8.935–2.200)	0.057	1.648 (–0.053–3.350)
Consanguinity of parents	0.410	–1.344 (–4.634–1.945)		
Echo	0.260	1.571 (–1.222–4.364)		
Height [7]	0.123	0.088 (–0.025–0.201)		
Weight [8]	0.541	0.037 (–0.084–0.157)		
BMI, kg/m^2	0.235	0.317 (–0.218–0.853)		
Hemoglobin, g/dL	0.918	–0.078 (–1.616–1.459)		
Calcium, mg/dL	0.450	0.736 (–1.225–2.697)		
P04, mg/dL	0.764	0.172 (–0.988–1.332)		
PTH, mg/dL	0.122	–0.003 (–0.008–0.001)		
Serum iron, mg/dL	< 0.001*	–0.213 (–0.250 – (–0.176))	< 0.001*	–0.203 (–0.240 – (–0.166))
Serum ferritin, ng/mL	0.687	–0.005 (–0.032–0.021)		
TIBC, mg/L	0.110	–0.002 (–0.004–0.0)		
Pulse	0.814	0.042 (–0.318–0.4020		
Dose of exogenous EPO, IU/week	0.460	0.0 (0.0–0.0)		

*Note. B – unstandardized coefficients; CI – confidence interval; # – all variables with p < 0.05 were included in the multivariate analysis; * – statistically significant at p ≤ 0.05.*

in both adults and children, from clinical experience and from expert opinion. The revised National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines for the management of anemia specifically for children have been recently published [13].

Biomarkers of iron metabolism like serum ferritin and hepcidin have been independently associated with the risk of death and CV events in this CKD patients [11].

In our study, there was no significant difference in the age or sex distribution between the controls and the CKD patients on regular hemodialysis (p = 0.775 and p = 0.313, respectively). In agreement with our results, Ogawa et al. [14] reported that there was no significant difference between the studied groups as regards age (years) and sex. In contrast to our results, Astor et al. [5] reported a statistically significant difference between the studied groups as regards age (years) and sex. In the study by Yu et al. [15], there was a highly statistically significant difference between the studied groups as regards age (years) and sex, which also disagrees with our results.

Our study showed a statistically significant difference in hemoglobin levels between the cases and controls (p < 0.001). The mean level of hemoglobin was 10.37 g/dL in the group of cases and 12.45 g/dL in the group of controls. In agreement with our results, Yu et al. [15] reported a highly statistically significant difference in the levels of hemoglobin between the studied groups (p > 0.001). In the study by Ogawa et al. [14], there also was a statistically significant difference in the levels of hemoglobin between the studied groups (p = 0.006). Hanudel et al. [16] showed that the mean hemoglobin level (g/dL) in non-dialysis CKD patients was 12.1 ± 1.7 SD, while in dialysis-dependent CKD patients it was 11.9 ± 1.5 SD.

In our study, there was a statistically significant difference in the levels of ERFE between the cases and the controls (p < 0.001). The mean ERFE levels were 17.37 ng/mL and 10.26 ng/mL in the groups of cases and healthy controls, respectively.

In the first study investigating ERFE in CKD patients, serum ERFE levels in hemodialysis patients were substantially similar to those in control subjects and 10 times lower than the levels in hemodialysis patients in the study by Spoto et al. [11] (0.5 ng/mL vs. 4.5 ng/mL). In the second study by Hanudel et al. [16], serum ERFE levels, measured by the recent assay by Ganz et al., were similar in 51 CKD and 161 healthy control subjects (6.1 (2.6–15.0) ng/mL and 7.8 (4.7–13.2) ng/mL, respectively) but twice lower than in 97 hemodialysis patients (15.7 (7.9–32.5) ng/mL).

Spoto et al. reported that ERFE emerged as a coherent direct risk factor of death and CV complications in two separate CKD cohorts. ERFE is strongly related in an inverse fashion to hepcidin in hemodialysis patients, which is a direct

correlate of CV events in such patients. In our study, echocardiographic examination showed that 12 (37.5%) cases had normal findings, 18 (56.3%) cases had left ventricular hypertrophy, and only 2 (6.3%) cases had cardiomyopathy.

Spoto et al. reported that the relationship between ERFE and the study outcomes was largely independent of major inflammation markers like C-reactive protein, serum iron, and ferritin, suggesting that interference with these factors does not explain the excess risk for death and CV events by relatively higher levels of ERFE in CKD and in hemodialysis patients. It is important to note that ERFE synthesized in the skeletal muscle in response to exercise (myonectin) has a protective role for the CV system in experimental models. Even though discrepancies among myonectin and ERFE assays still need to be understood and reconciled, it should be noted that other biomarkers that underlie a protective action for the CV system, like adiponectin – a paralogue to ERFE – are directly, rather than inversely, related to the risk of death in hemodialysis patients.

Our study showed a significant strong negative correlation between the levels of hemoglobin and ERFE ($r = –0.655$, $p < 0.001$).

ERFE is known to inhibit the induction of hepcidin. In the study by van Vuren et al., hepcidin values were unavailable, which limited the ability to study the link between erythropoiesis and iron metabolism in their cohort. Hepcidin itself was previously shown to be capable of inducing FGF23 production and its cleavage, independently of inflammation [19, 20].

Van Vuren et al. [20] underscore the importance of EPO-ERFE signaling in hemolytic anemia; however, ERFE is not simply an intermediary in EPO-FGF23 signaling. Their observation is in line with Clinkenbeard et al. [21] study that was performed in mice. Thereby, they confirm the persistence of a relationship between EPO and FGF23 regulation in the absence of iron deficiency.

In our study, we found a significant strong correlation between the levels of ERFE and serum iron ($r = –0.955$, $p < 0.001$). However, there was no significant correlation between the levels of ERFE and serum ferritin ($r = 0.074$, $p < 0.687$) and between the levels of ERFE and TIBC (mg/L) ($r = –0288$, $p < 0.110$)

Kalantar-Zadeh et al. indicated that low serum TIBC is related to protein-energy wasting, inflammation, poor quality of life, and mortality. They found that TIBC is positively associated with nutritional biomarkers such as serum albumin and negatively associated with several inflammatory markers such as log C-reactive protein [15].

The prevalence of anemia among patients with stage 3–5 CKD was 88.6% in the study by Thang et al. [23]. A similar Chinese cohort including 2420 patients with stage 1–5 CKD reported that 51.5% of patients had anemia, of which 1338 patients had stage 3–5 CKD. A Japanese cohort study showed that 32.3% of 2930 patients with stage 3–5 CKD were diagnosed as anemic. In a South Korean cohort study, 44.9% of 2198 patients with stage 1–5 CKD were diagnosed as anemic (1524 patients with stage 3–5 CKD) [24].

In the United States, the prevalence of anemia in patients with CKD was 15.4% in the NHANES study and 46% in the Chronic Renal Insufficiency Cohort study. [25]. Considering the discrepancy in anemia prevalence, the results obtained by Thang et al might have been higher than the aforementioned studies because 175 patients in their study were diagnosed as having stage 3–5 CKD for the first time (62.3% in stage 5 CKD).

The majority of the patients in that study had mild to moderate anemia. Thang et al found that the prevalence of moderate and severe anemia increased progressively with the deteriorating of renal function. These findings reflect that anemia severity increases with declining renal function, which can be attributed to various factors associated with the development of anemia in patients with CKD, such as EPO insufficiency, iron and vitamin deficiency, malnutrition, inflammation, platelet dysfunction, reduced red blood cell survival, and hemolysis. Most patients in their study had normochromic–normocytic anemia, comparable to the findings of other studies.

In the study by Thang et al. [23], the mean serum iron and ferritin levels and TIBC in patients with CKD were significantly different from the values in the control group. In particular, ferritin levels were significantly higher in the study group (259 ng/mL) than in the control group (160 ng/mL). TIBC was lower in the study group (50.4 μmol/L) than in the control group (66.0 μmol/L). An increase in ferritin levels can be explained by the nonspecific protein synthesis compensating for protein loss in advanced CKD as well as the progression of inflammation in CKD patients. Since the KDOQI 2006 workgroup recommended targeting serum ferritin levels of more than 100 ng/mL in patients with non-dialysis end-stage renal disease, some randomized control studies showed beneficial that iron treatment had erythropoietic effects in patients with stage 3–5 CKD and ferritin levels exceeding 100 ng/mL. Currently, the Vietnamese Nephrology Association covered the use of intravenous iron in patients with CKD and with transferrin saturation < 20.0% or ferritin < 100 ng/mL, and hemoglobin lower than 10 g/dL [23].

Alzaheb et al. [27] reported that iron deficiency anemia was prevalent among female university students in Saudi Arabia (12.5%) and that inadequate iron intake was a risk factor related to contracting

anemia. One of the most common factors influencing iron homeostasis is inflammation, which is present in CKD, especially in end-stage CKD.

However, Thang et al. also found a relationship between overall iron deficiency and serum hs-C-reactive protein in their study. The proportion of overall iron deficiency increased through stage 3 CKD to stage 5 CKD. The causes of iron deficiency in patients with CKD were multifactorial. Some had true iron deficiency, characterized by a decrease in both circulating iron levels and total body iron stores. Other patients had functional iron deficiency, characterized by a decrease in circulating iron that limits erythropoiesis, which can occur even in the context of normal or adequate body iron stores. A combination of these features was also sometimes presented. Factors predisposing patients with CKD to iron deficiency included increasing blood loss, increased iron utilization from ESA therapy, impaired dietary iron absorption, and impaired iron release from body storage sites.

When evaluating the correlation between TIBC and some para-clinical indices, Thang et al. [23] found that TIBC had a weak negative correlation with creatinine level, a weak positive correlation with hemoglobin concentration, a negative correlation with serum ferritin (ng/mL) and TIBC (mg/L). TIBC depends on the blood's capacity to bind iron with iron-bearing proteins including transferrin. TIBC denotes the quantity of iron transported to the body. TIBC is usually lower in patients with chronic diseases, inflammation, malnutrition, or proteinuria. In patients with CKD, malnutrition is often a major problem. Malnutrition leads to hypoproteinemia, which causes a decrease in TIBC and hemoglobin concentration. Overall iron deficiency is often characterized by decreased iron and transferrin saturation levels as well as increased ferritin and TIBC concentrations.

Our study has some limitations. First, we did not measure the target molecule of ERFE – hepcidin. Hepcidin is in the pathogenic pathway whereby ERFE impacts upon iron metabolism and anemia and, ultimately, on clinical outcomes. Another limitation is the small number of patients.

CONCLUSION

Serum ERFE levels in the children with CKD on regular hemodialysis were significantly higher than those in the controls. Serum ERFE levels in the cases were correlated negatively with hemoglobin and iron levels, with no significant correlation between the levels of ERFE and both serum ferritin and TIBC. These observations suggest that ERFE may be a part of the biological response to a high-risk condition like CKD, a hypothesis that remains to be tested in mechanistic studies.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

References

1. Abbaspour N., Hurrell R., Kelishadi R. Review on iron and its importance for human health. J Res Med Sci 2014; 19 (2): 164.
2. Rishi G., Wallace D.F., Subramaniam V.N. Hepcidin: regulation of the master iron regulator. Biosci Rep 2015; 35 (3): e00192. DOI: 10.1042/BSR20150014
3. Kautz L., Jung G., Valore E.V., Rivella S., Nemeth E., Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet 2014; 46 (7): 678–84.
4. Seldin M.M., Peterson J.M., Byerly M.S., Wei Z., Wong G.W. Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis. J Biol Chem 2012; 287 (15): 11968–80.
5. Astor B.C., Muntner P., Levin A., Eustace J.A., Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). Arch Int Med 2002; 162 (12): 1401–8.
6. Panwar B., Gutiérrez O.M. Disorders of iron metabolism and anemia in chronic kidney disease. Semin Nephrol 2016; 36 (4): 252–61. DOI: 10.1016/j.semnephrol.2016.05.002
7. Crowson C.S., Rollefstad S., Ikdahl E., Kitas G.D., Van Riel P.L., Gabriel S.E., et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis 2018; 77 (1): 48–54.
8. Libby P., Buring J.E., Badimon L., Hansson G.K., Deanfield J., Bittencourt M.S., et al. Atherosclerosis. Nat Rev Dis Primers 2019; 5 (1): 56. DOI: 10.1038/s41572-019-0106-z
9. Raichoudhury R. Spinowitz B.S. Treatment of anemia in difficult-to-manage patients with chronic kidney disease. Kidney Int Suppl 2021; 11 (1): 26–34.

10. Atkinson M.A., Warady B.A. Anemia in chronic kidney disease. Pediatr Nephrol 2018; 33 (2): 227–38.
11. Spoto B., Pizzini P., Torino C., Leonardis D., Cutrupi S., Tripepi G., et al. FP379 Erythroferrone Predicts Mortality and Cardiovascular Events in CKD and in Hemodialysis Patients: A Two Cohorts Study. Nephrol Dial Transplant 2019; 34 (Suppl_1): p.gfz106. FP379.
12. Kuriyama S., Maruyama Y., Honda H. A new insight into the treatment of renal anemia with HIF stabilizer. Renal Replacement Therapy 2020; 6 (1): 1–14.
13. Allen R.P., Picchietti D.L., Auerbach M., Cho Y.W., Connor J.R., Earley C.J., et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med 2018; 41: 27–44.
14. Ogawa C., Tsuchiya K., Kanda F., Maeda T. Low levels of serum ferritin lead to adequate hemoglobin levels and good survival in hemodialysis patients. Am J Nephrol 2014; 40 (6): 561–70.
15. Yu P.-H., Lin M.-Y., Chiu Y.-W., Lee J.-J., Hwang S.-J., Hung C.-C., Chen H.-C. Low serum iron is associated with anemia in CKD stage 1–4 patients with normal transferrin saturations. Sci Rep 2021; 11 (1): 1–10.
16. Hanudel M.R., Rappaport M., Chua K., Gabayan V., Qiao B., Jung G., et al. Levels of the erythropoietin-responsive hormone erythroferrone in mice and humans with chronic kidney disease. Haematologica 2018; 103 (4): e141.
17. Van der Weerd N.C., Grooteman M.P., Bots M.L., van den Dorpel M.A., den Hoedt C.H., Mazairac A.H., et al. Hepcidin-25 is related to cardiovascular events in chronic haemodialysis patients. Nephrol Dial Transplant 2013; 28 (12): 3062–71.
18. Honda H., Kobayashi Y., Onuma S., Shibagaki K., Yuza T., Hirao K., et al. Associations among erythroferrone and biomarkers of erythropoiesis and iron metabolism, and treatment with long-term erythropoiesis-stimulating agents in patients on hemodialysis. PLoS One 2016; 11 (3): e0151601.
19. David V., Martin A., Isakova T., Spaulding C., Qi L., Ramirez V., et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int 2016; 89 (1): 135–46.
20. Van Vuren A.J., Eisenga M.F., van Straaten S., Glenthøj A., Gaillard C.A., Bakker S.J., et al. Interplay of erythropoietin, fibroblast growth factor 23, and erythroferrone in patients with hereditary hemolytic anemia. Blood Adv 2020; 4 (8): 1678–82.
21. Clinkenbeard E.L., Hanudel M.R., Stayrook K.R., Appaiah H.N., Farrow E.G., Cass T.A., et al. Erythropoietin stimulates murine and human fibroblast growth factor-23, revealing novel roles for bone and bone marrow. Haematologica 2017; 102 (11): e427.
22. Bross R., Zitterkoph J., Pithia J., Benner D., Rambod M., Kovesdy C.P., et al. Association of serum total iron-binding capacity and its changes over time with nutritional and clinical outcomes in hemodialysis patients. Am J Nephrol 2009; 29 (6): 571–81.
23. Thang L.V., Kien N.T., Van Hung N., Kien T.Q., Dung N.H., Thu Huong N.T., et al., Serum total iron-binding capacity and iron status in patients with non-dialysis-dependent chronic kidney disease: A cross-sectional study in Vietnam. Asia Pac J Clin Nutr 2020; 29 (1): 48–54.
24. Ryu S.-R., Park S.K., Jung J.Y., Kim Y.H., Oh Y.K., Yoo T.H., Sung S. The prevalence and management of anemia in chronic kidney disease patients: result from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD). J Korean Med Sci 2017; 32 (2): 249–56.
25. Kurella Tamura M., Vittinghoff E., Yang J., Go A.S., Seliger S.L., Kusek J.W., et al. Anemia and risk for cognitive decline in chronic kidney disease. BMC Nephrol 2016; 17 (1): 1–7.
26. Lukaszyk E., Lukaszyk M., Koc-Zorawska E., Bodzenta-Lukaszyk A., Malyszko J. Fibroblast growth factor 23, iron and inflammation–are they related in early stages of chronic kidney disease? Arch Med Sci 2017; 13 (4): 845.
27. Alzaheb R.A., Al-Amer O. The prevalence of iron deficiency anemia and its associated risk factors among a sample of female university students in Tabuk, Saudi Arabia. Clin Med Insights Women's Health 2017; 10: 1179562X17745088.