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# Comparative analysis of iron metabolism proteins in the pathogenesis of anemia in chronic kidney disease

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Disturbances in iron metabolism play a key role in the pathophysiology of chronic kidney disease (CKD), contributing to clinical complications, particularly the development of anemia. Evaluating the diagnostic utility of iron metabolism proteins in CKD patients, depending on disease progression, is of great significance both diagnostically and therapeutically.

**Aim:** to evaluate the role of iron metabolism proteins in the pathogenesis of anemia and their clinical diagnostic value in patients with chronic kidney disease at both the conservative and terminal stages.

**Materials and methods.** The study included patients with stage II–III CKD (conservative group) and terminal-stage CKD undergoing hemodialysis (terminal group), as well as healthy controls. Serum levels of hemoglobin, iron, erythropoietin, ferritin, transferrin, lactoferrin, ferroportin, hepcidin, and haptoglobin were analyzed.

**Results.** In terminal-stage CKD, the concentrations of hemoglobin (22.1 %, $p < 0.001$ and 28.6 %, $p = 0.001$), erythropoietin (26.8 % and 32.5 %, $p < 0.001$), iron (18.3 %, $p = 0.004$ and 33.0 %, $p < 0.001$), TIBC (14.5 %, $p < 0.001$ and 17.3 %, $p = 0.003$), LIBC (14.4 %, $p = 0.006$ and 14.8 %, $p = 0.039$), and transferrin (11.3 %, $p = 0.042$ and 30.8 %, $p = 0.008$) were significantly lower in both men and women compared to the conservative group. In contrast, ferritin (2.3-fold and 2.1-fold, $p < 0.001$), hepcidin (82.2 % and 65.1 %, $p < 0.001$), ferroportin (50.0 % and 46.2 %, $p < 0.001$), and lactoferrin (2.2-fold and 87.5 %, $p < 0.001$) levels were significantly increased in the terminal stage group compared to the conservative group. Ferritin and hepcidin demonstrated the highest diagnostic performance in CKD, showing excellent sensitivity, specificity, and diagnostic efficiency. Lactoferrin and erythropoietin also showed strong diagnostic value, while ferroportin exhibited moderate diagnostic performance. Transferrin demonstrated the lowest diagnostic efficiency, indicating limited standalone clinical usefulness.

**Conclusions.** This study demonstrates that functional iron deficiency in end-stage renal disease is mediated by systemic inflammation. These findings underscore the pivotal role of iron metabolism proteins in the pathogenesis of renal anemia and validate their clinical utility as diagnostic biomarkers and therapeutic targets.

**Keywords:** chronic kidney disease, iron metabolism, erythropoietin, lactoferrin, hepcidin.

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## Порівняльний аналіз білків метаболізму заліза в патогенезі анемії при хронічній хворобі нирок

**Г. М. Ефендієва, Г. А. Джафарова**

Порушення метаболізму заліза відіграють ключову роль у патофізіології хронічної хвороби нирок (ХХН), спричиняючи клінічні ускладнення, як-от анемію. Дослідження інформативності білків метаболізму заліза у пацієнтів із ХХН залежно від прогресування захворювання має важливе діагностичне та терапевтичне значення.

**Мета роботи –** оцінити роль білків метаболізму заліза в патогенезі анемії та їхню клінічну інформативність у пацієнтів із ХХН на консервативній і термінальній стадіях.

**Матеріали і методи.** У дослідженні взяли участь 44 пацієнти з ХХН II–III стадії, які не отримували гемодіаліз (консервативна група), та 46 пацієнтів із ХХН термінальної стадії, яким регулярно виконували гемодіаліз (термінальна група). До контрольної групи залучили 20 практично здорових осіб. У всіх учасників аналізували рівень креатиніну, гемоглобіну, еритропоетину, заліза, гаптоглобіну, феритину, трансферину, лактоферину та гепсидину в крові.

**Результати.** У термінальній стадії ХХН концентрації гемоглобіну (22,1 %, $p < 0,001$ та 28,6 %, $p = 0,001$), еритропоетину (26,8 % та 32,5 %, $p < 0,001$), заліза (18,3 %, $p = 0,004$ та 33,0 %, $p < 0,001$), загальної залізозв'язувальної здатності сироватки (TIBC; 14,5 %; $p < 0,001$ та 17,3 %; $p = 0,003$), латентної залізозв'язувальної здатності (LIBC; 14,4 %, $p = 0,006$ та 14,8 %, $p = 0,039$), а також трансферину (11,3 %, $p = 0,042$ та 30,8 %, $p = 0,008$) статистично значущо нижчі і в чоловіків, і в жінок порівняно з консервативною групою. Натомість рівні феритину (у 2,3 та 2,1 раза, $p < 0,001$), гепсидину (82,2 % та 65,1 %, $p < 0,001$), феропортину (50,0 % та 46,2 %, $p < 0,001$) і лактоферину (у 2,2 раза та на 87,5 %, $p < 0,001$) статистично значущо підвищені в групі термінальної стадії порівняно з консервативною. Феритин і гепсидин мали найвищу діагностичну ефективність при ХХН, характеризуючись відмінною чутливістю, специфічністю та загальною діагностичною точністю. Лактоферин та еритропоетин також мали високу діагностичну цінність, а феропортин показав помірну діагностичну ефективність. Трансферин мав найнижчу діагностичну ефективність, що свідчить про його обмежену самостійну клінічну значущість.

**Висновки.** Функціональний дефіцит заліза виникає на фоні запалення при ХХН у термінальній стадії. Ці зміни підтверджують важливу роль білків метаболізму заліза в патогенезі анемії, що пов'язана з ХХН, та обґрунтовують їхнє клініко-діагностичне та практичне значення.

**Ключові слова:** хронічна хвороба нирок, метаболізм заліза, еритропоетин, лактоферин, гепцидин.

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Chronic kidney disease (CKD) continues to remain a serious public health problem worldwide. According to the World Health Organization, more than 800 million people are currently affected by this disease, and this number is increasing every year [1,2]. CKD is an irreversible, progressive condition defined by abnormalities of kidney structure or function, including renal parenchymal damage, albuminuria, or other markers of kidney damage, or a sustained reduction in glomerular filtration rate to below 60 mL/min/1.73 $m^2$ persisting for three months or longer [2,3]. The disease gradually leads to impairment of the filtration, excretory, and endocrine functions of the kidneys, ultimately resulting in acute or end-stage renal failure. Anemia, one of the major complications of CKD, not only worsens the course of the disease but also reduces quality of life, increases cardiovascular risks, and negatively affects survival rates [3,4,5].

In modern practice, relying solely on hemoglobin and hematocrit indices is not sufficient for the diagnosis of anemia. A more precise approach requires the analysis of iron metabolism proteins, their interactions, and their associations with inflammatory biomarkers. These biomarkers provide deeper insights into the etiopathogenesis of anemia in CKD and enable a more individualized approach.

Several complex mechanisms are involved in the development of anemia in CKD. One of the main causes is the reduced synthesis of erythropoietin (EPO) in the kidneys. EPO deficiency leads to the inhibition of erythropoiesis. On the other hand, under the influence of inflammatory cytokines, increased synthesis of hepcidin impairs the release of iron from stores and its absorption from the intestine, thereby exacerbating functional iron deficiency [6].

Disruption of iron metabolism plays a central role in the development of anemia. In recent years, the interactions of biomolecules and proteins involved in this process, erythropoietin, hepcidin, ferroportin, ferritin, transferrin, lactoferrin, and haptoglobin, have begun to be studied in greater detail. EPO is synthesized in type I interstitial peritubular cells located in the renal cortex and the outer medullary layer, and it ensures the differentiation of erythroid cells. EPO stimulates the production of red blood cells (erythrocytes) by inducing the synthesis of erythroferrone in erythroblasts, thereby regulating hepcidin levels. As a result, iron is released from storage sites and delivered to hematopoietic tissue. However, in CKD, reduced synthesis of EPO also leads to a decrease in erythroferrone levels, which in turn causes an increase in hepcidin. Consequently, iron mobilization is impaired and its availability for erythropoiesis becomes limited [3,6].

One of the key proteins in the regulation of iron homeostasis is hepcidin. This hormone is synthesized in the liver, and its levels are regulated by a feedback mechanism dependent on iron status, while its synthesis is controlled by iron levels, anemia, infection, inflammation, and erythropoietic activity [7]. Hepcidin binds to the iron exporter ferroportin, leading to its degradation. As a result of this mechanism, iron absorption from the intestine and iron release from macrophages and hepatocytes is significantly reduced. Activation of the inflammatory process, resulting in increased synthesis of inflammatory cytokines such as interleukin-6 (IL-6), stimulates hepcidin synthesis, thereby further exacerbating this pathological process [8,9].

Ferritin is the primary indicator reflecting the body's iron stores. However, since ferritin is an acute-phase reactant, its level does not accurately reflect actual iron reserves in chronic inflammation, including CKD. In such cases, the transferrin saturation (TSAT) can be considered a more objective indicator. A decrease in TSAT occurs against the background of reduced transferrin levels or low circulating iron and indicates functional iron deficiency. Transferrin participates in the transport of iron in plasma, and its saturation level reflects the functional iron status [10,11,12].

Lactoferrin is a glycoprotein with the ability to bind iron and regulate inflammation. It reduces hepcidin synthesis and also promotes iron mobilization from stores and stimulates erythropoiesis. Lactoferrin is a glycoprotein secreted by neutrophils and epithelial cells with a high affinity for iron. Additionally, it directly stimulates transferrin receptors, thereby accelerating the uptake of iron into cells [13,14,15].

Haptoglobin binds free hemoglobin, reducing oxidative stress that arises during hemolysis, and prevents the release of heme-bound iron, thereby decreasing the toxic effects of free iron. In CKD, its levels may vary depending on the degree of inflammation and hemolysis. Haptoglobin in these cases is considered a secondary defense mechanism. During hemolysis and chronic inflammation, haptoglobin levels can decrease, which may lead to increased toxicity of free iron, exacerbation of inflammation, and elevated hepcidin levels [16].

Although numerous studies have been conducted on iron metabolism in the pathogenesis of CKD, many questions remain unanswered. A deeper investigation of iron homeostasis physiology during CKD could help to better understand the disease's pathology and improve treatment efficacy [7]. These considerations highlight the importance of a comprehensive analysis of iron metabolism biomarkers for the timely detection of anemia, accurate differential diagnosis, and the development of effective therapeutic strategies in CKD.

## Aim

The aim of the study was to evaluate the role of iron metabolism proteins in the pathogenesis of anemia in patients with CKD at conservative and terminal stages, as well as their clinical diagnostic value.

## Materials and methods

The study included 44 patients aged 43–75 years (66.2 ± 1.7) with CKD stages II–III who were not receiving hemodialysis (conservative group), and 46 patients aged 19–77 years (60.8 ± 2.2) with terminal-stage CKD undergoing regular hemodialysis (terminal group). The control group consisted of 20 healthy individuals aged 20–75 years (62.5 ± 1.9). In the conservative group, 17 patients were women (68.9 ± 3.0 years) and 27 were men (64.5 ± 2.0 years), while among patients with terminal-stage CKD (tCKD), 24 were women (62.4 ± 2.8 years) and 22 were men (59.0 ± 3.4 years).

To assess the severity of anemia and renal functional activity in CKD patients, blood concentrations of creatinine, hemoglobin, erythropoietin, serum iron, ferritin, transferrin, lactoferrin, ferroportin, hepcidin, and haptoglobin were

analyzed. Hemoglobin levels in the blood were measured using a fully automated analyzer manufactured by Sysmex. The concentrations of serum iron, total iron-binding capacity (TIBC), creatinine, and urea were determined spectrophotometrically using reagent kits manufactured by Human (Germany) according to the manufacturer's instructions. Serum concentrations of erythropoietin, ferritin, transferrin, lactoferrin, and hepcidin were analyzed by the enzyme-linked immunosorbent assay (ELISA) method using reagent kits from BT LAB Bioassay Technology Laboratory (Shanghai, China). Serum ferroportin and haptoglobin levels were determined using commercially available ELISA kits (for example, Elabscience, USA; Cloud-Clone Corp., USA) suitable for semi-automated ELISA analyzers and available for international distribution. Only patients who met the following criteria were included in the study: no treatment with iron preparations (such as ferric gluconate, ferric sorbitol, ferric dextran, ferric carboxymaltose) during the last two weeks, no history of blood transfusion, and transferrin levels above 100 mg/dL. All analyses were performed according to the manufacturers' instructions using certified laboratory equipment.

After determining TIBC and serum iron, the latent iron-binding capacity (LIBC) was calculated using the following formula: LIBC = TIBC – iron. To determine the degree of transferrin saturation with iron in serum, the following formula was applied: TSAT = (iron / TIBC) × 100 %.

Statistical data processing was carried out using non-parametric testing (Mann–Whitney U test for between-group comparisons), one-way analysis of variance (ANOVA with Fisher–Snedecor F-distribution for multiple group comparisons), and Pearson's chi-square test. All statistical calculations were performed using MS Excel 2019 and IBM SPSS Statistics 26. Statistical significance was set at $p < 0.05$.

## Results

In the study, a comparative analysis of several clinical and laboratory parameters was performed across three groups (control, conservative, and terminal-stage CKD). In the conservative group, the median creatinine concentration (μmol/L) was 2.2-fold higher ($p < 0.001$) in men and 2.0-fold higher ($p < 0.001$) in women compared to the control group. In the terminal-stage group receiving hemodialysis, the median creatinine concentration (μmol/L) was 7.6-fold higher in men ($p < 0.001$) and 8.2-fold higher in women ($p < 0.001$) compared to the control group *(Tables 1, 2)*.

The progression of CKD was accompanied by functional iron deficiency and anemia in patients. In the conservative group, the concentrations of hemoglobin (g/L) and iron (μmol/L) decreased by 15.9 % ($p = 0.010$) and 40 % ($p < 0.001$) in men, and by 14.6 % ($p = 0.008$) and 30.7 % ($p < 0.001$) in women, compared to the control group. In the terminal group, the concentrations of hemoglobin and iron were significantly reduced by 34.5 % ($p = 0.010$) and 50 % ($p < 0.001$) in men, and by 39.0 % ($p < 0.001$) and 54.5 % ($p < 0.001$) in women, compared to the control group.

At the same time, significant alterations were also identified in the metabolism of proteins involved in iron transport and storage in the examined patients. In the conservative group, TIBC and LIBC (μmol/L) did not change significantly in either men or women compared to the control group. In the terminal stage group, TIBC (μmol/L) in men decreased by 23.8 % ($p < 0.001$), whereas LIBC showed a non-significant decrease of 12.6 % ($p = 0.073$), compared to the control group. In women, no significant changes in these parameters were observed.

In addition, a decrease in TSAT may be considered a marker of functional iron deficiency. In our study, TSAT levels showed a significant decline across the groups. Among males, the median TSAT decreased from 46.0 % in the control group to 25.0 % in the conservative group and 23.5 % in the terminal group ($p < 0.001$). A similar pattern was observed in females, with median TSAT values of 32.7 %, 19.3 % ($p = 0.001$) and 15.3 % ($p < 0.001$), respectively.

Haptoglobin (mg/dL) levels were significantly decreased in patients with CKD. In the conservative group, its concentration decreased by 41.0 % ($p < 0.001$) in men and by 17.3 % ($p = 0.002$) in women, whereas in the terminal stage group, it decreased by 38.0 % ($p < 0.001$) in men and by 37.3 % ($p < 0.001$) in women compared to the control group.

Ferritin (ng/mL) levels in the conservative group showed a relative decrease compared to the control group, decreasing by 17.9 % ($p = 0.010$) in men and by 28.6 % ($p = 0.009$) in women. In contrast, in the terminal stage group, ferritin levels were significantly increased, which may be associated with the intensification of the inflammatory process, by 66.3 % ($p < 0.001$) in men and by 52.7 % ($p < 0.001$) in women compared to the control group.

Transferrin (mg/dL) concentration in CKD patients was significantly reduced due to functional iron deficiency. In the conservative group, transferrin levels decreased by 11.7 % ($p = 0.021$) in men and by 15.8 % ($p = 0.001$) in women compared to the control group. In the terminal stage group, a more pronounced reduction was observed, by 21.6 % ($p = 0.001$) in men and by 41.7 % ($p < 0.001$) in women compared to the control group.

Erythropoietin (mIU/mL) levels showed a stage-dependent decrease during CKD. In the conservative group, erythropoietin concentration was significantly reduced by 2.1-fold ($p < 0.001$) in men and by 36.8 % ($p < 0.001$) in women compared to the control group. In the terminal stage group, a more pronounced reduction was observed, by 2.9-fold ($p < 0.001$) in men and by 2.3-fold ($p < 0.001$) in women compared to the control group.

Hepcidin (ng/mL) levels showed changes in CKD patients. In the conservative group, hepcidin demonstrated a non-significant increase by 19.4 % ($p = 0.260$) in men and by 8.5 % ($p = 0.359$) in women compared to the control group. In contrast, in the terminal stage group, a statistically significant increase was observed, by 2.2-fold ($p < 0.001$) in men and by 79.1 % ($p < 0.001$) in women compared to the control group.

Ferroportin (ng/mL) levels were significantly increased in patients with CKD. In the conservative group, ferroportin concentration increased by 86.7 % ($p < 0.001$) in men and by 44.4 % ($p = 0.004$) in women compared to the control group. In the terminal stage group, a more pronounced increase was observed, by 2.8-fold ($p < 0.001$) in men and by 2.1-fold ($p < 0.001$) in women compared to the control group.

Lactoferrin (ng/mL) levels were significantly increased in patients with CKD. In the conservative group, lactoferrin levels increased by 19.6 % ($p = 0.014$) in men and by 50 % ($p = 0.002$) in women compared to the control group. In the

**Table 1.** Concentration of iron metabolism proteins in male patients with CKD

| Parameter, units of measurement | Groups (male) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | | Conservative | | | | Terminal | | | |
| | M | Me | Q1 | Q3 | M | Me | Q1 | Q3 | M | Me | Q1 | Q3 |
| Creatinine, μmol/L | 81.6 | 81.0 | 71.0 | 94.0 | 197.3 | 181.0 | 123.0 | 238.0 | 674.8 | 618.5 | 472.0 | 789.0 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br><0.001 | | | |
| Hemoglobin, g/L | 14.4 | 14.5 | 12.9 | 16.5 | 12.4 | 12.2 | 10.9 | 14.1 | 9.7 | 9.5 | 8.0 | 11.2 |
| p<br>$p_1$1 | – | | | | 0.010 | | | | 0.010<br><0.001 | | | |
| Iron, μmol/L | 19.9 | 20.0 | 17.0 | 23.0 | 12.0 | 12.0 | 10.4 | 13.9 | 9.7 | 9.8 | 8.5 | 12.3 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br>0.004 | | | |
| TIBC, μmol/L | 64.9 | 66.0 | 57.0 | 73.0 | 59.0 | 58.6 | 54.7 | 64.7 | 49.0 | 50.3 | 42.7 | 53.6 |
| p<br>$p_1$ | – | | | | 0.055 | | | | <0.001<br><0.001 | | | |
| LIBC, μmol/L | 45.0 | 47.0 | 37.0 | 50.0 | 47.0 | 48.0 | 40.3 | 52.3 | 39.3 | 41.1 | 31.7 | 46.0 |
| p<br>$p_1$ | – | | | | 0.573 | | | | 0.073<br>0.006 | | | |
| Ferritin, ng/mL | 98.4 | 95.0 | 82.0 | 118.0 | 78.1 | 78.0 | 70.0 | 91.0 | 162.1 | 158.0 | 138.0 | 181.0 |
| p<br>$p_1$ | – | | | | 0.010 | | | | <0.001<br><0.001 | | | |
| Transferrin, mg/dL | 246.4 | 231.0 | 224.0 | 274.0 | 213.6 | 204.0 | 182.0 | 252.0 | 178.2 | 181.0 | 127.0 | 207.0 |
| p<br>$p_1$ | – | | | | 0.021 | | | | 0.001<br>0.042 | | | |
| TSAT, % | 46.6 | 46.0 | 32.6 | 52.5 | 26.6 | 25.0 | 21.2 | 31.2 | 26.7 | 23.5 | 18.0 | 34.7 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br>0.786 | | | |
| Haptoglobin, mg/dl | 159.6 | 166.0 | 148.0 | 170.0 | 99.9 | 98.0 | 88.0 | 108.0 | 95.4 | 103.0 | 76.0 | 113.0 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br>0.880 | | | |
| Erythropoietin, mIU/mL | 21.67 | 23.20 | 20.10 | 24.04 | 11.13 | 10.89 | 9.35 | 12.54 | 7.28 | 7.97 | 4.91 | 8.71 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br><0.001 | | | |
| Lactoferrin, ng/mL | 0.934 | 0.970 | 0.720 | 1.090 | 1.186 | 1.160 | 1.020 | 1.340 | 2.605 | 2.500 | 2.000 | 3.100 |
| p<br>$p_1$ | – | | | | 0.014 | | | | <0.001<br><0.001 | | | |
| Ferroportin, ng/mL | 0.31 | 0.30 | 0.27 | 0.35 | 0.58 | 0.56 | 0.49 | 0.66 | 0.95 | 0.84 | 0.72 | 1.13 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br><0.001 | | | |
| Hepcidin, ng/mL | 175.5 | 165.0 | 159.0 | 204.0 | 191.2 | 197.0 | 149.0 | 240.0 | 402.5 | 359.0 | 317.0 | 444.0 |
| p<br>$p_1$ | – | | | | 0.260 | | | | <0.001<br><0.001 | | | |

**M:** the mean value; **Me:** the median; **Q1:** the first quartile (25th percentile); **Q3:** the third quartile (75th percentile); **p:** compared to the control group; **p1:** compared to the conservative group.

terminal stage group, a more pronounced increase was observed, by 2.6-fold ($p < 0.001$) in men and by 2.8-fold ($p < 0.001$) in women compared to the control group.

In the terminal stage group, the concentrations of hemoglobin, erythropoietin, iron, TIBC, LIBC and transferrin were significantly lower in both men and women compared to the conservative group: hemoglobin by 22.1 % ($p < 0.001$) in men and 28.6 % ($p = 0.001$) in women; erythropoietin by 26.8 % ($p < 0.001$) in men and 32.5 % ($p < 0.001$) in women; iron by 18.3 % ($p = 0.004$) in men and 33.0 % ($p < 0.001$) in women; TIBC by 14.5 % ($p < 0.001$) in men and 17.3 % ($p = 0.003$) in women; LIBC by 14.4 % ($p = 0.006$) in men and 14.8 % ($p = 0.039$) in women; and transferrin by 11.3 % ($p = 0.042$) in men and 30.8 % ($p = 0.008$) in women.

Ferritin, hepcidin, ferroportin, and lactoferrin levels were significantly increased in the terminal stage group compared to the conservative group. Ferritin increased by 2.3-fold ($p < 0.001$) in men and 2.1-fold in women ($p < 0.001$); hepcidin by 82.2 % ($p < 0.001$) in men and 65.1 % in women ($p < 0.001$); ferroportin by 50.0 % ($p < 0.001$) in men and 46.2 % in women ($p < 0.001$); and lactoferrin by 2.2-fold ($p < 0.001$) in men and 87.5 % in women ($p < 0.001$).

The diagnostic utility of iron metabolism proteins in the diagnosis of CKD was studied. The obtained results are presented in *Table 3*.

According to the calculations, ferritin showed a cut-off value of >101 ng/mL with a sensitivity of 93.5 ± 3.6 %, specificity of 100.0 ± 0.0 %, and diagnostic efficiency of 96.7 ± 1.9 %, demonstrating excellent diagnostic performance *(Table 3)*.

Transferrin (cut-off <160 mg/dL) showed a sensitivity of 52.2 ±7.4 %, specificity of 84.1 ± 5.5 %, ODV of 67.8 ± 4.9 %, PPV of 77.4 ± 7.5 %, and NPV of 62.7 ± 6.3 %, indicating low diagnostic efficiency.

Lactoferrin (cut-off >1.8 ng/mL) demonstrated a sensitivity of 84.8 ± 5.3 %, specificity of 95.5 ± 3.1 %, ODV of 90.0 ± 3.2 %, PPV of 95.1 ± 3.4 %, and NPV of 85.7 ± 5.0 %, indicating high diagnostic value.

**Table 2.** Concentration of iron metabolism proteins in female patients with CKD

| Parameter, units of measurement | Groups (female) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | | Conservative | | | | Terminal | | | |
| | M | Me | Q1 | Q3 | M | Me | Q1 | Q3 | M | Me | Q1 | Q3 |
| Creatinine, μmol/L | 73.6 | 71.0 | 61.0 | 89.0 | 193.6 | 138.8 | 110.5 | 251.9 | 624.7 | 585.0 | 506.0 | 799.5 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br><0.001 | | | |
| Hemoglobin, g/L | 12.3 | 12.3 | 11.5 | 13.2 | 10.0 | 10.5 | 8.5 | 12.1 | 7.8 | 7.5 | 6.8 | 8.6 |
| p<br>$p_1$ | – | | | | 0.008 | | | | <0.001<br>0.001 | | | |
| Iron, μmol/L | 14.8 | 14.0 | 13.0 | 16.0 | 9.9 | 9.7 | 8.7 | 10.5 | 6.6 | 6.5 | 5.6 | 8.0 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br><0.001 | | | |
| TIBC, μmol/L | 54.4 | 52.0 | 49.0 | 65.0 | 57.1 | 58.4 | 51.2 | 60.8 | 48.7 | 48.3 | 43.2 | 54.7 |
| p<br>$p_1$ | – | | | | 0.608 | | | | 0.106<br>0.003 | | | |
| LIBC, μmol/L | 39.7 | 40.0 | 33.0 | 49.0 | 47.3 | 50.6 | 42.1 | 52.0 | 42.1 | 43.1 | 38.0 | 47.5 |
| p<br>$p_1$ | – | | | | 0.063 | | | | 0.467<br>0.039 | | | |
| Haptoglobin, mg/dl | 114.3 | 110.0 | 106.0 | 120.0 | 85.2 | 91.0 | 75.0 | 103.0 | 74.1 | 69.0 | 62.0 | 86.0 |
| p<br>$p_1$ | – | | | | 0.002 | | | | <0.001<br>0.062 | | | |
| Ferritin, ng/mL | 85.2 | 91.0 | 82.0 | 95.0 | 61.7 | 65.0 | 45.0 | 74.0 | 141.0 | 139.0 | 121.5 | 160.5 |
| p<br>$p_1$ | – | | | | 0.009 | | | | <0.001<br><0.001 | | | |
| Transferrin, mg/dL | 255.4 | 253.0 | 243.0 | 263.0 | 194.4 | 213.0 | 160.0 | 230.0 | 156.5 | 147.5 | 134.0 | 184.0 |
| p<br>$p_1$ | – | | | | 0.001 | | | | <0.001<br>0.008 | | | |
| TSAT, % | 39.9 | 32.7 | 30.0 | 51.5 | 22.0 | 19.3 | 17.2 | 22.9 | 16.2 | 15.3 | 12.8 | 18.0 |
| p<br>$p_1$ | – | | | | 0.001 | | | | <0.001<br>0.004 | | | |
| Erythropoietin, mIU/mL | 20.04 | 19.25 | 18.89 | 20.72 | 11.86 | 12.17 | 9.86 | 13.40 | 7.99 | 8.21 | 7.16 | 9.41 |
| p<br>$p_1$ | – | | | | <0.001 | | | | <0.001<br><0.001 | | | |
| Lactoferrin, ng/mL | 0.963 | 0.960 | 0.780 | 1.200 | 1.462 | 1.440 | 1.320 | 1.660 | 2.621 | 2.700 | 2.100 | 3.150 |
| p<br>$p_1$ | – | | | | 0.002 | | | | <0.001<br><0.001 | | | |
| Ferroportin, ng/mL | 0.36 | 0.36 | 0.34 | 0.38 | 0.53 | 0.52 | 0.38 | 0.63 | 0.86 | 0.76 | 0.68 | 0.93 |
| p<br>$p_1$ | – | | | | 0.004 | | | | <0.001<br><0.001 | | | |
| Hepcidin, ng/mL | 164.8 | 165.0 | 157.0 | 176.0 | 166.3 | 179.0 | 137.0 | 204.0 | 306.0 | 295.5 | 258.5 | 330.5 |
| p<br>$p_1$ | – | | | | 0.359 | | | | <0.001<br><0.001 | | | |

**M:** the mean value; **Me:** the median; **Q1:** the first quartile (25th percentile); **Q3:** the third quartile (75th percentile); **p:** compared to the control group; **p1:** compared to the conservative group.

Erythropoietin (cut-off <890 mIU/mL) showed a sensitivity of 71.7 ± 6.6 %, specificity of 95.5 ± 3.1 %, ODV of 83.3 ± 3.9 %, PPV of 94.3 ± 3.9 %, and NPV of 76.4 ± 5.7 %, demonstrating good diagnostic utility. Ferroportin (cut-off >0.66 ng/mL) exhibited a sensitivity of 91.3±4.2 %, specificity of 79.5±6.1 %, ODV of 85.6±3.7 %, PPV of 82.4±5.3 %, and NPV of 89.7±4.9 %, indicating moderate diagnostic performance. Hepcidin (cut-off >254.5 ng/mL) showed a sensitivity of 91.3 ± 4.2 %, specificity of 93.2 ± 3.8 %, ODV of 92.2 ± 2.8 %, PPV of 93.3 ± 3.7 %, and NPV of 91.1 ± 4.2 %, demonstrating excellent diagnostic value.

Among all studied biomarkers, ferritin and hepcidin demonstrated the highest diagnostic performance in CKD, while lactoferrin and erythropoietin showed strong additional diagnostic value. Ferroportin exhibited moderate performance, whereas transferrin showed the lowest diagnostic efficiency. These results indicate that ferritin and hepcidin are the most clinically relevant biomarkers in CKD-related iron metabolism disorders.

## Discussion

The results of our study have demonstrated that in the progressive stages of CKD, the main components of iron metabolism, iron, erythropoietin, ferritin, transferrin, ferroportin, lactoferrin, and hepcidin, undergo significant changes in various directions. These alterations play an important role in the pathogenesis of the disease and in the development of anemia. As the findings indicate, in patients with CKD, particularly those undergoing hemodialysis, severe impairments in renal functional activity are accompanied by anemia. Specifically, in patients with terminal-stage CKD, serum creatinine concentration significantly increased compared to the conservative group, whereas hemoglobin levels decreased.

The decrease in erythropoietin levels plays a key role in the pathogenesis of anemia. Absolute erythropoietin deficiency may result from impaired renal function, leading to reduced hormone synthesis. The development of

**Table 3.** Diagnostic value of iron metabolism proteins during CKD

| NN | Ferritin | Transferrin | Lactoferrin | EPO | Ferroportin | Hepcidin |
|---|---|---|---|---|---|---|
| n | 90 | 90 | 90 | 90 | 90 | 90 |
| min | 38 | 55 | 0.48 | 359 | 0.27 | 33 |
| max | 230 | 346 | 4.3 | 1590 | 1.67 | 757 |
| Cut-off point | 101 | 160 | 1.8 | 890 | 0.66 | 254.5 |
| | > | < | > | < | > | > |
| n+ | 46 | 46 | 46 | 46 | 46 | 46 |
| ++ | 43 | 24 | 39 | 33 | 42 | 42 |
| Sn | 93.5 | 52.2 | 84.8 | 71.7 | 91.3 | 91.3 |
| ±mp | 3.6 | 7.4 | 5.3 | 6.6 | 4.2 | 4.2 |
| n- | 44 | 44 | 44 | 44 | 44 | 44 |
| – | 44 | 37 | 42 | 42 | 35 | 41 |
| Sp | 100.0 | 84.1 | 95.5 | 95.5 | 79.5 | 93.2 |
| ±mp | 0.0 | 5.5 | 3.1 | 3.1 | 6.1 | 3.8 |
| ODV | 87 | 61 | 81 | 75 | 77 | 83 |
| % | 96.7 | 67.8 | 90.0 | 83.3 | 85.6 | 92.2 |
| ±mp | 1.9 | 4.9 | 3.2 | 3.9 | 3.7 | 2.8 |
| pPV | 100.0 | 77.4 | 95.1 | 94.3 | 82.4 | 93.3 |
| ±mp | 0.0 | 7.5 | 3.4 | 3.9 | 5.3 | 3.7 |
| nPV | 93.6 | 62.7 | 85.7 | 76.4 | 89.7 | 91.1 |
| ±mp | 3.6 | 6.3 | 5.0 | 5.7 | 4.9 | 4.2 |
| LR+ | >100 | 3.28 | 18.65 | 15.78 | 4.46 | 13.39 |
| | Excellent | Adequate | Excellent | Excellent | Adequate | Excellent |
| LR- | 0.07 | 0.57 | 0.16 | 0.30 | 0.11 | 0.09 |
| | Excellent | Negative | Good | Adequate | Good | Excellent |

The data obtained in this study; **n:** number of observations; **min:** minimum value; **max:** maximum value; **cut-off:** threshold value for the biomarker; **n+:** number of positive cases; **++:** number of correctly identified positive cases; **Sn:** sensitivity of the test (%); **±mp:** standard deviation or measurement error; **n-:** number of negative cases, **–:** number of correctly identified negative cases; **Sp:** specificity of the test (%); **ODV:** general diagnostic value (%); **pPV:** positive prognostic value (%); **nPV:** negative prognostic value (%); **LR+:** chance ratio of a positive test; **LR-:** chance ratio of a negative test.

inflammatory processes inhibits the hypoxia-induced synthesis of erythropoietin, thereby weakening the process of erythropoiesis [17].

Ferritin is the main protein responsible for iron storage in the human body [18]. Under physiological conditions, serum ferritin concentrations closely reflect body iron reserves, as confirmed by liver biopsy, which is considered the gold standard for assessing iron status. Nevertheless, inflammation can markedly influence ferritin levels, given that it functions as an acute-phase protein. When inflammation occurs, the rise in serum ferritin as an acute-phase reactant disrupts its correlation with actual iron availability [12]. The results indicate that ferritin levels decrease in the conservative group but increase significantly at the terminal stage, likely due to enhanced inflammation. During inflammation, elevated hepcidin levels reduce intestinal iron absorption and increase intracellular ferritin reserves. In CKD, chronic inflammation artificially elevates ferritin, which can also serve as an indicator of inflammation. It is suggested that in renal pathologies, high ferritin levels play a nephroprotective role in response to the progression of inflammation. Elevated ferritin reflects both the iron storage status and its role as an acute-phase reactant. Therefore, under inflammatory conditions, ferritin levels should be interpreted not only as an indicator of iron status but also as a marker of systemic inflammation. An increase in ferritin levels accompanied by a decrease in iron levels is a characteristic feature of inflammation-related anemia [19]. In our study, the elevation of ferritin alongside reduced serum iron and TSAT reflects a classic pattern of functional iron deficiency. In CKD, serum ferritin levels are usually elevated due to chronic inflammation, whereas serum iron parameters often do not correspond to normal values. The most commonly observed features include a decrease or normalization of serum iron and TIBC, an increase in ferritin levels, and a decrease in TSAT. Low ferritin levels most likely indicate iron deficiency, whereas high ferritin levels do not exclude iron deficiency in the context of CKD or chronic inflammation [4].

The transferrin protein binds iron and transports it to other cells, where it interacts with transferrin receptors. The bound iron is released, while iron-free transferrin is secreted back into the extracellular environment, and the intracellular iron is stored in the form of ferritin. A decrease in transferrin saturation together with an increase in ferritin is a typical indicator of functional iron deficiency [20].

Absolute iron deficiency arises as a result of the depletion of iron stores in the body, for example, in cases of blood loss. Functional iron deficiency, on the other hand, is characterized by the inability to mobilize iron from the stores despite its sufficient presence in the body. This condition may be observed in chronic inflammatory states or during high, supratherapeutic stimulation of erythropoiesis, such as during treatment with erythropoiesis-stimulating agents.

In the context of chronic inflammation, functional iron deficiency is distinguished by elevated hepcidin levels. In patients with anemia associated with CKD, absolute iron deficiency (due to blood loss during hemodialysis), functional iron deficiency (related to acute inflammation), or a combination of both conditions may be observed [20].

In CKD, disturbances in iron metabolism are associated with inflammation and dysfunction of the hepcidin–ferroportin axis. During inflammation, the accelerated synthesis of

pro-inflammatory cytokines stimulates hepatic hepcidin production, induces ferritin expression in macrophages, and inhibits ferroportin expression [21,22]. In addition, reduced glomerular filtration rate in the kidneys may lead to decreased clearance of hepcidin and, consequently, to its elevated levels in the blood [5].

An increase in hepcidin levels is one of the major consequences of chronic inflammation observed in CKD. By interacting with ferroportin, hepcidin blocks the release of iron from intestinal epithelial cells and macrophages into the plasma. As a result, in the setting of decreased circulating iron and elevated ferritin and hepcidin, classical inflammation-induced functional iron deficiency develops [23,24].

The increase in lactoferrin and ferroportin levels is considered an adaptive mechanism aimed at maintaining iron homeostasis in the body. Lactoferrin is a natural iron-containing glycoprotein synthesized in the epithelial cells of mucous membranes. In addition to its ability to bind iron, lactoferrin possesses anti-inflammatory and immunomodulatory effects, as well as antiviral, antibacterial, and antioxidant properties. Owing to its antioxidant activity, lactoferrin contributes to the protection of the kidneys from injury [25]. During CKD, the concentration of lactoferrin increases in a compensatory manner in response to decreased serum iron levels and the progression of inflammatory processes [26]. Recent studies indicate that lactoferrin may regulate hepcidin synthesis and positively influence the mobilization of iron from stores [27].

Although the increase in ferroportin levels may appear paradoxical, some studies have suggested that it represents a compensatory response against hepcidin. In other words, while the organism attempts to enhance ferroportin expression to facilitate iron utilization, elevated hepcidin levels block this effect, thereby impairing iron mobilization [24]. In chronic diseases (particularly in chronic kidney failure or anemia associated with inflammation), the simultaneous elevation of both hepcidin and ferroportin may be explained by compensatory mechanisms, the influence of inflammatory cytokines, tissue-specific differences, and disturbances in filtration–clearance [28].

Biomarkers such as lactoferrin, hepcidin, ferroportin, ferritin, and transferrin are of significance both as diagnostic and therapeutic indicators. Treatment strategies should be individualized according to the level of inflammation: intravenous iron is preferred in the presence of inflammation, whereas oral lactoferrin may be effective in patients without inflammation. Naoum F. A. et al. demonstrated that ferritin possesses high specificity and sensitivity in the diagnosis of iron deficiency anemia [29]. Similarly, T. Karlsson showed that hepcidin has high sensitivity and specificity in his study [30].

## Conclusions

1. In CKD, disturbances in iron metabolism, activation of inflammatory markers, and impaired erythropoiesis represent the principal pathogenic mechanisms jointly contributing to the development of anemia. As evidenced by the study results, complex and interrelated alterations exist among iron metabolism proteins. Physiological abnormalities arising in various tissues involved in iron metabolism disrupt the regulatory mechanisms of iron homeostasis.

2. In patients with CKD, on the one hand, the levels of iron, erythropoietin, transferrin and haptoglobin were significantly decreased, while on the other hand, increased levels of ferritin, ferroportin, lactoferrin, and hepcidin were observed. In addition, a decrease in TSAT may be considered a marker of functional iron deficiency. The more pronounced manifestation of these indicators in the terminal stage of CKD suggests that disease progression leads to more severe disturbances in iron metabolism.

3. Ferritin, lactoferrin, erythropoietin, and hepcidin are of great diagnostic importance due to their specificity and effectiveness in evaluating positive results, while ferritin and hepcidin also carry major practical significance. Accurate monitoring of these biomarkers is essential for the early diagnosis of anemia and the establishment of individualized treatment strategies.

**Ethical approval**
This study was approved by the Ethics Committee of the Azerbaijan Medical University based on Protocol No. 40 dated May 2, 2025. The research was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

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