течение 45 дней. Коррекцию осуществляли путем добавления в корм йодида калия (по 50 мг/сутки, 30 дней), селена (5 мкг/сутки, 20 дней), α-токоферола (20 мг/кг, 30 дней), L-аргинина (2,5 г/сутки, 20 дней). Контрольную группу составляли 30 интактных животных. Тиреоидный статус оценивали по содержанию свободных трийодтиронина - fT3 , тироксина - fT4 , тиреотропного гормона (ТТГ) в сыворотке крови и экскреции йода с мочой. Липидный спектр изучали по показателям уровня общего холестерина (ХС), триглицеридов (ТГ), липопротеидов низкой плотности (ЛПНП), липопротеидов высокой плотности (ЛПВП) и коэффициентом атерогенности (КА).

Результаты. Обнаружили, что дефицит селена отрицательно влияет на тиреоидный гомеостаз, о чем свидетельствует достоверное уменьшение содержания fT_3 в сыворотке крови и уменьшение содержания йода в моче животных 2-ой группы. ГД сопровождается нарушением липидного баланса, на что указывают изменения липидного спектра крови и увеличение КА. Установлено прогрессирование дислипидемии в условиях комбинированного дефицита йода и селена, что существенно увеличивает риск развития сердечно - сосудистых осложнений при гипотиреозе. Эффективным для коррекции $ГД_{I+Se}$ является йодид калия. Выяснена эффективность и целесообразность включения в схему терапии $ГД_{I+Se}$ селена, антиоксидантов (α-токоферола) и донаторов оксида азота (L-аргинина) для восстановления функционирования гипоталамо-гипофизарно-тиреоидной оси и липидного спектра крови.

Выводы. Развитие ГД сопровождается нарушением липидного спектра сыворотки крови, что носит более выраженный характер у животных в условиях комбинированного дефицита микроэлементов. Эффективными для коррекции тиреоидного статуса и липидного спектра крови являются препараты йода и селена. Включение в схему терапии антиоксидантов и донаторов оксида азота должна носить индивидуальный характер.

Ключевые слова: гипотиреоидная дисфункция, йод, липидный статус, селен, микроэлементный баланс.

L.V. Nykolyshyn

Peculiarities of Lipid Profile of Blood, Microelement Balance in Hypothyroid Dysfunction, Possible Ways of Correction

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Abstract. The aim of research: evaluation of lipid profile of blood in animals with hypothyroid dysfunction (HD) against the background of iodine and selenium deficiency and clarification of the effectiveness of correction of revealed changes by microelements, antioxidants and nitric oxide donators.

Material and methods. The research has been carried out on rates weighting 100-150g that were divided into five research groups: the 1st – animals with HD against the background of iodine deficiency (HD_I, n=30); the 2nd – animals with HD in conditions of combined deficiency of iodine and selenium (HD_{I+Se}, n=30); the 3rd – animals with correction of HD_{I+Se} with drugs containing iodine ($HD_{I+Se}+C_{KI}$, n=30); the 4th – animals with correction of HD_{I+Se} by iodine and selenium containing drugs ($HD_{I+Se}+C_{KI+Se}$, n=30); the 5th – animals with complex correction of HD_{I+Se} by iodine and selenium containing drugs, antioxidants (α-tocoperol), donators of nitric oxide (L-arginine) (HD_{I+Se}+CC, n=30). HD was modeled by adding Merkazolil to drinking water during 14 days (7.5 mg/100g of body weight). Animals of all research groups have been kept on iodine deficient diet throughout the study to reduce the income of iodine. Combined deficiency of iodine and selenium has been induced by the use of balanced ration of natural ingredients during 45 days. The correction has been performed by adding potassium iodide to the diet (50 mg/day, 30 days), selenium (5 mcg/day, 20 days), α-tocoperol (20 mg/kg, 30 days), L-arginine (2,5 g/day, 20 days). The control group was comprised of 30 intact animals. Thyroid status was estimated by the measurement of levels of free triiodothyronine – fT_3, thyroxin – fT_4, thyroid stimulating hormone of adenohypophysis (TSH) in blood serum and the excretion of iodine with urine. Lipid profile of blood has been studied by measuring the indexes of levels of total cholesterol, triglycerides, LDL- and HDL-cholesterol and quotient of atherogenicity.

Results. It has been revealed that selenium deficiency has negative influence on thyroid homeostasis that is proved by reliable decrease of fT_3 level in blood serum and the decrease of iodine level in the urine of animals of the 2nd group. HD was followed by the violation of lipid balance that was proved by the changes of lipid profile of blood and the increase of quotient of atherogenicity. There has been revealed the progression of dyslipidemia in conditions of combined deficiency of iodine and selenium that significantly increases the risk of development of cardio-vascular complications in hypothyroidism. Potassium iodide is effective for the correction of HD_{I+Se}. The rationale and the effectiveness of adding of selenium, antioxidants (α-tocoperol) and nitric oxide donators to the scheme of treatment of HD_{I+Se} has been shown for the restoring of functioning of hypothalamus-hypophysis-thyroid axis and the lipid profile of blood.

Conclusions. The development of HD is followed by the violation of lipid profile of blood serum that has more expressed character in animals in conditions of combined deficiency of microelements. The drugs containing iodine and selenium are effective for the correction of thyroid status and lipid profile of blood. Including antioxidants and donators of nitric oxide to the scheme of therapy should have an individual character.

Keywords: hypothyroid dysfunction, iodine, lipid status, selenium, microelement balance.

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Non-Heme Iron Panel in Patients with Anemia and Chronic Kidney Disease

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Abstract. **The objective of the study:** to improve the quality of diagnosis of anemia of renal origin by studying the non-heme iron state in patients with different stages of chronic kidney disease (CKD).

Material and methods: the study included 79 patients with CKD (28 – male, 51 – female) 33-72 years old. The patients were divided into two groups: group I included 24 patients without anemia, group II included 55 patients with anemia. Patients of group II were divided into 3 subgroups: 31 patients– with mild degree of anemia (subgroup 1), 18 patients – moderate degree (subgroup 2), 6 patients – severe degree (subgroup 3). The control group consisted of 20 healthy people. A complete hematology panel, urine tests, kidney ultrasound, serum urea and creatinine levels, glomerular filtration rate (GFR) by MDRD were performed. The serum iron levels, total and latent serum iron ability by ferritin and transferrin levels were measured.

Results: among patients CKD of II-III stages in 67% of cases and CKD of IV-V stages in 33% of cases were revealed. Anemia of mild degree was revealed in 56% of cases; moderate degree in 33% and severe degree in 11% of cases. It was found that in the case of anemia of renal origin serum creatinine and urea levels increased, and decreased GFR, serum hemoglobin, hematocrit, iron, transferrin, and ferritin levels deceased also. Intensive change of these parameters was the most pronounced in patients with severe anemia. This was confirmed by

exiting positive correlations between hemoglobin and serum iron and transferrin levels.

Conclusions: iron deficiency in the body is an important branch of the anemia pathogenesis in patients with CKD. For the diagnosis of anemia and its severity degree we should consider not only hemoglobin levels but the indicators of non-heme iron status in the patients with CKD. Decreasing serum iron, transferrin and ferritin levels determine severity of anemia and CKD. The lowest non-heme iron levels are typical for patients with CKD of IV-V stages and severe anemia.

Problem statement and analysis of recent research. Iron - essential elements, which is essential for the viability of the organism. Iron is a part of the functional groups of proteins that transport oxygen, enzymes catalyze the reaction of energy formation and control metabolic processes course in tissues [1, 2]. A number of proteins are involved in regulation of iron homeostasis that controls its absorption from food in the small intestine. Iron absorption occurs in the enterocytes, cells of duodenal epithelial layer of the intestine. Proteins are responsible for the metabolism of iron, expressed by the body needs it. In serum iron transport function performs the main iron transporting protein such as transferrin and accumulated reserves of iron in ferritin [1, 2, 10].

The term chronic kidney disease (CKD) suggests that the disease progresses with loss of renal function and in most cases irreversibly. Along with the main function of the kidneys urine formation it is important hematopoietic function through the formation of erythropoietin. Chronic kidney disease is associated with increased concentrations of potentially harmful toxic substances that can lead to anemia [3, 8, 9]. In patients with CKD pathogenesis of anemia is complex and multifactorial. Anemia develops in the early stages of chronic renal failure and increases in proportion to the reduction in glomerular filtration rate (GFR) [3, 4, 5, 6]. Therefore, anemia refers to the risk factors for end-stage CKD [5, 6, 7, 9]. At patients with CKD anemia is characterized by normochromic normocytic erythrocytes and low reticulocytes levels in peripheral blood and hypoplasia of erythroid cells in the bone marrow [9]. This is caused by three main reasons: deficiency of endogenous erythropoietin, reduced erythrocytes life expectancy and the presence of circulating hematopoiesis inhibitors in the blood, which include creatinine, polyamines, oligopeptides medium molecular, furancarboxylase acid, phenols [2, 9]. It is known that iron levels regulates hepsydyn producting. Hepsydyn has a blocking effect on iron transport including internal epithelial cells, macrophages, placenta and other cell types [2].

In the tissues most of the iron normally found in the form of heme proteins. Non-heme iron include iron of ferritin (hemosiderin) and transferrin and a small pool of iron in the form of low molecular weight complexes with ligands such as citrate, cysteine [1]. However, it remains poorly understood status non-heme iron in patients with CKD that caused purpose of our study.

Aim. Improving the quality of anemia diagnosis by studying the characteristics of non-heme iron status in patients with different stages of CKD.

Materials and methods

There were examined 79 patients with CKD II-V stages (28 male, 51 female), aged 33-72 years, among them 21 patients were with glomerulonephritis, 27 patients – with pyelonephritis, 18 patients – with diabetic nephropathy, 9 patients – with hypertensive nephropathy and 4 patients – with kidney abnormalities. Depending on the presence or absence of anemia patients were divided into two groups: group I included 24 patients without anemia, group II included 55 patients with anemia. Group II patients were divided into 3 subgroups depending on the severity of anemia: subgroup 1 included 31 patients with mild anemia (hemoglobin 110-90 g/L), subgroup 2 included 18 patients with moderate anemia (hemoglobin 89-70 g/L), subgroup 3 consisted of 6 patients with severe anemia (hemoglobin <69 g/L). The control group consisted of 20 healthy individuals of appropriate age.

For verify CKD hematology and urine tests, kidney ultrasound, plasma urea and creatinine levels by commonly accepted methods and GFR by MDRD (Modification of Diet In Renal Disease) were measured:

GFR = 186 × (SCr) - 1,154 x (age) - 0,203 × (0,742 women) × (1,210 - for African Americans),

where GFR – estimated glomerular filtration rate ml/min/1,73 m^2;
SCr - serum creatinine in mg/dL [8].

Laboratory methods included haematology tests such as hemoglobin, hematocrit, erythrocytes levels and biochemistry tests such as the plasma creatinine and urea levels, serum iron levels. Total and latent iron binding ability were assessed by serum ferritin and transferrin indexes by conventional methods using sets of reagents. Statistical analysis of the research results carried out by a computer program Microsoft Excel using the methods of variation statistics and Student t-test. Spending Doubles factor correlation analysis with Pearson correlation coefficient calculation (r) were measured.

Results and discussion

The examined patients have different CKD stages: II stages in 24 (30.4%); III – 29 (36.7%); IV – 9 (11.4%); V – 17 (21.5%) cases. As a result of renal ultrasound in all patients structural changes in the parenchyma or in the calyx-pelvis complex were revealed. In assessing the performance of kidney function (Table 1) creatinine and urea levels were higher by 2 times (group 1) and by 3-4 times (group 2) vs. the control group ($p<0.05$).

According to the general blood analysis in group 1 erythrocytes levels did not differ vs. the control group. In terms of complete blood count, biochemical iron status in 55 (69.6%) patients (group II) anemia of renal origin varying stages severity was revealed.

It is known that in the patients with CKD anemia is formed due to inhibition of erythropoiesis by uremic inhibitors, mechanical damage metabolically changed erythrocytes, shortening the duration of their life or because of erythrocytes hemolysis [8]. In group 2 hemoglobin and hematocrit were reduced by 26.19% and 33.33% compared with the levels in the control group ($p<0.05$). Number of erythrocytes also were reduced accordingly by 28.98% compared with the control group ($p<0.05$).

Analysis of iron status indicates its ambiguous changes in both groups of patients. Thus, in patients of group 1 the serum iron levels were within a healthy rate. In group 2 serum iron

Table 1. Parameters of hematology and biochemical blood tests in patients with CKD, M±m

Parameters, unit of measure	Control (n=20)	1 group (n=24)	2 group (n=55) The severity of anemia		
			Mild (n=31)	Moderate (n=18)	Severity (n=6)
Hemoglobin, g/l	127.32±8.51	123.71±7.42 p>0.05	104.59±11.67 p<0.05	83.13±5.54 p<0.05	63.00±8.87 p<0.05
Hematocrit, l/l	0.42±0.12	0.37±0.03 p>0,05	0.32±0.03 p>0.05	0.27±0.02 p<0.05	0.22±0.01 p<0.05
Red blood cells. × 10^{12}/ L	4.52±0.49	4.27±0.69 p>0.05	3.43±0.21 p<0.05	3.02±0.42 p<0.05	2.16±0.46 p<0.05
Serum iron. mg / dL	22.36±6.84	17.50±0.71 p>0.05	11.00±1.41 p<0.05	10.17±4.34 p<0.05	9.23±3.54 p<0.05
Ferritin. mg/l	147.35±38.84	105.0±31.77 p>0.05	90.00±8.49 p<0.05	68.83±30.60 p<0.05	58.50±28.49 p<0.05
Transferrin. g/l	3.11±0.14	2.55±0.07 p<0.05	2.28±0.49 p<0.05	2.23±0.16 p<0.05	1.50±0.07 p<0.05
Urea. mmol L	5.26±1.18	11.20±5.67 p<0.05	15.26±5.83 p<0.05	19.11±7.61 p<0.05	21.88±6.11 p<0.05
Creatinine. mmol/l	94.02±10.21	242.95±89.96 p<0.05	392.37±173.68 p<0.05	487.92±111.6 3 p<0.05	565.50±43.27 p<0.05
GFR ml/min/1.73m^2	115.32±12.42	69.32±17.42 p<0.05	52.18±16.87 p<0.05	31.11±4.72 p<0.05	14.25±2.99 p<0.05

Notes: 1. n - number of surveys; 2. p - the reliability of the difference compared to control

levels were lower by 47.18% and 32.51% compared with the levels in healthy subjects and in group 1 ($p<0.05$). Transferrin and ferritin parameters were not significantly different in group 1 vs. the control group ($p>0.05$). In group 2 transferrin levels were reduced by 31.83% and 16.86% vs. the control group and group 1 accordingly ($p<0.05$); ferritin indexes were reduced by 35.19% vs. the control group ($p<0.05$).

In patients of subgroups 2 and 3 plasma creatinine and urea levels were higher by 19.58% and 30.62% respectively vs. the patient of subgroup 1 ($p<0.05$). Indexes of GFR in subgroup 2 were reduced by 3.7 times; in subgroup 3 – by 8.0 times vs. the control group ($p<0.05$).

Absorption of iron from the intestine occurs through protein – mucous apotransferrin, which is synthesized in the liver and enters to the enterocytes. Transport iron from the intestinal wall to the precursors of red blood cells and cells depot is through plasma protein such as transferrin. A small portion of iron in enterocytes combined with ferritin, which can be considered a pool of iron in the mucosa of the small intestine [1, 2].

Iron circulates in the blood in combination with plasma protein transferrin which is synthesized primarily in the liver and a small amount in lymphoid tissue, mammary gland, testicles and ovaries. Transferrin carries iron from enterocytes with depots its in the liver and spleen. Transferrin – is an iron complex interacts with transferrin receptors located on cell membranes of erythrocariocytes, reticulocytes and in bone marrow by endocytosis and enters the cell. There's iron released from transferrin binds to an intracellular protein syderohilin that transports him into the mitochondria for the synthesis of heme (hemoglobin, myoglobin, cytochromes, enzymes – catalase, lactoperoxidase) and non-heme compounds (ferritin, hemosiderin, transferrin, enzymes – xanthine oxidase, NAD-H dehydrogenase aconitaze) [1].

Depending on the severity of anemia serum iron, transferrin and ferritin levels appeared to be reduced in varying degrees. The lowest rates were typical for patients with severe anemia. Thus, the rate of serum iron in the subgroup 3was not significally lower to 9.24% and 16.09% vs. subgroup 2 and 1 ($p<0.1$). In subgroup 3 the transferrin levels were reduced by 32.74% and 34.21% compared with subgroup 2 and 1 ($p<0.05$).

The concentration of serum ferritin evaluates the total iron stores in the body [1, 2]. In adult people the content of serum ferritin ranges from 20 to 350 mg/l. Decreasing of serum ferritin concentrations indicates the development of iron deficiency anemia [1]. In the patients of subgroup 2 serum ferritin levels were descreased by 1.5-3 times vs. the control group ($p<0.05$). In subgroup 3 the serum ferritin levels have tendency to decrease by 15.0% and 35.0% vs. subgroups 2 and 1 ($p>0.1$) accordingly.

We studied the correlation relationships between heme and non-heme iron parameters. There was revealed exesting direct correlation between hemoglobin and serum iron levels ($r=0.4751$; $p=0.0008$) and between hemoglobin and transferr levels ($r=0.1819$; $p=0.5003$) in the patients of group II. Between hemoglobin and ferritin levels there was a trend toward lowering ferritin levels ($r=0.1067$; $p=0.0008$).

Thus, for anemia of renal origin in terms of circulating creatinine, urea levels and decreasing of GFR, serum iron, transferrin have reduced levels and ferritin has downward trend. These changes depend on the severity of anemia and the most pronounced in patients with severe anemia and CKD IV-V degree as confirming direct correlation relationship between heme and non-heme iron.

Conclusions

1. Iron deficiency in an organism is an important branch of the anemia pathogenesis in patients with CKD.

2. For the diagnosis of anemia and its degree of severity in patients with CKD should be considered not only hemoglobin but also indicators of the blood non-heme iron status.

3 Decreasing of serum iron, transferrin and ferritin levels determine the severity of anemia in patients with CKD. The lowest grade of non-heme iron characteristic of patients with CKD stage IV-V and with severe anemia.

Prospects for further research in this direction

Further scientific research should focus on study dynamic of non-heme iron levels under in patients with anemia on the CKD ground influence treatment with including of different iron drugs.

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Показники негемового заліза при анемії у хворих на хронічну хворобу нирок

Резюме. Мета дослідження. Підвищення якості діагностики анемії на основі вивчення динаміки показників негемового заліза у хворих на хронічну хворобу нирок (ХХН) різних стадій.

Матеріал і методи. Обстежено 79 хворих на ХХН (28 – чоловіки, 51 – жінки) віком 33-72 років. Хворих розділено на 2 групи: I група – 24 хворих без анемії, II група – 55 хворих із анемією. Хворих II групи розподілено на 3 підгрупи: 31 хворий – легкий ступінь (1 підгрупа), 18 хворих – середній ступінь (2 підгрупа), 6 хворих – важкий ступінь анемії (3 підгрупа). Контроль – 20 здорових осіб відповідного віку. Проведено загальний аналіз крові, загальний аналіз сечі, ультразвукове дослідження (УЗД) нирок, визначення рівнів сечовини та креатиніну, заліза, трансферину та феритину в сироватці крові, розрахунок швидкості клубочкової фільтрації (ШКФ).

Результати. У 67% випадків виявлено ХХН II-III стадії та у 33% – ХХН IV-V стадії. Серед обстежених хворих у 70% випадках виявлено анемію: легкого ступеня тяжкості – у 56%, середнього ступеня тяжкості – у 33%, тяжкого ступеня – у 11% випадків. Встановлено, що паралельно з підвищенням креатиніну, сечовини в крові та зниженням ШКФ, зменшуються рівні гемоглобіну, гематокриту, сироваткового заліза, трансферину і відмічається тенденція до зниження феритину. Такі зміни найбільш виражені у хворих із тяжкою анемією та ХХН IV-V стадії.

Висновки. Дефіцит заліза в організмі є важливою ланкою патогенезу анемії у хворих на ХХН. Для встановлення діагнозу анемії та ступеня її тяжкості у хворих на ХХН необхідно оцінювати не лише рівень гемоглобіну, а й показники статусу негемового заліза в крові. Зниження рівнів сироваткового заліза, трансферину і феритину у хворих із ХХН обумовлюють ступінь тяжкості анемії. Найнижчі їх рівні – у хворих на ХХН IV-V стадії із анемією тяжкого ступеня.

Ключові слова: хронічна хвороба нирок, анемія, негемове залізо.

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