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Diagnosis of Anemia In Diffuse Toxic Goitre

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ABSTRACT

Diffuse toxic goitre (Graves' disease) is often accompanied by various hematological changes, including anemia. The diagnosis of anemia in this condition is based on blood count, iron studies, and thyroid function tests. Anemia may result from increased metabolism, iron deficiency, or autoimmune mechanisms. Early detection and treatment are essential for improving the patient's general condition and prognosis. Anemia was observed in 68.2% of patients with diffuse toxic goiter, of which 28.4% had iron deficiency anemia, 19.6% had megaloblastic anemia, 17.6% had normochromic anemia, and 34.4% had mixed anemia.

KEYWORDS: Diffuse Toxic Goiter, Iron Deficiency Anemia, Megaloblastic Anemia.

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INTRODUCTION

Diffuse toxic goiter (DTG) is a thyroid gland disorder that develops due to its damage and is characterized by excessive hormone production. Thyroiditis is one of the most common endocrine diseases, ranking second among endocrine pathologies after endemic goiter. In regions with normal iodine levels, the likelihood of thyrotoxicosis is high, whereas in iodine-deficient areas, endemic goiter is more prevalent [2].

According to various studies, the incidence of DTG averages 15–50 cases per 100,000 people annually. The disease is most commonly diagnosed in individuals aged 20–40 years. Women are 10–20 times more likely to suffer from DTG than men, but in recent years, the incidence among men has been increasing. In men, DTG tends to be more severe, complications develop more rapidly, and the remission period after thyrostatic therapy is shorter [7].

Thyrotoxicosis is a pathological response of the body that occurs due to an increase in the hormones thyroxine and triiodothyronine in organs and tissues. According to the literature, the symptoms of thyrotoxicosis in DTG are not always associated with an enlarged thyroid gland. In some cases, the thyroid gland remains small, yet severe thyrotoxicosis develops, while in other cases, a significantly enlarged thyroid gland may not result in thyrotoxicosis at all. In DTG, excessive production of triiodothyronine and thyroxine disrupts the functioning of all organs and systems in the body [3].

The primary clinical symptoms of DTG include general weakness, nervousness, sleep disturbances, palpitations, chest pain, and irregular heartbeat, which become more pronounced with rising air temperatures. Additionally, due to an increased metabolic rate, the patient experiences an increased appetite and eats more frequently, yet body weight decreases, and both physical and mental activity decline sharply. As the disease progresses, changes in the eyes become noticeable, leading to the development of thyrotoxic ophthalmopathy [8].

In DTG, an accelerated metabolism leads to excessive protein and fat breakdown, causing weight loss despite increased food intake. As the disease advances, retrobulbar tissue swells and thickens, resulting in eye protrusion, or exophthalmos [1].

At the same time, the sympathetic nervous system becomes hyperactive, causing excessive sweating and tremors of the hands and entire body, a condition known as Marie's symptom. The patient also exhibits symptoms characteristic of sideropenia, including hair thinning and dullness, as well as increased nail sensitivity. One of the early signs of thyrotoxicosis is muscle weakness due to thyrotoxic myopathy, along with metabolic disturbances. Gastrointestinal issues such as abdominal pain, vomiting, and diarrhea are also common. In 50% of patients, Nikolaev's triad—palpable thyroid enlargement, tachycardia, and

exophthalmos—is observed. Palpation helps assess the thyroid gland's size, smoothness or roughness, consistency, homogeneity or heterogeneity, mobility, and tenderness [4, 10].

Diagnosis is based on laboratory and instrumental tests that assess thyrotropin and thyroid hormone levels, as well as the condition of the thyroid gland. In severe cases of DTG, elevated levels of thyroxine and triiodothyronine increase metabolism by more than 60%, leading to disruptions in protein, carbohydrate, lipid, and water-salt metabolism. Blood tests typically reveal an increased erythrocyte sedimentation rate, a decrease in leukocytes, hemoglobin, and erythrocytes, along with an increase in lymphocytes [6, 9].

Anemia is commonly observed in patients with DTG due to metabolic changes. It is important to note that in DTG, endothelial dysfunction and thrombotic complications arise as a result of thyrotoxicosis. Additionally, increased catabolism in DTG leads to disruptions in protein metabolism. Diagnosing the type of anemia in DTG is a critical medical issue, as it allows for the timely application of appropriate pathogenetic treatment methods, ultimately improving the patient's quality of life.

It is worth mentioning that, although many studies have addressed the development of anemia and hematological changes in DTG, the clinical and laboratory methods for determining the type of anemia, as well as treatment approaches, have not been extensively studied. This methodological recommendation focuses on identifying the pathogenetic mechanisms of anemia development in DTG and implementing etiopathogenetic treatment strategies.

OBJECTIVE OF THE STUDY

The study aims to determine the type and severity of anemia in diffuse toxic goiter and enhance pathogenetic treatment methods.

MATERIALS AND METHODS

Clinical studies were conducted on DTG patients in the Department of Endohematology at the Multidisciplinary Clinic of the Tashkent Medical Academy between 2021 and 2024. The primary study group consisted of 94 patients aged 25–70 years with hemoglobin levels below 90 g/L, all diagnosed with DTG. Prior to participation, informed consent was obtained from all patients. Individuals with a history of other endocrine disorders, oncological, rheumatological, nephrological, gastroenterological, or other severe diseases, as well as those undergoing hormonal therapy, were excluded from the study.

The selected patients were categorized into four groups:

- **Group 1** – 29 patients with hypochromic iron deficiency anemia and DTG.
- **Group 2** – 20 patients with hyperchromic megaloblastic anemia (caused by vitamin B12 and folic acid deficiency) and DTG.
- **Group 3** – 18 patients with normochromic anemia and DTG.
- **Group 4** – 3–5 patients with mixed-etiology anemia (deficiencies of iron, vitamin B12, and folic acid) and DTG.

The control group included 20 healthy individuals aged 25–70 years with no hematological or endocrinological disorders.

HEMATOLOGICAL ANALYSIS

Blood samples were collected in purple-topped tubes and analyzed using the Mindray BC-5000 hematological analyzer for hematological assessments. A cytological evaluation of blood cells was also conducted. Initially, peripheral blood was examined for cytological diagnosis, and a myelogram was performed to assess blood production. Blood and myelogram samples were processed in the laboratory, where smears were prepared, fixed, and stained using Giemsa stain (Italy). The stained preparations were then examined under an Olympus BX53F2 microscope (Japan). During the evaluation of hematological smears, microscopic parameters such as cell count, size, shape, staining intensity, as well as cytoplasmic and nuclear inclusions, were analyzed.
To assess ferrokinetics and protein fractions, serum levels of iron and protein fractions were measured using the Mindray BS-200 biochemical analyzer (China) with Human (Germany) reagents. Levels of vitamin B12, folic acid, and erythropoietin were determined using a Snibe immunochemiluminescent analyzer (China) with Snibe reagents.

STUDY RESULTS

The analysis of DTG anamnesis revealed a correlation between the duration of thyrotoxicosis and hemoglobin levels, indicating the severity of anemia. As the duration of DTG increased, hemoglobin levels progressively declined. In patients with DTG lasting **1–3 years**, the average hemoglobin level was **88 ± 3.6 g/L**, and the erythrocyte count was **3.2 ± 0.05 × 10^{12}/L**. Among those with **DTG for 4–5 years**, these values dropped to **78 ± 5.6 g/L** and **2.8 ± 0.06 × 10^{12}/L**, respectively. In patients with **DTG for 6–10 years**, the hemoglobin level further decreased to **70 ± 4.0 g/L**, and the erythrocyte count averaged **2.4 ± 0.01 × 10^{12}/L**. By comparison, in the **control group**, hemoglobin was **124 ± 4.2 g/L**, and the erythrocyte count was **4.1 ± 0.04 × 10^{12}/L**.
Patients were categorized based on the type of anemia. The diagnostic approach included a **complete blood count, cytological analysis of blood smears, biochemical markers of iron metabolism**, and **immunological tests for ferritin, transferrin, vitamin B12, and folic acid**.

A. Anemia Types and Hematological Parameters.

Group 1 – Hypochromic Iron Deficiency Anemia (29 patients): hemoglobin 77 ± 5.5 g/L, e**rythrocyte** 3.1 ± 0.06 × 10^{12}/L, c**olor index** 0.74 ± 0.06, h**ematocrit** 29 ± 2.9%, m**ean corpuscular hemoglobin (MCH)** 24.8 ± 3.3 pg, m**ean corpuscular hemoglobin concentration (MCHC)** 265 ± 22 g/dL, e**rythrocyte anisocytosis:** 48 ± 3.8%.

Group 2 – Hyperchromic Megaloblastic Anemia (Vitamin B12/Folic Acid Deficiency, 20 patients): hemoglobin 72 ± 6.6 g/L, **erythrocyte** 1.7 ± 0.08 × 10^{12}/L, **color index** 1.27 ± 0.05, **hematocrit** 22 ± 3.1%, **MCH** 42.4 ± 3.5 pg, **MCHC** 327 ± 28 g/dL, **erythrocyte anisocytosis** 54 ± 4.2%.

Group 3 – Normochromic Anemia (18 patients): hemoglobin 78 ± 7.2 g/L, **erythrocyte** 2.6 ± 0.10 × 10^{12}/L, **color index** 0.9 ± 0.08, **hematocrit** 25 ± 2.5%, **MCH** 30.0 ± 2.7 pg, **MCHC** 312 ± 22 g/dL, **erythrocyte anisocytosis** 41 ± 4.4%.
Group 4 – Mixed-Etiology Anemia (35 patients with iron, vitamin B12, and folic acid deficiency): hemoglobin 74 ± 6.5 g/L, **erythrocyte** 2.4 ± 0.14 × 10^{12}/L, **color index** 0.93 ± 0.07, **hematocrit** 23 ± 2.0%, **MCH** 30.8 ± 2.1 pg, **MCHC** 322 ± 28 g/dL, **erythrocyte anisocytosis** 58 ± 4.7%.

There is no anemia in control group: **hemoglobin** 128 ± 11.2 g/L, **erythrocyte 4.**2 ± 0.10 × 10^{12}/L, **color index** 0.9 ± 0.06, **hematocrit** 45 ± 3.1%, **MCH** 30.0 ± 2.8 pg, **MCHC** 324 ± 31 g/dL, **erythrocyte anisocytosis** 38 ± 3.3%.

B. Morphological Study of Erythrocytes

The morphological characteristics of erythrocytes were analyzed, including **anisocytosis, staining intensity (anisochromy), poikilocytosis, and cytoplasmic inclusions.**

In the **control group**, erythrocytes had a **diameter of 7.7 ± 0.3 µm**, exhibited **normochromia**, retained a **round shape**, and showed **no cytoplasmic inclusions**.

Group 1 patients predominantly exhibited microcytes with an **erythrocyte diameter of 6.7 ± 0.4 µm**. Numerous annulocytes were present due to pronounced hypochromia, though no cytoplasmic inclusions were observed. Notably, **poikilocytosis** appeared in nearly half of the erythrocytes. The development of **erythrocyte hypochromia, microcytosis, and shape alterations** resulted from insufficient hemoglobin content **(Fig. 1).**

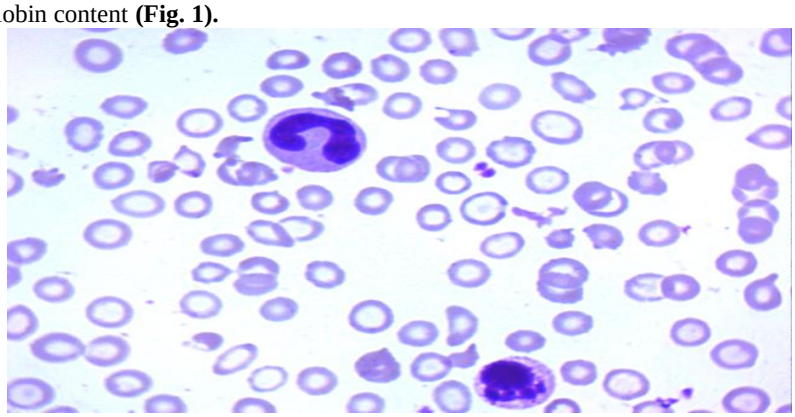

Fig.1. Morphology of erythrocytes in Group 1.

In contrast, **Group 2** patients exhibited **hyperchromic macrocytes with a diameter of 10.5 ± 0.7 µm** and **megalocytes measuring 12.6 ± 1.1 µm .**

Additionally, **large-nucleated erythrocytes (megaloblasts) with a diameter of 18.2 ± 1.5 µm** were observed. The nuclear chromatin structure of megaloblasts was **coarsely granular**, occupying almost half of the cell.

More than half of the erythrocytes in Group 2 also exhibited **various forms of poikilocytosis.** The **hyperchromia, macrocytosis, and shape alterations** were attributed to impaired erythrocyte division caused by excessive hemoglobin content. Additionally, nuclear remnants with cytoplasmic inclusions, such as **Jolly bodies and Cabot rings**, were detected in these patients (**Fig. 2**).

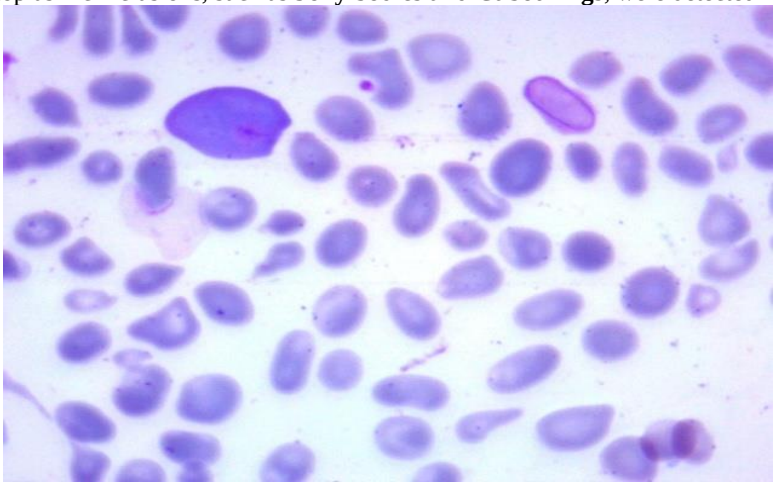

Fig. 2. Jolly bodies and Cabot rings in Group 2.

In **Group 3**, no significant morphological changes in erythrocytes were observed, though **moderate anemia** was present. The erythrocytes remained **normochromic and normocytic**, with normal shape characteristics (**Fig. 3**).

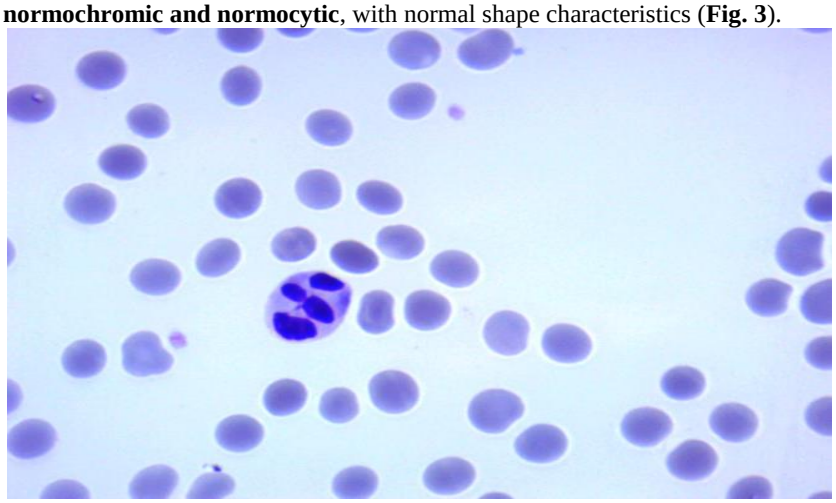

Fig. 3. Morphology of normochromic erythrocytes in Group 3.

In **Group 4**, erythrocytes displayed a mix of abnormalities, exhibiting both **hypochromia and hyperchromia, as well as macrocytosis and microcytosis**. Additionally, **nucleated erythrocytes, Cabot rings, and Jolly bodies** were present in a single smear (**Fig. 4**).

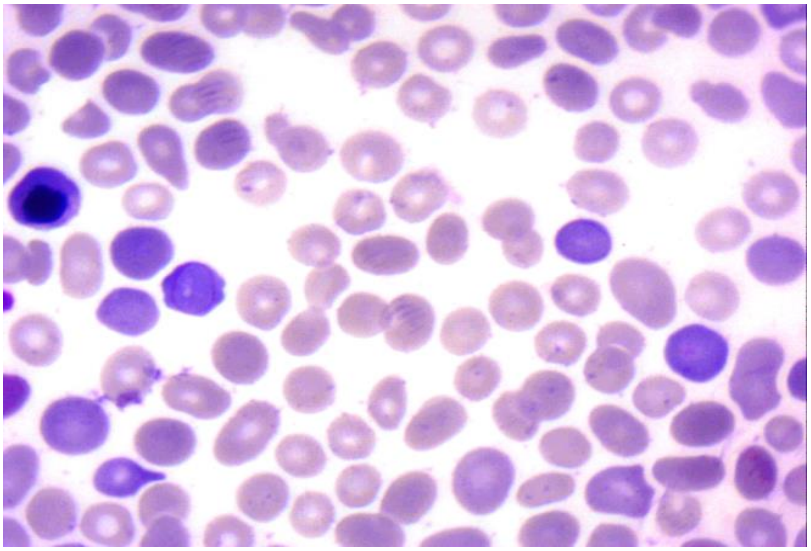

Fig. 4. Morphology of erythrocytes in Group 4.

In conclusion, anemia of different etiologies can be observed in patients with DTP. By analyzing hematological studies, the type of anemia can be identified based on erythrocyte indices and morphology.

C. Biochemistry parametres

To examine iron metabolism in patients with DTG and anemia, serum levels of iron, ferritin, and transferrin were measured. Ferrokinetic analysis revealed a severe iron deficiency in group 1 patients, with serum iron levels of 6.4 ± 1.1 μmol/L ***, ferritin levels of 7.8 ± 1.9 ng/mL ***, and transferrin levels of 2.3 ± 0.2 g/L *.

In group 2, two distinct subgroups were identified: six patients exhibited serum iron levels of 37.9 ± 4.1 μmol/L ***, ferritin levels of 245.1 ± 16.3 ng/mL ***, and transferrin levels of 2.4 ± 0.3 g/L *, while the remaining 14 patients had serum iron levels of 18.5 ± 1.1 μmol/L, ferritin levels of 77.8 ± 1.9 ng/mL, and transferrin levels of 2.6 ± 0.3 g/L *.

Similarly, group 3 patients displayed two different outcomes: in 10 patients, serum iron levels were 48.1 ± 3.6 μmol/L ***, ferritin levels were 228.1 ± 12.0 ng/mL ***, and transferrin levels were 2.5 ± 0.2 g/L *, whereas in the remaining eight patients, serum iron levels were 19.0 ± 1.1 μmol/L, ferritin levels were 58.3 ± 5.3 ng/mL, and transferrin levels were 2.4±0.3 g/L* (table 1).

TABLE 1. INDICATORS OF IRON METABOLISM IN ANEMIA AND DIFFUSE TOXIC GOITER

Groups	Patients	Iron, mkmol/l	Ferritin, ng/ml	Transfer-rin, g/l
Control group	n=20	16,8 ± 2,3	66,1 ± 7,8	3,2 ± 0,3
1 group	n=29	6,4±1,1***	7,8±1,9***	2,3 ± 0,2*
2 group	n=6	37,9±4,1***	245,1±16,3***	2,4 ± 0,3*
	n=14	18,5±1,1	77,8±1,9	2,6 ± 0,3*

3 group	n=10	48,1±3,6***	228,1±12,0***	2,5 ± 0,2*
	n=8	19,0±1,1	58,3±5,3	2,4 ± 0,3*
4 group	n=35	8,1±0,9***	12,5±1,6***	2,1 ± 0,2*

Note: - differences in relation to control group indicators are significant (*- P<0.05, * * - P<0.01, * * * - P<0.001

As shown in Table 1, group 4 patients had serum iron levels of 8.1 ± 0.9 µmol/L ***, ferritin levels of 12.5 ± 1.6 ng/mL ***, and transferrin levels of 2.1 ± 0.2 g/L *. In contrast, the control group had serum iron levels of 16.8 ± 2.3 µmol/L, ferritin levels of 66.1 ± 7.8 ng/mL, and transferrin levels of 3.2 ± 0.3 g/L.

Iron metabolism analysis indicated that groups 1 and 4 exhibited iron deficiency, whereas elevated iron and ferritin levels were observed in six patients from group 2 and 10 patients from group 3. However, transferrin levels were significantly reduced in all DTG patients with anemia.

To assess protein metabolism, total protein, albumin, and globulin levels in serum were measured. In group 1 patients, the average total protein level was 60.2 ± 5.8 g/L *, serum albumin was 29.7 ± 2.8 g/L *, alpha-1-globulins were 1.4 ± 0.1 g/L, alpha-2-globulins were 5.1 ± 1.0 g/L, beta-globulins were 7.6 ± 0.8 g/L, and gamma-globulins were 16.4 ± 1.3 g/L *.

In group 2, the average total protein level was 61.0 ± 5.1 g/L *, serum albumin was 28.2 ± 2.2 g/L **, alpha-1-globulins were 1.3 ± 0.2 g/L, alpha-2-globulins were 5.8 ± 1.1 g/L, beta-globulins were 6.8 ± 0.8 g/L, and gamma-globulins were 18.9 ± 2.0 g/L **. For group 3 patients with DTG and normochromic anemia, the average total protein level was 56.7 ± 4.2 g/L **, serum albumin was 23.3 ± 1.9 g/L ***, alpha-1-globulins were 1.3 ± 0.1 g/L, alpha-2-globulins were 5.1 ± 1.6 g/L, beta-globulins were 6.2 ± 0.7 g/L *, and gamma-globulins were 20.8 ± 2.1 g/L **.

Similar changes were observed in group 4 patients with mixed anemia: the average total protein level was 59.9 ± 4.6 g/L *, serum albumin was 26.3 ± 2.0 g/L **, alpha-1-globulins were 1.4 ± 0.2 g/L, alpha-2-globulins were 5.2 ± 1.4 g/L, beta-globulins were 6.5 ± 0.6 g/L, and gamma-globulins were 20.5 ± 1.6 g/L **.

In the control group, the corresponding values were: total protein 74.1 ± 6.9 g/L, serum albumin 42.5 ± 4.3 g/L, alpha-1-globulins 1.5 ± 0.2 g/L, alpha-2-globulins 7.3 ± 0.7 g/L, beta-globulins 8.1 ± 0.8 g/L, and gamma-globulins 11.7 ± 1.3 g/L.

Based on these findings, it can be concluded that protein metabolism and its fractions are disrupted in DTG patients with anemia, with the most pronounced disturbances observed in group 3. Specifically, there was a significant reduction in total protein and albumin levels, while gamma-globulin levels increased, likely due to the autoimmune mechanism involved in DTG pathogenesis. A marked decrease in albumin and a substantial increase in globulins indicate the presence of dysproteinemia in these patients.
The determination of erythropoietin, a key stimulator of erythropoiesis, revealed low levels in all patient groups, with the most significant decrease in group 3. Erythropoietin levels were 8.9 XB/L in the control group, 5.0 ± 0.7 XB/L *** in group 1, 4.6 ± 0.5 XB/L *** in group 2, 2.2 ± 0.6 XB/L *** in group 3, and 4.8 ± 0.4 XB/L *** in group 4 (Figure 5).

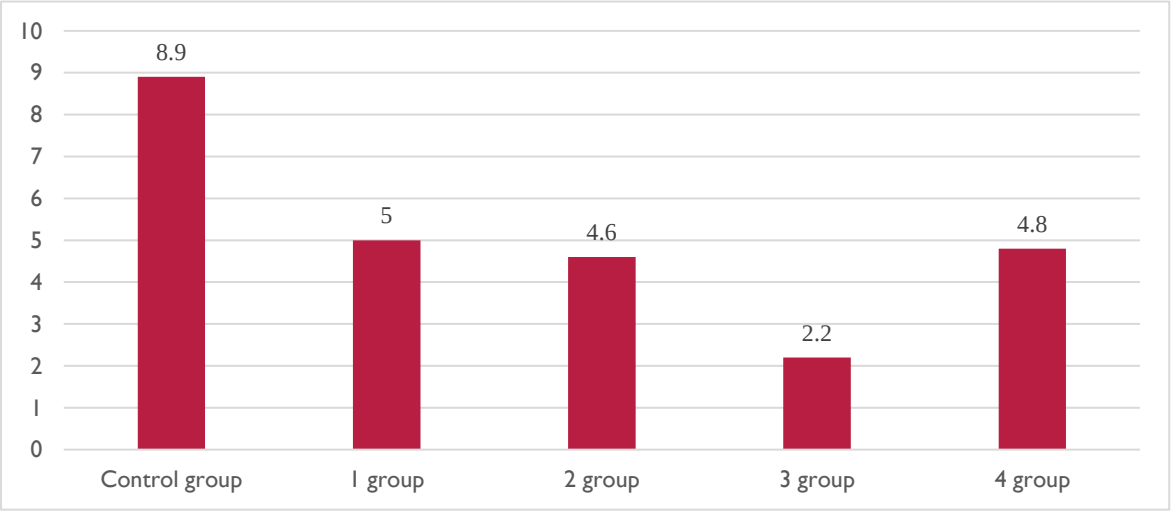

Fig. 5. Erythropoietin levels in patients with anemia and DTG.

The observed decrease in hematopoietic factor in all DTG patients with anemia highlights the need for erythropoietin therapy in treatment protocols. Based on the analysis of examinations conducted in patients with DTG and anemia, the following diagnostic criteria were developed to determine the type of anemia in DTG and establish pathogenetic treatment strategies.

To determine the resistance of erythrocytes to external influences, their osmotic resistance was examined. For this purpose, sodium chloride solutions of different concentrations were prepared using the titration method.

To assess the osmotic resistance of erythrocytes, six test tubes were numbered and placed on a stand, and sodium chloride solutions with decreasing concentrations were added.
In each test tube, 40 µL of native blood is added and mixed, then left on the stand for one hour or centrifuged at 3000 rpm for 5 minutes. Complete hemolysis is assessed based on the color of the solution, sedimented erythrocytes, and microscopy (Table 2).
The study of erythrocyte osmotic resistance in patients with anemia and tuberculosis revealed that in groups 2, 3, and 4, erythrocyte osmotic resistance was severely impaired. This indicates that these erythrocytes break down rapidly under the influence of the external environment.

TABLE 2. ASSESSMENT OF ERYTHROCYTE OSMOTIC RESISTANCE IN PATIENTS WITH ANEMIA AND DTG.

Groups	Patients	1	2	3	4	5	6
		0,6	0,5	0,45	0,4	0,35	0,3
Control group	n=20	-	-	-/+	+	+	+
1 group	n=29	-	-/+	+	+	+	+
2 group	n=6	-/+	+	+	+	+	+
	n=14	-	-/+	+	+	+	+
3 group	n=10	-/+	+	+	+	+	+
	n=8	-	-/+	+	+	+	+
4 group	n=35	-/+	+	+	+	+	+

The study of erythrocyte osmotic resistance in patients with anemia and tuberculosis revealed that in groups 2, 3, and 4, erythrocyte osmotic resistance was severely impaired. This indicates that these erythrocytes break down rapidly under the influence of the external environment.

DIAGNOSTIC CRITERIA

1. Evaluation of erythroid row scabies through hematological studies (hemoglobin, erythrocyte, color indicator, hematocrit, hemoglobin content in erythrocytes (MCH), hemoglobin concentration in erythrocytes (MCHC), erythrocyte anisocytosis).
2. Study of erythrocyte morphology (erythrocyte anisocytosis, anisochromia, poykilocytosis, inclusions in erythrocytes).
3. Ferrokinetic studies (determination of iron, ferritin and transferrin levels in whey).
4. Determination of vitamin V12, folic acid in whey.
5. Assessment of protein metabolism (total serum protein, albumin and gamma-globulins content).
6. Examination of osmotic resistance of erythrocytes.
7. Examination of the hematopoietic factor of erythropoietin.

CONCLUSIONS

1. Assessment of erythroid parameters using hematological studies (hemoglobin level, red blood cell count, color index, hematocrit, average hemoglobin content in red blood cells (MCH), average hemoglobin concentration in red blood cells (MCHC), erythrocyte anisocytosis) is the main diagnostic criterion for anemia in DTG.
2. The study of erythrocyte morphology (erythrocyte anisocytosis, anisochromia, poikilocytosis, inclusions in erythrocytes) is of great importance for determining the type of anemia in DTG.
3. Anemia was observed in 68.2% of patients with diffuse toxic goiter, of which 28.4% had iron deficiency anemia, 19.6% had megaloblastic anemia, 17.6% had normochromic anemia, and 34.4% had mixed anemia.
4. In patients with anemia and diffuse toxic goiter, total protein and albumin are significantly reduced by 17.7-19.5%, which requires the addition of amino acid preparations to the complex treatment of the disease.
5. In patients with anemia and diffuse toxic goiter, erythropoietin, a stimulator of erythropoiesis, decreased almost 2-fold in all groups of patients, while in group 3 this indicator decreased sharply by 4-fold, therefore, the duration of treatment with erythropoietin in patients with normochromic anemia lasts up to 1 month.

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