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Changes in complete blood count parameters influenced by endocrine disorders

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Abstract

Complete blood count is one of the most common diagnostic methods used in everyday practice. Hormonal status is known to affect blood count parameters. The aim of this study is to summarize changes in blood count that may indicate endocrine disorders, based on a literature review. Red cell parameters deteriorate in thyroid disorders including autoimmune thyroiditis and tend to resolve with appropriate treatment implementation. The most frequent form of anaemia associated with thyroid dysfunction is normocytic anaemia. Macrocytic anaemia is more typical of autoimmune thyroiditis-induced hypothyroidism, while microcytic anaemia is more common in hyperthyroidism. Unexplained anaemia or an increase in red cell distribution width should prompt the investigation of thyroid disorders. Cushing's disease may manifest as an increase in white blood cells and platelets. In the blood smear, neutrophilia is often present, while lymphocytes and eosinophils may be within the lower normal range. Hypercortisolism may induce both hyperaemia and anaemia. In hypopituitarism, a decrease in red blood cell count, haemoglobin, haematocrit, and platelets is observed. Acromegaly may be accompanied by an increase in mean corpuscular volume of erythrocytes. Testosterone deficiency is manifested by a decrease in red cell parameters, whereas hyperandrogenism may lead to polycythaemia. In polycystic ovary syndrome an increase in white blood cell count reflects an underlying inflammatory state. Complete blood count analysis is an easily available and cost-effective additional tool in the diagnosis and treatment monitoring of endocrine disorders. **(Endokrynol Pol 2021; 72 (2): 261–270)**

Key words: *complete blood count; endocrine diseases; hyperthyroidism; hypothyroidism; acromegaly; Cushing's disease*

Introduction

Peripheral blood count is one of the most accessible, cost-effective, and frequently performed diagnostic tests in medical practice. Both venous whole blood sampling and subsequent laboratory analysis are technically simple, allowing the results to be obtained very quickly. Abnormal results may direct further differential diagnosis.

The measured parameters include the following: red blood cells (RBC), haemoglobin (HGB), white blood cells (WBC), platelets (PLT), and haematocrit (HCT). Both manual and automatic blood smears enable quantitative and qualitative assessment of blood cells subpopulations. For leukocytes the proportion of each type in the total pool of white blood cells is determined. The types are as follows: granulocytes — neutrophils, eosinophils and basophils, and agranulocytes: lymphocytes and monocytes. We also receive information on red blood cells parameters — mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV) and detailed platelets parameters including MPV — mean platelet volume, PDW — platelet distribution width, which is a platelet volume variability index, PCT — plateletcrit, and P-LCR — platelet large cell ratio, describing the percentage of large platelets in the total number of thrombocytes.

The hormonal status may influence the parameters assessed in the blood count, thus their changes may reflect endocrine diseases. The aim of this study is to summarise current literature on blood count changes that should prompt diagnosis towards endocrine disorders not only by endocrinologists but by all physicians.

Thyroid disorders

Hypothyroidism and thyroiditis

In countries well supplied with iodine, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease), which is included in a wider group of autoimmune thyroid diseases

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(AITDs) [1]. The thyroid hormones stimulate erythropoiesis through increased expression of the erythropoietin (EPO) gene and its production in kidneys [2]. Previous research confirmed that increased triiodothyronine (T3) stimulates a colony of erythrocytes in contrast to hypothyroidism that decreases activity of erythroid cells in the bone marrow and erythropoiesis. In up to 60% of hypothyroid patients, normocytic anaemia of different aetiology can be observed, while in Hashimoto's thyroiditis a macrocytic anaemia is the most common [1]. It might be explained with accompanying Addison-Biermer anaemia associated with the presence of autoantibodies against the parietal cells or Castle's internal factor, which leads to the vitamin B12 malabsorption. On the other hand, iron deficiency in the course of hypothyroidism further exacerbates anaemia by reducing the synthesis of thyroid hormones and deteriorating the viability of erythrocytes. In microcytic iron deficiency anaemia an increase in in the degree of erythrocytes anisocytosis (red cell distribution width, RDW) is observed. The exact pathomechanism of iron homeostasis disturbances in patients with Hashimoto's thyroiditis is not well elucidated. Proper L-thyroxine replacement therapy normalises haematological parameters [1]. Additional iron substitution in subclinical hypothyroidism increases the effectiveness of L-thyroxine treatment. According to Shakir et al., in patients with anaemia the tolerance of L-thyroxine therapy may be worse [3]. Therefore, it is advised to initiate treatment with iron substitution, then add L-thyroxine. The study by Bremner et al. confirmed that even subtle changes in thyroid function in euthyroid patients may influence the red cell indicators [4]. Hernik et al. observed changes in blood count parameters, especially a gradual reduction of RDW in hypothyroid patients upon restoration of euthyroid state, which reflects improvement of erythropoiesis [1]. In another paper an increased RDW was also observed in the course of hypothyroidism due to Hashimoto's thyroiditis [5]. Interestingly, Aktas et al. suggested that increased RDW may be indicative of Hashimoto's thyroiditis even in euthyroid patients [6]. Additionally, both MCV and MCH may be lower in hypothyroidism in comparison to euthyroid state [1].

Subacute thyroiditis (SAT) is a specific type of thyroiditis, which comprises hyper- and hypothyroid phases accompanied by essential changes in complete blood count. The following parameters: RDW, HGB, HCT, MCV, MCH, and MCHC were found to be lower in comparison to healthy subjects [7].

Pregnancy is another state predisposing to anaemia. In the 4th week of pregnancy, an increase in plasma volume and number of erythrocytes is observed, but it is proportionally less pronounced than the increase in the volume of plasma. The physiological anaemia in pregnant women improves haemodynamic circulation in the course of increased resistance of blood vessels and increased blood flow through uteroplacental vessels occurring during pregnancy, which provides a better blood supply. Additionally, the level of iron is decreased due to increased utilization and transport to the foetus. On the other hand, iron deficiency is often linked to thyroid diseases, as less iron reduces the activity of thyroid peroxidase — an enzyme essential for the production of thyroid hormones. Concluding, in pregnant women a complete blood count should be monitored, and in case of anaemia, diagnostics directed towards thyroid diseases should be initiated, even if they were not diagnosed before pregnancy [8].

Keskin et al. described differences in haematological parameters between patients with Hashimoto's thyroiditis and a healthy control group, both being euthyroid [9]. They observed higher levels of lymphocytes in comparison to the control group. Additionally, Hashimoto's group presented lower level of HGB and higher MPV but with no difference in WBC. Next, they confirmed a significantly higher neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in Hashimoto's patients. The research of Erikci et al. demonstrated higher MPV and PDW in subclinical hypothyroidism compared to euthyroidism [10]. The study by Hernik et al. did not demonstrate changes in platelet count in hypothyroid state [1]. In patients suffering from SAT an increased level of platelets and decreased PDW, MPV, and P-LCR were observed. Increased platelet count may result from a decreased level of megakaryocytes that accumulate iron, which leads to increased synthesis of poliploidal megakaryocytes. Thrombocytosis may also be explained by an inflammatory reaction [7]. Kutluturk et al. described the impact of changes in the level of thyroid hormones on platelets in 58 patients with papillary thyroid carcinoma in three phases of treatment: preoperative (euthyroidism), in hypothyroidism before radioiodine treatment (RAI), and subclinical hyperthyroidism after RAI (up to 6 months). They did not notice significant differences in the level of plates, MPV, NLR, or PLR in the hypothyroid phase [11].

Hyperthyroidism

Hyperthyroidism may have different aetiology, but in countries well supplied with iodine the most common cause is Graves' disease. In 1988, Ford and Carter noticed a significant impact of thyrotoxicosis on all haematopoietic cell lines [12]. In thyrotoxicosis, changes

of complete blood count depend on the cause. The mechanism of changes is not fully understood.

In a thyrotoxic state, anaemia concerns 10-34% of all patients with cytopaenia [13]. One of the possible explanations is that excess thyroid hormones increase body metabolism and demand for oxygen [14]. Next, hypoxia stimulates the erythropoietin gene expression and its synthesis in the kidneys [13]. The erythropoietin potentiates erythropoiesis and increases demand for iron, folic acid, and vitamin B12. The most likely theory is a mixed aetiology of anaemia [2]. In hyperthyroidism, the most common type of anaemia is microcytic anaemia, which results from iron deficiency [13, 15]. Parameters that enable the diagnosis include increased RDW and decreased MCV. Normocytic anaemia may occur in Graves' disease with concomitant bone marrow hypoplasia [13]. Macrocytic anaemia occurs due to deficiency of folic acid and vitamin B12 [13, 15], whereas treatment with antithyroid drugs may induce iatrogenic aplastic anaemia [13].

The potential link between anaemia and thyroid diseases may be hepcidin, which is an important regulator of iron homeostasis. According to Krygier et al., the hepcidin concentration decreases during the treatment of Graves' disease [16]. Additionally, they observed an improvement in haematological parameters, especially increase in MCV and MCH.

Leukopaenia accounts for 15–30% of all cytopaenia cases, while neutropaenia concerns 5–18% [13, 17]. The pathomechanism is not well recognized. On one hand, granulopoiesis is limited by a decreased amount of granulocytes in bone marrow. On the other hand, there is a hypothetical immunological mechanism linked to the identification of antibodies directed against neutrophils in patients with thyrotoxicosis [13].

Agranulocytosis is often a result of therapy with anti-thyroid drugs (ATD). According to Japanese researchers, the lower level of granulocytes may occur in up to 70% patients receiving ATD therapy [18]. Therefore, before introduction of ATD, it is crucial to evaluate complete blood count and monitor this parameter, particularly in the case of fever or throat angina [19].

Thrombocytopaenia accounts for 2-5% of all cytopaenia cases [13]. Previous studies described the occurrence of antibodies against platelets in patients with thyrotoxicosis. Bagir et al. estimated the significance of MPV to predict the recurrence of Graves' disease; a higher level of MPV was confirmed in the group with recurrence of hyperthyroidism in comparison to the group of patients in remission [20]. The authors explain this phenomenon by an increased metabolic rate due to hyperthyroidism rather than an autoimmune reaction. Turan et al. reported higher level of platelets in patients with untreated Graves' disease [17]. Franchini et al. underlined the correlation between hyperthyroidism and idiopathic thrombocytopaenic purpura [17]. Ford et al. observed no changes in platelet count in hyperthyroidism. They demonstrated a significant decrease in MPV and PCT and slight increase in PDW upon euthyroidism restoration after the phase of hyperthyroidism [12]. Similarly, in the study by Kutluturk et al., MPV, which reflects the pace of plates production and activation, was significantly elevated in subclinical hyperthyroidism compared to euthyroidism [11].

Previously, pancytopaenia in the course of Graves' disease was described occasionally [13]. Initially, pancytopaenia was linked to deficiency of iron, vitamin B12, and coexisting diseases, but in most described cases those disturbances were not observed. Pancytopaenia is generally chronic and well tolerated [13, 22]. Pincet and Gorostidi reported no severe anaemia complications such as intensive bleeding in the course of thrombocytopaenia or infection due to leukopaenia [22]. Next, the parameters of complete blood count returned to normal range after euthyroidism was achieved [13, 14, 23, 24]. For authors the hyperthyroidism was an obvious explanation of the previous unexplained pancytopaenia [22].

A Polish study on 59 children with de novo diagnosed Graves' disease confirmed the previously presented observations. Neutropaenia was noted in 37.3% of patients, the decreased level of MCV occurred in 32.2% of children, and 22% of them had elevated haemoglobin. The decreased levels of RBC, WBC, and PLT were observed in 13.6%, 8.5%, and 5% of patients, respectively. Higher RDW occurred in 15.3% of the study group. In most cases, the changes in the studied parameters were not significant and severe anaemia, neutropaenia, or thrombocytopaenia were not found. The studies showed statistically significant improvement after ATD therapy. Additionally, no changes in MCV, WBC, or neutrophils were noticed [25].

Pituitary disorders

Acromegaly

Acromegaly is a rare endocrine disorder with two to four new cases per million persons per year and the incidence of 50-70 cases per million inhabitants [26, 27]. The most common cause of acromegaly is a growth hormone (GH)-secreting pituitary adenoma [28]. Changes in the blood count commonly accompany acromegaly [29]. Regular observation of basic blood parameters may be of value considering the high morbidity and mortality due to cardiovascular

diseases in this group of patients [30]. Current studies have demonstrated alterations in RDW, MCV, and MPV in acromegaly. Uçler et al. compared RDW between patients with active and inactive disease treated either only surgically or with adjuvant somatostatin analogues (SSA) [31]. RDW was significantly higher among patients with inactive acromegaly receiving SSA following surgery. For surgical treatment alone, the results did not reach significance. Strauch et al. observed increased MCV values in male patients with active acromegaly compared to female patients and healthy controls [32]. MCV correlated positively with the GH concentration, suggesting that excessive endogenous GH secretion is responsible for a reversible increase in MCV in acromegaly.

MPV has aroused interest as a useful indicator of cardiovascular risk [33]. Research on MPV in acromegaly is inconclusive. Several studies have shown an increased MPV in acromegaly compared to healthy individuals [34–36], while another demonstrated no significant differences [37, 38]. Surgical treatment with concomitant use of SSA was found to either increase or decrease MPV, whereas in patients treated only surgically no changes of MPV were noted [31, 37]. The treatment with SSA may thus increase MPV and be associated with greater risk of cardiovascular diseases. Demirpence et al. demonstrated a significant decrease in MPV following surgery without adjuvant therapy [35]. MPV values remained unchanged in the active phase of the disease and in patients in remission who received SSA after surgery. These results suggest that, although acromegaly is pharmacologically controlled with SSAs, the risk of cardiovascular diseases may remain elevated.

Cardiovascular diseases are associated with chronic inflammation. The ratios of neutrophils to leukocytes and platelets to leukocytes are good indicators of inflammation [39]. Üçler et al. demonstrated a positive correlation between the ratio of neutrophils to lymphocytes and insulin-like growth factor 1 (IGF-1), as well as between the ratio of platelets to lymphocytes and IGF-1 [40]. The authors concluded that an inflammatory state due to uncontrolled IGF-1 secretion may increase the risk of mortality and morbidity in the course of acromegaly.

Hypopituitarism

Hypopituitarism comprises a group of symptoms related to the deficiency of one or more pituitary hormones. Most commonly it results from damage to the pituitary or hypothalamus due to the sellar lesions, autoimmune diseases, or iatrogenic injuries. Less frequently, it is caused by congenital or developmental defects [41].

Valerio et al. investigated the effect of rhGH treatment on erythropoiesis by assessing RBC, HGB, HCT, and MCV in 19 children with isolated GH deficiency (12 cases) and multiple pituitary hormone deficiency (MPHD; 7 cases). During rhGH treatment HGB, HCT, and RBC increased, which indicates the erythropoietic effects of GH *in vivo*. The authors hypothesised that the deterioration of red cell parameters in hypopituitarism is mainly attributable to GH deficiency. Balancing the other pituitary axes does not fully restore normal erythropoiesis until the GH deficiency has been corrected [42].

In adults a prolonged administration of rhGH also increased HGB [43]. Haemoglobin concentration peaked at week 120 of the treatment, with mean increase of 0.73 ± 0.2 mmol/L. The fold of increase was higher in men. HGB concentration changes correlated with IGF-1. The maximum concentration of HGB was observed in the majority of patients with IGF-1 values close to the normal range. Leukocyte and platelet counts remained unchanged throughout the treatment.

Anaemia is a common feature of hypopituitarism. Nishioka and Haraoka investigated the influence of hydrocortisone and/or levothyroxine replacement therapy on HGB concentration in patients with hypopituitarism [44]. HGB concentrations were significantly lower in patients with hypopituitarism in the corticoid, thyroid, somatotropic, and gonadotropic axes compared with healthy controls. The HGB concentration decreased with the disease duration. In some patients, hydrocortisone and levothyroxine supplementation improved HGB concentrations; however, it was not sufficient in all. These results confirm previous observations that additional rhGH and/or androgen replacement therapy is necessary to obtain further improvement.

Additionally, the study focused on the morphotic elements of blood. The RBC, HCT, and platelets were significantly lower in patients with hypopituitarism compared to the control group. No differences in WBC or reticulocytes were observed.

Beshyah et al. demonstrated that haemostasis in adult patients treated for hypopituitarism is not disturbed [45]. Twenty-one patients with hypopituitarism, treated with thyroxine, hydrocortisone, and sex hormones, participated in the study. All subjects were GH-deficient and had decreased IGF-1 concentrations compared to the control group. Blood count parameters including HGB, WBC, PLT, and HCT did not differ significantly between groups.

Cushing's disease

ACTH (adrenocorticotropic hormone)-secreting pituitary adenomas are the most common underlying condition of endogenous hypercortisolaemia [46, 47].

Numerous blood count abnormalities are associated with Cushing's syndrome, including an increased or decreased RBC and haemoglobin, as well as elevated WBC and PLT.

Possible explanations of erythrocytosis and elevated haemoglobin include decreased erythrophagocytosis caused by glucocorticoid (GCS) excess and stimulation of erythropoietin synthesis or positive regulation of erythropoiesis (e.g. participation in stress erythropoiesis or blood-loss associated erythropoiesis). Erythrocytosis may be reflected as a typical Cushing's syndrome appearance, namely a red, moon-shaped face [48]. Fluctuations in testosterone concentration in hypercortisolism may also affect blood count. Patients suffering from Cushing's syndrome due to GCS excess are likely to have decreased LH and testosterone concentrations. Because testosterone stimulates RBC proliferation (influence stronger than GCS), the blood count may show decreased HCT, RBC, and HGB [48, 49]. Polycythaemia observed in Cushing's disease occurs more frequently among women due to the less important role of testosterone in the erythropoiesis regulation. As Cushing's disease occurs predominantly in women, polycythaemia is considered a typical symptom [48].

Another blood count abnormality reported in hypercortisolism is a considerable or slight increase in WBC. Most commonly we observe neutrophilia with eosinophils and lymphocytes below or in lower normal range [48]. The mechanisms responsible for leukocytosis include prolonged half-life and postponed neutrophil apoptosis, decreased migration to tissues, and increased inflow of granulocytes into the bloodstream induced by stress factors such as cortisol or catecholamines [50].

Platelet concentration is either normal or increased [50]. An increased risk of venous thrombo-embolic disease must be considered [51].

Hyperprolactinaemia

The largest proportion of pituitary adenomas are prolactinomas. They are considered the main cause of hyperprolactinaemia, which is the most common hormonal abnormality among the hypothalamic and pituitary disorders [52, 53].

The most frequent blood count abnormality observed in hyperprolactinaemia is thrombocytosis [54], although the research on this topic is limited. The change of platelet parameters is not observed in the pregnancy-induced hyperprolactinaemia [54]. On the other hand, changes in haemostasis parameters are observed more frequently and include, e.g., increased platelet activation and an increased fibrinogen concentration, which, taken together, contribute to the increased risk of thrombosis, atherosclerosis, and heart disease [55, 21]. This also applies to patients with macroprolactinaemia [55]. Hyperprolactinaemia does not affect total white blood cell counts or other blood count parameters [56].

Adrenal disorders

Adrenal insufficiency

In Addison's disease (primary adrenal insufficiency), the most common abnormality regarding blood count parameters is eosinophilia. Eosinophilia in Addison's disease was described in early works from the 1970s [57]. Eosinophil concentration above 500/mm^3 was found in 4 out of 26 subjects. In one 21-year-old patient the concentration reached 800/mm^3 in the absence of any parasitic infection. Oral administration of cortisol reduced eosinophilia in this patient, while daily use reduced the myeloid production of eosinophils and restored eosinophil concentration. Eosinophilia has also been described in a patient with adrenal insufficiency due to tuberculosis [58]. However, it cannot be clearly stated that eosinophilia is caused solely by low plasma cortisol levels, because it is not present in all patients with Addison's disease.

In patients with adrenal insufficiency, treatment with dehydroepiandrostenedione sulphate (DHEA-S) has an immunomodulatory effect, increasing the number of T cells by stimulating their proliferation. A 12-week exposure of cultured lymphocytes to DHEA-S increased their number by more than 10 times while reducing the number of NK cells by 37–43%. Additionally, in one trial, the treatment increased the number of B cells and monocytes [59]. However, an experimental study in mice showed that long-term use of DHEA-S in these animals did not affect the T-cell subpopulation or the production of antibodies after erythrocyte immunization [60].

Addison's disease may coexist with other autoimmune disorders as a part of the autoimmune polyglandular syndrome [61]. Then it may be accompanied by pernicious anaemia — a macrocytic anaemia due to vitamin B12 deficiency.

Pheochromocytoma and hyperaldosteronism

Blood count changes are also reported in pheochromocytoma - a tumour originating from the adrenal medulla. Experimental studies have shown that high-dose catecholamine administration increases WBC and PLT, and promotes platelet activation, which is also observed in chronic stress [62, 63]. Neutrophilia was reported in a patient with phaeochromocytoma and non-cardiac pulmonary oedema [64]. The authors hypothesised that elevated WBC may lead to respiratory failure by increasing the permeability of pulmonary vessels and promoting the development of that complication [64].

Zelink et al. compared blood count parameters between patients with pheochromocytoma, primary hyperaldosteronism, and idiopathic arterial hypertension [65]. WBC in pheochromocytoma was significantly higher compared to the group of patients with primary aldosteronism or the control group. On the other hand, the number of platelets was higher in patients with phaeochromocytoma compared to primary hyperaldosteronism, but lower than in the control group. There were no significant differences in RBC and HGB among the studied subgroups. After surgical treatment and normalization of catecholamine concentrations, WBC, neutrophils, and platelets decreased. The influence of catecholamines on the blood morphotic elements is explained by their direct interaction with cell surface receptors: PLT — alpha receptors stimulated by epinephrine, and WBC — adrenoreceptors.

An elevated HGB concentration has also been described in a 20-year-old patient with late diagnosis of Bartter's syndrome type IV. Other morphological parameters (leukocytes, platelets), as well as plasma iron, transferrin, and erythropoietin concentration were within the normal ranges [66]. The reasons for this phenomenon remain unclear. A similar clinical situation, described by Erkelens many years ago, was interpreted by the author with the hypertrophy of the glomerular apparatus, which led to the overproduction of renin and an increase in the synthesis of erythropoietin [67]. It is now known that the glomerular apparatus is not the main site of erythropoietin synthesis, the concentration of which in the described case was within the normal range. The occurrence of erythrocytosis may be the result of polyuria, which, however, also did not apply to this patient.

Premature adrenarche

Adrenarche is the process of adolescence in which the child's adrenal cortex begins secreting androgen precursors. These mainly include dehydroepiandrosterone and androstenedione. This phenomenon is considered premature when it occurs before the age of 8 years in girls and before the age of 9 years in boys. Adrenal hormones promote secondary sex characteristics such as the appearance of pubic and underarm hair, acne, and sweat with a characteristic smell. When accompanied by gonadarche, it is classified as premature puberty. Adrenarche praecox (AP) is more common in girls — 9/10 patients [68]. Reports indicate a relationship between AP and altered values of blood count parameters in patients compared to the group of healthy people. It has been shown that the RBC level is higher in girls with AP than in the same sex in the control group. Such a relationship did not occur in the group of boys. At the same time, the remaining blood count parameters did not differ significantly between the affected and healthy subjects of both sexes [68].

Disorders of the secretory function of the gonads

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder that affects 5 to 25% of women in reproductive age [69–72]. Characteristic features for this disease include oligo- or anovulation, polycystic ovaries on ultrasound imaging, and clinical and biochemical hyperandrogenism. PCOS is also associated with metabolic disorders such as glucose intolerance, insulin resistance, and obesity. In patients with PCOS, an increase in many markers of inflammation is also observed [72]. Chronic inflammation is a significant risk factor for the development of atherosclerosis and cardiovascular diseases.

WBC is an indicator of inflammation and is routinely measured in the blood count. In PCOS patients a significantly higher WBC was observed compared to healthy women, matched for age and BMI. Increased concentration of leukocytes is an independent predictor of inflammation and atherosclerosis [72]. Research indicates a correlation between WBC, CRP, insulin resistance, BMI, and visceral fat. However, it is still not fully understood whether inflammation is directly related to PCOS or reflects the insulin resistance and obesity associated with the syndrome [72]. Other morphological parameters considered as inflammation indicators include PLT, MPV, PDW, and PCT. Cardiovascular, cerebrovascular, and inflammatory diseases influence PLT counts. MPV, PLR and NLR indices have also been considered as markers of inflammation. However, studies in PCOS patients demonstrated no changes in the above-mentioned blood count parameters, and thus they are not applicable in this syndrome [72]. Due to the limited research in this field, further studies are necessary to confirm those findings. Metformin therapy in PCOS reduces WBC (including lymphocyte and monocyte count) and thereby reduces inflammation and the risk of atherosclerosis and cardiovascular diseases [69].

Male hypogonadism

Male hypogonadism results in gonadal dysfunction. Due to its aetiology, hypogonadism is classified as:

— hypergonadotropic (primary) hypogonadism, in which the testes are unable to perform an endocrine or reproductive function due to damage to their structure. This group includes among others: gonadal dysgenesis, congenital lack of testes, Klinefelter syndrome;

— hypogonadotropic (secondary) hypogonadism, resulting from hypothalamic-pituitary insufficiency and decreased gonadotrophins. It occurs in the course of hyperprolactinaemia, Kallmann's syndrome, hypopituitarism, isolated FSH deficiency or might be idiopathic;
— mixed hypogonadism — late-onset hypogonadism (LOH)
— syndromes associated with the target tissue resistance to sex hormones — aromatase deficiency, androgen insensitivity syndrome [73].

Clinical presentation of male hypogonadism results from testosterone deficiency. Erythropoiesis is an androgen-dependent process. Therefore, a mild anaemia is common in hypogonadal patients. Substitution of testosterone restores proper erythropoiesis and might induce polycythaemia in up to 25% of patients [73–76]. Blood count is one of the basic tests allowing indirect assessment of the effectiveness of the treatment of hypogonadism. Regular blood count monitoring, with particular attention paid to HCT, is recommended during testosterone therapy [73, 74, 76]. If HCT increases above 54%, the dose should be reduced or the intramuscular drug administration route changed to transdermal [74]. In some cases, a phlebotomy is recommended. If the aforementioned actions are unsuccessful in decreasing HCT, testosterone therapy should be discontinued and restarted after normalization of this parameter.

In idiopathic hypogonadotropic hypogonadism (IHH) HGB, HCT, and MCV were reported to decrease compared to the healthy individuals. Conversely, RDW in patients with IHH was higher than in healthy people, which reflects a greater anisocytosis of red blood cells. In IHH PLT increased significantly compared to the control group. The study cited above concerned newly diagnosed, untreated IHH patients, thus changes in the erythropoiesis are a direct consequence of this disease [75].

Doping

Doping involves the use of methods aimed at increasing the physical performance of athletes, which at the same time go beyond the limits of conventional training. Due to gradual blurring of boundaries between "proper" training and doping, the latter can be considered as methods that require medical intervention.

According to the 2015 World Anti-Doping Agency (WADA) definition, doping is a breach of at least one of the anti-doping rules included in the Anti-Doping Code. These include: the presence of a Prohibited Substance, its metabolites or markers in a sample collected from an Athlete, use / attempted use by an Athlete of a prohibited substance or method, and evasion or refusal to collect samples for doping testing. The code also lists the following: possession of prohibited substances, trade or attempted trade in such substances, as well as administering or attempting to administer them to an athlete [77].

In order to detect doping and disqualify athletes using illegal methods, WADA has developed the Athlete Biological Passport (ABP). It includes, inter alia, haematological parameters. Peripheral blood counts include parameters listed in the haematological ABP: HCT, HGB, MCH, MCV, MCHC, PLT, RBC, WBC, and RET [63]. In view of the above, an endocrinologist can assess certain abnormalities characteristic for doping on the basis of morphology.

Androgenic anabolic steroids (AAS) are a widely used method of doping, both in professional athletes and amateurs, being synthetic testosterone derivatives. They are mainly applied to increase the muscle mass; therefore, their use is often associated with sports that require significant muscle strength in a short time, e.g. weight lifting or sprinting. Smaller doses of anabolic steroids are taken by cyclists to increase the erythrocyte count and haematocrit, which increases the supply of oxygen to the cells [78].

Chrostowski et al. investigated the effect of high-dose ASS administration on the renin-angiotensin-aldosterone axis. Forty bodybuilders were enrolled and divided into ASS-urine positive and negative groups. In individuals using AAS, significantly higher levels of RBC, HGB, and HCT were reported compared to the group not taking ASS [79]. These results confirm both the effectiveness of AAS as a doping agent and their influence on blood count parameters. Properly performed differential diagnosis should include doping as one of the potential causes of abnormally high blood count parameters.

Conclusions

In the course of thyroid dysfunction and AITD, the worsening of RBC parameters is observed, which improve following successful therapy. Agranulocytosis may be one of side effects of ATD used for hyperthyroidism therapy. The most common form of anaemia in the case of thyroid dysfunction is normocytic anaemia. Macrocytic anaemia is more typical of hypothyroidism, while microcytic is more typical for hyperthyroidism. Unexplained anaemia or an increase in RDW should prompt the diagnostics directed towards thyroid diseases. In the course of Cushing's disease an increase in PLT and WBC is observed. The most common is neutrophilia, while the concentration of eosinophils and lymphocytes may be in the lower reference ranges. In hypercortisolism, both anaemia and hyperaemia may

occur. In hypopituitarism, a decrease in RBC, HGB, HCT, and PLT is observed. In patients with acromegaly, an increase in the MCV parameter is detected. Testosterone deficiency is accompanied by a decrease in RBC parameters, while androgen excess may induce polycythaemia. Routine control of blood count is recommended during the therapy with testosterone. In women with PCOS features of chronic inflammatory state are detected, which may be reflected by an increase in WBC. Evaluation of complete blood count is a useful tool in the basic diagnostics and monitoring of endocrine disorders.

Conflict of interest

Authors declare there is no conflict of interest.

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REVIEW

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