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СОВРЕМЕННЫЕ ПОДХОДЫ К ВЕДЕНИЮ БОЛЬНЫХ С ГИПЕРКАЛИЕМИЕЙ

E.V. Reznik*[1,2,3], A.I. Selivanov[1,2], A.R. Lutsenko[1], L.K. Garanina[2], G.N. Golukhov[1,3]

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Modern Approaches to the Management of Patients with Hyperkaliemia

Резюме

Гиперкалиемия — наиболее часто встречающееся нарушение электролитного баланса в клинической практике. Гиперкалиемия может быть обусловлена повышенным поступлением калия в организм, выходом его из клеток и нарушением экскреции почками. Данное состояние ассоциировано с высоким риском смерти от аритмий, поэтому даже незначительное отклонение уровня калия в сыворотке крови от нормы нуждается в немедленной коррекции. Современные подходы к лечению гиперкалиемии включают устранение провоцирующих факторов и применение калийснижающих препаратов. Хотя ингибиторы ренин-ангиотензин-альдостероновой системы являются в настоящее время самыми лучшими препаратами с кардионефропротективным эффектом, их назначение также может приводить к гиперкалиемии, особенно при сердечной недостаточности, хронической болезни почек и сахарном диабете. В статье подробно рассмотрены вопросы физиологии калиевого обмена, возможные провоцирующие факторы гиперкалиемии, современные подходы к профилактике и лечению этого состояния.

Ключевые слова: *гиперкалиемия, калий, ЭКГ, острое почечное повреждение, хроническая болезнь почек, блокаторы ренин-ангиотензин-альдостероновой системы*

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Abstract

Hyperkalemia is the most common electrolyte imbalance in clinical practice. Hyperkalemia can be caused by an increased intake of potassium into the body, the shift of potassium out of cells or an abnormal renal potassium excretion. This condition is associated with a high risk of death from arrhythmias; therefore, even a slight deviation of the serum potassium level from the norm requires immediate correction. Modern approaches to the treatment of hyperkalemia include the elimination of predictors and the potassium-lowering drugs. Although inhibitors of the renin-angiotensin-aldosterone system are currently the best cardionephroprotective drugs, their administration can lead to hyperkalemia too, especially in heart failure, chronic kidney disease and diabetes mellitus. The article discusses in detail the physiology of potassium metabolism, possible predictors, prevention and treatment of hyperkalemia.

Key words: *hyperkalemia, potassium, ECG, acute kidney injury, chronic kidney disease, renin–angiotensin–aldosterone system inhibitors*

Conflict of interests

The authors declare no conflict of interests

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ACE—angiotensin-converting enzyme, ARA—angiotensin receptor antagonist, ARI—acute renal injury, ARNI—angiotensin receptor antagonist and neprilysin inhibitor, ATP—adenosine triphosphate, AV—atrioventricular, CBV—circulating blood volume, CKD—chronic kidney disease, CPS—calcium polystyrene sulfonate, CVD—cardiovascular disease, DM—diabetes mellitus, ECG—electrocardiogram, ESC—European Society of Cardiology, GFR—glomerular filtration rate, GIT—gastrointestinal tract, HF—heart failure, K^+—potassium, MCRA—mineralocorticoid receptor antagonist, NSAIDs—non-steroidal anti-inflammatory drugs, RAAS—renin-angiotensin-aldosterone system, SPS—sodium polystyrene sulfonate.

Introduction

Hyperkalemia is common in clinical practice, especially in patients with heart failure (HF), diabetes mellitus (DM), and chronic kidney disease (CKD). It significantly increases the risk of sudden death due to the development of fatal arrhythmias. It significantly worsens the quality of life and prognosis and is an indication for starting renal replacement therapy in patients with end-stage renal disease [1]. This article provides a detailed description of the physiology of potassium metabolism, causes of hyperkalemia, and methods of its prevention and correction.

Definition

Normal concentration of extracellular potassium (K^+) is in the range 3.5–5.0 mmol/L (for potassium, 1 mmol/L = 1 mEq/L). Hyperkalemia is defined as serum or plasma potassium > 5.0 mmol/L [2]. Laboratory potassium values may vary slightly depending on the population and accuracy of the potassium determination method.

Potassium is usually measured in clotted blood serum. However, it is now mostly measured in plasma of heparinized blood. Serum levels can be 0.5 mEq/l higher than plasma levels. Unfortunately, in many studies, it is unclear whether potassium was measured in serum or plasma [2].

Classification

Hyperkalemia can be divided into the following groups by severity:

- mild (> 5.0 < 5.5 mmol/L),
- moderate (5.5–6.0 mmol/L),
- severe (> 6.0–6.9 mmol/L), and
- extremely severe (> 7.0 mmol/L) [2, 3].

In recent decades, the clinical approach to assessing hyperkalemia and its classification into two groups of severity has become the leading approach:

- life-threatening hyperkalemia (> 6.5 mmol/L and/or the presence of ECG signs typical for hyperkalemia) and
- non-life-threatening hyperkalemia (< 6.5 mmol/L and the absence of ECG signs typical for hyperkalemia).

Fatal arrhythmias and sudden death in patients with hyperkalemia can develop at different potassium levels. Hyperkalemia < 6 mmol/L can often be asymptomatic, especially in patients with DM, CKD, and HF [2].

Hyperkalemia can be classified as acute or chronic (or recurrent) depending on the onset and number of past episodes of hyperkalemia. Chronic hyperkalemia means a high potassium level > 5.0 mmol/L detected periodically throughout the year [2].

Pseudohyperkalemia means a high potassium level in a test tube without a high potassium level in the blood [2]. It is caused by the mechanical release of potassium from cells during phlebotomy or sample processing [4]. Hemolysis is more common when blood is taken with a syringe than with a vacuum device. Fist clenching, using a tight tourniquet or a small-bore needle for phlebotomy can also cause pseudohyperkalemia [4]. Reverse pseudohyperkalemia is a phenomenon when plasma potassium level is falsely elevated, but its serum level is within normal. This is described in cases of hematological diseases with severe leukocytosis when malignant cells are prone to lysis with minimal mechanical stress due to increased fragility or changes in the activity of sodium-potassium ATPase [4].

Epidemiology

The exact incidence of hyperkalemia is unknown [5]. According to different authors, hyperkalemia develops in 2–4% of the population, 10–55% of hospitalized patients, 7.7–73% of patients with CKD, and 40% of patients with chronic HF [2, 5]. Men are more prone to hyperkalemia than women. Infants and the elderly are at high risk of hyperkalemia. In-hospital mortality among patients with hyperkalemia is approximately 14%, with K^+ level ≥ 7 mmol/L—28%, and with K^+ level ≤ 6.5 mmol/L—9%.

Physiology of Potassium Metabolism

Potassium is the most common cation in the human body (50–75 mEq/kg of body weight) [2]. Under physiological conditions, 98% of potassium is inside cells, and 2%—in extracellular space [4]. Intracellular potassium concentration is **higher** than extracellular concentration. A high transmembrane potassium concentration gradient is important for the function of excitable tissues. Therefore, abnormal potassium concentration leads to life-threatening disorders of the heart and nervous system [4]. The most important factors involved in potassium distribution between the intra- and extracellular space are insulin and catecholamines [4]. Insulin release after meals not only regulates blood glucose concentration, but also promotes the transportation of potassium into cells. During physical exertion, potassium is released from skeletal muscles and accumulates in intercellular space, leading to vasodilation. A simultaneous increase in the concentration of circulating catecholamines contributes to the uptake of potassium by cells via beta-adrenergic receptors. Kidneys excrete 90–95% of excessive potassium, and the gastrointestinal tract excretes a small amount [4].

Etiology

Hyperkalemia often develops in cases of CKD and urinary tract pathology, acute renal injury (ARI), cardiovascular diseases (CVD), DM, and oncological diseases (Fig. 1).

There are three main causes of hyperkalemia (Table 1):

1) hyperkalemia associated with increased intake (consumption/administration) of potassium into the body;
2) hyperkalemia associated with increased release of potassium from cells; and
3) hyperkalemia due to the impaired excretion of potassium by the kidneys.

The release of potassium from cells results in a temporary increase in the potassium level, and decreased renal excretion—to persistent hyperkalemia.

Increased dietary potassium intake rarely leads to hyperkalemia in adults with normal renal function. However, it may result in hyperkalemia in patients with renal or adrenal disease. Dried fruits, seaweed, nuts, molasses, avocado, etc., contain large amounts of potassium. The following foods are also rich in potassium: spinach, jacket potatoes, tomatoes, broccoli, beets, carrots, kiwi, mangoes, oranges, bananas, melons, and red meat. These foods should be excluded from the diet of patients with severe renal impairment. Salt substitutes (sodium chloride replaced with potassium chloride) and dietary supplements can also be a source of potassium [2]. Drug products with high potassium level (especially when administered intravenously), herbs, parenteral nutrition, and massive blood transfusion can significantly increase serum potassium levels.

When cells are destroyed, potassium can move from cells into extracellular space. The release of 2% intracellular potassium can double the potassium concentration in blood serum. This happens in cases of hemolysis, trauma, and rhabdomyolysis. Tumor lysis syndrome can also cause acute hyperkalemia due to the mass death of cancer cells [4].

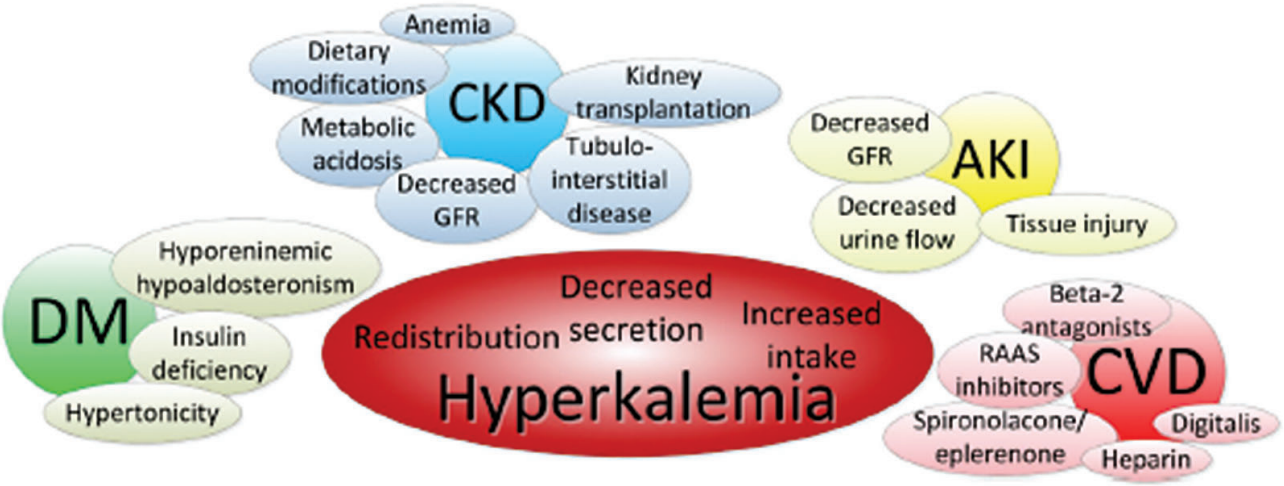

Figure 1. *Factors of the development of hyperkalemia in patients with different conditions[5].*
Note: AKI — acute kidney injury, RAAS — renin-angiotensin-aldosterone system, CVD — cardiovascular disease, DM — diabetes mellitus, CKD — chronic kidney disease, GFR — glomerular filtration rate

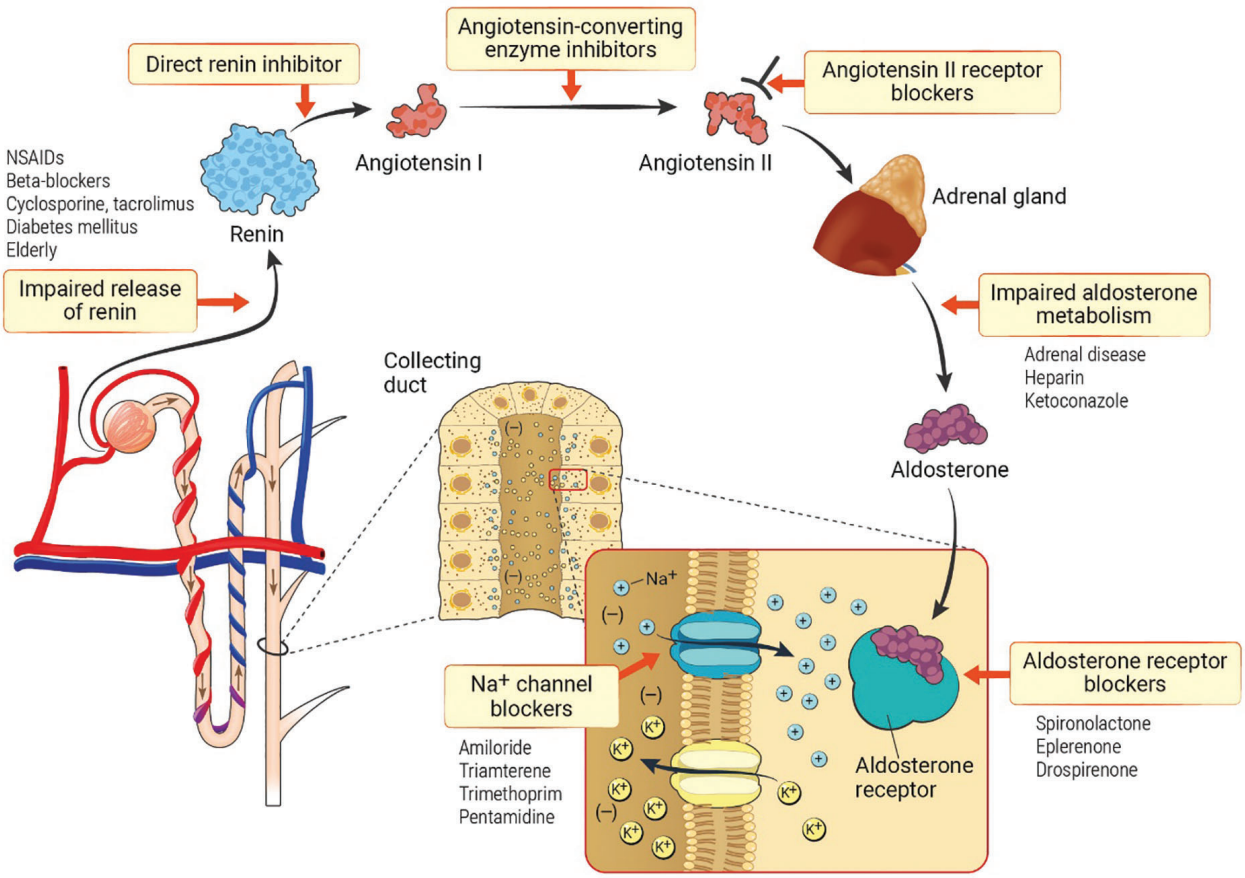

Figure 2. *A number of pharmocologic agents and conditions can interfere with the renin-angiotensin-aldosterone system, altering renal potassium excretion.*
Note: Reabsorbtion of sodium in the collecting duct increases the luminal electronegativity, providing a more favorable gradient for potassium secretion. In some patients, more than one distrurbance may be presents. NSAIDs=nonsteroidal anti- inflammatory drugs.
The picture was kindly provided by Biff F. Palmer (Professor of Internal Medicine, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX) [4] and permitted for reproduction on conditions of the licence Creative Commons CC-BY-NC-ND

Table 1. *Possible causes of hyperkalemia [2, 4]*

Category	Examples of
Increased intake of K into the body	
Oral	Food products (dried fruits, seaweed, nuts, molasses, avocados, spinach, jacket potatoes, tomatoes, broccoli, beets, carrots, kiwi, mangoes, oranges, bananas, melons, red meat)
	Salt substitutes (KCl instead NaCl)
	Oral potassium supplements
	Amino acids (aminocaproic acid, arginine, lysine)
	Medicinal plants (alfalfa, dandelion, hawthorn berry, horsetail, lily of the valley, spurge, nettle, Siberian ginseng, noni juice)
	Potassium preparations
Parenteral	Blood transfusion
	Introduction of solutions with additives K
	K-containing drugs (for example, penicillin G)
	Full parenteral nutrition
Enhanced potassium exit from cells (potassium redistribution)	
Medicines	Succinilcholine
	Beta blockers
	Digoxin
Enhanced tissue catabolism	Tumor lysis syndrome
	Hemolysis
	Hemorrhage in soft tissue or bleeding from the gastrointestinal tract
	Burns
	Injury
	Rhabdomyolysis
Insulin deficiency	Diabetes mellitus
	Hunger
Genetic disease	Hyperkalemic family periodic paralysis
Other	Exercise
	Metabolic acidosis
Reducing potassium excretion	
Medicines	Angiotensin converting enzyme inhibitors
	Receptor blockers for angiotensin II
	Direct renin inhibitors (aliskiren)
	Sakubitril/Salsartan
	Cyclosporine or tacrolimus
	Heparin
	Glycosides
	K-saving diuretics (spironolacton, eplerenone, triamterene, amyloid)
	Nonsteroidal anti- inflammatory drugs
	Calcinevrine inhibitors
	Beta blockers
	Trimethoprim
	Pentamidine
	Mannitol
	Penicillin G
Hypoaldo-steronism	Adrenal insufficiency
Kidney pathology	Acute kidney damage
	Chronic kidney disease
	Renal tubal acidosis, type IV

Metabolic acidosis, which is often due to impaired blood supply to tissues (including sepsis or dehydration), can also facilitate potassium release from cells. The severity of hyperkalemia depends on the type of acidosis. Hyperchloremic acidosis (mineral acidosis) most often contributes to hyperkalemia due to the relative impermeability of the cell membrane to the chloride anion. Hydrogen ions move into cells due to the accumulation of hydrogen chloride or ammonium chloride; electroneutrality is maintained by potassium release from cells with the development of hyperkalemia [4]. Organic acidosis (associated with lactic, beta-hydroxybutyric, methylmalonic acid) does not usually lead to the release of potassium since most organic anions easily move into cells along with hydrogen ions. In lactic acidosis, potassium release from cells is often caused by the violation of membrane integrity due to ischemia. In diabetic ketoacidosis, hyperkalemia is often associated with insulin deficiency [4]. Hyperglycemia contributes to the movement of fluid from intracellular to extracellular space, which increases the concentration of potassium in cells and creates favorable conditions for its release through membrane channels. A similar picture can be observed in neurosurgical patients receiving large amounts of hypertensive mannitol. Repeated doses of immunoglobulin can result in extracellular accumulation of sorbitol, maltose or sucrose, which are added to the agent to prevent aggregation of immunoglobulins, with the development of hyperkalemia [4].

Certain agents, such as succinylcholine, can cause severe acute elevations of the potassium level, especially in cases of subacute neuromuscular diseases.

Hyperkalemic periodic paralysis is a rare autosomal dominant condition when potassium is transferred into extracellular space due to mutations in the SCN4 gene that encodes the alpha-subunit protein of the sodium channel, its dysfunction, prolongation of action potential, and abnormal muscle fiber membrane repolarization.

Decreased potassium excretion may be due to:

1) decreased sodium delivery;
2) lack of mineralocorticoids (hypoaldosteronism); and
3) dysfunction of collecting ducts.

Some cases include all three of these reasons.

Normally, potassium is freely filtered by glomeruli, then reabsorbed, mainly in proximal tubules and in the thick ascending limb of Henle's loop. Potassium secretion starts in the distal convoluted tubule and increases in the collecting ducts. Secretion is regulated according to physiological needs. Decreased GFR and decreased mass of active nephrons lead to a reduced number of collecting ducts and decreased potassium secretion. However, the increased capacity of the remaining nephrons to secrete potassium can work against it. Hyperkalemia often develops in cases of oliguria due to decreased distal sodium and water delivery. Also, the underlying pathology can contribute to increased catabolism and hyperkalemia in such patients [4]. Decreased renal function leads to the increased excretion of potassium by the colon. In patients with end-stage renal failure, potassium excretion with feces is three times higher than in patients with normal renal function [2]. This allows maintaining potassium concentration in plasma within the normal range until GFR drops below 10–15 mL/min/1.73 m^2 [4].

Decreased concentration or action of mineralocorticoids reduces renal potassium secretion and leads to hyperkalemia. Aldosterone deficiency can be isolated or accompanied by decreased cortisol levels. This is observed in cases of adrenal insufficiency. Heparin also leads to a reversible disorder of adrenal aldosterone synthesis. Blockers of renin-angiotensin-aldosterone system (RAAS: direct renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, sartans, mineralocorticoid receptor antagonists, angiotensin receptor antagonists and neprilysin inhibitors (ARNI), Figure 2, Table 2) reduce aldosterone levels and can lead to hyperkalemia.

Table 2. *Potential risk factors for hyperkalemia in patients taking renin-angiotensin-aldosterone system inhibitors [3]*

Risk factors	Mechanism
Age	Disruption of renin release followed by hypoaldosteronism (hyporenemic hypoaldosteronism)
Diabetes	Diabetic nephropathy Hyporenemic hypoaldosteronism Impaired ability of cortical collective tubes to secrete potassium Insulin deficiency
Kidney pathology	Impaired ability of cortical collective tubes to secrete potassium Hyporenemic hypoaldosteronism

The syndrome of hyporeninemic hypoaldosteronism is the most common cause of hyperkalemia in patients with GFR of 40–60 mL/min/1.73 m^2 [4].

Hyperkalemia can develop at underlying interstitial kidney diseases when the distal nephron is affected. In this case, GFR decreases slightly and the level of circulating aldosterone is within normal range. After kidney transplantation, with systemic lupus erythematosus, amyloidosis, urinary tract obstruction, or sickle cell anemia, impaired renin release may be combined with impaired tubular secretion [4].

Potassium-sparing diuretics impair the ability of collecting ducts to secrete potassium. In particular, amiloride and triamterene block sodium channels and inhibit sodium reabsorption. This reduces the negative charge in the lumen of tubules and potassium secretion [4]. Trimethoprim and pentamidine have similar effects [4].

Spironolactone and eplerenone compete with aldosterone at the mineralocorticoid receptor level and may cause hyperkalemia. Drospirenone, a non-testosterone progestin derivative found in several oral contraceptives, blocks the effects of mineralocorticoids similar to spironolactone [4].

Non-steroidal anti-inflammatory drugs can cause hyperkalemia by suppressing renin release and reducing sodium delivery to the distal nephron [4].

Calcineurin inhibitors reduce potassium secretion by suppressing renin release and directly affecting renal tubules [4].

Beta-1 and, to a lesser extent, beta-2 adrenergic blockers can also lead to a hyporeninemic state and hyperkalemia [4].

Special attention should be paid to plasma potassium level monitoring when these agents are administered, especially in polypharmacy [4].

Clinical Picture

Hyperkalemia has no specific symptoms; symptoms of the underlying disease may dominate in the clinical presentation. Patients may be asymptomatic or complain of weakness, fatigue, less often—paresthesia, fasciculations of the arms and legs, muscle cramps, rarely—ascending flaccid paralysis with quadriplegia. The most life-threatening symptoms of hyperkalemia are the signs of cardiac arrhythmias and conduction disorders—palpitations, irregular heart function, dizziness, and syncope. The severity of symptoms is determined not only by the concentration, but also by the rate of potassium level buildup in plasma. First clinical manifestations can appear only in fatal increase in potassium level [4]. In rare cases, hyperkalemia is accompanied by arterial hypotension, shortness of breath, mental changes, and confusion.

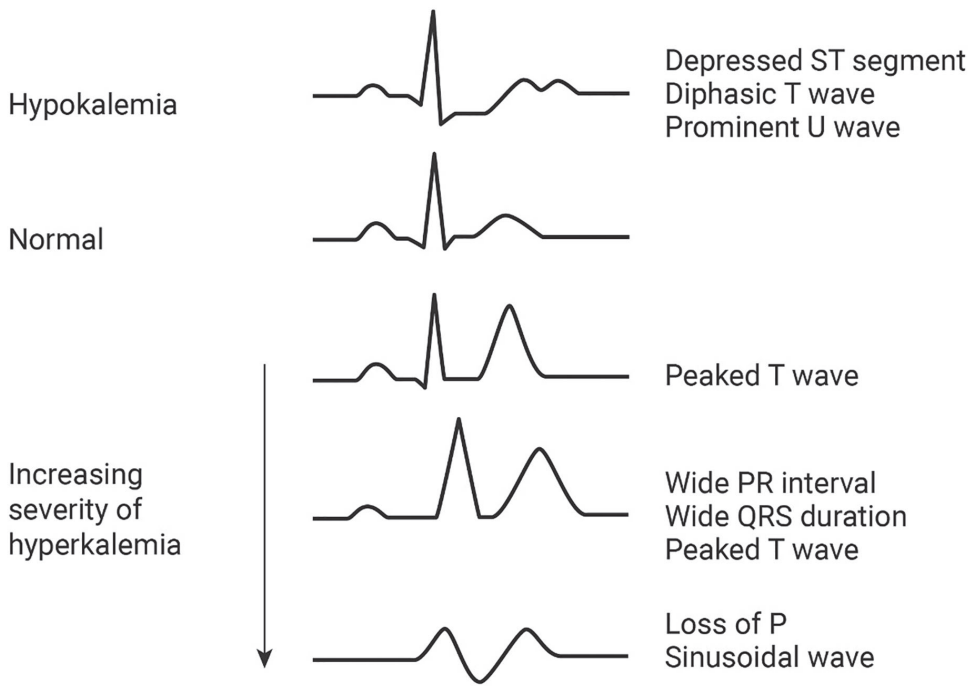

Figure 3. *Electrocardiographic signs of hyperkalemia.*
Note: The picture was kindly provided by Biff F. Palmer (Professor of Internal Medicine, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX) [4] and permitted for reproduction on conditions of the licence Creative Commons CC-BY-NC-ND

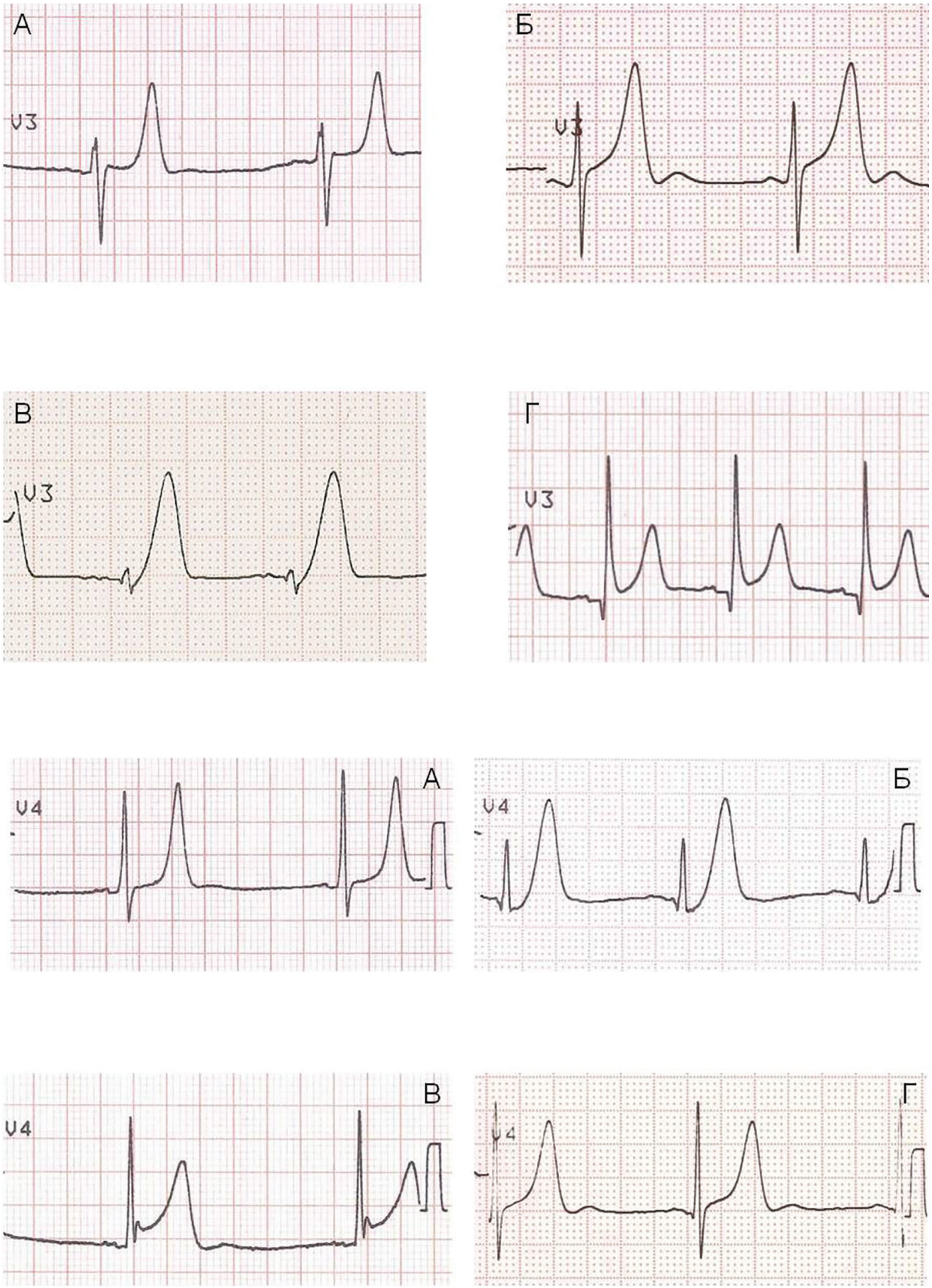

Figure 4. *T wave types in hyperkaliemia*

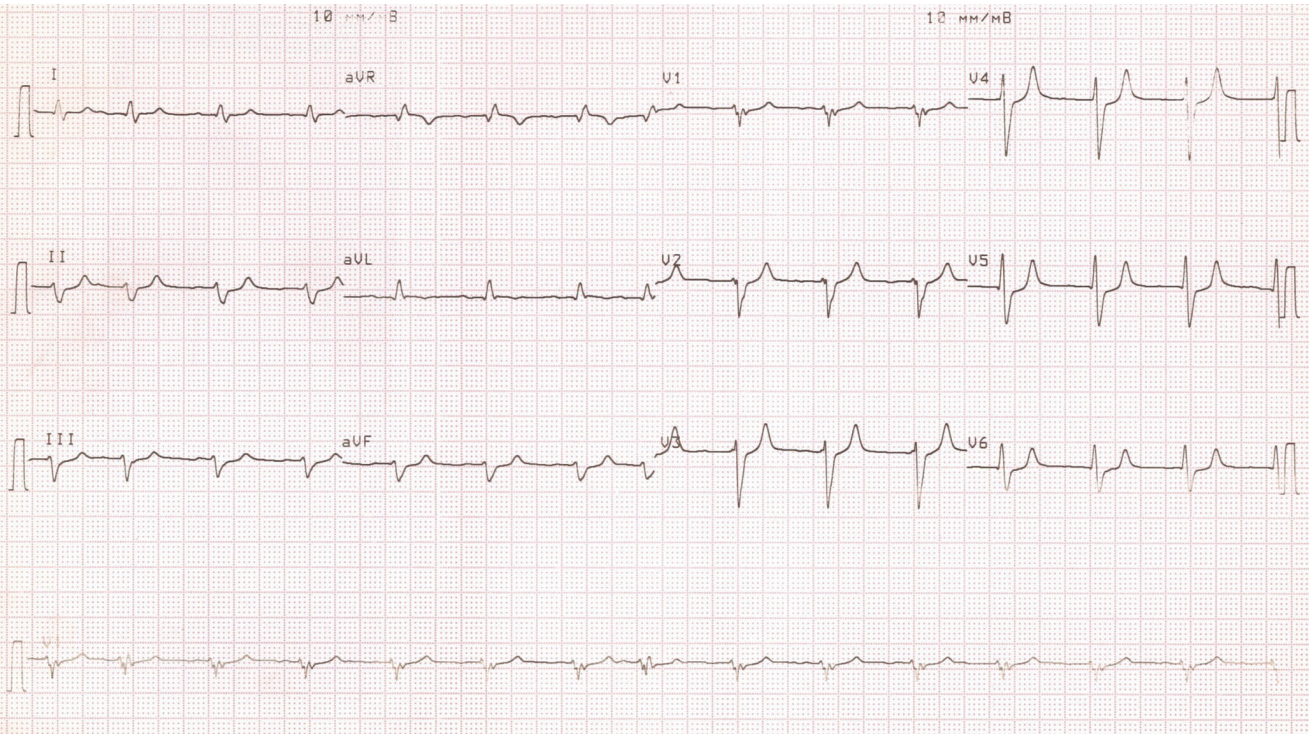

Figure 5. *ECG of 78-year old patient with acute renal injury and hyperkalemia 6,8 mmol/L. AV-block I, loss of P wave, QT 320 ms, QTc 363ms (Framingham), peaked T wave*

Diagnosis

The diagnosis of hyperkalemia requires the ongoing monitoring of blood potassium level, assessment of the renal excretion of potassium, and ECG.

Renal potassium excretion is best assessed by measuring the amount of potassium in daily urine or determining the potassium/creatinine ratio in urine. Daily potassium excretion of less than 15 mmol/L or potassium–creatinine ratio of less than 1 indicates an extrarenal cause of hypokalemia. A ratio of more than 20 corresponds to renal hyperkalemia [4].

Early ECG signs of hyperkalemia are often found in asymptomatic patients. Therefore, knowledge of the electrocardiographic manifestations of hyperkalemia becomes critical.

The severity of ECG changes depends on the potassium concentration in blood (Fig. 3). However, there is no linear dependence of electrocardiographic abnormalities on the potassium level. The ratio of cation content in the cell to extracellular fluid, the rate of transmembrane transportation of ions, not only potassium, changes in transmembrane potential due to ischemia, impaired acid-base balance, fluctuations in sympathetic tone and concentration of insulin, various medications, etc., largely determine the ECG presentation. This is also confirmed by our experience.

In case of hyperkalemia, P waves are flattened and widened, atrioventricular conduction slows down, the ventricular complex expands, and high peaked narrow T waves appear ("pinched T," Fig. 4 and 5). Such T waves are the most specific ECG changes in case of hyperkalemia and sometimes become its earliest manifestations. This form of T waves is associated with the reduction of the cardiomyocyte action potential, mainly of its second phase. This initially shortens the duration of the electrical ventricular systole, QT interval, as well as the effective refractory period, which contributes to arrhythmogenesis. With the progression of hyperkalemia, the ECG shape may resemble a sinusoid, which is a precursor of ventricular fibrillation and asystole (Fig. 6, 7, and 8).

Retrospective analysis revealed typical ECG changes only in 16 out of 90 cases of hyperkalemia. Thirteen patients demonstrated no changes in T wave. Only 1 of 14 patients with arrhythmia or asystole had ECG changes typical for hyperkalemia [4]. In cases of hyperkalemia, atrioventricular (AV) block of different degrees, paroxysmal ventricular tachycardia, ventricular fibrillation, bradycardia, and asystole can develop.

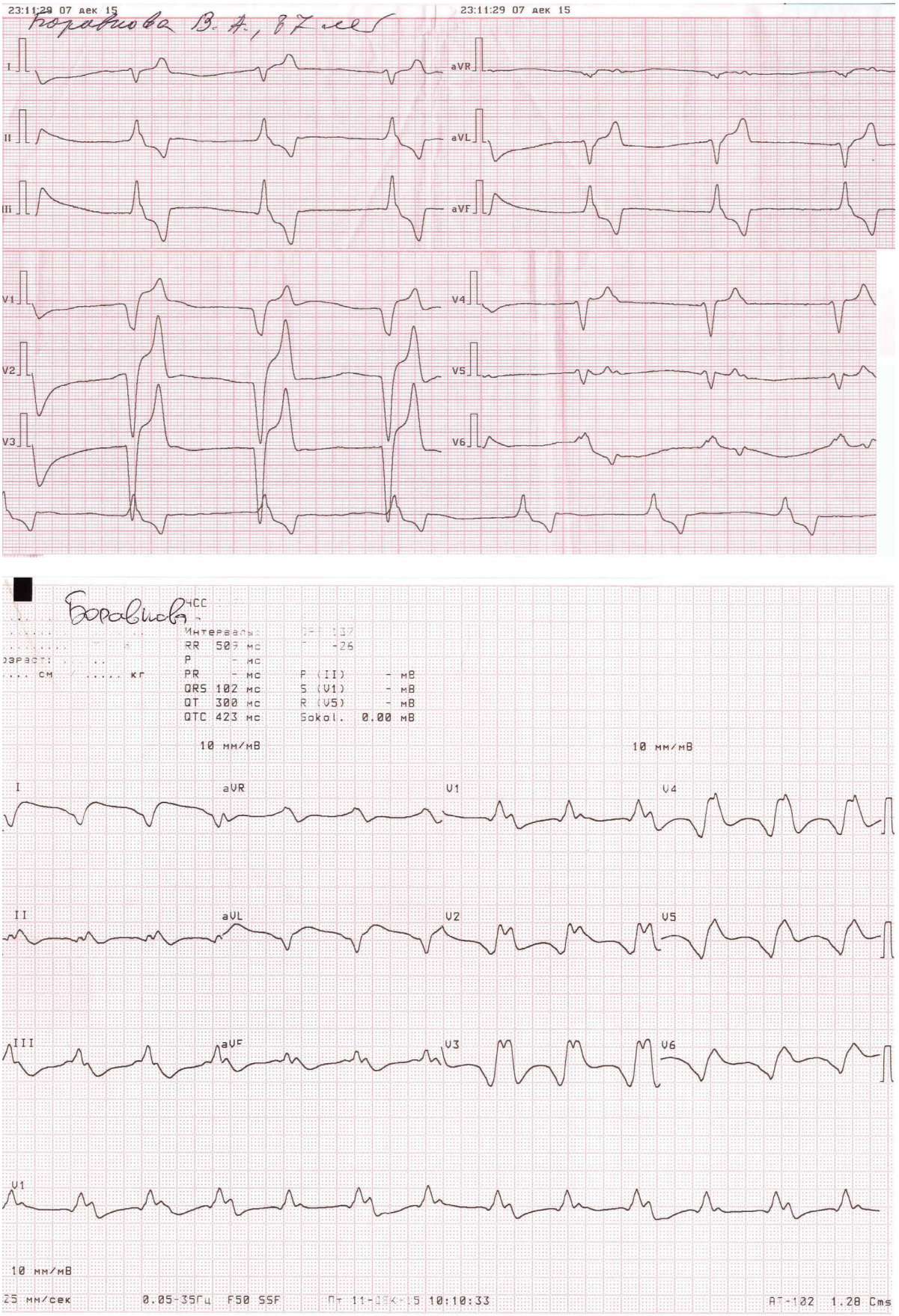

Figure 6. *ECG of 87-year old woman.*

A. *Wide QRS duration, junctional rhythm with abberant conduction and retrograde atrial excitation, hyperkalemia 8,6 mmol/L.*

Б. *Sinusoidal curve before death, potassium not determined.*

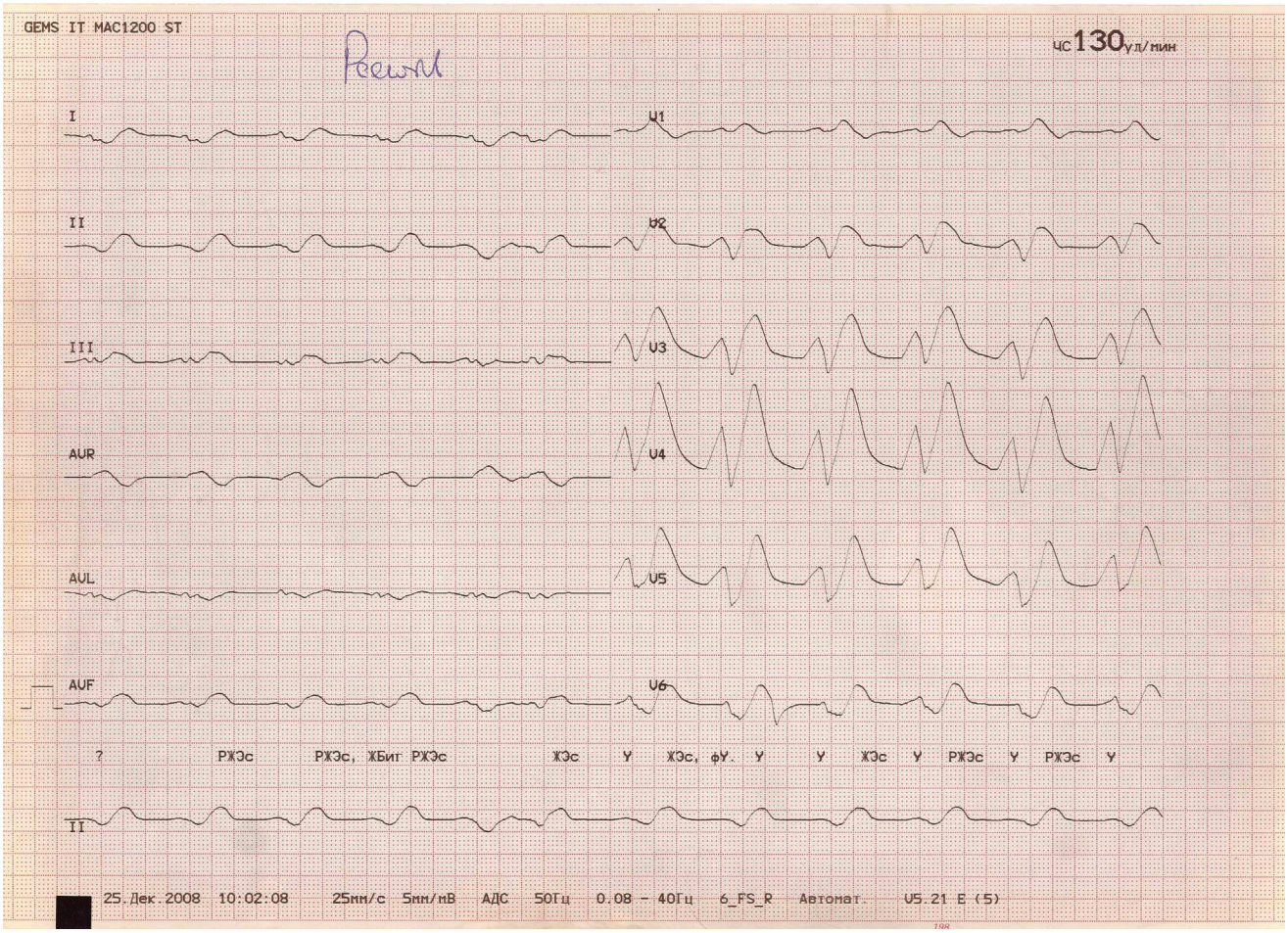

Figure 7. *ECG of a patient who died from terminal CHF (decompensation of aortic stenosis), potassium — 7.0. Sinusoidal curve*

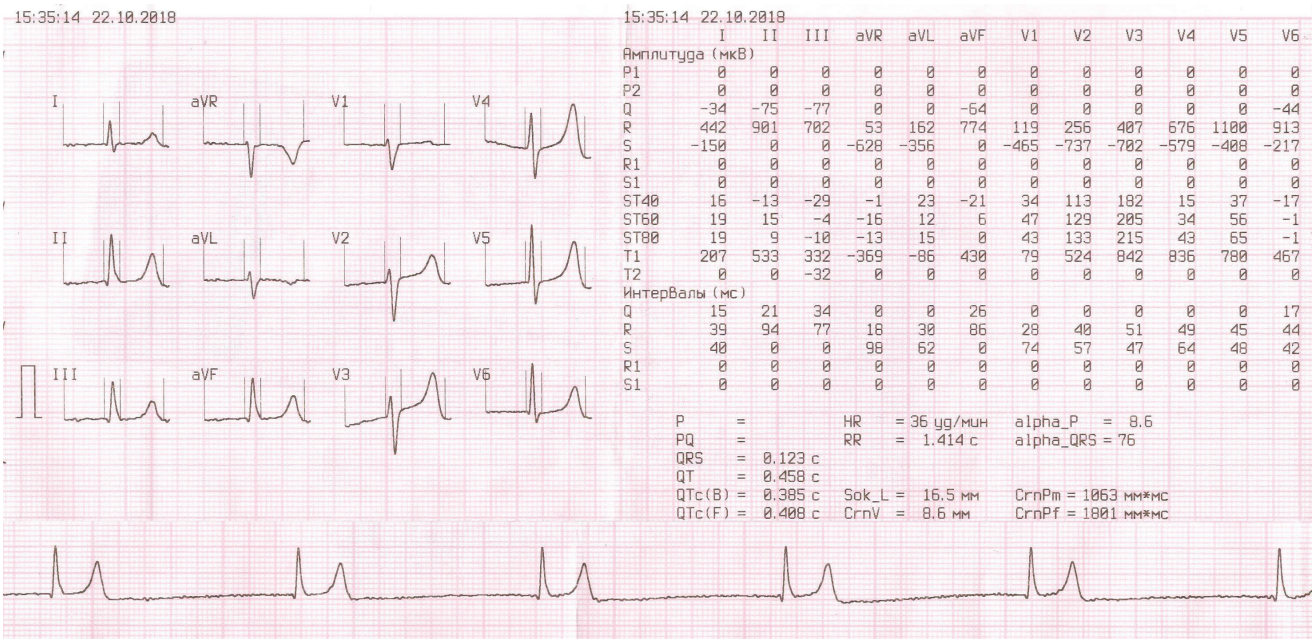

Figure 8. *ECG of a patient with hyperkalemia 7.7 mmol/L. Nodular bradycardia, tall, peacked T waves*

Table 3. *Treatment of acute and chronic hyperkalemia [2]*

Mechanism	Therapeutic approach
Promoting the transition of potassium into intracellular pro-day	Stimulation of Na/K-ATFase: Beta2 agonists (intravenously, via nebulizer) Insulin (intra-glucose) Sodium bicarbonate (in metabolic acidosis)
Heart membrane stabilizers	Calcium chloride or gluconate (intravenous) Hypertensive saline solution (3-5%)
Increased potassium withdrawal	Loop diuretics (intravenous, oral) to increase renal potassium excretion Hemodialysis Cationexchange resins (sodium polystyrolosulfonate — oral, rectal) Sodium bicarbonate alkalizes urine and increases potassium excretion with urine Patiromer Ciklosilicate sodium zirconium
Other	Fludrocortisone (oral) in aldosterone deficiency

Management of Acute Hyperkalemia

The management of hyperkalemia (Table 3) depends on the degree to which plasma potassium concentration increases, the presence or absence of ECG changes, or neuromuscular symptoms. Emergency treatment is indicated for severe ECG changes or severe muscle weakness [4].

For emergency correction of hyperkalemia, calcium chloride (3–5 mL 10% for 2 minutes) or calcium gluconate (10 mL 10% for 2 minutes) should be administered. The effect of calcium gluconate starts 1–2 minutes after administration and lasts for 30–60 minutes; if changes in ECG persist 5 minutes after administering calcium gluconate, the agent is re-administered at the same dose. Intravenous calcium quickly normalizes membrane excitability. However, it has no effect on potassium concentration in blood.

A more prolonged antihyperkalemic effect is achieved by infusing glucose solution with insulin, which should be started after calcium gluconate administration. For this purpose, 40-% glucose solution is commonly used in an amount of up to 300 mL adding 8–12 U of insulin for every 100 mL of 40-% glucose solution. The administration of glucose with insulin ensures the transfer of potassium from blood plasma into cells; its antihyperkalemic effect starts 5–10 minutes after the infusion and lasts up to 4–6 hours. Potassium concentration in blood decreases by 0.5–1.5 mmol/L within 15–30 minutes; a decrease in potassium concentration, although not so fast, is also observed with the administration of glucose only (due to the secretion of endogenous insulin).

Beta-2 adrenergic receptor agonists have a similar effect. Potassium moves into cells due to insulin and beta-2 agonists by increasing the activity of sodium-potassium ATPase, primarily of skeletal muscles [4]. For this purpose, salbutamol 10 mg through a nebulizer can be prescribed for 15 minutes every 60 minutes; its effect starts in 15–30 minutes and lasts for 2–4 hours; K^+ concentration in plasma decreases by 0.5–1.5 mmol/L. The procedure can be repeated until 20 mg of salbutamol is administered during 120 minutes. Alternatively, salbutamol 0.5–2.5 mg can be administered intravenously (except for patients with coronary heart disease) [6].

Sodium bicarbonate (NaHCO3) 1.4% or 8.4% infusion, 10–20 mEq/h with no acidosis in the patient, only slightly reduces potassium concentration in plasma. It should be prescribed to patients with severe metabolic acidosis after administration of glucose with insulin, adrenergic agents and calcium [4, 6]. Sodium bicarbonate 50 mmol IV during 15 minutes contributes to the movement of potassium into cells; it should be administered with an isotonic solution. It increases potassium excretion by the kidneys by increasing sodium delivery to collecting ducts [4].

These emergency hyperkalemia correction methods should be accompanied by treatment aimed at reducing the amount of potassium in the body, including the administration of diuretics and potassium-binding agents [4]. For patients with hypervolemia, it is recommended to administer furosemide (1 mg/kg of body weight as an IV push (up to 80 mg), then 10–20 mg/h as a continuous infusion) and thiazides or thiazide-like diuretics (for example, metolazone 5–10 mg orally) [6].

Hemodialysis is the fastest and most effective way to reduce K^+ concentration in plasma; it is indicated when other procedures have no effect.

Management of Chronic Hyperkalemia

If hyperkalemia is detected, treatment should be revised first, and agents that may contribute to hyperkalemia should be excluded [4].

Diet (Table 4). Patients should be advised to reduce their dietary potassium intake and avoid potassium-containing salt substitutes and herbs that might increase potassium levels. In the early stages of CKD, potassium restriction to 4.7 g/day is required to prevent hyperkalemia. In serum potassium level > 5.3 mmol/L, potassium intake should be limited to 2–3 g/day [1].

Diuretic therapy is efficient in minimizing the risk of hyperkalemia in patients with CKD. Thiazide and loop diuretics increase potassium excretion by increasing sodium delivery to collecting ducts. Thiazide diuretics should only be given for GFR > 30 mL/min/1.73 m^2 [4].

Sodium polystyrene sulfonate (SPS) is a cation-exchange resin that binds potassium in the gastrointestinal tract in exchange for sodium (1 g of the agent binds 1 mmol K^+) and is used to manage hyperkalemia. This agent is most often prescribed with sorbitol for the management of acute hyperkalemia. Despite that this agent is widely used, its potassium-lowering effect in most cases is due to the increased stool volume caused by sorbitol [4]. Long-term use of the agent is poorly tolerated due to the development of constipation, diarrhea, hypernatremia, hypokalemia, hypocalcemia, or hypomagnesemia. Long-term use should be avoided due to possible gastrointestinal (GI) adverse effects such as colon necrosis [1]. No rigorous placebo-controlled studies of this agent were performed. Since sodium is an anti-exchange ion when administering SPS, this agent should be prescribed with caution in case of HF, arterial hypertension, edemas [2].

Calcium polystyrene sulfonate (CPS, Veltassa VR) has a number of advantages over SPS because it binds potassium in the distal colon in exchange for calcium and does not cause sodium retention. Like for SPS, long-term efficacy and safety data for this agent are scarce [1].

Patiromer and sodium zirconium cyclosilicate are two new potassium-binding agents that have proved effective in lowering plasma potassium concentrations along with the continued use of RAAS blockers (Table 5).

Patiromer is a non-absorbable polymer approved for clinical use in the management of hyperkalemia.

Table 4. *Approaches to the treatment of chronic hyperkalemia*

Approach to treatment	Diet	Sodium (SPS) and calcium polystyrene sulfonate (CPS)-non-selective cation — exchange resins	Increased urinary K excretion	Increased urinary K excretion
Mechanism of sK decreas	Restricted intake of K-rich foods	Increased fecal K excretion	Increased urinary K excretion	Increased potassium levels in urine
Efficiency	Variable, depending on prescription and patient compliance	Can decrease sK concentration by 0.7–1.1 mEq/L	Variable, depending on dose and state of effective arterial blood volume	Withdrawal can decrease sK concentra-tion by 0.2–0.5 mEq/L
Side effects/ tolerability	Poor patient compliance in the long term, due to difficult preparation and poor palatability	Bind calcium and magnesium May cause hypomagnesemia, hypocalcemia and sodium overload GI side effects (constipation, nausea) FDA warning for the risk of colonic necrosis (SPS)	May cause further deterioration of kidney function due to volume depletion May cause/worsen electrolyte and acid–base disorders (e.g. hyponatremia, hypomagnesemia, metabolic alkalosis)	-
Limitations	Need for skilled health professionals (renal dietician) May interfere with the prescription of protein-restricted diet in advanced CKD	Poor tolerability and adhernce due to GI side effects Slow effect onset	Inappropriate in the absence of fluid overload May be poorly effective in advanced stage of CKD	Dose reduction or withdrawal reduce renal and cardiovascular benefits of treatment

Table 5. *Characterization of K-binding agents for the treatment of hyperkalemia [8]*

Drug	SPS	Patiromer	Sodium zirconium cyclosilicate
Type of molecule	Non-specific cation binding, sodium-containing organic resin	Selective, calcium-containing sodium-free, organic polymer	Highly selective, sodium- and zirconium-containing, inorganic crystalline silicate
Mechanism of action	Non-specific binding of K in exchange for sodium	Non-specific binding of K in exchange for calcium	Selective K binding in exchange for Sodium or Hydrogen
Linked cations	Potassium, magnesium, calcium	Potassium, magnesium	Potassium
Route of administration/ formulation	Oral or rectal suspension	Oral suspension	Oral suspension
Site of action	Colon	Dystal colon	Entire intestinal tract
Onset of effect	1–6 h	4-7 h	1–6 h
Duration	Variable, 4-6-24 hours	12-24 hours	Unclear
Dosing	15–60 g/day orally in 100 ml 20% sorbitol solution — to prevent constipation); 30-50 g/day rectally (50 ml 70% sorbitol solution, 150 ml water); Up to 4 receptions per day	8.4-25.2 g/day once	Initial dose: 10 grams 3 times a day for 48 hours, supportive — 5-15 g/day
Destination features	Separate from the appointment of other oral drugs: 3 hours before or 3 hours after; gastroparares — 6 hours	Separate from the prescribing of other oral drugs: 3 hours before or 3 hours after	Separate from the prescribing of other oral drugs with clinically significant pH-dependent bioavailability: 2 hours before or 2 hours after
Most common adverse events	Gastrointestinal intolerance Hypokalemia Hypernatremia Hypocalcemia Volume overload Colonic necrosis	Gastrointestinal intolerance Hypokalemia Hypomagnesemia	Gastrointestinal intolerance Hypokalemia Oedema
Serious adverse events	Colon necrosis	None	None

This medication binds potassium in exchange for calcium in the gastrointestinal tract, mainly in the distal colon, and increases potassium excretion with feces [1]. It reduces plasma potassium concentration in a dose-dependent manner, with maximum decrease observed in patients with higher baseline values. Patiromer demonstrated effective control of plasma potassium concentrations in a one-year randomized study in high-risk patients taking RAAS blockers. Common adverse events observed during clinical trials were constipation and hypomagnesemia, which required correction of magnesium levels in several patients. However, this medication was well tolerated overall [4, 7].

Sodium zirconium cyclosilicate (SZC, ZS-9, Lokelma) is a non-absorbable microporous inorganic compound that does not adsorb and binds potassium in exchange for sodium throughout the gastrointestinal tract. It was shown to be effective in lowering plasma potassium concentration in a dose-dependent manner in high-risk patients, most of whom received RAAS blockers. Adverse events observed during clinical trials were generally comparable to the placebo; however, edema developed more frequently with higher doses. This is because the agent contains a large amount of sodium—800 mg in a 10 g dose [1, 4].

Prevention of Hyperkalemia in Patients Receiving RAAS Blockers

In patients with arterial hypertension with no risk factors, the incidence of hyperkalemia along with monotherapy with a RAAS blocker is ≤ 2%; it increases to 5% along with a two-component RAAS blockade, and up to 5–10% with a two-component RAAS blockade prescribed in patients with HF or CKD. In the RALES study, hyperkalemia developed in 13.5% and 40% of patients receiving 25 mg and 50 mg of spironolactone, respectively. This suggests that limiting the dose to 25 mg per day may reduce the risk of hyperkalemia. In actual clinical practice, the incidence of hyperkalemia during

treatment with mineralocorticoid receptor antagonists (MCRA) is 6–12% in cases of chronic HF with reduced left ventricular ejection fraction; sometimes, it reaches 50% [2]. Interestingly, during treatment with RAAS blockers, hyperkalemia develops even in patients with anuria who are on long-term hemodialysis, probably due to decreased gastrointestinal excretion [5]. Hyperkalemia was the reason why ACE/ARA and MCRA inhibitors were not administered in 8.5% and 35.1%, respectively [2].

In the PARADIGM-HF study in patients receiving MCRA, the incidence of hyperkalemia demonstrated no differences between the enalapril group and the sacubitril/valsartan group. However, severe hyperkalemia was more common in the enalapril group (3.1–3.3 vs 2.2 per 100 patient-years) [9].

To reduce the risk of hyperkalemia with underlying intake of agents blocking RAAS, treatment should be started with low doses and potassium level should be monitored after 1–2 weeks from the start / dose titration. If potassium concentration in the blood is higher than 5.5 mmol/L, despite the above precautions, the use of a potassium binder can be considered before discontinuing agents that block RAAS [4]. Some guidelines recommend prescribing a K-lowering agent for potassium levels > 5.0 mmol/L (Table 6). If it is ineffective, the dose of the RAAS inhibitor should be reduced or withdrawn [1]. Mortality in patients with CKD, HF, and type 2 DM is minimal at serum potassium values of 4.0–4.5 mmol/L and significantly increases at values > 5.0 mmol/L and < 4.0 mmol/L [1]. In accordance with the European Society of Cardiology (ESC) guidelines for the management of patients with HF, low-dose MCRA followed by titration should be started in patients with serum potassium level < 5.0 mmol/L. If potassium level increases > 5.5 mmol/L, the MCRA dose should be halved; if it is > 6.0 mmol/L, MCRA should be immediately withdrawn [10]. Serum potassium and creatinine levels should be monitored 1 and 4 weeks after treatment start/ dose increase, then after 8 and 12 weeks, 6, 9, and 12 months, then once every 4 months. The recommended potassium level during treatment with ACE inhibitors and sartans, when the patient should consult a specialist, is > 5.0 mmol/L; drug withdrawal is recommended when serum potassium increases > 5.5 mmol/L [1, 10].

A recent consensus published by the ESC Working Group on Cardiovascular Pharmacotherapy recommends a diet with reduced potassium intake and a higher dose of non-potassium-sparing diuretics for the prevention and management of hyperkalemia. Treatment with approved potassium binders is recommended when the potassium level rises above 5.0 mmol/L in patients taking targeted doses of RAAS blockers to continue this life-saving treatment. Potassium binders can be started earlier, at potassium level < 5.0 mmol/L, to allow titration of doses of RAAS blockers to target or maximum tolerated doses. Preference should be given to patiromer and sodium zirconium cyclosilicate, although there are no data on their efficacy and safety in administration for more than 12 months [2]. A secondary analysis performed

Table 6. *Existing recommendations on renin-angiotensin-aldosterone system inhibitors use according to K+ levels*

K^+ level, mmol/L	Recommendation
>6	Stop RAASi (ESC HF, ESC CVPT, NICE)
>5,5	Reducing the dose of/stop ACE/ARA inhibitors (K/DOQI)
5,0-5,5	K/DOQI :take measures to lower K+ when initiating RAASi
>5	Do not start RAASi if >5,0 (K/DOQI, HFSA HF, NICE) Reduce dose of/stop RAASi>5,0 (ACCF/AHA HF, ESC HF, K/DOQI) MRA not recommended if >5,0 (HFSA HF) Maintain MRA between 4,0-5,0 (ACA/AHA) Do not routinely offer a RAASi to people with CKD in their pre-treatment K+ levels are >5,0 mmol/L A K+ lowering agent should be started
4,5-5,0	In patients not on maximal guideline-recommended target dose of RAASI therapy, it is recommended to up-titrate/start RAASi therapy and closely monitor Kю levels.

Note: ACA — American College of Cardiology, AHA — American Heart Association, ESC — European Society of Cardiology, CKD — chronic kidney disease, ESC CVPH — the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology, ESC HF — Heart Failure Association of the European Society of Cardiology, HF — Heart Failure, HFSA HF — heart failure Society of America, K/DOQI — Kidney Disease Outcomes Quality Initiative, NICE — National Institute for Health and Care Excellence, RAASi — renin angiotensin aldosterone system inhibitor; ARB — angiotensin II receptor blocker; K^+ — potassium; MRA — mineralocorticoid receptor antagonists

in the Randomized Aldactone Evaluation Study and EMPHASIS-HF study demonstrated a beneficial effect of MCRA on cardiovascular outcomes in HF patients with serum potassium level 5.0–5.5 and > 5.5 mmol/L [11–13]. However, the main clinical trials of MCRA in cases of HF did not include patients with serum potassium level > 5.0 mmol/L and creatinine level > 2.5 mg/dL or GFR < 30 mL/min/1.73 m^2 [1]. According to the Italian Society of Nephrology, serum potassium level > 5.0 mmol/L with underlying CKD is considered abnormal and requires careful monitoring and preventive and therapeutic approaches aimed at maintaining potassium levels in the range of 4.0–4.5 mmol/L [6].

Conclusion

Hyperkalemia is a common and serious disease, especially in the management of patients with CKD, DM, HF, and cardiorenal syndrome of different types [14, 15]. Previously, withdrawal of RAAS blockers was the main strategy for preventing/correcting hyperkalemia. Other approaches to preventing or managing chronic hyperkalemia are associated with low adherence (diet), unfavorable efficacy and safety profile (SPS), and potential adverse effects (intensive treatment with diuretics). Patiromer and sodium zirconium cyclosilicate are the new effective and well-tolerated agents for the long-term treatment of patients with hyperkalemia or at risk of its development. They may allow wider use of RAAS blockers at recommended doses in patients with CKD, DM, and HF and may delay the start of renal replacement therapy required due to the development of hyperkalemia in patients with end-stage renal disease.

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ПЕРИОПЕРАЦИОННОЕ ВЕДЕНИЕ ПАЦИЕНТОВ С РЕВМАТОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ: РЕКОМЕНДАЦИИ ПО ПРИМЕНЕНИЮ ГЛЮКОКОРТИКОСТЕРОИДОВ, БОЛЕЗНЬ-МОДИФИЦИРУЮЩИХ АНТИРЕВМАТИЧЕСКИХ ПРЕПАРАТОВ, ГЕННО-ИНЖЕНЕРНЫХ БИОЛОГИЧЕСКИХ ПРЕПАРАТОВ, НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ ПРЕПАРАТОВ

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Perioperative Management of Patients with Rheumatic Diseases: DMARDs, Biological Agents, Steroids, and NSAIDs

Резюме

Пациенты с ревматологическими заболеваниями характеризуются рядом особенностей, которые необходимо учитывать в процессе периоперационного ведения. В частности, ревматологические заболевания приводят к двигательным ограничениям, нарушению структуры и снижению функции многих органов и систем, необходимости постоянного приёма иммуносупрессивных и других лекарственных средств. В связи с этим у пациентов отмечается повышенный риск разнообразных интраоперационных и послеоперационных осложнений.

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Целью данной публикации является рассмотрение современных рекомендаций по периоперационному ведению пациентов с ревматологическими заболеваниями. В данной публикации рассматривается один из наиболее сложных вопросов — периоперационное применение лекарственных препаратов: глюкокортикостероидов, базисных болезнь-модифицирующих антиревматических препаратов, генно-инженерных биологических препаратов и нестероидных противовоспалительных препаратов.

Ключевые слова: *ревматоидный артрит, периоперационное ведение, базисные болезнь-модифицирующие антиревматические препараты, БМАРП, метотрексат, генно-инженерные биологические препараты, системная красная волчанка, глюкокортикостероиды, ГКС*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The rheumatic patients are characterized by various structural and functional changes, caused by chronic disease, the necessity of constant medication intake, including anti-inflammatory drugs and immunosuppressants. In this regard, the rheumatic patients have an increased risk of intraoperative and postoperative complications. The purpose of this publication is to review current recommendations on the topic of perioperative management of rheumatic patients. The publication consists of two parts. In the first part we review the issues of perioperative administration of disease-modifying antirheumatic drugs, biologics, steroids, and nonsteroidal anti-inflammatory drugs.

Key words: *rheumatoid arthritis, perioperative management, perioperative care, disease-modifying anti-rheumatic drug, methotrexate, biological agents, systemic lupus erythematosus, glucocorticoids, surgical intervention, NSAIDs*

Conflict of interests

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AAHKS — American Association of Hip and Knee Surgeons, ACR — American College of Rheumatology, ACTH — adrenocorticotropic hormone, AI — adrenal insufficiency, COX — cyclooxygenase, DMARDs — disease modifying anti-rheumatic drugs, GC activity — glucocorticoid potency of steroids, HPAA — hypothalamic-pituitary-adrenal axis, IRD — inflammatory rheumatic diseases, IV — intravenous, MC activity — mineralocorticoid potency of steroids, NSAIDs — non-steroid anti-inflammatory drugs, OR — operating room, PDE-4 — phosphodiesterase-4, PO — peroral, RD — rheumatic diseases, SLE — systemic lupus erythematosus, SQ — subcutaneous, TNF — tumor necrosis factor, WBC — white blood cells, WHO — world health organisation

Introduction

Rheumatic Diseases (RD) are characterized by chronic course and systemic involvement, leading to significant structural alterations and functional deficiency in many organs. The treatment of RD includes long-term use of various anti-inflammatory agents and immunosuppressants such as non-steroidal anti-inflammatory drugs (NSAIDs), steroids, disease-modifying anti-rheumatic drugs (DMARDs) and biological agents. Both the impact of the disease itself and the adverse effects of medications result in an increased risk of infectious and cardiovascular complications in rheumatic patients. This has to be considered perioperatively.

Well before the elective surgery, the RD patients should be carefully assessed by rheumatologist in regard to the disease activity and organ involvement, which may affect the course of the surgical procedure and postoperative recovery. It is recommended to schedule the operation for the period of remission or minimal activity of the disease. If necessary, the doses of constant medications should be adjusted. Cardiovascular and thrombo-

Table 1. *Guideline for the perioperative use of antirheumatic drugs [1]*

DMARDs: CONTINUE these medications through	**Dosing interval**	**Continue/withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGIC AGENTS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.	**Dosing interval**	**Schedule Surgery (relative to last biologic agent dose administered) during**
Adalimumab	Weekly or every 2 weeks	Week 2 or 3
Etanercept	Weekly or twice weekly	Week 2
Golimumab	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab	Every 2 or 4 weeks	Week 3 or 5
Rituximab	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra	Daily	Day 2
Secukinumab	Every 4 weeks	Week 5
Ustekinumab	Every 12 weeks	Week 13
Belimumab	Every 4 weeks	Week 5
Tofacitinib: STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing interval**	**Continue/withhold**
Mycophenolate mofetil	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications 1 week prior to surgery	**Dosing interval**	**Continue/withhold**
Mycophenolate mofetil	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Withhold

embolic risk management as well as infectious complications prevention in RD patients are implemented within the framework of generally accepted guidelines. Besides, there are special recommendations for certain types of operations and certain diseases.

In case of an emergency operation, the perioperative management should be considered individually on the basis of available guidelines.

The literature review consists of two parts. This part highlights the issues of perioperative use of DMARDs, biologics, steroids and NSAIDs.

DMARDs and biologics

The most detailed information on perioperative use of DMARDs is presented in the guidelines of the American College of Rheumatology [1]. The summary is given in Table 1 and illustrated by schemes 1 and 2. The guidelines relate to the knee and hip joint replacement surgery in patients with rheumatoid arthritis, seronegative spondyloarthritis and systemic lupus erythematosus (SLE) and thus may well be extrapolated to other major operations in RD patients.

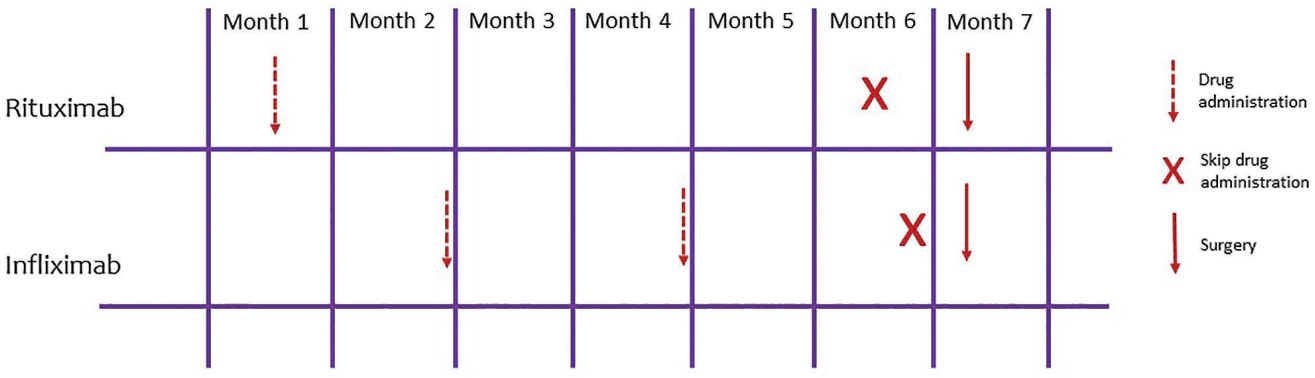
Following from Table 1, it is not required to withdraw the DMARDs perioperatively. In the case of mild SLE however, it is recommended to stop DMARDs a week before surgery.

The administration of biologics should be discontinued prior to the surgery and the procedure should be scheduled for the end of the dosing cycle of a particular drug [2]. This recommendation is internationally agreed on [3]. The temporary withdrawal of the biologics aims to reduce the risk of infectious complications [4, 5], as the avoidance of postoperative infection is more important for the RD patients than the potential exacerbation of their disease [1]. In addition, it is known that 5 half-life periods are necessary for the complete elimination of the drugs [3]. Given the comparatively short period of perioperative pausing, the risk of exacerbation is very low.

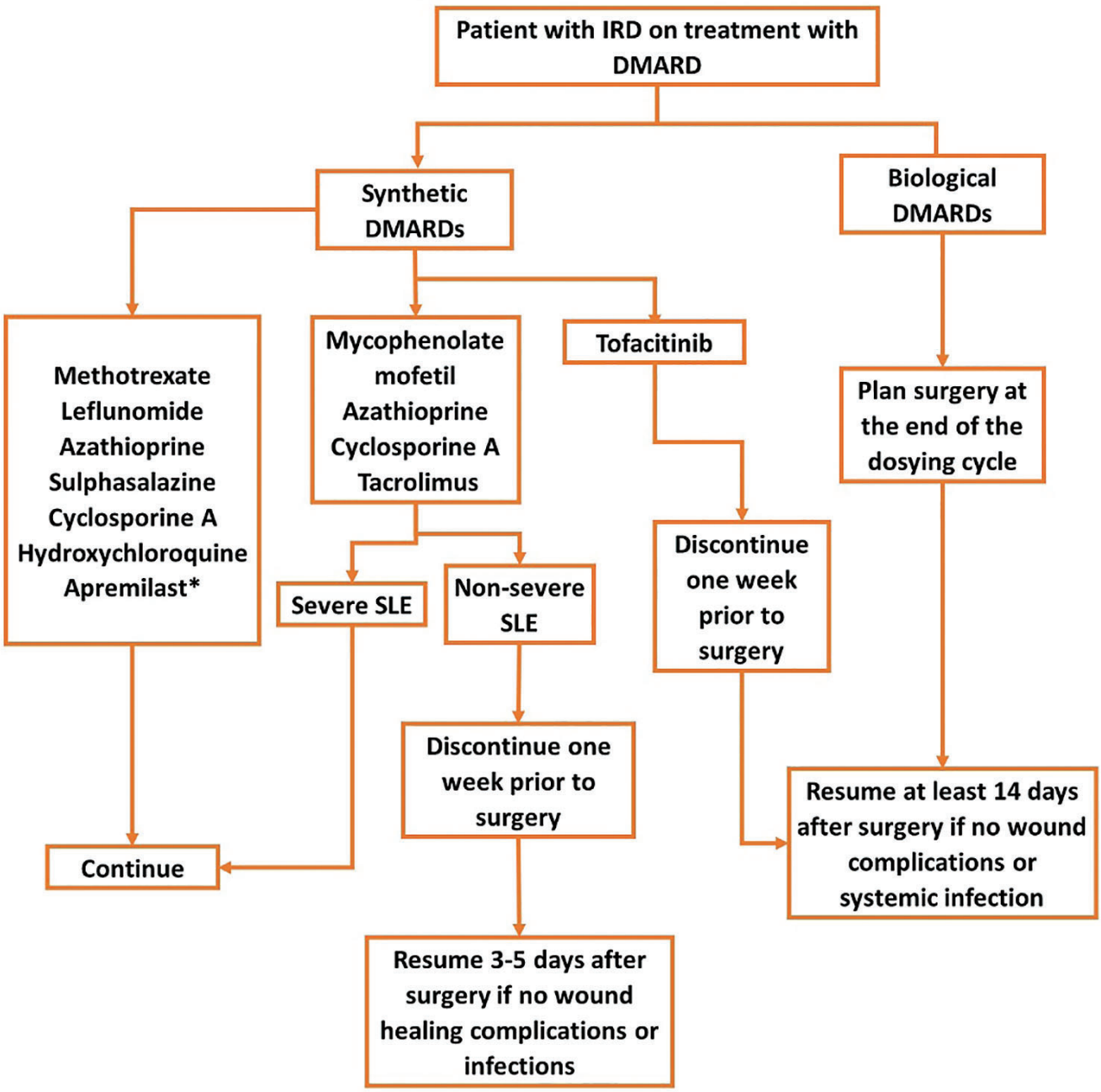
The timing of preoperative withdrawal of biologics is based on the cycle of their dosing, rather than their half-life period. This is justified by the fact that the half-life period of biologics may not correspond to the duration of their immunosuppressive effect. Moreover, the duration has not been established for some of them. In this regard, the dosing cycle was chosen as a more reliable criterion for determining the pausing interval [1].

The perioperative dosing of biologics is illustrated in Scheme 1 by the examples of rituximab and infliximab. In patients receiving rituximab every 6 months, the surgery has to be scheduled on the week following the missed dose (i.e., the second week of the seventh month, or during the seventh month). In patients receiving infliximab every 8 weeks the operation has to be scheduled on the 9th week after the last injection. In case of adalimumab — on the 3rd week and belimumab — on the 5th week. [1]

Resuming the normal medication after the surgery is recommended in the healing stage of the wound (which usually occurs 14 days after surgery) and in the absence of any signs of infection and inflammation of the wound. Besides, the renal and hepatic functions should be sufficient [1]. Resuming the treatment in RD patients should be considered individually, based off the condition of the wound and the general condition of the patient.



Scheme 1. *Biological agents withdrawal on the example of rituximab and infliximab (author's illustration)*



Scheme 2. *The use of DMARDs in the perioperative period [2]*

Note: IRD — Inflammatory rheumatic diseases
DMARD — disease-modifying anti-rheumatic drugs
SLE — systemic lupus erythematosus
*No evidence, in high-risk patients suspend 3 days before surgery

In addition to the general guidelines on the resumption of the drugs, there are particular recommendations for some biologics. For tumor necrosis factor (TNF) inhibitors and rituximab the recommended time of resumption is 4 weeks after surgery, while tocilizumab can be continued immediately after surgery, provided that the wound healing process is normal and there are no infections [3].

Currently, there are no guidelines for the perioperative administration of apremilast (a PDE-4 inhibitor), which is used for the treatment of psoriatic arthritis. There is evidence that this is a generally safe drug characterized by the low risk of infectious complications. In high risk patients however, apremilast may be discontinued 3 days before surgery, based on its half-life period [2].

There are some specific recommendations for perioperative management in SLE (see Scheme 2).

According to American College of Rheumatology/ American Association of Hip and Knee Surgeons (ACR/ AAHKS) guidelines, the patients with severe and non-severe forms of SLE should be distinguished [2].

The severe SLE implies that the patient has the most severe involvement of the organs such as the skin syndrome, central nervous system involvement, hemolytic anemia, thrombocytopenia, vasculitis (except for mild cutaneous vasculitis), myocarditis, pneumonitis, myositis (including oculomotor muscle myositis), enteropathy, lupus pancreatitis, cholecystitis or hepatitis, severe keratitis, posterior severe uveitis/retinal vasculitis and optic neuritis [6].

In patients with severe SLE it is recommended to continue the normal dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus perioperatively, since the risk of exacerbation exceeds the risk of infectious complications. The ACR/AAHKS group also recognizes however the importance of making decisions on a case-by-case basis.

In mild SLE, it is recommended to stop the normal dose of mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus treatments 1 week before surgery in order to restore the immune response. These drugs should be resumed 3-5 days after the operation, provided that the wound healing process is normal and there are no infections. [1]

Steroids

1. *General information*

The basic secretion of adrenal glands is equivalent to 20-30 mg of cortisol a day (5-7.5 mg of prednisone). With high level stress, such as major surgery under general anesthesia, this amount increases tenfold, up to 200-300 mg of cortisol (50-75 mg of prednisone). Usually, the peak of cortisol levels is observed within 24 hours after surgery and returns to normal after 72 hours [9].

Steroid intake can affect the normal function of the hypothalamic-pituitary-adrenal system and suppress the endogenous production of cortisol. This can result in adrenal insufficiency (AI) which means a lack of cortisol secretion under stress and the inability to adequately maintain physiological functions, such as vascular tone and blood pressure. The risk of AI justifies the supraphysiological dosing of steroids in the perioperative period (aka stress dosing). The use of 300 mg of hydrocortisone daily for several days has become a common perioperative practice for patients receiving steroid therapy [7].

The contemporary understanding however states that the perioperative dosage of steroids should be considered on a case-by-case basis. The decision should be based on steroid intake history, hypothalamic- pituitary-adrenal axis (HPAA) function, as well as the type and duration of the surgery. In addition, it is necessary to take into account whether etomidate will be used for anesthesia (currently not registered in Russia) [7].

2. *Assessment of the patient's steroid status*

Based off the history of steroid intake the patients are viewed in three distinctive categories. The first group includes the patients with low risk of HPAA suppression and AI. The second group is characterized by the high risk of AI. The third group involves the patients with intermediate risk and several special subgroups.

Group 1. Low risk of AI; suppression of HPAA is not expected in the following cases [7]:

- **a.** Intake of any dose of steroids in the past for less than three weeks
- **b.** Morning intake of less than 5 mg a day of prednisone or its equivalent for any period of time in the past
- **c.** Current intake of less than 10 mg of prednisone or its equivalent every other day.

The patients of the low-risk group do not require any additional administration of steroids perioperatively. This means that they either do not need steroids at all (as for 1a and 1b), or they should continue taking

Table 2. *Perioperative use of stress doses of glucocorticoids [9]*

Level of surgical Stress	Surgical procedure	Stress-dose steroids
Superficial procedure	Skin biopsy	Continue daily dose of corticosteroids.
Minor	· Procedures under local anesthesia and <1 hour; · colonoscopy; · cataract surgery; · carpal tunnel release; · tenosynovectomy; · knee arthroscopy; · most minor podiatry/orthopedic foot procedures (hammer toe correction, toe fusion).	Continue daily dose of corticosteroids Hydrocortisone on call to OR for urgent use if necessary.
Moderate	· unilateral total joint replacement; · complex foot reconstruction; · lower extremity vascular surgery; · uncomplicated appendectomy; · gallbladder removal.	Hydrocortisone 50–100 mg IV intraoperatively in OR, then 50 mg IV every 8 hours for 24 hours. On the second postoperative day, hydrocortisone may be tapered over an additional 24 hours or preoperative daily oral dosing may be resumed.
Major	· multiple trauma; · colon resection; · bilateral joint replacement; · revision arthroplasty; · multiple level spinal fusion; · any surgery requiring cardiopulmonary bypass.	Hydrocortisone 100 mg IV intraoperatively in OR, then 100 mg IV every 8 hours for 24 hours, then 50 mg IV every 8 hours for the next 24 hours, then resume the preoperative daily dose on third postoperative day.

Note: OR — operating room, IV — intravenous

Table 3. *Comparative activity of glucocorticoids for systemic administration*

Steroids	Equivalent doses (mg)	GC* potency	MC** potency	Half-life	
				serum (minutes)	tissue (days)
Short-acting (8–12 hours):					
Hydrocortisone	20	1	1	90	0,5
Cortisone	25	0,8	1	30	0,5
Intermediate-acting (12–36 hours):					
Prednisolone	5	4	0,8	200	0,5-1,5
Prednisone	5	4	0,8	60	0,5-1,5
Methylprednisolone	4	5	0,5	200	0,5-1,5
Long-acting (36–72 hours):					
Triamcinolone	4	5	-	> 200	1-2
Dexamethasone	0,75	30	-	> 300	1,5-3
Betamethasone	0,75	30	-	> 300	1,5-3

Note: *GC activity — glucocorticoid potency of steroids, **MC activity — mineralocorticoid potency of steroids

their usual dose. The HPAA function test is not advised in these patients, since it does not predict the development of AI after surgery [8]. During the operation, the low-risk patients require standard hemodynamic monitoring.

Group 2. High risk of AI; suppression of the HPAA function is assumed in the following cases:

a. Current intake of prednisolone is 20 mg daily (or equivalent) for more than three weeks

b. Current steroid intake accompanied by Cushing's syndrome.

Patients with high risk require additional doses of steroids perioperatively in accordance with the type of operation (Table 2):

Besides the low and high-risk groups, there are also special categories of patients with a history of steroid intake.

Group 3. Special groups of patients with a history of steroids intake

a. Patients in whom it is impossible to judge the HPAA function confidently (so called "intermediate risk") [7]:

In patients who have been taking 5 to 20 mg/day of prednisone (or equivalent) for more than three weeks, the HPAA function varies significantly. This variability is possibly related to differences in the metabolising rate of steroids.

In addition, doses lower than the equivalent of 5 mg/day of prednisone taken in the evening can disrupt normal daily fluctuations of steroids and distort the patient's response to surgical stress [10].

It is recommended to assess the HPAA in the patients of the "intermediate group" (See "Assessment of the HPAA")

b. Patients who stopped taking steroids less than a year before surgery

The full recovery of HPAA takes one year. In this regard, the perioperative steroid administration in these patients should be based off the same rules as for the high, low and intermediate groups.

c. Patients who receive inhaled or topical steroids

Long-term use of inhaled or topical steroids can potentially cause suppression of HPAA, although it rarely results in AI [11]. The degree of HPAA suppression depends on the class of activity, dose, duration, frequency and time of administration of steroids.

It is recommended to evaluate the adrenal function preoperatively in patients with the following history:

- ≥ 750 mcg/day of fluticasone (≥1500 mcg/day for other inhaled steroids) for more than three weeks before surgery;
- ≥ 2 g/day of topical steroids with high or ultra-high activity (classes I-III) for more than three weeks before surgery (Table 4);

In addition, the HPAA should be evaluated in all the patients with Cushing's syndrome or any symptoms of AI [12].

d. Patients who received intra-articular or spinal injections of steroids.

The HPAA suppression has been described following intra-articular as well as spinal injections of steroids since the certain amount of the medication enters the bloodstream [13-15]. It is known that the degree of suppression depends on the dose, the interval between and the number of steroid injections, but is also possible with a single administration of a small dose.

The risk of perioperative AI in patients of this group is considered relatively low, however it is recommended to assess the HPAA function in those who received three or more intra-articular or spinal steroid injections within three months before surgery [14], as well as in the case of Cushing's syndrome [16].

Table 4. *Classification of local glucocorticoids by potential activity (according to WHO)*

Ultra-high potency topical corticosteroids (class I) — clobetasol propionate cream (0.05 %) and others;
High potency topical corticosteroids (classes II-III) — betamethasone valerate ointment (0.1 %), betamethasone dipropionate ointment or cream (0.05 %), triamcinolone acetonide ointment (0.1 %) and others;
Moderate potency topical corticosteroids (classes IV-V) — hydrocortisone valerate ointment 0.2 %, triamcinolone acetonide cream 0.1 %, betamethasone dipropionate lotion 0.02 %, betamethasone valerate cream 0.1 %, fluocinonide acetonide cream 0.025 %, hydrocortisone butyrate cream 0.1 %, hydrocortisone valerate cream 0.2 %, triamcinolone acetonide lotion 0.1 % and others;
Low potency topical corticosteroids (classes VI-VII) — betamethasone valerate lotion 0.05 %, fluocinolone acetonide solution 0.01 %, hydrocortisone acetate cream (1 %), methylprednisolone acetate cream 0.25 % and others.

3. *Evaluation of the HPAA function*

It is important that in case of urgent or emergent surgery no HPAA evaluation is necessary. All patients therefore who have a risk of perioperative AI require empirical additional doses of steroids.

The additional dosing is based off the type and expected duration of the operation and presented in Table 2.

4. *Evaluation of morning serum cortisol*

The evaluation of morning (before 8 am) serum cortisol is proposed as a screening method for assessing the probability of secondary AI [17, 18]. It is extremely unreliable however and is uninformative in steroid taking patients, so it is rarely used in clinical practice.

5. *ACTH Stimulation Tests*

A so — called "short" test implies the use of synacten which is an ACTH synthetic analog (currently not registered in Russia). The test can be carried out at any time of day regardless of meals. First, a blood sample is obtained to determine the initial level of cortisol. Then, a solution of synacten (250 mcg in 5 ml of saline) is injected intravenously, slowly, in the course of two minutes. After 30 minutes, a second blood sample is obtained and the cortisol level is measured.

The cortisol level >18 mcg/dl (497 nmol/l) in the second sample indicates a sufficient reserve of the adrenal glands, and additional doses are not required perioperatively [19, 20]. Patients with an insufficient adrenal reserve should receive additional doses (Table 2).

The ACTH stimulation test may be normal in patients with acute ACTH deficiency (for example, within 2-4 weeks after pituitary surgery). In this case the indicators of the HPAA function will be distorted [21]. In these patients, an insulin tolerance test or metyrapone stimulation can be performed to assess the HPAA. These tests however are difficult to perform in real clinical practice. Therefore, patients who have recently undergone pituitary surgery and have a risk of acute ACTH deficiency are recommended empirical additional doses of steroids.

6. *Application of etomidate*

Etomidate was previously widely used in anesthesia; however, it showed an inhibitory effect over the steroid synthesis, resulting in acute AI [22]. In this regard, etomidate should be avoided, especially in patients with a risk of adrenal suppression and AI. If etomidate is still used, the patients should receive steroids perioperatively and/or be carefully monitored for any clinical signs of AI [23].

In patients with possible suppression of the HPAA function, the presence of unexplained nausea, vomiting, hypotension, orthostatic hypotension, changes in mental status, hyponatremia or hyperkalemia require a random cortisol test. Regarding the urgency, empirical therapy with additional steroids may be required. It is important that the numerous postoperative stressors, such as infection, myocardial infarction, bleeding or other complications, may call for the introduction of additional steroids.

7. *Assessment of the type and duration of the operation.*

The most common schemes of perioperative steroid dosing the approximate doses are indicated in Table 2.

8. *Potential side effects of steroids in the perioperative period*

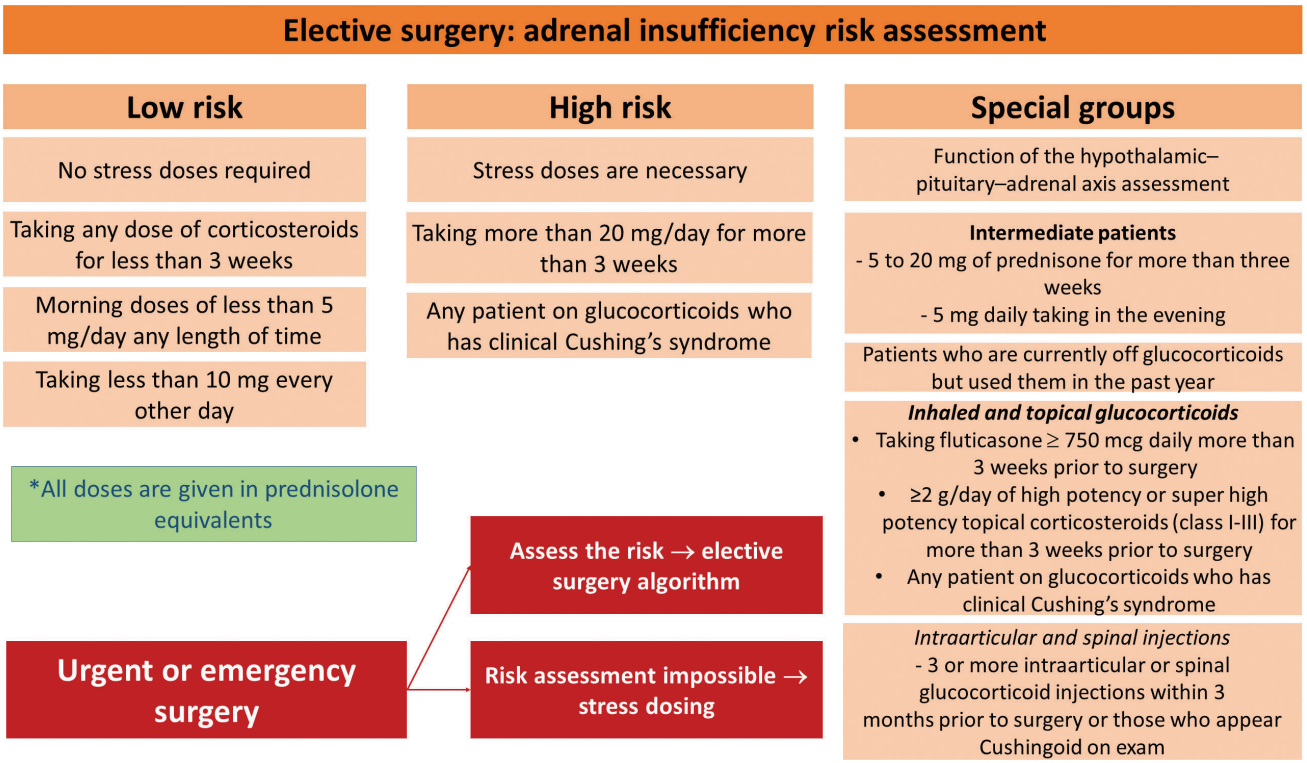
In addition to the increased risk of infectious complications and suppression of the HPAA function, there are some other potential adverse effects of steroids, affecting the results of surgical intervention [7]:

- poor wound healing;
- thinning of the skin, easy tissue injury, fragility of superficial blood vessels (for example, moderate pressure can cause a hematoma or ulceration of the skin, removing the patch can tear the skin, and sutures can tear the intestinal wall);
- increased risk of fractures, gastrointestinal bleeding or ulcers, hyperglycemia; arterial hypertension; fluid retention.

9. *The risk of infectious complications against the background of the use of steroids.*

In steroid taking patients a careful monitoring is required postoperatively for the timely detection of infectious complications. This includes the control of WBC, C-reactive protein and procalcitonin levels. It also shouldn't be omitted that steroids can suppress a febrile reaction.

In knee and hip replacement surgery, the "safe dose" in regard to the risk of infectious complications should not exceed 10 mg of prednisone a day [3] or 20mg a



Scheme 3. *Perioperative risk assessment of adrenal insufficiency*

day according to other sources [1]. This applies to patients who have been taking steroids for a long time. It remains unclear whether there is a "safe period" for short-term steroid use in the preoperative period. The data, although limited, shows the detection of immunosuppression after two weeks of 20 mg of prednisone a day [1].

Thus, to reduce the risk of infectious complications, it is advisable to adjust the dose of steroids to the 10 mg/day target. Dose adjustment should be started 3-6 months before the elective surgery [24].

In patients who cannot reduce the dose because of the risk of deterioration, it is especially important to ensure thorough sterility and treatment of the skin, tight covering and proper antibiotic prophylaxis [2].

A normal dose of steroids exceeding 10-20 mg/day is not only associated with the risk of infections, but also indicates high activity of the disease, which in itself carries a risk [3]. In patients undergoing high-dose steroid therapy, the elective surgery is recommended to be postponed until better control of the disease activity, allowing to reduce the dose of steroids. If the surgery is performed for emergency indications, it is necessary to provide enhanced prevention of infectious complications, as well as AI. [2]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

It is recommended to cancel NSAIDs before surgery for a period of time amounting to 3-5 half-lives (Table 5) with the aim of platelet function recovery. Temporary withdrawal of NSAIDS allows to avoid the most common side effect of this class (an increased risk of bleeding; in particular, gastrointestinal bleeding as well as bleeding in the area of the surgical wound).

It is believed that celecoxib does not affect the function of platelets, thus assumed the safest NSAID in terms of the risk of bleeding [26].

At the same time, it is known that there is a poor correlation between the half-life and COX-1 inhibition and decrease in platelet function. In addition, the relationship between the duration of NSAIDs withdrawal and intra- and postoperative clinically significant bleeding is not clearly defined. It was found that for most NSAIDs, platelet function normalizes within three days after pausing, which suggests that NSAIDs should be discontinued at least three days before surgery. Ibuprofen can be discontinued 24 hours before surgery [27].

It is possible to resume taking NSAIDs 2-3 days after surgery, provided the patient's condition is stable [2].

Table 5. *The half-life of NSAIDs [24]*

NSAIDs	Half-life, h	Withdrawal time before surgery
Ibuprofen	1,6-1,9	10 hours
Naproxen	12-15	3 days
Diclofenac	2	10 hours
Indomethacin	4.5	1 days
Piroxicam	30	6 days
Etodolac	6-7	1,5 days
Nabumetone	24-29	6 days
Celecoxib	11	Withdrawal not required
Meloxicam	15-20	5 days

If the patient needs NSAIDs perioperatively and the risk of adverse effects is high, it is possible to switch from a medication with a long-lasting effect to the one with a shorter half-life (Table 5). At the same time, it is not recommended to use selective COX-2 inhibitors for the reasons of cardiovascular safety.

If pain relief is necessary and NSAIDs use is objectionable, it is recommended to consider paracetamol, tramadol or opioids as an alternative.

In addition, it is necessary to check with patients whether they take any medications and supplements on their own. Many supplements can affect platelet function, increasing the risk of bleeding or interact with anesthesia (such as ginkgo biloba, ginger, etc.) [9]

Conclusion

This article provides a review of current guidelines and recommendations for the perioperative administration of the main medications used in rheumatology. The dose adjustment for NSAIDs and steroids is recommended to be carried out in advance. It is not required to withdraw or adjust DMARDs in most cases, and there are special instructions for the perioperative use of biologics.

The perioperative management of infectious, thromboembolic and cardiovascular risks, as well as the impact of some special conditions characteristic to RD, will be reviewed in the second part of the publication.

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РЕГУЛЯЦИЯ ИММУННОЙ СИСТЕМЫ ПРИ СТАРЕНИИ: В ФОКУСЕ — ЭПИГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ

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Regulation of the Immune System in Aging: Focus on Epigenetic Mechanisms

Резюме

Эпигенетика изучает процессы, приводящие к изменению активности генов без изменения последовательности ДНК. Эпигенетические механизмы, такие как метилирование ДНК и модификации гистонов, формируются в период эмбрионального развития, а эпигенетические профили стабильно наследуются при митозе, обеспечивая дифференцировку клеток и их дальнейшую судьбу в процессе развития. Под действием внутренних и внешних факторов, таких как метаболический профиль, гормоны, питание, наркотики, курение и стресс, эпигенетические механизмы активно модулируются и, в этом смысле, образ жизни может существенно влиять на эпигеном, а следовательно, и на профиль экспрессии генов и функцию клетки. Показано, что развитие и функции клеток как врожденной, так и адаптивной иммунной системы, также регулируются эпигенетическими механизмами, а негативные эпигенетические изменения являются отличительной чертой старения и онкологических заболеваний. Учитывая эти данные, можно полагать, что возрастные изменения профиля эпигенетических меток могут привести к снижению иммунной функции и способствовать увеличению заболеваемости у пожилых людей. Поэтому, чтобы обеспечить здоровую старость, необходимо лучше понять, как избежать эпигенетических изменений, которые связаны со старением иммунной системы. В данном обзоре мы попытались обобщить последние достижения в этой области исследований и рассмотреть возможность их использования в качестве средств диагностики, профилактики и лечения заболеваний.

Ключевые слова: *иммунное старение, эпигенетика, метилирование ДНК, модификации гистонов, окружающая среда, возрастные заболевания*

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Abstract

Epigenetics studies processes leading to changes in the activity of genes without changing the DNA sequence. Epigenetic mechanisms, such as DNA methylation and histone modifications, are formed during embryonic development, and epigenetic profiles are stably inherited in mitosis, providing cell differentiation and their further fate in the development process. Under the influence of internal and external factors such as metabolic profile, hormones, nutrition, drugs, smoking and stress, epigenetic mechanisms are actively modulated and, in this sense, a lifestyle can significantly affect the epigenome, and consequently, the gene expression profile and function of cells. It is shown that the development and function of cells of both congenital and adaptive immune systems are also regulated by epigenetic mechanisms, and negative epigenetic changes are a distinctive feature of aging and cancer. Given these data, it can be assumed that age-related changes in the profile of epigenetic labels can lead to a decrease in immune function and contribute to an increase in morbidity in the elderly. Therefore, to ensure healthy aging, better understanding of how to avoid epigenetic changes that are associated with aging of the immune system is needed. In this review, we tried to generalize the latest achievements in this field of research and consider the possibility of using them for diagnosis, prevention and treatment of diseases.

Key words: *immune aging, epigenetics, DNA methylation, histone modifications, environment, age-related diseases*

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Introduction

Aging is a process of gradual failure of all normal physiological functions of the body [1] that eventually ends in death. This process is understudied, although many different theories exist, including the following: accumulation of genetic damage [2]; free radicals [3]; cell apoptosis [4]; immunological theory [5], and others that are aimed at shedding light upon its origin. Unfortunately, none of them can fully explain all aspects of this complex biological process. In humans, aging is characterized by decreased immune function, chronic inflammation, sarcopenia, and, most importantly, increased susceptibility to several diseases such as cancer, cardiovascular, metabolic, and neurodegenerative diseases. Despite their systemic nature, these phenotypes are the result of changes in different cellular processes, such as the response to DNA damage, mitochondrial and proteasome function, and regulation of cell death. Dysregulated transcription that develops in aging leads to significant changes in gene expression. Studies have shown that these changes in transcriptome, known as "epigenetic drift," are significantly affected by modifications of the epigenetic mechanisms of regulation of gene activity.

Epigenetic Mechanisms of Regulation of Gene Activity

As is known, all cells of an organism have an identical genome. However, they are very different in cytomorphological traits and function. These differences are a consequence of "epigenetic processes" in cells that can modulate the pattern of gene expression. Epigenetic processes are direct hereditary changes in gene expression with no alterations in the DNA sequence when active or silent states of genes are controlled by adding or removing chemical modifications in chromatin [6]. These modifications include the following: 1) DNA methylation; 2) various post-translational modifications of histone (acetylation, methylation, phosphorylation, etc.); and 3) binding of messenger RNAs to non-coding RNAs (ncRNAs). In this review, we will discuss the latest advances in investigating the role of epigenetic mechanisms in the regulation of gene activity in cell aging, including immune cells, focusing on the significance of two types of epigenetic modification—DNA methylation and histone modifications.

DNA Methylation: In mammals, DNA methylation is mainly associated with the attachment of methyl groups (-CH3) to cytosine residues in CpG sites. This reaction is catalyzed by DNA methyltransferases (DNMT)—DNMT1, 3A and 3B—that transfer a methyl group from S-adenosyl methionine (SAM) on the 5th carbon of cytosine forming 5-methylcytosine (5mC). In mammalian cells, methylation usually develops in CpG islands, and such methylated sites amount to 70–80% [7]. Hypermethylation of gene promoter regions usually induces transcriptional silencing, while hypomethylation stimulates gene expression.

Histone Modifications: In nucleosomes, which are the basic structural units of chromatin, not only a DNA

molecule but also histone proteins can carry chemical modifications that are fundamental for chromatin-dependent gene regulation [8]. Post-translational modifications (PTMs) of histones regulate chromatin structure, thereby affecting internucleosomal interactions, and recruit proteins and complexes that not only affect gene transcription but also mediate processes such as DNA replication, DNA repair, alternative splicing, and recombination [6]. PTMs of histones such as acetylation, methylation, ubiquitination, phosphorylation, sumoylation, and poly-ADP-ribosylation develop mainly in the N-terminal tails of histones that are readily available for covalent post-translational modifications and constitute a potential "histone code"—a hypothesis which argues that histone modifications can result in activation or repression of gene transcription [9]. For example, acetylation and phosphorylation reduce the positive charge of histones and thus weaken the interaction between histones and DNA, thereby facilitating the access of transcription factors to DNA transcription mechanisms. As a result of these and other PTMs of histones, the chromatin structure changes, leading to the activation or suppression of target genes due to modulation of the binding of transcriptional agents to their respective promoter elements of the nucleus [10].

Changes in Epigenetic Marks with Aging

DNA Methylation: It has been demonstrated that global DNA hypomethylation develops in advanced years. Repetitive DNA sequences that are usually "silenced" by epigenetic marks become expressed with age and may be partially responsible for the loss of heterochromatin during aging [11]. Besides, aging is accompanied by hypomethylation of the promoters of certain genes, for example, IL17RC, which induces its transcription and leads to the expression of inflammatory chemokines and cytokines [12]. At the same time, the promoters of some other genes become hypermethylated and abnormally "silent." Regarding 5-hydroxymethylcytosine (5hmC) generated during active demethylation of 5-methylcytosine, it was demonstrated that although the global level of 5hmC in the brain increases with aging in mice and humans, its level decreases in other tissues, such as blood. Despite that age-related changes in DNA methylation develop more frequently in CpG islands, tissue-specific changes were also found in other genomic regions. In their comprehensive study of DNA methylation, Yuan et al. [13] showed that, in addition to hypermethylated CpG islands, a large number of differentially methylated sites were found in regions with low CpG content. These authors also identified large aging-related hypomethylated blocks similar to those described in cancer cases. Based on the study of the genomic profile of whole blood methylation in 656 individuals across a wide age range (from 19 to 101 years), a quantitative model was constructed not only for more accurate determination of the biological age of a person but also for predicting his/her risk of death from senile diseases and, in particular, the probability of cancer development [14].

Histone Modifications: Global DNA hypomethylation seen in advanced years has been closely associated with changes in histone modification patterns. Moreover, with aging, changes were observed in the activity, functions, and number of enzymes of the epigenetic apparatus. For example, the genes identified as hypermethylated were associated with bivalent chromatin domains (genes carrying two types of histone H3 marks—active and inactive—are located on these domains) in embryonic stem cells, and those with repressive histone marks H3K27me3 and H3K9me3—in differentiated cells [15]. With age, there was a global loss of histones, as well as an imbalance between activating and repressive histone marks. There was a decrease in acetylated H3K9 and trimethylated H3K27 marks in old cells. Histone lysine methyltransferase expression also decreased with age, contributing to a decrease in the level of H3K9me3 marks and loss of heterochromatin. Age-related decrease in HP1 and DNMT expression may contribute to DNA demethylation in heterochromatin. Another change that may contribute to a more open chromatin state is increased H4K16Ac level with replicative age, as described in human fibroblast culture. H4K16 is a target of histone deacetylase SIRT1, which is associated with the rate of aging and genome maintenance in different organisms.

Changes with aging develop not only in canonical histones but also in the attachment of histone variants that do not depend on replication. The replication-independent histone variant H3.3 becomes more common with age not only in non-replicating cells (such as neurons) but also in other cells; this fact also contributes to the greater availability of chromatin for transcription apparatus. Another replication-independent histone variant associated with aging is H2A.Z; its knockout leads to premature aging in fibroblasts [16]. Finally, the macroH2A variant of histone H2A is associated with aging. An age-related increase in macroH2A level has been described both during replicative aging of human fibroblast culture and in many other tissues of aged animals [17].

Effect of Environment and Lifestyle: The classic study conducted by Fraga et al. [18] demonstrated, on the one hand, significant differences in the level of epigenetic marks in elderly monozygotic twins and, on the other hand, their general indistinguishability in very young twins. An even more interesting thing in this study was that the greatest differences in epigenetic marks

were found in elderly twins who lived together for a little time. The data obtained on the dominant effect of the environment on the variability of phenotypic traits are confirmed by studies in the human population, which showed that genetic factors are responsible for only 20–30% of the variability observed in identical twins, and most of the variability is due to the epigenetic drift that develops throughout the life of twins [19]. These studies also demonstrate how age and various environmental factors impact on changes in epigenetic marks. Generally speaking, these modifications of epigenetic marks alter the state of chromatin, making it more open and accessible to transcriptional regulators and leading to abnormal gene transcription and genomic instability. Therefore, they were proposed as key regulators of the aging process that contribute to the development of age-related diseases and even as predictors of chronological age.

It should be emphasized that the epigenome acts as a molecular interface between the genome and the environment. This means that lifestyles, including eating habits, exercise, stressors, smoking, alcohol or drug abuse, and exposure to chemicals, can alter the epigenetic landscape, affecting the structure and function of chromatin, thereby contributing to the development of phenotypes of age-associated diseases. It was found that physical exercise results in the reconstruction of epigenetic marks in human skeletal muscles and adipose tissue. Increased cardiorespiratory performance and endurance and decreased low-density lipoprotein levels that are observed during physical exercise were accompanied by demethylation of CpG islands, in contrast to methylation changes observed in aging. At the same time, such bad habits as smoking [20] and alcohol abuse [21] had negative effects on the processes associated with changes in epigenetic marks. For example, prenatal smoking affected blood cell DNA methylation in children of smoking mothers. Epigenetic changes caused by chronic exposure to cigarette smoke contributed to the sensitization of bronchial epithelial cells to malignant transformation. Tobacco smoking caused changes in DNA methylation in the cells of both innate and adaptive immune systems. Alterations in fetal DNA methylation were also associated with alcohol abuse of the mother.

The way how many of these environmental factors obtained in both human and animal models have an impact on aging is associated with oxidative stress. Although severe acute or chronic stress effects accelerate aging, contributing to the accumulation of cellular damage due to the depletion of defense mechanisms, moderate stress, on the contrary, slows down this process, activating defense mechanisms and preventing and/or eliminating such cellular damage [22]. Recent research has demonstrated the relationship between cellular stress and epigenetic changes. As is known, reactive oxygen species (ROS) lead to oxidized DNA damage, which can contribute to changes in DNA methylation. In this regard, the results of studies on 8-hydroxy-2'-deoxyguanosine (8-oxo-dG), one of the main oxidative products of DNA damage, and its level in tissues are especially noteworthy. It was demonstrated that this modified nucleotide is accumulated in the DNA of various organs and tissues of mammals with age [23]. Also, reducing caloric intake, which is known to slow aging and increase longevity, caused a significant decrease in the level of 8-oxo-dG in the DNA of all tissues in mice [24]. It was also established that ROS can interfere with TET (ten-eleven translocation)-mediated DNA demethylation [25].

Sirtuins, i.e., histone deacetylases that catalyze the removal of the acetyl group of histones, play a key role in responses to various stresses, such as oxidative or genotoxic stress. Sirtuins modify histones and alter chromatin conformation, making DNA packaging denser and less accessible for transcription factors, leading to transcriptional repression. However, this is not the only function of sirtuins. In the event of DNA damage caused by ROS, sirtuins move to these damage sites and participate in its restoration. O'Hagan et al. [26] demonstrated that this process can result in stable aberrant epigenetic and gene transcriptional changes similar to those observed in cancer diseases. In mouse embryonic mesenchymal fibroblasts, elevated levels of hydrogen peroxide induced SIRT1 to move from repressed DNA sequences to DNA breaks in order to facilitate repair; this resulted in transcriptional changes similar to those seen in the brains of aged rats. However, in response to environmental stress, sirtuins appear to promote cell survival, thereby extending the replicative and chronological lifespan. This assumption is based on the following: 1) calorie reduction, which induces SIRT1 deacetylase, increased the viability of mammalian cells; 2) sirtuin activity was a prerequisite for increasing physical activity and increasing life expectancy with calorie reduction [27]; 3) the health and survival of mice on a high-calorie diet improved after treatment with resveratrol, which activates SIRT1 [28]. This evidence of the important role of sirtuins in extending the lifespan of various model organisms under caloric restriction apparently shows that epigenetic mechanisms play an essential role in this process. In this regard, new and known compounds were tested as "calorie restriction mimetics," including sirtuin-activating compounds such as resveratrol. Compounds that inhibit histone acetylation, such as spermidine, also helped to increase lifespan.

As mentioned earlier, ROS can modify TET-mediated DNA demethylation [25]. Increasing endogenous antioxidants and reducing calorie intake reduces high 5hmC levels in the brains of aged mice. Demethylase activity

of TET enzymes can be stimulated with nutrients such as ascorbic acid. Since the activity of many epigenetic enzymes depends on the intracellular levels of metabolites (methionine, iron, ketoglutarate, NAD^+, acetyl coenzyme A, SAM), cell metabolism controls epigenetic modifications and can regulate longevity [29].

Other studies in human cohorts have demonstrated that life-threatening stressors, especially during early development, can cause long-term changes in the epigenome. Human and animal studies also demonstrated that stress and glucocorticoids can induce long-term changes in DNA methylation both at the genomic level and at the level of individual gene loci.

Epigenetic Regulation of Immune System

The most important feature of the immune system is its ability to distinguish what is "friendly" from what is "hostile" and then attack and neutralize the "hostile" (potentially pathogenic agents or substances) in order to protect the body from harmful effects. Protection from a potentially dangerous environment is provided by several populations of immune cells using both innate and adaptive mechanisms. However, these immune cells can exercise their protective functions to the full extent only under strictly controlled regulation of the differentiation of hematopoietic cells from which they originate. A growing number of studies show the critical role of epigenetic mechanisms in the development and differentiation of cells of the immune system and the pathologies associated with them. It is widely known that immunocompetence, i.e., the functional state of the immune system that provides effective protection of the body against infectious agents, tumor cells and chemicals with antigenic properties, becomes defective with age. It turns out that one of the leading causes for this is the repression of immune cell differentiation genes, along with the activation of autoimmunity genes due to changes in DNA methylation.

Cells of the Innate Immune System: The innate immune system, which includes macrophages, neutrophils, dendritic cells (DCs) and natural killer cells (NKs), is the first line of defense against pathogenic agents. Macrophages and dendritic cells are professional antigen-presenting cells (APCs) that can capture antigens for processing and presentation to lymphocytes. When activated, resident macrophages can act either directly, thereby destroying their targets, or indirectly by initiating an acute inflammatory response by producing cytokines, chemoattractants, and inflammatory mediators, as well as recruiting neutrophils, monocytes, and DCs. Activated macrophages produce different factors in response to the extracellular environment and can acquire functionally different phenotypes: classically activated M1 and alternatively activated M2. Activated M1 macrophages are induced by cytokine interferon-gamma (IFN-γ) as well as bacterial products and have a pro-inflammatory profile, playing an important role in host defense. Unlike M1 macrophages, M2 macrophages are induced by interleukin-4 and -10 (IL-4 and IL-10) as well as helminth products and have an anti-inflammatory profile that promotes tissue repair. Since mature cells of the immune system should quickly respond to pathogens, the contribution of epigenetic mechanisms to the regulation of genes involved in such response was described to a large extent. In this context, it was established that epigenetic mechanisms were involved in modulating the polarization of macrophages mainly through the presentation of histone marks in the enhancers of specific genes.

The fact that inflammation is regulated by epigenetic mechanisms was first demonstrated in the study conducted by Sakkani and Natoli [30]. They found that the loss of H3K9 methylation in the promoter regions of cultured human monocytes after exposure to bacterial lipopolysaccharide (LPS) endotoxin induced inflammatory cytokines such as IL-8 and macrophage inflammatory protein 1-alpha (MIP-1α). Innate immune cells have a certain degree of specificity through the presentation on their surfaces of pattern recognition receptors (PRRs) targeted at the recognition of molecular structures associated with pathogens. Recent studies demonstrate that, in contrast with previous ideas, cells of the innate immune system can form the memory of past stimuli. This phenomenon, called "trained immunity," allows the cells of the innate immune system to change their response to repeated stimuli, reacting more strongly or reacting to a larger number of microbes compared to the baseline level [31]. This immunological "memory" includes changes in transcriptional programs made by reprogramming epigenetic marks. For example, metabolic changes in monocytes triggered by β-glucan from *Candida* are associated with increased levels of active histone marks, trimethylation of H3K4, and acetylation of H3K27, which leads to increased production of cytokines IL-6 and TNF, inflammation, and the development of "trained immunity" [32]. Macrophages re-stimulated by LPS induce a more attenuated inflammatory response while maintaining an intact antimicrobial response. Foster et al. [33] demonstrated that genes involved in LPS tolerance lost active histone marks H3K4me3 and H4Ac in their promoters during re-stimulation with LPS, while intolerant genes, on the contrary, retained these active marks. Under certain stimuli, epigenetic mechanisms also regulate the differentiation of human monocytes into DC. For example, the increase in CD209 expression observed during differentiation was shown to be a result of the acquisition

of H3K9Ac and the loss of H3K9me3, H4K20me3, and DNA methylation in its promoter [34].

T Lymphocytes: Age-related decline in the function of the immune system, called "immune aging," is accompanied by changes in epigenetic marks. Kuwahara et al. [35] demonstrated that CD4 T-cell senescence and homeostasis of cytokines were controlled by maintaining histone acetylation at the Bach2 gene locus (encodes a protein of the same name, i.e., a transcription factor), which was stimulated by binding to *menin*, a nuclear protein. Also, genomic instability in the thymus, which increases with age, was associated with the loss of heterochromatin markers, including H3K9me3, with a corresponding reduction in the expression of the SUV39H1 gene. This suggests that aging is stimulated by DNA hypomethylation, which is observed particularly in aging but not in immortal cells, and inhibition of DNA methylation leads immortal cells to stop the cell cycle.

Cells of the innate immune system present antigens to both B lymphocytes and T lymphocytes, activating them for proliferation and differentiation into effector cells. APCs activate T-cell receptor and costimulatory molecules of naive T cells, initiating T-cell differentiation by activating the nuclear factor of activated T cells (NFAT) and the production of interleukin-2 (IL-2). Activation of naive T cells triggers the synthesis and secretion of IL-2 and the simultaneous expression of its receptor on the cell surface. By interacting with its own receptor, IL-2 provides rapid multiplication and subsequent differentiation naive T cells into mature effector cells. Naive and resting CD4 + T cells do not express IL-2. However, this cytokine is expressed in T cells upon antigenic stimulation. Murayama et al. [36] demonstrated that demethylation of a single specific CpG site in the enhancer region of the human IL-2 gene was sufficient for IL-2 transcription and, more interestingly, this single epigenetic change was the memory that CD4 + T cells had encountered an antigen.

Peptide antigens are presented to T cells by APCs in combination with the major histocompatibility complex (MHC). Cytotoxic T cells that express CD8 recognize antigens presented by normal cells in regard to MHC class I molecules, and can directly kill infected cells. Activated CD8 + T cells have increased levels of H3Ac in the IFN-γ promoter and enhancer. This epigenetic modification is maintained through the memory of CD8 + T cells and provides a faster and stronger cytotoxic response to additional antigen stimulation. MHC class II molecules are MHC molecules involved in the presentation of CD4 + antigen to T-helper cells. A class II transactivator (CIITA) is a key factor that controls MHC-II expression; both CIITA expression and CIITA-dependent MHC-II expression are epigenetically regulated. An analysis of chromatin availability in peripheral blood mononuclear cells defined the memory of CD8 + T cells as a subpopulation with the deepest chromatin remodeling with aging.

After antigen recognition, naive T lymphocytes differentiate into effector T-helper cells (Th1, Th2, and Th17) or regulatory (Treg) CD4 + T cells depending on the cytokine environment, and coordinate specific immune responses by generating different sets of cytokines. Differentiation towards the Th1 profile is induced by IFN-γ, IL-12, or IL-15, while differentiation towards the Th2 profile is induced by IL-4, IL-10, or IL-13; both pathways include the regulated expression of several effector genes. Transforming growth factor beta and IL-6 are responsible for the induced differentiation of naive T cells into Th17 cells. CD4 + T cell differentiation into these different profiles is tightly regulated in order to provide specific cytokine profiles; changes in epigenetic marks are essential for completing this process. The IFNG gene promoter, which is hypermethylated in naive human T cells, is demethylated during differentiation into the Th1 profile. Specific histone marks were identified throughout the entire IFNG locus: H4Ac and H3K4me3 in Th1 cells, and H3K27me2 and H3K27me3 in Th2 cells. Naive and Th1 cells had a highly methylated IL-4-gene promoter, while Th2 cells had a partially demethylated IL-4-intron 2. Th17 cells were characterized by the expression of IL-17 cytokine and RAR-related orphan receptor C (RORC). Demethylation of both IL-17A and RORC locus correlates with gene expression in human Th17 cells; active histone marks H3Ac and H3K4me3 were found in the IL-17 locus. Demethylation of the Foxp3 locus, as well as histone hyperacetylation, was shown to be important for maintaining stable expression of the transcription factor FOXP3 (has an impact on the development and functioning of regulatory T lymphocytes) and stabilization of the regulatory phenotype in Treg cells.

B Lymphocytes: After binding to an antigen and induction by T-helper cells, B cells differentiate into antibody-secreting plasma cells. Antibodies bind to a specific antigen, leading to better recognition and destruction of pathogens (e.g., bacteria, viruses, and tumor cells) by activating complement and/or interacting with lytic cells. During B-cell differentiation, lineage-specific genes are expressed, while genes associated with multipotent progenitors and alternative lines are suppressed. Complex epigenetic regulatory mechanisms coordinate the differentiation and function of B cells, including monoallelic V(D)J rearrangement and determination of antibody diversity. The key transcription factor involved in B-cell commitment is the PAX-5 (paired box 5) transcription factor, which, in addition to the expression of this cell being regulated by epigenetic mechanisms, recruits chromatin-modifying proteins to regulate the

expression of its targets. For example, the CD79a-gene promoter, which is hypermethylated at the precursor stage, is demethylated at the early stages of B-cell differentiation, followed by the action of histone acetyltransferase recruited by Pax5, which allows gene expression [37]. Pax5 can also interact with chromatin-modifying enzymes to repress genes specific to other lines [38]. V(D)J rearrangement and determination of antibody diversity are essential for the production of effective antibodies and require activation-induced cytidine deaminase (AID) expressed by B cells at certain stages of differentiation. In naive B cells, the AID-gene promoter is hypermethylated and the gene is not expressed. When B cells are activated, the AID gene becomes demethylated and acquires higher levels of the active histone H3Ac mark. The uptake of this histone mark by active promoters and distal enhancers is also critical for changes in gene expression during B-cell differentiation into plasma cells. Blimp-1, a transcriptional repressor that maintains plasma cell identity, has its epigenetically induced expression and epigenetically downregulates mature B-cell gene expression by recruiting histone modifiers. After V(D)J rearrangement processes and determination of antibody diversity, B cells can differentiate into memory B cells that acquire additional epigenetic marks in addition to those obtained upon activation of B cells. Various epigenetic modifications, as well as epigenetic enzymes, such as the enhancer of zeste homolog 2, monocytic leukemia zinc finger protein histone acetyltransferase, and DNMT3a, are observed in resting and activated B cells that demonstrate that the epigenome of B cell memory may contribute to faster and more efficient activation than the epigenome of naive cells.

Involvement of Epigenetic Modifications in the Aging of Cells of the Immune System

Age-related defects are observed in all cells of the immune system and affect their activation and cytokine production.

Innate Immune Cells: It was shown that many immune responses are inhibited with aging. However, several responses are hyperreactive. Age-related epigenetic changes seem to affect monocyte differentiation since the hypomethylation of genes associated with differentiation was observed in older hematopoietic progenitor cells (HPCs) compared to progenitor cells from umbilical cord blood. This is possibly due to a decrease in pluripotency and decreased HPC differentiation potential in elderly donors. At the same time, methylation *de novo* in a subgroup of genes associated with the repressive Polycomb complex was observed in older HPCs, which could contribute to a decrease in the phenotypic plasticity of old stem cells. Moreover, according to Kramer a. Challen [39], epigenetic dysfunction may be a precursor of hematological disease in elderly individuals. In the elderly, epigenetic mechanisms also contribute to decreased expression of MHC-II in macrophages. Although the number of NK cells in the elderly increases, their cytotoxic activity decreases. The regulation of DNA methylation by IFN-γ and IL-2 appears to contribute to this defective NK-cell function. With aging, there is an imbalance between inflammatory and anti-inflammatory responses, which can be described by high levels of inflammatory mediators such as IL-6 and tumor necrosis factor alpha (TNF-α), even with no acute infection or another physiological stress (a process known as "subclinical systemic inflammation") [40]. Expression of TNF-α increases with aging; this is associated with the demethylation of its promoter. This epigenetic modification contributes to increased levels of TNF-α and IL-1α, thereby initiating subclinical systemic inflammation associated with resting neutrophils in elderly donors.

The primary cause of morbidity of elderly individuals worldwide is diseases of the circulatory system and inflammatory lung diseases. In this regard, hypomethylation of the promoter of inflammatory genes such as toll-like receptor 2, carnitine O-acetyltransferase, and coagulation factor III were associated with decreased lung function [41]. Zinc is an essential trace mineral for the development and functioning of the immune system. Its deficiency, which often comes with aging, contributes to a wide range of immune defects, including increased inflammatory response by inducing demethylation of the IL-6 promoter. Using C-reactive protein (CRP) as an inflammatory biomarker, Ligthart et al. [42] conducted a meta-analysis of large-scale associative studies of DNA methylation in chronic subclinical inflammation. In that study, the authors demonstrated that several inflammation-associated CpG sites were associated with the expression of adjacent genes, and that many of these CpGs showed associations with cardiometabolic phenotypes and cases of coronary heart disease. These genes also include the AIM2 gene that plays a critical part in innate immune responses (it is involved in the host's defense mechanisms against bacterial and viral pathogens); it was found to be hypermethylated and expressed at low levels in samples with low CRP levels.

T Lymphocytes: Involution of the structure and function of the thymus, which is characterized by the decreased number and functional defects of naive thymic T cells, is another process that contributes to immune aging. The analysis of CD4 + T-cell methylome in neonates and centenarians performed by Heyn et al. [43] revealed that these immune cells had the same changes in DNA methylation observed in other tissues during

aging—global DNA hypomethylation and higher variability of DNA methylation.

More recently, a comprehensive analysis of transcriptome, methylome, and the totality of all miRNAs in the same CD4 + T cells conducted by Zhao et al. [44] revealed a potential link between gene transcription and DNA methylation for age-related or immune genes, indicating the involvement of DNA methylation in the regulation of transcription associated with the development and functions of T cells during aging. Mice with heterozygous *Dnmt1* null mutation had hypomethylated DNA and were phenotypically normal. However, they showed signs of immune aging and early development of autoimmunity compared with normal mice of the same age. In the analysis of naive CD4 + T cells in 74 healthy (19 to 66 years) individuals [45], Dozmorov et al. identified sites that were hypomethylated with age and demonstrated a specific enrichment of active T-cell enhancers H3K27Ac and H3K4me1 with marks. This indicates a progressive age-related shift in T-cell epigenomes towards a pro-inflammatory and T-cell activated phenotype, which may contribute to increased autoimmunity with age. It was also demonstrated that the elderly with higher levels of autoantibodies had T cells with demethylation and overexpression of the same genes as in patients with lupus [46]. Progressive loss of the co-stimulatory molecule CD28 in CD4 + T-lymphocytes during aging is associated with impaired immune response. A unique DNA methylation landscape in CD28 null T cells that leads to the expression of genes associated with inflammation was recently described. Another recent study revealed two CpG sites in the promoter region of the KLF14 gene (transcription factor), which is involved in CD4 + T-cell differentiation through suppression of FOXP3 (transcription factor that functions as a regulator of the development and functioning of regulatory T cells); they demonstrated stable methylation in early age and a sharp increase in methylation at the end of life in peripheral whole blood, monocytes, and isolated CD4 + T cells [47]. Dysfunctional Treg cells are thought to be involved in immune aging and increased susceptibility to age-related diseases by suppressing T-cell responses. Garg et al. [48] demonstrated that a large number of Treg cells observed in aged mice was associated with the hypomethylation of the FoxP3 enhancer, which caused its increased expression. They also demonstrated that Treg cells from aged mice produced more IL-10 and were more effective in reducing the co-stimulatory molecule CD86 on Dcs; they also modulated the extracellular redox environment by suppressing T-cell proliferation.

Immune aging is also described by the loss of naive T cells and central memory cells, as well as the proliferation of effector memory cells in the CD8 + T-cell compartment. The transition to a more differentiated state of chromatin openness that provides DNA accessibility for transcriptional regulators was observed in naive T cells and central memory cells in the elderly; there was also loss of chromatin availability on gene promoters in old naive cells, which was partly mediated by the loss of nuclear respiratory factor 1 (NRF1). An analysis of methylation data of peripheral blood mononuclear cells (PBMCs) among the Italian population performed by Horvath et al. [49] revealed that the biological age of centenarians was less than their chronological age. While studying the profile of immune cells among "the Nikoyans" (a population from Costa Rica characterized by longevity), McEwen et al. [50] found that this population had a significantly higher number of predicted CD8 + T naive cells and a lower content of CD8 + T memory cells compared to "non-Nikoyans," which indicates a younger profile of immune cells. Also, they demonstrated that the epigenetic characteristic of longevity in Nikoyans is a lower variability in their DNA methylation compared to non-Nikoyans.

B Lymphocytes: Considering the role of epigenetic mechanisms in the differentiation and functioning of B cells, age-related epigenetic changes may be responsible for decreased humoral immunity in the elderly. Loss of function of B cells and their precursors, reduction of immunoglobulin diversity and affinity, and shifts in the ratio of naive and committed subpopulations of peripheral B cells are typical for the aging of the immune system. Hematopoietic stem cells (HSCs) lose their ability to differentiate with age, and epigenetic modifications are critically involved in these changes. Aged mice had HSCs with aberrant gene expression profiles due to epigenetic deregulation. With aging, defects were observed both in the early and late stages of the maturation and differentiation of B cells.

Conclusion and Perspectives

According to the review data, a lot of new information was obtained in recent years regarding the understanding of the role of epigenetic mechanisms in the regulation of genome activity, including genes associated with the immune system. After analyzing and summarizing this information, we can draw the following basic conclusions: 1) epigenetic mechanisms modulate chromatin states and determine gene expression profiles; 2) epigenetic mechanisms play a critical role in the development and functioning of immune system; 3) strictly regulated functioning of the immune system is essential to maintain a healthy state of the body; 4) the environment modifies epigenetic marks throughout the entire life cycle; and 5) epigenetic marks are potentially reversible.

As for the role of epigenetic modifications in the aging of body cells and, particularly, immune cells, despite the

abundance of data on their involvement in aging processes, there are still gaps and questions in this area that require thorough investigation. In particular, the epigenetic changes causally related to the aging process, and how and via what mechanisms they cause immune aging should be determined. Solving these problems undoubtedly requires great efforts. However, these efforts are justified. Given that epigenetic marks are potentially reversible, knowledge about how the environment contributing to the development of age-related pathology modulates the immune system via epigenetic mechanisms can lead to the development of innovative strategies for the prevention and management of human diseases.

Finally, since several age-related epigenetic changes are similar in different tissues, they can already potentially be used as biomarkers of phenotypes of age-related diseases in biological samples such as blood or saliva. However, most importantly, considering that both internal and external factors change epigenetic marks throughout life, we should clearly realize that a healthy lifestyle that positively modulates our epigenome could be the most effective method of preventing age-related diseases and ensuring healthy aging today.

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КОРРЕКЦИЯ МЕТАБОЛИЧЕСКОГО ПРОФИЛЯ ПАЦИЕНТОВ С ОБСТРУКТИВНЫМ АПНОЭ СНА В ЗАВИСИМОСТИ ОТ ДЛИТЕЛЬНОСТИ СЕАНСОВ CPAP-ТЕРАПИИ

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Metabolic Profile Correction in Patients with Obstructive Sleep Apnea Depends on the Duration of CPAP Therapy Sessions

Резюме

Обструктивное апноэ сна (ОАС) является распространённым гетерогенным хроническим заболеванием с фрагментацией сна, метаболическими и сердечно-сосудистыми нарушениями. Терапия постоянным положительным воздухоносным давлением (CPAP-терапия) служит основным методом лечения пациентов ОАС. Однако, воздействие длительно проводимой CPAP-терапии с ночными сеансами более 6 часов остается малоизученным. Целью исследования явилось изучение эффектов различной длительности ночных сеансов CPAP-терапии на «метаболический профиль» пациентов с тяжёлым течением ОАС. **Материалы и методы.** В ретроспективное исследование «случай-контроль» сравнения двух режимов CPAP-терапии путём подбора пар из числа пациентов с верифицированным тяжёлым ОАС (индекс апноэ-гипопноэ >30/ч), артериальной гипертензией, ожирением I-II степени по классификации ВОЗ (1997), подписавших информированное согласие, были сформированы две группы по 18 человек в каждой, сопоставимые по возрасту, антропометрическим и сомнографическим показателям, использующие CPAP-терапию 4-6 ч/ночь и более 6 ч/ночь соответственно. Пациенты получали CPAP-терапию в течение года, визиты осуществлялись на 3, 6 и 12 месяцы. Характер и тяжесть апноэ сна верифицировалась в ходе ночной компьютерной сомнографии (КСГ) на аппаратном комплексе WatchPAT-200 (ItamarMedical, Израиль) с оригинальным программным обеспечением zzzPAT™SW ver. 5.1.77.7 (ItamarMedical, Израиль) путём регистрации основных респираторных полиграфических характеристик в период 23:00 — 7:30. Оптимальный лечебный уровень CPAP-терапии титровался в домашних условиях с использованием аппаратов для автоматического выбора лечебного давления («PR System One REMstar Auto CPAP Machine with A-Flex» (Philips Respironics, США)) в течение 7 дней после диагностического исследования. Для оценки показателей комплаенса пациентов использовалось оригинальная программа анализа комплаентности Encore Pro v.2.14 (Philips Respironics, США). **Результаты.** При исходной сопоставимости групп уже к 3-му месяцу терапии пациенты группы CPAP >6 ч/ночь демон-

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стрировали статистически значимое преимущество перед пациентами группы с сеансами 4-6 ч по показателям сонливости (ESS), окружности шеи и тестостерона. К 6-му месяцу в группе CPAP >6 ч/ночь возникали статистически значимые различия групп по индексу массы тела, индексу висцерального ожирения, пероральному глюкозотолерантному тесту, индексу инсулинорезистентности, показателям липидного обмена (липопротеиды высокой и низкой плотности, триглицериды, Апо-В), лептина, инсулина натощак. К 12-му месяцу терапии группа CPAP >6 ч/ночь имела улучшение показателей по окружности талии, глюкозы крови натощак и мочевой кислоты. Возникшие различия между группами сохранялись на протяжении всего периода терапии. **Выводы.** Длительно (в течение 12 мес.) проводимая в домашних условиях CPAP-терапия сеансами >6 ч/ночь имеет преимущество над терапией с сеансами 4-6 ч/ночь в достижении более быстрого, выраженного и клинически значимого улучшения показателей метаболического профиля и гормонального фона у пациентов ОАС тяжёлого течения.

Ключевые слова: *обструктивное апноэ сна, ОАС, CPAP-терапия, WatchPAT-200, компьютерная сомнография, КСГ, метаболический профиль, гормональный фон*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Obstructive sleep apnea (OSA) is a common, heterogeneous chronic disease with sleep fragmentation, metabolic and cardiovascular disorders. Continuous Positive Air Pressure (CPAP) therapy is the primary treatment for patients with OSA. However, the effects of long-term CPAP therapy with night sessions > 6 hours remain poorly understood. The aim of the study was to study the effects of different durations of night sessions of CPAP therapy on the "metabolic profile" of patients with severe OSA. **Materials and methods.** In a retrospective case-control study comparing two CPAP-therapy regimens by matching pairs from among patients with verified severe OSA (apnea-hypopnea index> 30/h), arterial hypertension, obesity of I-II degrees according to the WHO classification (1997), signed informed consent, 2 groups of 18 people each were formed, comparable in age, anthropometric and somnographic indicators, using CPAP therapy 4-6 hours / night and more than 6 hours / night, respectively. Patients received CPAP therapy for a year, visits were carried out at 3, 6 and 12 months. The severity of sleep apnea was verified during nighttime computed somnography (CSG) on WatchPAT-200 hardware (ItamarMedical, Israel) with original software zzzPAT™SW ver. 5.1.77.7 (ItamarMedical, Israel) by registering the main respiratory polygraphic characteristics from 11.00 PM to 7:30 AM. The optimal therapeutic level of CPAP therapy was titrated at home using devices for automatic selection of therapeutic pressure (PR System One REMstar Auto CPAP Machine with A-Flex (Philips Respironics, USA)) within 7 days after the diagnostic study. To assess the compliance of OSA patients at 3-6-12 months of CPAP-therapy, we used the original compliance analysis program Encore Pro v.2.14 (Philips Respironics, USA). **Results.** With the initial comparability of the groups, by the 3rd month of therapy, patients with CPAP > 6 h/night showed a statistically significant advantage over the patients with 4-6 h CPAP-therapy in ESS, neck circumference and testosterone. By the 6th month, statistically significant differences of BMI, VAI, leptin, oral glucose tolerance test, fasting insulin, HOMA-IR, lipid metabolism (HDL, LDL, triglycerides, Apo-B) appeared. By the 12th month of therapy, the CPAP group > 6 h/night had a statistically significant advantage in waist circumference, fasting blood glucose and uric acid. Differences between groups at control points persisted throughout the observation period. **Conclusions.** Long-term home-based CPAP therapy with sessions > 6 h/night has an advantage over therapy with sessions 4-6 h/night in achieving a rapid and pronounced improvement in metabolic profile and hormonal levels in patients with severe OSA.

Key words: *obstructive sleep apnea, OSA, CPAP-therapy, WatchPAT-200, computer somnography, CSG, metabolic profile, hormonal levels*

Conflict of interests

The authors declare no conflict of interests

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AHI — apnea-hypopnea index, BMI — body mass index, BP — blood pressure, CPAP — constant positive air pressure, DI — desaturation index, ESS — Epworth Sleepiness Scale, GCP — good clinical practice, HDL — high-density lipoproteins, HOMA-IR — insulin resistance index, HR max — maximum night heart rate, HR min — minimum night heart rate, LDL — low density lipoproteins, NSG — night somnography, NC — neck circumference, OGTT — oral glucose tolerance test, OSA — obstructive sleep apnea, REM sleep — rapid eye movement sleep, SpO_2 mean — mean night saturation, SpO_2min — minimum night saturation, STOP-BANG — obstructive sleep apnea marker scale, TSat90 — time at saturation less than 90%, URT — upper respiratory tract, WC — waist circumference

Introduction

Obstructive sleep apnea (OSA), a common heterogeneous chronic disease with cyclic respiratory pauses (apnea) and nocturnal hypoxemia/desaturation, is characterized by sleep fragmentation, excessive daytime sleepiness (EDS), and metabolic and cardiovascular disorders [1, 2]. Also, OSA is directly associated with an increased risk of fatal and nonfatal cardiovascular complications (CVC) [2, 3]. Continuous positive airway pressure (CPAP) therapy is the main treatment method for patients with OSA of different severity. Compliance with the CPAP therapy regimen is critical for patients with OSA in improving their quality of life, controlling blood pressure (BP), and eliminating EDS [4]. An analysis of 82 randomized clinical trials (RCTs) by Rotenberg B.W. et al. (2016) showed that non-compliance with the CPAP therapy regimen reduced its effectiveness in 1/3 of treated patients with OSA. Compliance with treatment was low in patients with OSA who had minimal severity of symptoms, heterogeneous metabolic disorders, or comorbidities in the form of neurological disorders [5]. Paradoxically, most RCTs were performed in patients with moderate OSA, on CPAP therapy for no more than three months, without assessing the "metabolic profile" even in the presence of carbohydrate and lipid metabolism disorders [6]. Our study sought to analyze the "metabolic profile" of patients with severe OSA taking into account the duration of night CPAP sessions during 12 months of treatment.

Materials and Methods

Study Design. In a retrospective case-control study for comparing two CPAP therapy regimens by matching pairs from patients with verified severe OSA (apnea-hypopnea index > 30/h), arterial hypertension, obesity of grade I-II according to the WHO classification (1997), who signed informed consent, two groups were formed, each with 18 subjects, comparable in age, anthropometric and somnographic parameters; using CPAP therapy 4–6 h/night, or more than 6 h/night, respectively. Patients received CPAP therapy for one year; visits were made in 3, 6, and 12 months. The inclusion criteria were the following: 1) males; 2) apnea-hypopnea index (AHI) > 30/h; 3) duration of CPAP therapy > 4 hours/night during one year of follow-up; and 4) signed informed consent. Matching of pairs of patients was performed according to the following criteria: 1) age ±5 years; 2) BMI ±1 kg/m^2; 3) neck circumference (NC) ±1 cm; 4) AHI ±10/h; 5) desaturation index (DI) ±5 events/hour; 6) time at saturation less than 90% (TSat90) ±5%.

This study was carried out at the Department of Phthisiology and Pulmonology of the Faculty of Medicine of A.I. Evdokimov Moscow State Medical and Dental University (A.I. Evdokimov MSMDU of the Russian Ministry of Health) at the Central Union Hospital of the Russian Federation (Moscow); it met good clinical practice (GCP) standards and the principles of the Helsinki Declaration and was approved by the Interacademic Ethics Committee of A.I. Evdokimov MSMDU. Patients were recruited from 2017 to 2020.

Night Somnography (NSG). To detect obstructive sleep apnea, we performed night somnography using a computer-based somnography (CSG) method based on the technology for determining apnea episodes and their consequences by varying changes in peripheral arterial tone (PAT technology) in accordance with the unified rules and recommendations of the American Academy of Sleep Medicine (AASM) [7, 8]. OSA was found using a WatchPAT-200 portable CSG devicer (ItamarMedical, Caesarea, Israel) with original zzzPAT™SW software, ver. 5.1.77.7 (ItamarMedical, Caesarea, Israel) by measuring the main respiratory polygraphic parameters between 11:00 p.m. and 7:30 a.m. Sleep apnea-hypopnea index (AHI) of more than 30/h corresponded to severe OSA. Assessment of nocturnal oxygen desaturation index (ODI), mean and minimum nocturnal saturation (SpO_2), heart rate (HR), and sleep stages was performed in accordance with international guidelines [9, 10].

CPAP Therapy. The optimal therapeutic level of CPAP was titrated at home using devices for automatic selection of therapeutic pressure (PR System One REMstar Auto CPAP Machine with A-Flex (Philips Respironics, USA)) within 7 days after the diagnostic study. To assess the compliance parameters of patients with OSA at months 3–6–12 of CPAP therapy, we used the original compliance analysis software Encore Pro v. 2.14 (Philips Respironics, USA). The main analyzed parameter was the duration of the night session of CPAP therapy with the function of auto-adaptation to the patient's inspiration and expiration (A-Flex); according to this parameter, the patients were divided as: 1) low-compliant < 4 h/night; 2) medium-compliant—4–6 h/night; 3) highly compliant > 6 h/night [11].

Laboratory Tests. Venous blood sampling was carried out in the morning, in a fasting state, after 12 hours of fasting. Laboratory tests were standardized and were carried out on the same laboratory equipment using INVITRO reagent kits for the determination of total cholesterol (TC), low (LDL) and high-density lipoproteins (HDL), triglycerides, uric acid, apolipoprotein B (Apo-B), C-reactive protein (CRP), leptin, testosterone, insulin, and glucose— in a fasting state and 2 hours after the standard oral glucose tolerance test (OGTT). HOMA-IR index was calculated using the following formula: fasting

glucose (mmol/L) × fasting insulin (μU/mL)) ÷ 22.5. Sensitivity to insulin was considered to be within the normal range at HOMA-IR value ≤ 2.77.

Statistical Analysis. Statistical data analysis was carried out using commercial software packages STATISTICA 13.0 (TIBCO Software Inc., USA) and PASW Statistics v.18 (IBM, USA). The distributions of quantitative and qualitative ordinal characteristics (with more than 5 ranks) are represented by medians (Me) and quartiles (lower, Q1, and upper, Q3); qualitative characteristics—in the form of the absolute number of observations (n) and the percentage (%) of the total number of patients in the group. Pairwise comparison of unrelated groups in terms of quantitative and qualitative ordinal (with more than 5 ranks) characteristics was carried out using the nonparametric Mann–Whitney test. The threshold level of statistical significance was considered to be 0.05; for multiple comparisons, the Bonferroni correction was applied.

Results

Intergroup comparison of the parameters of the "metabolic profile" (anthropometric, metabolic, hormonal) before starting CPAP therapy showed the comparability of groups (Table 1).

Further, the groups were compared according to the studied parameters at three subsequent visits.

Таблица 1. *Характеристика групп пациентов до начала терапии*
Table 1. *Baseline patients' parameters*

Parameter	CPAP 4-6 hrs (n=18)	CPAP >6 hrs (n=18)	P, Mann-Whitney test
Age, yars	47 [43; 50]	46 [43; 47]	0,45
BMI, kg/m^2	34,35 [31,6; 35,5]	33,1 [32,2; 35,3]	0,54
Neck circumference, cm	44,8 [43,5; 45,5]	45,0 [44,0; 45,5]	0,65
Waist circumference, cm	111,75 [107; 117]	111,75 [108; 115]	0,70
Epworth sleepiness scale (ESS), score	12 [9; 12]	12 [12; 13]	0,22
Visceral Adiposity Index, (VAI)	3,21 [2,98; 3,58]	3,3 [2,81; 3,49]	0,96
Computer somnography data			
Apnoea-hypopnea index (AHI) (h^{-1})	50,2 [38,4; 56,2]	50,1 [39,4; 54,68]	0,87
Oxygen desaturation index (ODI), (h^{-1})	38,25 [24,1; 51,3]	39,2 [21,2; 47,1]	0,55
Percentage of time with oxygen saturation < 90%, (TSat90), %	23,0 [15,2; 29,1]	23,75 [5,2; 37,0]	0,95
SpO_2 mean, %	91,0 [89,0; 92,0]	91,5 [89,0; 94,0]	0,42
SpO_2min, %	76,5,0 [73,0; 81,0]	73,5 [66,0; 83,0]	0,41
HR min, min^{-1}	46,5 [45,0; 48,0]	46,5 [43,0; 50,0]	0,99
HR max, min^{-1}	101,5 [94,0; 108,0]	101,0 [99,0; 102,0]	0,43
REM sleep, %	15,0 [13,6; 26,5]	14,6 [13,3; 20,4]	0,53
Light sleep, %	74,4 [59,3; 80,65]	75,7 [60,6; 81,1]	0,66
Deep sleep, %	10,0 [6,03; 13,5]	7,6 [6,2; 11,6]	0,95
Laboratory data			
Fasting blood glucose, mmol/l	5,6 [5,4; 5,9]	5,6 [5,4; 5,8]	0,75
Oral glucose tolerance test, mmol/l	7,2 [6,2; 8,0]	7,4 [6,0; 8,0]	0,90
Fasting insulin, μU/ml	16,9 [14,5; 20,3]	18,4 [15,3; 19,8]	1,00
HOMA-IR	4,5 [3,52; 5,14]	4,77 [3,6; 5,04]	0,96
HDL, mmol/l	0,98 [0,92; 0,99]	0,95 [0,91; 1,0]	1,00
LDL, mmol/L	3,49 [3,09; 3,72]	3,43 [3,11; 3,71]	0,91
Triglycerides, mmol/L	2,29 [2,16; 2,42]	2,16 [2,11; 2,42]	0,48
Apolipoprotein B, g/L	1,3 [1,26; 1,34]	1,36 [1,24; 1,44]	0,14
Uric acid, μmol/L	452,5[430,0;471,0]	460,5[432,0;470,0]	0,65
Testosterone, nmol/l	7,93 [7,1; 8,79]	8,13 [7,44; 8,72]	0,41
Leptin, ng/ml	25,1 [19,8; 32,6]	27,7 [22,5; 34,5]	0,99

Note: data are presented as medians and quartiles, Me [Q1; Q3]

Clinical and Anthropometric Parameters

Comparison of patients of the studied groups in terms of sleepiness (ESS) and neck circumference shows a statistically significant difference by month 3 (Table 2).

A clinically and statistically significant advantage of CPAP > 6 h/night compared to 4–6 h sessions was observed at Month 6 in terms of BMI and VAI, and at Month 12 of therapy—in terms of decreased waist circumference. Differences between the groups that arose at the control points persisted throughout the follow-up period. Established patterns indicate the advantage of CPAP > 6 h/night in improving anthropometric parameters and reducing the volume of visceral fat.

Laboratory Parameters of Metabolic Disorders

The comparison of patients of the studied groups in terms of carbohydrate, lipid, purine metabolism, and hormonal levels is presented in Table 3.

A clinically and statistically significant advantage of CPAP > 6 h/night before shorter sessions was observed as early as Month 3, in terms of testosterone; at Month 6, in terms of OGTT, HOMA-IR, lipid metabolism parameters (HDL, LDL, triglycerides, Apo-B), leptin, and fasting insulin; at Month 12, in terms of uric acid. Differences between the groups that arose at the control points persisted throughout treatment. The patterns established indicate the advantage of CPAP > 6 h/night in improving the "metabolic profile" and hormonal levels in patients with OSA.

Results and Discussion

CPAP therapy, the first-line therapy for patients with moderate and severe OSA, is deemed capable of effectively eliminating sleep disorders, nocturnal hypoxemia, and excessive daytime sleepiness (EDS). Also, CPAP therapy has a positive effect on the activity of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS), which is closely related to the overall energy balance [12]. However, a contradiction was found: patients with OSA either lost weight [13] or did not [14]. A meta-analysis conducted by Drager LF et al. (2015) included 25 RCTs summarizing data on 3,181 patients with OSA who did not use CPAP therapy for more than three months. This study demonstrated the possibility of a slight increase in BMI and body weight in such patients in connection with CPAP therapy, which could worsen "cardiometabolic health" with prolonged (more than six months) use of respiratory support [15]. Results of our study of the positive effect of one-year CPAP therapy on the metabolic profile of patients with severe OSA contradict previous data [15]. However, they are fully in line with the results of recent studies that showed that the duration of night sessions of CPAP therapy is an important prognostic factor of a positive effect on the metabolic profile of

Table 2. *Comparison of clinical and anthropometric parameters of OSA patients on CPAP therapy*

Parameter	Study group / P, test Mann-Whitney	3 months	6 months	12 months
Сонливость (ESS), points	CPAP 4-6 ч. (n=18)	9,5 [8; 11]	8 [7; 8]	7 [7; 8]
	CPAP >6 ч. (n=18)	7,5 [7; 9]	5 [4; 6]	3 [2; 5]
	P	**0,0068**	**<0,0001**	**<0,0001**
BMI, kg/m^2	CPAP 4-6 ч. (n=18)	34,3 [31,6; 35,5]	33,6 [31,1; 34,7]	32,7 [30,7; 34,1]
	CPAP >6 ч. (n=18)	32,3 [31,6; 34,0]	30,7 [29,4; 32,5]	29,1 [27,7; 31,5]
	P	0,11	**0,0075**	**0,0009**
Neck circumference, cm	CPAP 4-6 ч. (n=18)	44,8 [43,5; 45,5]	43,0 [43,0; 45,0]	43,0 [42,0; 44,0]
	CPAP >6 ч. (n=18)	43,0 [43,0; 44,0]	42,5 [42,0; 43,0]	42,0 [42,0; 42,0]
	P	**0,0027**	**0,0025**	**0,0005**
Waist circumference, cm	CPAP 4-6 ч. (n=18)	111,75 [107; 117]	110,0 [104; 116]	109,0 [104; 114]
	CPAP >6 ч. (n=18)	111,0 [107; 114]	108,5 [104; 111]	105,0 [99; 107]
	P	0,45	0,22	**0,02**
Visceral Adiposity Index, (VAI)	CPAP 4-6 ч. (n=18)	3,21 [2,83; 3,58]	2,78 [2,53; 3,24]	2,52 [2,37; 2,89]
	CPAP >6 ч. (n=18)	2,94 [2,54; 3,19]	2,19 [2,01; 2,6]	1,76 [1,57; 1,96]
	P	0,21	**0,0002**	**<0,0001**

Note: data are presented as medians and quartiles, Me [Q1; Q3]

patients with OSA when it is carried out at home for a long time [16–18]. Our study is unique in the establishment of a threshold value for nocturnal respiratory support that lasts more than 6 h/night, which can effectively control and restore the "metabolic profile" of patients with severe OSA. In our opinion, this will allow practitioners to change the treatment strategy of CPAP therapy towards extending its duration and to plan the follow-up of patients with OSA, which can be carried out in an outpatient setting.

Table 3. *Comparison of biochemical parameters of metabolic disorders in OSA patients on CPAP therapy*

Parameter	Study group / P, test Mann-Whitney	3 months	6 months	12 months
Carbohydrate metabolism				
	CPAP 4-6 ч. (n=18)	5,6 [5,4; 5,8]	5,6 [5,4; 5,8]	5,6 [5,4; 5,8]
Fasting blood glucose, mmol/l	CPAP >6 ч. (n=18)	5,6 [5,4; 5,7]	5,5 [5,2; 5,7]	4,95 [4,6; 5,4]
	P	0,45	0,12	**0,0002**
	CPAP 4-6 ч. (n=18)	7,2 [6,2; 8,0]	7,2 [5,9; 8,0]	7,2 [5,9; 7,6]
Oral glucose tolerance test, mmol/l	CPAP >6 ч. (n=18)	7,1 [6,0; 7,7]	5,95 [5,5; 6,5]	5,95 [5,5; 6,2]
	P	0,56	**0,0089**	**0,0034**
	CPAP 4-6 ч. (n=18)	16,2 [14,0; 19,5]	15,0 [12,9; 17,4]	14,2 [12,4; 16,8]
Fasting insulin, μU/ml	CPAP >6 ч. (n=18)	16,2 [12,5; 18,2]	12,5 [10,2; 14,3]	9,4 [8,5; 10,8]
	P	0,34	**0,019**	**<0,0001**
	CPAP 4-6 ч. (n=18)	4,24 [3,42; 4,94]	3,85 [3,01; 4,48]	3,64 [2,88; 4,25]
HOMA-IR	CPAP >6 ч. (n=18)	4,11 [3,06; 4,59]	3,01 [2,42; 3,72]	2,01 [1,72; 2,59]
	P	0,33	**0,02**	**<0,0001**
Lipid metabolism				
	CPAP 4-6 ч. (n=18)	0,98 [0,92; 1,00]	0,99 [0,92; 1,06]	0,99 [0,96; 1,06]
HDL, mmol/l	CPAP >6 ч. (n=18)	0,98 [0,96; 1,07]	1,13 [1,03; 1,17]	1,19 [1,09; 1,24]
	P	0,25	**0,0016**	**<0,0001**
	CPAP 4-6 ч. (n=18)	3,49 [3,08; 3,72]	3,48 [3,05; 3,71]	3,38 [2,98; 3,65]
LDL, mmol/L	CPAP >6 ч. (n=18)	3,33 [3,03; 3,65]	2,9 [2,75; 3,21]	2,58 [2,38; 2,83]
	P	0,57	**0,018**	**0,0003**
	CPAP 4-6 ч. (n=18)	2,25 [2,08; 2,42]	2,04 [1,93; 2,17]	1,86 [1,83; 1,97]
Triglycerides, mmol/L	CPAP >6 ч. (n=18)	2,04 [2,00; 2,34]	1,65 [1,61; 1,85]	1,51 [1,36; 1,57]
	P	0,12	**<0,0001**	**<0,0001**
	CPAP 4-6 ч. (n=18)	1,3 [1,26; 1,34]	1,29 [1,26; 1,33]	1,29 [1,23; 1,33]
Apolipoprotein B, g/L	CPAP >6 ч. (n=18)	1,24 [1,19; 1,32]	1,19 [1,16; 1,26]	1,15 [1,13; 1,18]
	P	0,15	**0,0017**	**<0,0001**
Purine metabolism				
	CPAP 4-6 ч. (n=18)	452,5[427,0;471,0]	438,5[420,0;455,0]	429,5[414,0;448,0]
Uric acid, μmol/L	CPAP >6 ч. (n=18)	452,0[428,0;462,0]	425,0[402,0;429,0]	381,0[361,0;401,0]
	P	0,84	0,053	**<0,0001**
Hormonal levels				
	CPAP 4-6 ч. (n=18)	7,93 [7,1; 8,79]	8,26 [7,61; 9,0]	9,11 [8,22; 10,1]
Testosteron, nmol/l	CPAP >6 ч. (n=18)	9,63 [9,08; 10,68]	14,87 [12,46; 15,89]	19,22 [15,67; 22,17]
	P	**0,0008**	**<0,0001**	**<0,0001**
	CPAP 4-6 ч. (n=18)	24,9 [19,5; 32,6]	23,05 [18,2; 32,0]	23,7 [16,8; 26,7]
Leptin, ng/ml	CPAP >6 ч. (n=18)	26,4 [20,1; 30,5]	19,9 [17,3; 22,6]	12,6 [10,4; 13,6]
	P	0,70	**0,031**	**<0,0001**

Note: data are presented as medians and quartiles, Me [Q1; Q3]

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ФАКТОРЫ РИСКА РАЗВИТИЯ РАННИХ СТРУКТУРНЫХ ИЗМЕНЕНИЙ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ У ПАЦИЕНТОВ ПЕРВИЧНЫМ ГИПОТИРЕОЗОМ

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Risk Factors Promoting Early Cardiovascular Structure Disorders in Patients with Primary Hypothyroidism

Резюме

Цель. Выявление факторов, способствующих развитию ранних структурных изменений сердечно-сосудистой системы у пациентов первичным гипотиреозом в зависимости от компенсации заболевания. **Материалы и методы.** Обследовано 163 женщины с первичным гипотиреозом в возрасте 62 [55;67] лет, которые были разделены на группы: 1 группа — 54 пациентки в возрасте 62,0 [57;68] лет с субкомпенсированным заболеванием, 2 группа — 15 пациенток в возрасте 59 [53;66] лет с некомпенсированным заболеванием и 3 группа — 94 пациентки в возрасте 63 [53;66] лет с компенсированным гипотиреозом. Всем пациенткам выполнено физикальное обследование, трансторакальная эхокардиография, оценка продольной сократительной функции левого желудочка методом «speckle tracking», оценка функции эндотелия, липидного профиля. Проводился регрессионный анализ с использованием в качестве предикторов тиреотропного гормона, свободного Т4, возраста, давности заболевания, причины гипотиреоза, наличия менопаузы и натурального логарифма тиреотропного гормона, а в качестве зависимых переменных — ряда параметров состояния сердца и липидного обмена. **Результаты.** При проведении математического моделирования показано, что наибольшее значение в процессах ремоделирования миокарда левого желудочка у пациентов первичным гипотиреозом имеет сочетание таких параметров, как возраст, давность заболевания и уровень тиреотропного гормона. В то же время, значимое влияние на показатель величины комплекса интима медиа оказывает только возраст. **Заключение.** Модифицируемыми факторами, определяющими ремоделирование левого желудочка, морфофункциональное состояние стенки сосудов у пациентов гипотиреозом, являются индекс массы тела и уровень тиреотропного гормона, а немодифицируемыми — возраст и давность заболевания.

Ключевые слова: *первичный гипотиреоз, модель поражения сердца, ремоделирование левого желудочка, липидный обмен*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Objective. To develop the pattern of early cardiovascular disorders in patients with primary hypothyroidism based on the analysis of relationship between patient's thyroid status and some functional cardiovascular parameters depending on compensation status. **Materials and methods.** The examination of 163 women aged 62 [55;67] years with primary hypothyroidism was performed. The patients were divided into groups: 1 group included 54 patients aged 62.0 [57;68] years with subcompensated disease, 2 group consisted of 15 patients aged 59 [53;66] years with non-compensated disease and 3 group included 94 patients aged 63 [53;66] years with compensated hypothyroidism. Physical examination, transthoracic echocardiography, assessment of global left ventricle longitudinal strain by speckle tracking method, endothelial function and laboratory tests were performed to all patients. Regression analysis using thyroid stimulating hormone, free T4, age, duration of the disease, cause of hypothyroidism, menopause presence and natural thyroid stimulating hormone logarithm as predictors and some cardiovascular parameters of heart condition and lipid metabolism as dependent valuables was made. **Results.** Mathematic modeling demonstrated that the combination such factors as age, duration of disease and thyroid stimulating hormone level is the most important in left ventricle remodeling processes. However, the age only has significant influence on intima media thickness. **Conclusion.** Left ventricle remodeling, morphologic functional status of blood vessel wall and decrease of glomerular filtration rate are basically determined by such modified and non-modified factors as body mass index, age, duration of hypothyroidism and thyroid stimulating hormone level.

Key words: *primary hypothyroidism, heart disorder pattern, left ventricle remodeling, lipid metabolism*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BA — brachial artery, BMI — body mass index, DBP — diastolic blood pressure, EF — ejection fraction, fT4 — free T4, GFR — glomerular filtration rate, GLPS AVRG — averaged global longitudinal peak systolic strain, HDL-C — high-density lipoprotein cholesterol, IARH — increase in artery diameter in reactive hyperemia test, IMT — intima media thickness, LDL-C — low density lipoprotein cholesterol, LVMMI — left ventricular myocardial mass index, LV — left ventricle, Me — median, non-HDL-C — non-high density lipoprotein cholesterol, RWT — relative wall thickness, SBP — systolic blood pressure, TC — total cholesterol, TG — triglycerides, TSH — thyroid stimulating hormone, Q1 — 25th percentile, Q3 — 75th percentile

Diseases of the circulatory system are the leading cause of death not only in the Russian Federation but in the whole world [1]. In recent years, the role of other possible risk factors that affect the development and progression of cardiovascular pathology was studied, along with already well-established factors (smoking, arterial hypertension (AH), hypercholesterolemia, etc.) [1]. Thyroid insufficiency may be one of the risk factors. Opinions still differ on whether primary hypothyroidism is a risk factor for cardiovascular events. The role of subclinical hypothyroidism as a predictor of cardiovascular morbidity and mortality is especially debatable. This is probably because such an effect is most often assessed via surrogate markers, for example, impaired lipid metabolism, endothelial dysfunction, increased rigidity of the vascular wall, and cardiac function [2–4].

Results of several observational studies supported the hypothesis that hypothyroidism accelerated the course of atherosclerosis of coronary arteries [4]. However, according to a number of authors, subclinical hypothyroidism is associated with an increased risk of heart failure but not with the risk of coronary heart disease or peripheral vascular atherosclerosis; and the normalization of TSH (thyroid stimulating hormone) in elderly patients leads to no significant changes in intima media thickness and manifestations of the atherosclerosis of carotid arteries [5].

In recent decades, the role of hypothyroidism in the development of vascular endothelial dysfunction was demonstrated, as well as the association between thyroid hormone deficiency and the development of AH and left ventricular (LV) dysfunction [3–5].

A number of authors describe a moderate increase in triglycerides and low-density lipoprotein cholesterol (LDL-C) levels in patients with subclinical hypothyroidism compared with euthyroid subjects [5]. On the

contrary, a population-based study in 1,350 participants demonstrated no difference in mean total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) in patients with subclinical hypothyroidism compared with euthyroid subjects even after adjustment for sex, age and body mass index (BMI) [6]. However, the same study showed that average TSH levels were higher in individuals with dyslipidemia, suggesting the relationship between TSH and TC, as well as TSH and LDL-C in overweight women [6].

Data on the effect of substitution therapy on the cardiovascular system in patients with hypothyroidism of different types are also inconclusive. A number of studies demonstrated that the administration of levothyroxine in patients with subclinical hypothyroidism leads to a significant decrease in TC and LDL-C levels [5]. Other authors claim that replacement therapy with levothyroxine increases the risk of general and cardiovascular mortality in patients 80+ with primary hypothyroidism and heart failure [7]. There are no data describing the state of the cardiovascular system depending on the degree of disease compensation.

Objective of the study: to establish the key risk factors for the development of structural changes in the heart and blood vessels in patients with primary hypothyroidism depending on its compensation.

Materials and Methods

One hundred and sixty-three women with primary hypothyroidism were examined (diagnosed in accordance with the recommendations of the Russian Association of Endocrinologists, 2021); the primary hypothyroidism was caused by autoimmune thyroiditis in 104 (63.2%) patients (39 in Group 1 (72.2%), 11 in Group 2 (73.3%), and 64 in Group 3 (68.0%)), by postoperative hypothyroidism—in 54 (33%) patients (15 (27.8%), 4 (26.7%), and 29 (31.6%), respectively), and by diffuse goiter—in 3 (1.8%) patients (3 (3.19%) only in Group 1).

The study was open-label, prospective, with three groups. Inclusion criteria for this study were consent to participate, the presence of subcompensated, uncompensated, or compensated primary hypothyroidism, age 18+, female. Exclusion criteria were the presence of oncological, systemic diseases, decompensated heart and lung failure, diabetes mellitus. The study was carried out in accordance with the principles of the World Medical Association Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the Izhevsk State Medical Academy.

All 163 patients meeting the inclusion and exclusion criteria were divided into three groups. Group 1 included 54 patients aged 62.0 [57; 68] with subcompensated hypothyroidism (TSH level > 4.0 μIU/L, free T4 (fT4) > 10 pmol/L); Group 2 included 15 patients aged 59 [53; 66] years with uncompensated hypothyroidism (TSH > 10 μIU/L, fT4 < 10 pmol/L), and Group 3 included 94 patients aged 63 [53; 66] with a disease compensated due to replacement therapy with levothyroxine (TSH > 4 μIU/L and fT4 > 10 pmol/L) [2]. All patients took levothyroxine agents. The patients received no menopausal hormone therapy.

Evaluation of concomitant treatment showed that statins were almost not prescribed for patients in all examined groups; beta blockers were prescribed significantly more often in the group of patients with decompensated hypothyroidism, while the number of patients receiving treatment with angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, calcium antagonists, diuretics, and combination therapy did not differ significantly between groups 1, 2, and 3 (Table 4).

All patients underwent a comprehensive general clinical examination with BMI calculation, determination of TC, TG, LDL-C and high-density lipoprotein cholesterol (HDL-C) levels, as well as cholesterol that is not related to high-density lipoprotein cholesterol (non-HDL-C). Transthoracic echocardiography was performed in accordance with the recommendations of the European and American Association of Echocardiography using Vivid 7 Dimension ultrasound device (GE Healthcare, USA) with an M4S phased array sector transducer and scanning frequency of 1.5–4.3 MHz [8]. Relative LV wall thickness (LVWT), Simpson's ejection fraction (EF), LV myocardial mass (according to the recommendations of the American Association of Echocardiography, ASE, 2016), LV myocardial mass index (LVMMI) were calculated. LV longitudinal strain was assessed using the ECHOPAC workstation version BT-08 integrated in an ultrasound scanner in an automated functional imaging application. This software is based on Speckle Tracking technology. Averaged global longitudinal peak systolic deformity (GLPS AVRG) was considered a parameter of global longitudinal LV systolic function [9]. Endothelial function was assessed by Doppler scanning of the brachial artery (BA) using an Esaote MyLab 70 device (Italy) with ultrasound at rest and in case of reactive hyperemia after three-minute clamping of shoulder vessels with a cuff. Flow-dependent dilation was calculated as the ratio of the change in BA diameter during reactive hyperemia to the diameter of the artery at rest expressed as a percentage of the initial diameter. Artery diameter increase by 10% or more was considered normal when conducting a reactive hyperemia test (IARH). Intima media thickness (IMT) was also determined [10].

Statistical processing was carried out in MS Excel, STATISTICA 10.0 Statsoft and RStudio using nonparametric criteria. To describe the quantitative criteria in

the group, median, 1st and 3rd percentiles (Me [1Q; 3Q]) were calculated. To compare independent samples, the Mann–Whitney test and the Kruskal–Wallis test for multiple comparisons were used. Nonparametric correlation analysis was performed using Spearman's rank correlation coefficient. The conclusion about statistical significance was made at $p < 0.05$.

Regression analysis was carried out in the RStudio statistical package based on the stats standard library. Linear and quadratic models were constructed by a search method among all possible combinations of factors. After creating quadratic models, insignificant interactions were excluded step by step. When carrying out regression analysis, the factors presented in Table 1 and designated as X_i, $i = \overline{1.7}$ were taken as the parameters that presumably affect the cardiovascular system. The following parameters were used as dependent variables (responses), which parameters are shown in Table 2 and designated as Y_i, $i = \overline{1.11}$. The quality of models was determined by the adjusted coefficient of determination R^2_{adj}, and the closer the value R^2_{adj} to 1, the better the model described the relationship between the response and factors. Response variation explained by the studied factors was also evaluated using R^2_{adj} [11].

Table 1. *The Factors Probable Affected Cardiovacular System in Patients with Hypothyroidism*

Symbol	Name
X_1	TSH
X_2	fT4
X_3	Age
X_4	Duration
X_5	Diagnosis
X_6	Menopause
$X_8 = ln\ X_1$	TSH_ln

Note: TSH — thyroid stimulating hormone, fT4 — free L-thyroxine, TSH_ln — linear logarithm of thyroid stimulating hormone

Table 2. *Dependent Variables Studied in Patients with Hypothyroidism*

Symbol	Name	R^2_{adj}	p-value
Y_1	Diameter increase in reactive hyperemia test	0,338	<0,001
Y_2	Total cholesterol	0,118	0,007
Y_3	Triglycerides	0,001	0,277
Y_4	Cholesterol LDL	0,123	0,003
Y_5	Cholesterol HDL	0,050	0,042
Y_6	Cholesterol non-HDL	0,040	0,044
Y_7	Glomerular filtration rate	0,241	<0,001
Y_8	Body mass index	0,049	0,023
Y_9	GLPS AVRG	0,064	0,024
Y_{10}	Relative wall thickness	0,099	<0,001
Y_{11}	Left ventricular mass index	0,513	<0,001
Y_{12}	Complex intima media value	0,306	<0,001

Note: GLPS AVRG — global left ventricle longitudinal strain average

Results

Comparative clinical and demographic characteristics of the examined patients are presented in Table 3. The average age of the examined patients was 62 [55; 67] years; no significant differences were found between the groups. Disease duration on average was 5 [1; 13] years; patients with compensated hypothyroidism had had that condition reliably longer than the patients in other groups. The average dose of levothyroxine was 50 [50; 100] μg; the dosage of levothyroxine in the group of compensated and subcompensated hypothyroidism differed significantly. Despite the absence of compensation, patients in Group 2 took a relatively high dose of levothyroxine (Table 3). The causes and duration of decompensation or subcompensation cannot be determined since patients in Groups 1 and 2 were examined irregularly and occasionally missed taking medications.

BMI in the examined patients averaged 29.14 [25.2; 32.9] kg/m^2; body weight in the group of uncompensated hypothyroidism was significantly higher than in other groups. Seventy-one of the examined patients (43.5%) had obesity of Grade 1 and higher; 49 (30.0%) patients were overweight; differences in the incidence of obesity and overweight between the groups were insignificant (Table 4).

Average office systolic blood pressure (SBP) was 140 [130; 159] mm Hg, diastolic (DBP)—85 [80, 92] mm Hg; however, blood pressure did not depend on disease compensation.

In general, AH was found in 114 (69.9%) examined patients; there were no significant differences between the groups. In 92 (56.4%) patients, AH was observed before the development of primary hypothyroidism.

Exertional angina of different functional classes was diagnosed in 55 (33.7%) patients. Eight (4.2%) patients had myocardial infarction, 8 (4.7%) patients had acute cerebrovascular accident; there were no significant differences in the frequency of these events in the examined groups (Table 4).

Assessment of lipid profile revealed increased average values of total cholesterol up to 6.1 [5.4; 7.0] mmol/L. Patients with uncompensated hypothyroidism demonstrated a tendency towards a more pronounced increase in total cholesterol compared with compensated and subcompensated disease, as well as a significant increase

in LDL-C up to 5.1 [4.8; 5.3] mmol/L compared to the other two groups. Also, non-HDL-C increased to 4.51 [3.7; 5.3] mmol/L in the entire population of examined patients, while TG and HDL-C levels were within the reference range: 1.4 [1.0; 1.96] mmol/L and 1.64 [1.32; 1.9] mmol/l, respectively (Table 5).

Table 3. *Clinical and Demographic Characteristics of Examined Patients*

Parameter	All sample (n=189)	Group 1 (n=70)	Group 2 (n=25)	Group 3 (n=94)	Kraskell-Wallis test, H, p	p-value
Age, years	62[55;67]	62,0[57;68]	59[53;66]	63[53;66]	1,4 p=0,49	p_{12}=0,15 p_{13}=0,9 p_{23}=0,2
Duration, years	5 [1;13]	4 [1;10]	5[0,4;10]	8,0 [4;15]	9,2 p=0,001	p_{12}=0,33 p_{13}=0,02 p_{23}=0,014
Levothyroxine dose, μg	50 [50;100]	50 [50;75]	75 [50;100]	50 [50;100]	8,3 p=0,01	p_{12}=0,1 p_{13}=0,006 p_{23}=0,8
Thyroid stimulating hormone, mIU/L	4,1 [1,97;9,1]	8 [5,06;10,6]	30 [17,9;44,0]	1,96 [0,74;2,8]	117,73 p=0,000	p_{12}=0,0001 p_{13}=0,0001 p_{23}=0,0001
Free T4, pM/L	13,6 [11,2;16,0]	13,8 [11,2;17,5]	7,9 [6,5;10,2]	14,4 [13,1;17,2]	19,59 p=0,0001	p_{12}=0,0002 p_{13}=0,05 p_{23}=0,001
Body mass index kg/m^2	29,14 [25,2;32,9]	29,3 [25,0;32,8]	35,17 [26,9;38,9]	28,6 [25,9;32,7]	5,4 p=0,05	p_{12}=0,003 p_{13}=0,85 p_{23}=0,0006
Systolic blood pressure, mm Hg	140 [130; 159]	140,0 [127;157]	140,0 [120; 165]	144,5 [132; 160]	1,57 p=0,45	p_{12}=0,95 p_{13}=0,43 p_{23}=0,69
Dyastolic blood pressure, mm Hg	85 [80, 92]	80,0 [77; 90]	90 [80; 94]	83,5 [75; 92]	2,6 p=0,26	p_{12}=0,95 p_{13}=0,43 p_{23}=0,69

Note: p_{12}, p_{13}, p_{23} — *p*-values– significant differences between respective groups

Table 4. *Qualitative characteristics in examined groups*

Parameter	Total sample n=163	Group 1 n=54	Group 2 n=15	Group 3 n=94	Chi-square, p-value
Arterial hypertension (n, %)	114 (69,9%)	36 (66,6%)	9 (60%)	69 (73,4%)	χ^2 12=0,23, p12=0,63 $\chi^2$13=0,76, p13=0,38 χ^2 23=1,14, p23=0,28
Obesity (n, %)	71 (43,5;)	22 (40,7%)	9 (60%)	40 (42,5%)	χ^2 12=1,76, p12=0,18 $\chi^2$13=0,05, p13=0,83 χ^2 23=1,76, p23=0,18
Overweight (n, %)	49 (30,0%)	13 (24,07%)	6 (40%)	30 (31,9%)	χ^2 12=1,49, p12=0,22 $\chi^2$13=1,02, p13=0,31 χ^2 23=0,38, p23=0,53
Angina (n, %)	55 (33,7%)	21 (38,8%)	5 (33,3%)	29 (30,8%)	χ^2 12=1,24, p12=0,26 $\chi^2$13=1,02, p13=0,31 χ^2 23=0,04, p23=0,84
History of myocardial infarction (n, %)	7 (4,3%)	3 (5,5%)	0 (0%)	4 (4,2%)	χ^2 12=0,87, p12=0,35 $\chi^2$13=0,13, p13=0,72 χ^2 23=0,66, p23=0,41
History of Stroke (n, %)	8 (4,9%)	4 (7,4%)	0)0%)	4 (4,2%)	χ^2 12=1,18, p12=0,27 $\chi^2$13=0,67, p13=0,41 χ^2 23=0,66, p23=0,41

Note: χ^2 12, χ^2 13, χ^2 23 — Chi-square values between respective groups, p_{12}, p_{13}, p_{23} — p-values– significant differences between respective groups

Table 5. *Lipid Parameters in Examined Patients*

Parameter	All sample	Group 1	Group 2	Group 3	Kraskell-Wallis test, H, p	p-values
Total cholesterol, mM/L	6,1 [5,4;7,0]	6,05 [5,3;6,9]	7,1 [6,0; 8,5]	6,1 [5,4;6.7]	4,26, p=0,23	p_{12} = 0,16 p_{13}=0,8 p_{23}=0,12
Triglycerides, mM/L	1,4 [1,0;1,96]	1,35 [0,99; 1,98]	1,45 [1,1; 2,4]	1,4 [1,0; 1,9]	0,7, p=0,7	p_{12} = 0,29 p_{13}=0,63 p_{23}=0,48
LDL cholesterol, mM/L	3,9 [3,26;4,8]	3,9 [3,4; 4,9]	5,1 [4,8; 5,3]	3,8 [3,2; 4,58]	6,64, p=0,03	p_{12} = 0,04 p_{13}=0,65 p_{23}=0,016
HDL cholesterol, mM/L	1,64 [1,32;1,9]	1,6 [1,4; 1,82]	1,73 [1,3; 2,05]	1,67 [1,25; 1,98]	0,24, p=0,88	p_{12} = 0,66 p_{13}=0,68 p_{23}=0,49
Non-HDL cholesterol, mM/l	4,51 [3,7;5,3]	4,67 [3,59; 5,47]	4,98 [3,7; 5,76]	4,4 [3,8; 5.13]	0,69, p=0,7	p_{12} = 0,61 p_{13}=0,95 p_{23}=0,52

Note: p12, p13, p23 — p-values– significant differences between respective groups, LDL — low density lipids, HDL — high density lipids

Table 6. *Investigated Parameters of Echocardiography, Endothelium Function in Patients with Hypothyroidism*

Parameter	All sample	Group 1	Group 2	Group 3	Kraskell-Wallis test, H, p	p-values
Ejection fraction, % by Simpson	65,7 [62,0; 69,0]	66,5 [62,5; 70,0]	61,0 [60,5; 68,0]	66,0 [63,0; 69,0]	5,19, p=0,07	p12 =0,03 p13=0,84 p23=0,03
Left ventricular mass index, mg/m^2	96,8 [81,2; 113,2]	98,5 [85,4; 116]	130,7 [113,1; 160,4]	96,6 [81,1; 112,0]	9,2 p=0,0098	p_{12} =0,001 p_{13}=0,86 p_{23}=0,001
Relative wall thicknes, cm	0,38 [0,35;0,41]	0,38 [0,35; 0,40]	0,44 [0,35; 0,45]	0,39 [0,36; 0,42]	6,5, p=0,03	p_{12} =0,03 p_{13}=0,12 p_{23}=0,053
GLPS AVRG, %	-19,8 [-21,6; -18,3]	-19,4 [-20,4; -16,6]	-17,0 [-20,0; -14,2]	-20,0 [-21,9; -18,5]	5,07, p=0,07	p_{12} =0,78 p_{13}=0,37 p_{23}=0,03
Diameter increase in reactive hyperemia test, %	8,0 [4,65; 12,8]	6,8 [3,2; 12,9]	11,1 [6,5; 13,3]	7,8 [4,9, 12,1]	0,8,p=0,8	p_{12} =0,89 p_{13}=0,80 p_{23}=0,90
Complex intima media value, mm	1,1 [0,9; 1,2]	1,1 [1,1, 1,2]	1,1 [0,7; 1,2]	1,1 [0,9; 1,2]	1,9 p=0,38	p_{12} =0,20 p_{13}=0,31 p_{23}=0,43
Ve/Va	0,78 [0,66; 0,87]	0,76 [0,64; 0,87]	0,71 [0,59, 1,19]	0,79 [0,66; 0,88]	0,4, p=0,81	p_{12} =0,28 p_{13}=0,56 p_{23}=0,44

Note: p_{12}, p_{13}, p_{23} — *p*-values — significant differences between respective groups, GLPS AVRG — global left ventricle longitudinal strain average

As seen in Table 6, an increase in the average value of IMT to 1.1 [0.9; 1,2] mm was detected in all groups of examined patients, regardless of TSH level.

Endothelial dysfunction in the form of a reduced average value of the increase in the diameter of the brachial artery in a reactive hyperemia test (IDRH) less than 10% was found in all groups of examined patients, including the general sample, regardless of TSH level; differences between the groups were insignificant (Table 6).

Ejection fraction in all groups was within the reference range; in the group of patients with uncompensated hypothyroidism, there was a decrease in the parameter compared to that in the group with subcompensated and compensated hypothyroidism (Table 6).

Signs of left ventricular remodeling were found in patients of all of the compared groups; average LVMMI in examined subjects was 96.8 [81.2; 113.2] g/m^2, and average RWT was 0.38 [0.35; 0.41] (Table 6). In the group

Table 7. *Significant ratios for Quadratic Model of the Left ventricular mass index* $\hat{Y}_{11}$

Variables	Regression Ratio b_i	p-value
X_3	1,296	<0,001
X_4	2,426	0,067
$X_{5.1}$	803,8	0,009
$X_{5.2}$	45,19	0,318
X_8	-32,99	0,002
$X_1 \cdot X_3$	0,028	0,017
$X_1 \cdot X_4$	-0,094	<0,001
$X_1 \cdot X_{5.1}$	-0,947	0,821
$X_1 \cdot X_{5.2}$	1,196	0,006
$X_2 \cdot X_8$	1,133	0,010
$X_3 \cdot X_{5.1}$	-14,23	0,012
$X_3 \cdot X_{5.2}$	-0,830	0,233

Note: X_3 — Age, X_4 — Duration, X_5 — Diagnosis, X_8 — linear logarithm TSH_ln

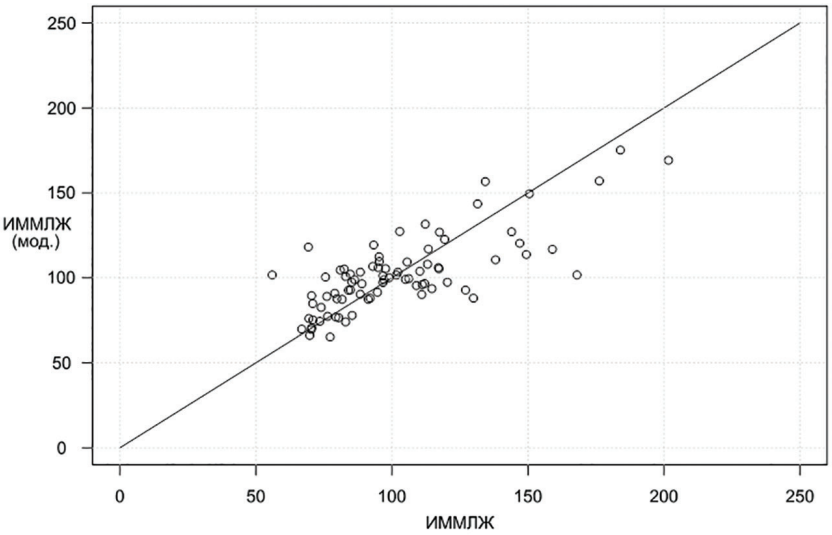

Figure 1. *Relationship Between the Model and Actual Values of the Left ventricular Mass Index*

Note: ИММЛЖ (мод.) — Left ventricular mass index model, ИММЛЖ — Left ventricular mass index

of uncompensated hypothyroidism, LVMMI was significantly higher than in the other two groups.

Impaired LV diastolic filling in the form of decreased Ve/Va ratio less than 1.0 was found in 121 (74.2%) patients (39 (72.24%), 11 (73.3%) and 78 (82.9%) patients in groups 1, 2, and 3, respectively); differences between the groups were not significant (Table 6).

Global contractility of the left ventricular myocardium in the entire examined sample was −19.4 [−20.4; −16.6]%; in the group of subcompensated hypothyroidism this parameter was significantly lower than in patients with disease compensation. In Group 1, a decrease in GLPS AVRG of less than 19% was revealed in 17 (31.4%) patients, in Group 2: in 4 (26.6%) patients, and in Group 3: in 27 (28.7%) patients.

The following significant correlations were registered: between age and IMT (r = 0.54, p = 0.00006), between BMI and GLPS AVRG (r = 0.32, p = 0.0009), between IMT and RWT (r = 0.36, p = 0.0004), as well as negative correlations between age and between HDL-C level and BMI (r = −0.33, p = 0.00006), between the level of fT4 and LVMMI (r = −0.39, p = 0.0002).

Quadratic models for LVMMI, IARH and IMT had the highest values R^2_{adj} and were significant at the level p < 0.001. Response variation, which can be explained by the studied factors, was as follows: for LVMI 51.3%, IARH 33.8%, and IMT 30.5%.

Significant coefficients (p < 0.05) of the regression model of the relationship between LVMMI and the studied factors are presented in Table 6.

As seen in Table 6, the most significant factors at the level p < 0.001 that affect LVMMI were the age factor and the interaction of TSH and disease duration factors. Nominal discrete variables X_5 and X_6 were converted to binary dummy variables ($X_{5.1}$, $X_{5.2}$) and ($X_{6.1}$, $X_{6.2}$), respectively, to be included in the regression model (Table 6).

As seen in Figure 1, the model allows satisfactory reproduction of LVMMI values from the studied factors for the group of patients under consideration.

Only the age factor turned out to be a significant factor at the level p < 0.001 that has an effect on IMT.

Discussion

According to a number of studies, patients with hypothyroidism have a different incidence of arterial hypertension, coronary heart disease, and heart failure; the effect of substitution therapy on surrogate markers of progression of cardiovascular lesions is inconclusive [3, 4, 5, 14]. Authors also have different opinions on the nature and severity of hemodynamic and lipid disorders, depending on the degree of thyroid insufficiency [5, 7, 15]. According to our data, patients with hypothyroidism are most often women in postmenopausal period; AH is found in 69.9%, CHD—in 33.7%, a history of MI and acute cerebrovascular accident—in of 4.3% and 4.9%, respectively.

Also, patients with primary hypothyroidism have such risk factors as obesity (43.5%), overweight (30%),

increased levels of total cholesterol, LDL cholesterol, non-HDL cholesterol with normal HDL cholesterol and triglyceride levels, which is consistent with the data obtained by other authors [6, 12].

It should be noted that the degree of thyroid insufficiency has a significant influence on the severity of lipid metabolism disorders and structural changes in the left ventricle. However, with compensated disease, these parameters do not normalize completely. In addition, the levothyroxine dose has no significant effect on the severity of the identified structural and functional changes. Correlation analysis showed that the level of free T4 significantly affects LVMMI and, consequently, the severity of left ventricular hypertrophy.

Assessment of correlations revealed that age is the main factor affecting LVMMI and IMT in patients with primary hypothyroidism with thyroid insufficiency of various degrees.

With age, the body replaces parenchymal cells with connective tissue, morphological changes develop in the myocardium, cardiomyocytes die, total peripheral vascular resistance increases, and collagen rigidity increases; all this leads to impaired myocardial extensibility and contractility [13]. The combination of impaired relaxation of the left ventricular myocardium, increased LVMMI, signs of endothelial dysfunction, and thickening of the intima media of peripheral vessels, typical for damage to the cardiovascular system in both hypothyroidism and aging, probably aggravates the severity of pathological changes [6].

The revealed relationship between BMI and global longitudinal contractility of the left ventricular myocardium in the examined patients is consistent with the data obtained by other authors who studied the relationship between BMI and longitudinal LV deformity in patients with chronic kidney disease [14]. This is probably because obesity leads to negative metabolic and neurohumoral changes that can intensify myocardial remodeling. Probable reasons for this are the activation of peroxidation processes, which increases oxygen consumption by the myocardium and decreases myocardial contractility, which is aggravated by thyroid insufficiency.

Mathematical modeling showed that the combination of such parameters as age, disease duration and TSH level is of greatest importance in the processes of the remodeling of the left ventricular myocardium in patients with primary hypothyroidism. At the same time, only age has a significant effect on IMT.

It should be noted that despite the disease compensation, changes in the cardiovascular system in patients with hypothyroidism persist. The development of hypothyroidism may trigger such processes as oxidative stress, inflammation and dyslipidemia, and routine replacement therapy does not lead to a complete normalization of cardiovascular parameters [15]. Apparently, it is the combination of these factors that leads to persistent cardiovascular changes. Additional research is required to find additional factors affecting structural and functional changes in the cardiovascular system in patients with primary hypothyroidism.

Conclusion

1. The most significant risk factors for LV and vascular wall remodeling in patients with primary hypothyroidism are TSH level > 4 mIU/L, disease duration over 6 years, and elderly age (65+).

2. As part of a cardioprotective strategy for managing patients with hypothyroidism, it is advisable to achieve reference ranges of TSH, free T4, and correction of excess body weight.

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ТРЕНИРОВКА ДЫХАТЕЛЬНОЙ МУСКУЛАТУРЫ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ПАЦИЕНТОВ С ОСТРОЙ ДЕКОМПЕНСАЦИЕЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Respiratory Muscles Training in the Complex Treatment of Patients with Acute Decompensated Heart Failure

Резюме

Цель: оценить эффективность тренировки дыхательной мускулатуры в комплексном лечении пациентов с острой декомпенсацией сердечной недостаточности. **Материал и методы.** В проспективное рандомизированное исследование были включены 120 пациентов (71 мужчина и 49 женщин, средний возраст 73,6±5,8лет), госпитализированных с острой декомпенсацией сердечной недостаточности. Основными критериями исключения были: необходимость лечения в условиях отделения интенсивной терапии; гемодинамическая нестабильность; тяжелая бронхопульмональная и другая сопутствующая патология. После прохождения процедур исходного обследования все пациенты были рандомизированы в группу дыхательной гимнастики, выполняемой в дополнение к стандартной медикаментозной терапии (основная группа, n=60) либо в группу только стандартной медикаментозной терапии (контрольная группа, n=60). Пациенты основной группы были обучены технике полного йоговского дыхания, состоящего из трех последовательных фаз: брюшного, грудного и ключичного. Участники практиковали полное дыхание ежедневно не менее 3 раз в день по 10 минут под наблюдением инструктора. Первичной конечной точкой исследования было изменение выраженности одышки согласно модифицированной шкале Борга (в модификации Мареева В.Ю.) на 7-й день лечения. **Результаты.** На фоне лечения у пациентов обеих групп значимо уменьшилась выраженность одышки, в большей степени в группе дыхательной гимнастики (с 6 (5; 6) до 3 (2; 3)) баллов) по сравнению с контрольной (с 6 (5; 6) до 4 (3; 4), p <0,05). Значимые различия между группами были получены и по вторичным переменным эффективности: дистанции теста с шестиминутной ходьбой, частоте сердечных сокращений и дыхания в покое, насыщению крови кислородом (p <0,05). У пациентов, выполнявших дыхательную гимнастику, масса тела снижалась быстрее (0,72±0,06 кг/сут против 0,53±0,06 кг/сут, p <0,001), хотя объемы выделенной жидкости между группами не различались. В среднем в основной группе влажные хрипы в легких были купированы к шестому дню от момента госпитализации (интерквартильный интервал 5-7 дней), а в контрольной — к восьмому (интерквартильный интервал 7-9 дней), p=0,024. Продолжительность активной фазы диуретической терапии и среднесуточные дозы диуретиков были ниже в основной группе по сравнению с контрольной (p <0,05). За вре-

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мя госпитализации в обеих группах больных наблюдалось заметное улучшение качества жизни, однако степень его была более выражена у пациентов, практикующих полное дыхание (p <0,01). Госпитальная летальность и частота переводов в отделение интенсивной терапии не различались между группами. Средние сроки госпитализации у выживших пациентов оказались значимо меньше в основной группе, чем в контрольной (14,2±2,5 против 17,3±2,9, p <0,001). **Заключение.** Тренировка дыхательной мускулатуры с помощью полного йоговского дыхания в дополнение к стандартной медикаментозной терапии пациентов с острой декомпенсацией сердечной недостаточности приводит к более значимому уменьшению выраженности одышки, увеличению толерантности к физической нагрузке, улучшению насыщения крови кислородом и снижению потребности в диуретиках. Применение полного дыхания ассоциируется с заметным улучшением качества жизни пациентов, более быстрым достижением компенсации и уменьшением сроков пребывания в стационаре, однако не приводит к улучшению госпитальных исходов заболевания.

Ключевые слова: *хроническая сердечная недостаточность, декомпенсация, полное йоговское дыхание, одышка, качество жизни, диуретики, сроки госпитализации, летальность*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The aim: to evaluate the efficacy of respiratory muscles training in the complex treatment of patients with acute decompensated heart failure. **Material and methods.** A prospective randomized study included 120 patients (71 men and 49 women, mean age 73,6±5,8 years) hospitalized with acute decompensated heart failure. The main exclusion criteria were: requirement for treatment in intensive care unit; hemodynamic instability; severe pulmonary and other concomitant pathology. After initial procedures all patients were randomized to breathing exercises performed in addition to standard therapy (main group, n=60) or to standard therapy only (control group, n=60). Patients of the main group were trained in the technique of complete yogic breathing, which consists of three successive phases: abdominal, thoracic and clavicular. The participants practiced full breathing daily at least 3 times a day for 10 minutes under the supervision of instructor. The primary endpoint of the study was the change in dyspnea according to the modified Borg scale (modified by V.Yu. Mareev) on the 7th day of treatment. **Results.** During treatment the severity of dyspnea decreased in both groups, more significantly in the main group (from 6 (5; 6) to 3 (2; 3) points) compared to control (from 6 (5; 6) to 4 (3; 4) points, p <0,05). Significant differences between the groups were also obtained for the secondary variables of efficacy: six-minute walk distance, heart rate and breathing rate at rest, blood oxygen saturation (p <0,05). In patients who performed breathing exercises, body weight decreased faster (0,72±0,06 kg/day versus 0,53±0,06 kg/day, p <0,001), although the volumes of excreted fluid did not differ between the groups. In the main group moist rales in the lungs were stopped by the sixth day of hospitalization (interquartile range of 5-7 days), and in the control group — by the eighth (interquartile range of 7-9 days), p=0,024. The duration of active diuretic phase and the average daily doses of diuretics were lower in main group compared to control (p <0,05). During hospitalization quality of life improved in both groups, more significantly in respiratory muscles training group (p <0,01). In-hospital mortality and the rate of transfers to the intensive care unit did not differ between groups. The average hospital stay in surviving patients was significantly shorter in main group than in control (14,2±2,5 versus 17,3±2,9 days, p <0,001). **Conclusion.** Respiratory muscles training with full yogic breathing in addition to standard medical therapy for patients with acute decompensated heart failure leads to a more significant reduction in the severity dyspnea, increased exercise tolerance, improved blood oxygen saturation, and reduced need for diuretics. The use of full breathing is associated with significant improvement in the quality of life and decrease in the length of hospital stay, but does not lead to improvement in hospital outcomes.

Key words: *chronic heart failure, decompensation, full yogic breathing, dyspnea, quality of life, diuretics, duration of hospitalization, mortality*

Conflict of interests

The authors declare no conflict of interests

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Sips-059 ADHF — acute decompensated heart failure, AH — arterial hypertension, CHF — chronic heart failure, FC — functional class, HR — heart rate, LV — left ventricle, 6MWT — 6-minute walk test, RM — respiratory muscles, RR — respiratory rate, SACS — scale for assessing clinical state

Chronic heart failure (CHF) is one of the most common diseases in the world. Despite the significant progress achieved in recent decades in the management of this pathology, mortality and re-hospitalization rate in patients with CHF remains high. According to information from large registries, currently CHF is found in 26 million people worldwide; its prevalence in the next 30-40 years is expected to increase by 40–60% [1].

Limited physical activity, dyspnea, and fatigue are the main complaints of patients with CHF [2]. For a long time, intracardiac hemodynamics disorders were considered the primary cause of CHF symptoms. It was subsequently demonstrated that there was no clear relationship between the volume and ejection fraction of the left ventricle on the one hand and exercise tolerance on the other [2]. This led to the hypothesis that skeletal muscle weakness makes a crucial contribution to the onset of CHF symptoms [3, 4]. Pathological changes in muscle tissue manifest as systemic vasoconstriction, deterioration of endothelial function, increased myocyte apoptosis, redistribution of the ratio of muscle fibers towards an increase in type II fibers, a decrease in the number and volume of mitochondria, and activation of pro-inflammatory cytokines. Currently, there are convincing evidences that morphological and functional disorders in muscles accompany CHF course with both reduced and preserved left ventricular (LV) systolic function They lead to excessive neurohumoral activation and are an important factor in worsening the prognosis [5, 6].

Muscle disorders are not limited to motor muscles. The remodeling of the respiratory system plays an essential role in the pathogenesis of CHF. Sarcopenic changes in the diaphragm, increased inspiratory muscle metaboreflex, changes in the sensitivity of pulmonary stretch receptors cause decreased perfusion of respiratory and skeletal muscles, leading to increased dyspnea, decreased exercise tolerance, and deterioration in patients' quality of life.

Aerobic exercise is an important component of the rehabilitation of patients with CHF. Numerous studies in recent years convincingly demonstrated that exercise of various intensity contributes to the improvement of cardiorespiratory parameters, functional ability, vegetative balance, sleep, and quality of life of patients [7–9]. Some studies suggest the positive effect of physical activity on the incidence of cardiovascular events, hospitalizations, and prognosis for patients with CHF [10]. According to the current guidelines [11], aerobic physical activity should be recommended for all patients with CHF, provided they have no contraindications. At the same time, breathing exercise can be an alternative to physical training for patients with severe decompensated CHF; this is also recommended by current guidelines.

Most often, training respiratory muscles (RM) requires using special devices that create resistance on exhalation or inhalation [11, 12]. However, costs and additional equipment required (often for individual use) limit the practical application of these techniques. Also, elderly patients often have difficulty using these devices due to impaired cognitive and visual functions, preventing them from performing breathing exercises independently. Therefore, there is an urgent need to develop alternative methods of RM training that would not require any additional devices and could be used by a patient at home or in a hospital without involving medical staff. Full yogic breathing could be one of these methods.

Full yogic breathing is a slow, deep breathing that includes three successive phases—abdominal, thoracic, and clavicular. This type of breathing exercise reportedly [13] contributes to increased exercise tolerance, decreased neurovegetative imbalance, and improvement in the quality of life in relatively healthy individuals. However, the study of its effectiveness and safety in patients with CHF has only just started.

This study sought to assess the effectiveness of full yogic breathing in the comprehensive treatment of patients with acute decompensated heart failure (ADHF).

Material and Methods

Study Design: In a prospective, randomized, open-label, blinded, parallel-group study, 120 patients were enrolled (71 males and 49 females, average age 73.6 ± 5.8 years). Investigators were categorized according to their specific roles in this study: (1) RM training coaches—they teach RM exercises to patients, monitor their execution and do not consider performance; (2) medical evaluators—staff responsible for conducting clinical trial procedures (blinded with respect to groups, but not results); and (3) analysts—responsible for the statistical analysis of the results obtained (blinded with respect to both groups and results).

Inclusion and Exclusion Criteria: The inclusion criteria were the following: age 18+; hospitalization due to ADHF; and consent to participate in the study. The exclusion criteria were the following: treatment in intensive care unit; hemodynamic instability; acute coronary syndrome (ACS) ≤ 3 months; percutaneous coronary angioplasty ≤ 3 months; coronary artery bypass grafting ≤ 3 months; acute cerebrovascular accident ≤ 3 months; severe bronchopulmonary pathology; severe gastroesophageal reflux disease, diaphragmatic hernia;

uncontrolled arterial hypertension (AH); life-threatening heart rhythm and conduction disorders; intracardiac thrombosis; acute myocarditis and/or pericarditis; severe valve stenosis; comorbidities in the stage of decompensation; active systemic diseases; malignancies; pregnancy; alcohol and drug addiction; mental illnesses; and inability or unwillingness to comply with the study procedures.

Definition of Inclusion Criteria: CHF was diagnosed in accordance with the criteria recommended by the European Society of Cardiology for the diagnosis and treatment of acute and chronic heart failure in 2016 [14]. ADHF was defined as an acute or gradual buildup in clinical signs and symptoms of hypervolemia (breathlessness, peripheral edema, and pulmonary crackles), which requires additional immediate treatment (intravenous administration of furosemide) and/or hospitalization.

Screening Procedures: Initially, all patients underwent general clinical examination; they were diagnosed with the underlying disease that caused CHF; their comorbidities were analyzed, and the following parameters were assessed: clinical status, quality of life, severity of dyspnea according to the Borg scale, exercise tolerance assessed by 6-minute walk test, and blood oxygen saturation.

Randomization: After the initial examination procedures, all patients were randomized in a 1:1 ratio to a group of breathing exercises performed in addition to standard drug therapy (treatment group, n = 60), or to a group of standard drug therapy only (control group, n = 60). Patients were monitored until they were discharged from the hospital.

End Points: The primary endpoint of this study was the change in dyspnea severity according to a modified Borg scale (modified by V.Yu. Mareev) on Day 7 of treatment. Secondary efficacy variables were the following: changes in clinical status parameters, test distance in 6-minute walk test (6MWT), heart rate (HR), respiratory rate (RR) at rest, and oxygen saturation, quality of life, duration of hospital stay; and hospitalization outcome (discharge, death, or transfer to intensive care unit).

Discharge Criteria: Patients were discharged from the hospital when ADHF symptoms were resolved, euvolemia and stabilization of hemodynamic parameters were achieved, and the renal function and clinical condition of the patient while taking oral medications remained stable for at least the recent 24 hours.

Study Methods

Clinical Status: The clinical status of patients was assessed using the scale for assessing clinical state (SACS) for CHF as modified by V.Yu. Mareev.

6MWT. 6-minute walk test was performed after a 10-minute rest in a sitting position. Patients were advised not to exercise and smoke for 2 hours before the test. For this test, the length of the hospital corridor was measured and a distance of 30 m was defined; chairs were placed at 10-m intervals. The time was counted using a watch with a second hand. The patient was asked to walk in an empty corridor for 6 minutes at his/her own convenient pace, trying to cover the maximum distance. Patients were verbally motivated to perform the exercise twice during the test; current information about the testing phase was also given. Due to significantly reduced exercise tolerance, patients were allowed to take short breaks from walking. The time for forced rest was included in the allocated 6 minutes. In the end, the distance (in meters) covered by the patient in 6 minutes was determined. If such symptoms as chest pain, sudden or severe dyspnea, severe fatigue appeared, 6MWT was stopped.

Severity of Dyspnea: After completing 6MWT, the severity of dyspnea was assessed according to the modified Borg scale.

Quality of Life: The Minnesota Living with Heart Failure Questionnaire was used to assess the quality of life. Patients were asked to answer 21 questions, each related to the factors affecting the quality of life. Patients had to evaluate the effect of any factor on a scale of 0 to 5 depending, on its intensity. The total score was determined at the end of the test: 0 points corresponded to the best quality of life, 105 points—to the worst quality of life.

Pulse Oximetry: Arterial blood oxygen saturation and resting HR were determined by a non-invasive method of percutaneous pulse oximetry using a wrist pulse oximeter (BIOLIGHT CO., LTD, China).

Rate of Fluid Loss: Rate of fluid loss was assessed by measuring body weight daily in the morning in fasting state after emptying the bladder and by calculating the difference between the volumes of fluid consumed and excreted every day.

Drug Therapy: All patients received adequate drug therapy in accordance with the existing standards for CHF management [14]. According to the recommendations, the active phase of diuretic therapy was carried out until physical euvolemia was achieved. Then, the patients were transferred to maintenance diuretic therapy.

Fluid and Electrolyte Balance: During active diuretic therapy, patients were recommended to moderately restrict sodium consumption with food (< 3 g/day) after condition compensation—according to the functional class (FC) of CHF. In the case of CHF FC I, patients were advised not to eat salty food (sodium consumption restriction to 3 g/day), in case of FC II—not to add salt to

food (sodium consumption restriction to 1.5–2 g/day), in case of FC III–IV—use products with low salt content and prepare meals without salt (sodium consumption restriction to 1 g/day). During active diuretic treatment, patients were told to limit fluid intake to 1.5 L/day, after complete compensation of CHF—less than 2 L/day.

The study was completed by 108 patients (53 patients in Group 1 and 55 in Group 2). Twelve subjects discontinued participation in the study: 5 died during their hospital stay, 7 were excluded from the study due to transfer to another department (n = 5) or refusal to participate (n = 2).

RM Training Technique. Patients of the treatment group were trained in the technique of deep yogic breathing, which includes three consecutive phases: abdominal, thoracic, and clavicular. Inspiration was carried out slowly through the nose, in a deep wave-like manner, with the successive involvement of abdominal muscles and the diaphragm, intercostal muscles, and then shoulder girdle muscles. Expiration was carried out in the same sequence. Patients were recommended to breathe as deeply and as slowly as they could tolerate. Participants practiced full breathing in a comfortable sitting position, in a quiet room, at least 3 times every day for 10 minutes under the supervision of an instructor.

Statistical Analysis. Processing was performed on a personal computer using the MedStat statistical analysis software package. At normal distribution, the quantitative characteristics were presented as mean ± standard deviation (m ± σ), in a case other than normal distribution—as median and 1st, 3rd quartiles (Me (Q1; Q3)). To compare two samples of continuous variables subject to the normal distribution law, paired and unpaired Student's t-tests were used, while the Wilcoxon test was used for other distribution than normal distribution. To compare relative values, we used standard contingency table analysis with the χ^2 criterion. In all cases of hypothesis testing, differences were considered significant at $p < 0.05$.

Results

Initially, both studied groups of patients were comparable in relation to the main clinical and demographic characteristics: gender, age, severity of CHF, and comorbid conditions (Table 1).

In the course of treatment, patients of both groups demonstrated significantly improved parameters of clinical status and exercise tolerance, and decreased severity of dyspnea according to the Borg scale. In the group of breathing exercises, all these changes were more pronounced in comparison with the control group (Table 2).

Changes in the subjective perception of CHF symptoms were accompanied by improved objective cardiorespiratory parameters. A more pronounced slowdown in HR and RR at rest and improved blood oxygen saturation were observed in patients performing breathing exercises (Table 3).

When comparing the rate of fluid loss, it was found that body weight in patients who performed breathing exercises decreased faster, although there was no difference in the volume of fluid excreted between the groups. The decrease in body weight in the treatment group averaged 0.72 ± 0.06 kg/day, in the control group—0.53 ± 0.06 kg/day ($p < 0.001$).

Crackles during auscultation were initially heard in 93.1% of patients in the treatment group and in 86.7% of patients in the control group, $p > 0.05$. In patients practicing full breathing, more rapid regression of the signs of stagnation in pulmonary circulation was observed. On average, pulmonary crackles in the treatment group had stopped by Day 6 from the moment of hospitalization (interquartile interval of 5–7 days), and in the control group—by Day 8 (interquartile interval of 7–9 days), $p = 0.024$.

We analyzed the duration of the active phase of diuretic therapy and the average dose of the loop diuretic for the entire period of hospitalization. It was revealed that the duration of active diuretic therapy in the treatment group lasted on average 7 days (interquartile range 5–8), in the control group—9 (8–10) days ($p = 0.034$). The median dose of the loop diuretic during the active phase was significantly ($p = 0.003$) lower in the treatment group than in the control group, and averaged 60 (40; 80) and 80 (70; 110) mg/day equivalent to furosemide, respectively. During transfer to maintenance treatment, when compensation was achieved, the fixed dose of diuretic was also significantly lower in the treatment group (on average 30 (20; 40) mg/day equivalent to furosemide) in comparison with the control group (on average 40 (30; 60) mg/day), $p = 0.018$ (Table 4).

During hospitalization, both groups of patients demonstrated notable improvement in the quality of life. However, the improvement was more pronounced in patients practicing full breathing (from 82.2 ± 8.6 to 62.2 ± 7.6 points) compared with the standard therapy group (from 79.6 ± 8.4 to 69.3 ± 6.7 points, $p < 0.01$).

To assess the effect of full breathing on the course and hospital prognosis of the disease, mortality and the frequency of transfers to the intensive care unit were analyzed (Table 5). In the treatment group, one patient died and two patients were transferred to the intensive care unit, while in the control group, unfavorable outcomes were observed in three and four patients, respectively. The above differences did not reach statistical significance. Nevertheless, the average hospital stay for surviving patients was significantly shorter in the full respiration group than in the standard therapy group.

Table 1. *Initial clinical characteristics of patients*

Parameter	Main group (n=58)	Control group (n=60)	P
BAge, years, Me (Q1; Q3)	73 (66,5; 78)	72 (67; 78,5)	H3/ NS
Male, number of patients (%)	36 (62,1%)	35 (58,3%)	H3/ NS
Arterial hypertension, number of patients (%)	50 (86,2%)	49 (81,7%)	H3/ NS
Myocardial infarction, number of patients (%)	36 (62,1%)	39 (65,0%)	H3/ NS
Atrial fibrillation, number of patients (%)	21 (36,2%)	18 (30,0%)	H3/ NS
Stroke, number of patients (%)	5 (8,6%)	5 (8,3%)	H3/ NS
Chronic obstructive pulmonary disease, number of patients (%)	17 (29,3%)	21 (35,0%)	H3/ NS
Diabetes mellitus, number of patients (%)	23 (39,7%)	21 (35,0%)	H3/ NS
Anemia, number of patients (%)	8 (13,8%)	12 (20,0%)	H3/ NS
NYHA class, Me (Q1; Q3)	III (III; IV)	III (III; IV)	H3/ NS
Signs of fluid retention in two circles of blood circulation, number of patients (%)	51 (87,9%)	48 (80,0%)	H3/ NS
Anasarca, number of patients (%)	7 (12,1%)	5 (8,3%)	H3/ NS
BMI, kg/m^2, m±σ	30,5±3,6	29,4±3,9	H3/ NS
SBP, mmHg, m±σ	131,2±3,9	129,3±4,6	H3/ NS
DBP, mmHg, m±σ	74,9±2,9	76,4±3,2	H3/ NS
Left ventricular ejection fraction %, m±σ	42,8±8,2	44,6±6,2	H3/ NS
Sodium serum level, mmol/l, m±σ	133,5 (132; 137,5)	134,5 (133; 137,5)	H3/ NS
Potassium level, mmol/l, m±σ	4,20±0,36	4,32±0,42	H3/ NS
Blood hemoglobin concentration, g/l m±σ	114,6±7,8	117,3±6,2	H3/ NS
GRF, ml/min, m±σ	44,6±7,9	48,2±8,4	H3/ NS

Note: BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; GRF — glomerular filtration rate, NS — not significant

Table 2. *Dynamics of clinical status, severity of dyspnea and 6-minute walk test distance (M±σ, Me (Q1;Q3))*

Parameter	Main group		Control group	
	Baseline (n=58)	7th day (n=55)	Baseline (n=60)	7th day (n=53)
Severity of dyspnea according to the Borg scale, score, Me (Q1; Q3)	6 (5; 6)	3 (2; 3)$^{*,\#}$	6 (5; 6)	4 (3; 4)*
Clinical assessment scale, score, Me (Q1; Q3)	9 (8; 10)	4 (3; 5)$^{*,\#}$	8 (8; 10)	6 (5; 7)*
6-minute walk test distance, m, m±σ	159,4±20,3	209,2±19,6$^{*,\#}$	168,5±22,8	188,6±20,4*

Note: * — differences are significant (p <0.05) compared to baseline values, # — differences are significant (p <0,05) compared to the control group

Table 3. *Dynamics of office heart rate, respiration rate and blood oxygen saturation (M±σ, Me (Q1;Q3))*

Parameter	Main group		Control group	
	Baseline (n=58)	7th day (n=55)	Baseline (n=60)	7th day (n=53)
Respiration rate, at rest, bpm, Me (Q1; Q3)	23 (21; 24)	19 (18; 20) *,#	24 (22; 25)	21 (20; 22) *
HR at rest, bpm, Me (Q1; Q3)	86,8±6,6	72,6±4,8*,#	84,9±6,8	77,4±4,5*
SpO_2, %	91 (88; 94)	97 (95; 97) *,#	90 (88; 92)	94 (93; 96)*

Note: HR — heart rate, SpO_2 — blood oxygen saturation, * — differences are significant (p<0.05) compared to baseline values, # — differences are significant (p<0.05) compared to the control group

Table 4. *Average daily doses of diuretics in terms of furosemide, mg Me (Q1; Q3)*

Therapy phase	Main group (n=58)	Control group (n=60)	P
On the day of hospitalization	80 (80; 120)	80 (70; 110)	p=0,49
Active phase	60 (40; 80)	80 (70; 110)	p=0,003
Maintenance phase	20 (20; 40)	40 (40; 80)	P <0,001

Table 5. *Hospital outcomes and terms of hospitalization*

Parameter	Main group (n=58)	Control group (n=60)	P
Hospital mortality, number of patients (%)	1 (1,72%)	3 (5,00%)	insignificantly
Transfer to the intensive care unit, number of patients (%) (%)	2 (3,44%)	4 (6,67%)	insignificantly
Average terms of hospitalization, days, m±σ	14,2±2,5	17,3±2,9	P <0,001

Discussion

Respiratory system remodeling plays an important role in the onset of CHF symptoms and disease progression [6, 15]. The diaphragm is a muscle that makes the greatest contribution to ensuring effective gas exchange; it is subject to numerous pathological changes, including increased protein degradation processes, decreased number of mitochondria, and impaired oxidative metabolism. Diaphragm biopsy in patients with heart failure reveals a transition from fast-twitch muscle fibers (type II) to slow-twitch ones (type I), increased apoptosis, and, as a result, replacement of muscle fibers with adipose and connective tissue [16, 17]. This remodeling of RM leads to decreased inspiratory strength and dyspnea [18].

Weakness of RM not only limits the functional capabilities of patients but also exacerbates excessive neurohumoral activation. Owing to the significant changes in the diaphragm, inspiratory metaboreflex in patients with CHF is activated with slight physical exertion. However, it does not improve gas exchange and cardiac output; it just causes sympathetically mediated vasoconstriction [18, 19]. In turn, a persistent increase in sympathoadrenal activity leads to a further increase in afterload on the myocardium, closing the vicious circle and worsening the prognosis [20].

RM training is currently regarded as a key rehabilitation measure to ease CHF symptoms and to improve patients' quality of life. Our study demonstrated that the addition of RM training to standard ADHF therapy is associated with a more significant decrease in dyspnea, improved clinical status, increased blood oxygen saturation, and exercise tolerance compared with the standard therapy. Our results are confirmed by other studies. Results of randomized controlled trials in patients with CHF showed that the addition of breathing exercises to aerobic exercise improved cardiovascular response to exercise and its tolerance [21–23]. Experimental models of heart failure demonstrated that training respiratory muscles improved hemodynamic parameters and reduced vegetative disbalance [24].

Mechanisms for implementing the positive effects of breathing exercises vary, and their study is just starting. First of all, they are the result of increasing the reserve of RM. A specific feature of full deep breathing is that during expiration, the diaphragm is pushed up by abdominal muscles, which increases its effectiveness as an inspiratory muscle [24]. By increasing the strength and endurance of respiratory muscles and by increasing the efficiency of

gas exchange, full yogic breathing increases not only the tidal volume but also the saturation of arterial blood with oxygen. This is likely the reason for increased exercise tolerance and reduced dyspnea achieved during this study.

Another mechanism of the effect of breathing exercises is to improve the neurovegetative regulation of cardiovascular and respiratory systems. It is known that CHF course is characterized by a decreased tone of the parasympathetic division of the autonomic nervous system and, therefore, increased activity of its sympathetic division. Hypoxia and hypercapnia that develop in the case of HF activate chemoreceptors in the carotid zone [25]. Signals from these receptors enter the respiratory center in the medulla oblongata and cause the activation of the sympathoadrenal system to maintain adequate blood oxygenation. Increased sympathetic tone primarily manifests as increased respiratory rate, increased systemic blood pressure and HR. There are data on the optimization of the balance of the autonomic nervous system in connection with RM training [26]. By affecting the baroreceptors of lung tissue, as well as stretch receptors located in the smooth muscle layer of large airways, slow deep yogic breathing activates the parasympathetic nervous system and reduces the sensitivity of chemoreceptors [27]. This mechanism is probably responsible for the decrease in HR and RR recorded during this study. A central effect of yogic breathing on the respiratory and vasomotor centers in the medulla oblongata can also not be ruled out. This phenomenon may be based on a network that is common to several respiratory and cardiomotor neurons [28].

We established that full breathing contributes to faster achievement of euvolemia and less need for diuretics. Reducing stagnation is one of the primary goals of treating patients with ADHF. According to current guidelines, intravenous loop diuretics are recommended for patients with no severe arterial hypotension and signs of hypoperfusion immediately after hospitalization. It is recommended to evaluate signs associated with fluid overload on a daily basis (dyspnea, congestive pulmonary crackles, peripheral edema, body weight, and diuresis). We found that body weight in patients who performed breathing exercises decreased faster, although there was no difference in the volume of fluid excreted between the groups. Apparently, full yogic breathing contributed to increased respiratory fluid loss, which explains the more rapid regression of pulmonary congestion in patients of the treatment group [29].

Dyspnea and decreased exercise tolerance in many ways affect the life of patients with CHF. We hypothesized that full breathing, on the contrary, may contribute to a better quality of life. To assess the quality of life, we used the Minnesota Living with Heart Failure Questionnaire; patients were asked to complete it upon admission and at discharge. During hospitalization, both groups of patients demonstrated notable improvement in the quality of life. However, improvement was more pronounced in patients practicing full breathing compared with the standard therapy group ($p < 0.01$). The positive effect of breathing techniques on the quality of life was confirmed in many studies [30] and is primarily associated with improved exercise tolerance. Improvement in the psychoemotional state of patients, decreased anxiety, and restoration of breath control can also make a certain contribution to this process [26].

Most studies on RM training did not analyze hard endpoints, that is, survival and cardiovascular event incidence. A distinctive feature of our work was the analysis of the effect of full breathing on the course and hospital prognosis of the disease. We analyzed mortality and the frequency of transfers to the intensive care unit. Full breathing did not lead to an improvement in hospital outcomes. Nevertheless, the average hospital stay in surviving patients was significantly shorter in the full breathing group than in the standard therapy group. It cannot be ruled out that the absence of statistical differences in patient survival is associated with a small sample of patients. Further larger studies are required to investigate this hypothesis.

Conclusion

Full breathing in addition to standard drug therapy in patients with ADHF leads to a more significant reduction in the severity of dyspnea, increased exercise tolerance, and improved blood saturation. RM exercise contributed to faster regression of pulmonary congestion and the decreased need for diuretics. Full breathing is associated with a significant improvement in patients' quality of life, i.e., more rapid achievement of compensation and shorter hospital stay. However, it does not lead to improvement in hospital outcomes of the disease.

Full yogic breathing is an affordable and relatively easy-to-perform method that does not require additional costs or special equipment. It is important to emphasize that in our study, adherence to breathing exercises increased along with its practice, and patients noted the affordability and effectiveness of this method.

A definite limitation of this study was the lack of blinding with respect to the RM training technique, which, to a certain extent, reduced the validity of the results obtained. Dividing patients into additional subgroups depending on CHF type and severity would help determine the role of full breathing for certain cohorts of patients. Large and well-designed studies to assess the objective determinants of CHF and hard endpoints will help clarify the role of breathing exercises as an important non-pharmacological treatment for CHF.

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КОЖНЫЕ ПРОЯВЛЕНИЯ COVID-19 В ПРАКТИКЕ ДЕРМАТОЛОГА

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Skin Manifestations of COVID-19 Infection in the Practice of Dermatologist

Резюме

В начале 2020 года Всемирная организация здравоохранения объявила о появлении заболевания — новой коронавирусной инфекции (COVID-19). Высокая контагиозность и бессимптомная передача вируса привели к стремительному распространению инфекции и развитию пандемии. Вирус SARS-CoV-2 тропен к нижним отделам дыхательного тракта. Вместе с тем наблюдаются внелегочные проявления, в том числе высыпания на коже, которые характеризуются чрезвычайным многообразием. Некоторые авторы поражения кожи описывают как первый, а иногда и единственный симптом новой коронавирусной инфекции. Таким образом, кожные проявления должны быть тщательно оценены дерматологами при осмотре, особенно в период продолжающейся пандемии.

В статье представлено шесть клинических случаев с различными кожными проявлениями в острый период инфекции COVID-19. Первыми, к кому обратились с жалобами пациенты, были дерматологи. Высыпания на коже характеризуются многообразием и распространенностью: полиморфный васкулит, ливедо-ангиит, уртикарные, пятнисто-папулёзные, папуло-везикулёзные, папуло-сквамозные элементы. Все случаи объединяет присутствие основных симптомы коронавирусной инфекции, характерных для острого периода: слабость, быстрая утомляемость, гипертермия, головная боль, миалгии, частичная или полная аносмия, агевзия.

Таким образом, в период продолжающейся пандемии обмен клиническим опытом развития кожных проявлений при COVID-19 инфекции крайне актуален. Анализ накопленных данных позволит оценить прогноз при наблюдении таких пациентов.

Ключевые слова: *SARS-CoV-2, COVID-19, дерматология, кожные проявления*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

In early 2020, the World Health Organization announced the emergence of the disease-a new coronavirus infection (COVID-19). High contagiousness and asymptomatic transmission of the virus led to a rapid spread of infection and reached the scale of a pandemic. It was found that the SARS-CoV-2 virus

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is pathogenic to the lower respiratory tract. At the same time, there are extrapulmonary manifestations, including skin rashes, which are characterized by an extreme variety. Some authors describe skin lesions as the first, and sometimes the only, symptom of a new coronavirus infection. Thus, skin manifestations should be carefully evaluated by dermatologists during the examination, especially during the ongoing pandemic.

This article presents 6 clinical cases with various skin manifestations in the acute period of COVID-19 infection. The first patients to complain were dermatologists. Rashes on the skin are characterized by a variety and prevalence: polymorphic vasculitis, livedo-angiitis, urticary, spot-papular, papulo-vesicular, papulo-squamous elements. All cases are united by the presence of the main symptoms of coronavirus infection characteristic of the acute period — hyperthermia, headache, fatigue, myalgia, partial or complete anosmia, ageusia.

Thus, the exchange of clinical experience of skin manifestations in COVID-19 infection is extremely relevant during the ongoing pandemic. The analysis of the accumulated data will provide an understanding of the diagnostic significance and the ability to assess the prognosis when observing such patients.

Key words: *SARS-CoV-2, COVID-19, dermatology, skin findings*

Conflict of interests

The authors declare no conflict of interests

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ACE2 — angiotensin converting enzyme 2, BMI — body mass index, BP — blood pressure, CBC — complete blood count, COVID-19 — novel coronavirus infection caused by SARS-CoV-2, CT — computed tomography, DNA — deoxyribonucleic acid, ESR — erythrocyte sedimentation rate, HR — heart rate, PAF — platelet-activating factor, PCR — polymerase chain reaction, RNA — ribonucleic acid, SARS-CoV-2 — coronavirus that causes COVID-19

In December 2019, cases of pneumonia of unknown etiology were detected in the People's Republic of China in the city of Wuhan [1]. Later, it was found that the pneumonia was caused by a new pathogen named by the Committee on Taxonomy SARS-CoV-2, which was isolated from the lower respiratory tract of patients [2]. In early February 2020, the World Health Organization defined this disease as a novel coronavirus infection (COVID-19). The high contagiousness and asymptomatic transmission of the virus led to the rapid spread of infection and resulted in a pandemic [3, 4].

SARS-CoV-2 is a single-stranded RNA virus with surface "corona-like" proteins and belongs to the coronavirus family. This virus has tropism to the lower respiratory tract [5, 6]. The main symptoms of acute coronavirus infection include fever, cough, shortness of breath, chest congestion, headache, fatigue, myalgia, anosmia, and ageusia [6, 7]. Extrapulmonary manifestations are also observed; one of these manifestations is skin rash of vast diversity [8, 9].

Some authors cite skin lesions as the first and sometimes the only symptom of novel coronavirus infection. Other rinvestigators concluded that skin rash appeared more often in the first four weeks after the onset of the main symptoms of COVID-19 [8, 10].

The course of infection caused by SARS-CoV-2 may be asymptomatic (no main symptoms of coronavirus infection) [11]. Some authors say skin lesions may precede COVID-19 symptoms [12]. Even if there is no confirmed COVID-19 diagnosis, skin signs should be carefully evaluated by dermatologists upon examination, especially during the ongoing pandemic. The correct interpretation of symptoms can result in the earlier verification of the diagnosis.

A.S. Dvornikov et al. (2020) analyzed pathological skin changes associated with COVID-19 and divided them into seven groups; five of these groups were considered as manifestations of novel viral infection [13]. Group 1 was defined as skin vasculitis. It is thought to be directly caused by coronavirus infection, as a result of which the walls of small vessels of the dermis are damaged by immune complexes circulating in blood. Group 2 includes papulo-vesicular rash that resembles sweat rash; it develops with underlying high temperature and increased sweating for several days. Group 3 includes such skin lesions as pityriasis rosea and papulosquamous rash, which are infectious and allergic skin lesions associated with COVID-19 infection. Group 4 includes morbilliform rash. Group 5 includes toxidermia. This rash is not directly associated with coronavirus infection; it develops due to the individual intolerance of patients to certain medications. Scientists include urticaria in Group 6 of skin manifestations of coronavirus; in some cases, it can be a precursor symptom of the onset of COVID-19. Group 7 includes trophic changes in facial tissues that develop in patients due to prolonged lying in a prone position [13, 14].

The average incidence of skin manifestations in patients with SARS-CoV-2, according to different sources, ranges from 0.2% to 19.6% [7, 15]. Rash in the cases of coronavirus infection is characterized by its vast diversity; its pathogenesis is not quite clear and is poorly known [10–15]. Therefore, the awareness of professionals about such manifestations of the disease is relevant in order to reduce erroneous diagnosis and improve subsequent treatment approach. The awareness and alertness of physicians during the visit will contribute to early and timely diagnosis of the disease, which will significantly

accelerate the implementation of treatment and sanitary and epidemiological measures.

This article describes six clinical cases of skin manifestations in patients with confirmed SARS-CoV-2 infection. All patients consulted a dermatologist in the acute phase of their disease before laboratory confirmation and treatment for COVID-19.

The patients were familiarized with the stages of examination and signed informed voluntary consent for medical intervention and publication of data in sciebtific literature.

Case Report No. 1

Patient D., female, 72, consulted a dermatologist with complaints of swelling and rash on the skin of feet, lower legs, skin soreness in the area of rash accompanied by severe weakness, tiredness, fever up to 38°C. Rash appeared on Day 7 after reporting high temperature, weakness, and malaise. The patient took antihistamines (levocetirizine 5 mg) on her own for three days; however, her general condition continued to deteriorate: weakness increased, anosmia developed.-

Life history: The patient has acute respiratory diseases once or twice a year; she is under follow-up with a diagnosis of chronic cholangiocholecystitis with mixed biliary dyskinesia, chronic gastroduodenitis without exacerbation; she has been taking ursodeoxycholic acid 500 mg in capsules before bedtime at night for three months; there is no drug intolerance.

Epidemiological history: The patient lives alone, had no contact with patients with confirmed COVID-19. She returned from Moscow a week ago.

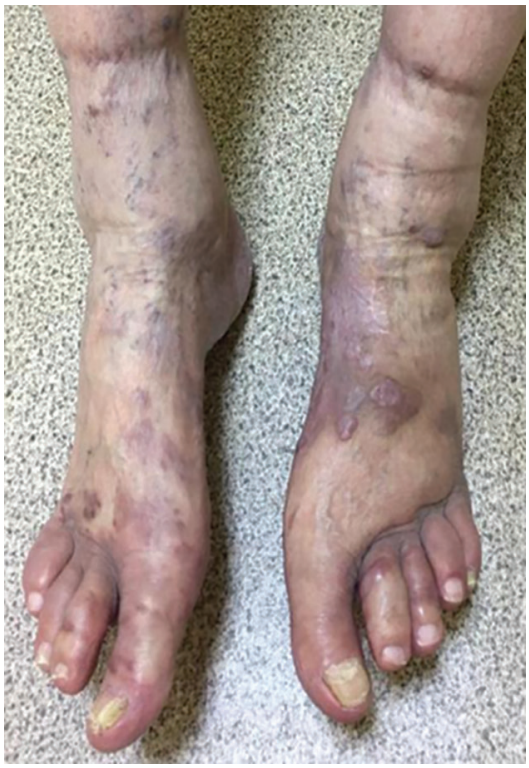

Figure 1. *Patient S., 72 years old. Polymorphic vasculitis*

Objective status: Clear consciousness, active position. Satisfactory condition. Body temperature 37.2°C. Regular body type, weight 82 kg, height 165 cm, BMI 30.1 kg/m^2. Mucosa of the oral cavity is pink, no rash, posterior pharyngeal wall is hyperemic, tonsils are not enlarged, no dental caries, the root of tongue is coated with yellowish plaque. Vesicular breathing, respiratory rate 17/min. Heart rhythm is regular, heart tones are clear, rhythmic, heart rate (HR) 84/min, blood pressure 145/85 mm Hg on both arms, saturation 96%. Abdomen is soft, moderately painful with deep palpation in the area of gallbladder projection; liver + 0.5 cm below the costal margin. On examination, edematous inflammatory purple spots and superficial edematous papules with moderate infiltration of a brown-violet color were observed on the skin of both lower legs and feet. (Figure 1). The patient was diagnosed with polymorphous vasculitis (ICD-10: L95.9 Vasculitis limited to the skin, unspecified).

CBC on appointment: hemoglobin 145 g/L, RBC 5.92 × 10^{12}/L, color index 0.73, hematocrit 48.0%, WBC 4.56 × 10^9/L, neutrophils 50.9%, lymphocytes 41.5%, monocytes 4.7%, eosinophils 2.6%, basophils 0.3%, ESR 25 mm/h, platelets 307 × 10^9/L. Blood biochemistry: total protein 67.2 g/L, creatinine 48 μmol/L, glucose 6.4 mmol/L, urea 4.0 mmol/L, uric acid 174.9 μmol/L, total bilirubin 18.0 μmol/L, direct bilirubin 3.2 μmol/L, aspartate aminotransferase 25 U/L, alanine aminotransferase 29 U/L, total cholesterol 5.8 mmol/L, C-reactive protein 2 mg/L. Antistreptolysin O 20 IU/mL, circulating immune complexes 3.9 RU/mL (reference range: 0.0–20.0 RU/mL). Waaler–Rose test and latex test negative, microprecipitation reaction negative. Common urinalysis within normal range.

Smear from nasal and oropharyngeal mucosa for COVID-19. After receiving positive results that confirmed coronavirus infection, the patient was referred to an infectious disease specialist and hospitalized. In addition to the management of the underlying disease, the therapeutic complex included topical glucocorticosteroids in the form of 0.05% betamethasone cream. The course of the viral infection turned out to be severe; according to the computed tomography data, lung damage was more than 50%; the patient required mechanical ventilation. Positive changes regarding skin rash were seen during Week 3 of hospitalization: swelling gradually decreased, no new rash appeared, and current rash turned pale. After elimination of the etiological factor (COVID-19) on Day 37 of the disease, skin lesions regressed.

Case Report No. 2

Patient O., female, 32, **consulted** a dermatologist with complaints of weakness, rash on the skin of thighs, and loss of taste. From medical history: complaints of weakness, fever, and rash appeared two days ago. In the evening before the visit, the patient's temperature increased to 37.8°C. She took an acetylsalicylic acid tablet on her own. The patient denies any constant use of medications.

Life history: The patient has acute respiratory diseases 2-3 times a year; chickenpox—at the age of 5; there is no drug intolerance.

Epidemiological history: She lives with her husband, who has been in self-isolation for 7 days after returning a positive PCR test for COVID-19.

Objective status: Clear consciousness, active position, satisfactory state, body temperature 37.5°C. Regular body type, weight 61 kg, height 167 cm, BMI 21.9 kg/m^2. Mucosa of the oral cavity is pink, no rash, posterior pharyngeal wall is hyperemic, tonsils are not enlarged, no dental caries, the root of tongue is coated with whitish plaque. Vesicular breathing, respiratory rate 17/min. Heart rhythm is regular, heart tones are clear, HR 88/min, blood pressure 125/75 mm Hg on both arms, saturation 97%. Abdomen is soft, painless; liver does not protrude below the costal margin. On examination, pink spots of various sizes and outlines were observed that formed a bizarre reticular pattern on the skin of thighs (Fig. 2). The following clinical diagnosis was established: Livedo vasculitis (ICD-10: L95.9 Vasculitis limited to the skin, unspecified).

CBC on appointment: hemoglobin 120 g/L, RBC 4.5 × 10^{12}/L, color index 0.80, hematocrit 43.0%, WBC 4.6x10^9/L, neutrophils 51.8%, lymphocytes 41.5%, monocytes 5.0%, eosinophils 1.6%, basophils 0.1%, ESR 23 mm/h, platelets 300 × 10^9/L. Blood biochemistry: total protein 66.2 g/L, creatinine 47 μmol/L, glucose 5.4 mmol/L, urea 4.0 mmol/L, uric acid 140.9 μmol/L, total bilirubin 17.0 μmol/L, direct bilirubin 3.2 μmol/L, aspartate aminotransferase 23 U/L, alanine aminotransferase 24 U/L, total cholesterol 4.8 mmol/L, C-reactive protein 3 mg/L. Antistreptolysin O 10 IU/mL, circulating immune complexes 2.9 RU/mL (reference range: 0.0–20.0 RU/mL). Antibodies to double-stranded DNA (anti-dsDNA) 5 IU/mL (reference range: 0.0–25.0 IU/mL). Microprecipitation reaction negative. Common urinalysis within normal range.

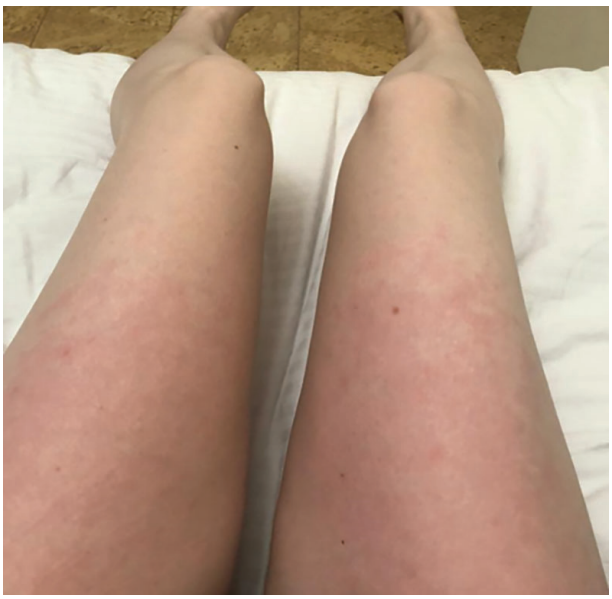

Figure 2. *Patient O., 32 years old. Livedo-angiitis*

Smear from nasal and oropharyngeal mucosa for COVID-19. After receiving positive results that confirmed coronavirus infection, the patient was referred to an infectious disease specialist. Outpatient treatment with self-isolation was prescribed. According to CT results, the lesion of lung parenchyma was more than 15%; the course of COVID-19 was regarded as moderate. Positive changes regarding skin rash (spots became pale pink with blurred outlines, no new ones appeared) were seen during Week 2 of treatment for the underlying disease. After elimination of the etiological factor (COVID-19) on Day 29 of the disease, skin lesions regressed.

Case Report No. 3

Patient M., male, 39, consulted a dermatologist with complaints of severe weakness, malaise, increased temperature in the evenings up to 38°C for 5 days; rash on the skin of arms accompanied by itching, loss of taste and smell. The patient linked the rash with a single intake of an acetylsalicylic acid tablet.

Life history: The patient rarely has acute respiratory diseases; chickenpox—at the age of 2; there was no drug intolerance before.

Epidemiological history: a week ago he came into contact with his neighbor who was hospitalized with viral pneumonia (COVID-19 test results unknown).

Objective status: Clear consciousness, active position, satisfactory state, body temperature 37.1°C. Regular body type, normosthenic, weight 75 kg, height 188 cm, BMI 21.2 kg/m^2. Mucousa of the oral cavity is pink, no rash, posterior pharyngeal wall is extremely hyperemic, tonsils are not enlarged, no dental caries. Vesicular breathing, respiratory rate 17/min. Heart rhythm is regular, heart tones are clear, HR 84/min, blood pressure 115/75 mm Hg on both arms, saturation 97%. Abdomen is soft, painless, liver does not protrude below the costal margin. On examination, heavy bright pink confluent maculopapular elements were observed in the area of hands, forearms, with a tendency to spread to the skin of shoulders (Fig. 3). Considering the complaints, the nature of the rash, and intake of acetylsalicylic acid the day before, the clinical diagnosis of maculopapular toxidermia, a moderately severe course was established (ICD-10: L27.1 Localized skin eruption due to drugs and medicaments taken internally).

CBC on appointment: hemoglobin 140 g/L, RBC 5.5 × 10^{12}/L, color index 0.76, hematocrit 46.0%, WBC 4.2 × 10^9/L, neutrophils 49.8%, lymphocytes 44.5%, monocytes 6.1%, eosinophils 1.6%, basophils 0.1%, ESR 25 mm/h, platelets 280 × 10^9/L. Blood biochemistry: total protein 76.3 g/L, glucose 4.4 mmol/L, urea 4.1 mmol/L, uric acid 139.0 μmol/L, total bilirubin 20.0 μmol/L, direct bilirubin 3.5 μmol/L, aspartate aminotransferase 25 U/L, alanine aminotransferase 22 U/L, total cholesterol 4.9 mmol/L, C-reactive protein 7 mg/L. Antistreptolysin O 5 IU/mL, circulating immune complexes 8.9 RU/mL (reference range: 0.0–20.0 RU/mL).

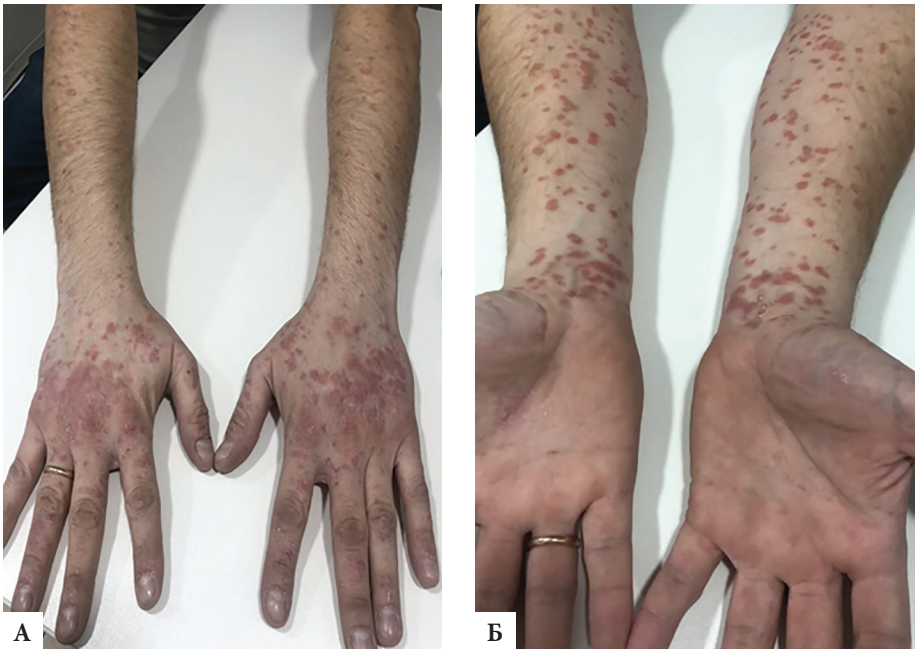

Figure 3. *Patient M., 39 years old. Spotty-papular rashes on the skin of A) the back of the hands Б) the forearms*

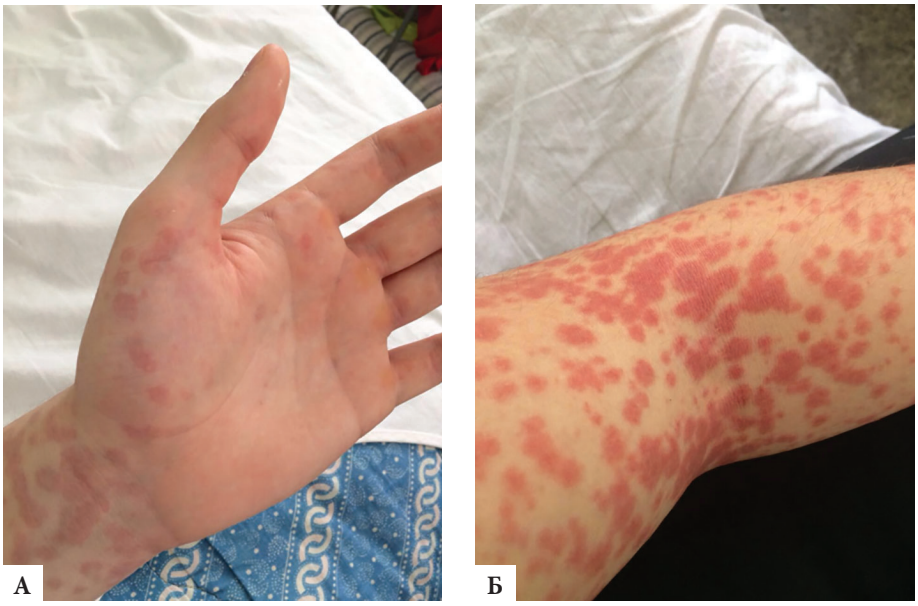

Figure 4. *Patient M., 39 years old. Spot-papular rashes on the skin of A) hands Б) forearms after 10 days of treatment in a hospital*

Antibodies to double-stranded DNA (anti-dsDNA) 10 IU/mL (reference range: 0.0–25.0 IU/mL). Microprecipitation reaction negative. Common urinalysis within normal range.

Smear from nasal and oropharyngeal mucosa for COVID-19. After receiving positive results that confirmed coronavirus infection, the patient was referred to an infectious disease specialist and hospitalized. According to CT results, lung damage was more than 75%. The course of COVID-19 infection was severe; the patient was on oxygen support. Sorbents were added to the management of the underlying disease: polymethylsiloxane polyhydrate (Enterosgel) for 10 days. In the course of treatment, on Day 5 in hospital, skin rash started to regress (color intensity decreased, as well as the infiltration of maculopapular elements; there was no tendency to spread along the periphery) (Fig. 4).

At the time of discharge from the hospital (Day 40 of the disease), skin lesions had regressed completely.

Case Report No. 4

Patient S., female, 23, consulted a dermatologist with complaints of weakness, sweating, and rash on the skin of the trunk accompanied by slight itching, which developed after three days of increased body temperature to 38.2°C. The patient regarded these symptoms as an acute respiratory disease, took Supradin vitamin complex and antipyretics on her own, with temporary effect. Negative epidemiological history: The patient denies contact with patients with COVID-19; she worked from home during the last 14 days and only visited a grocery store once every three days. On examination, multiple isolated papulovesicular elements with a red crown were

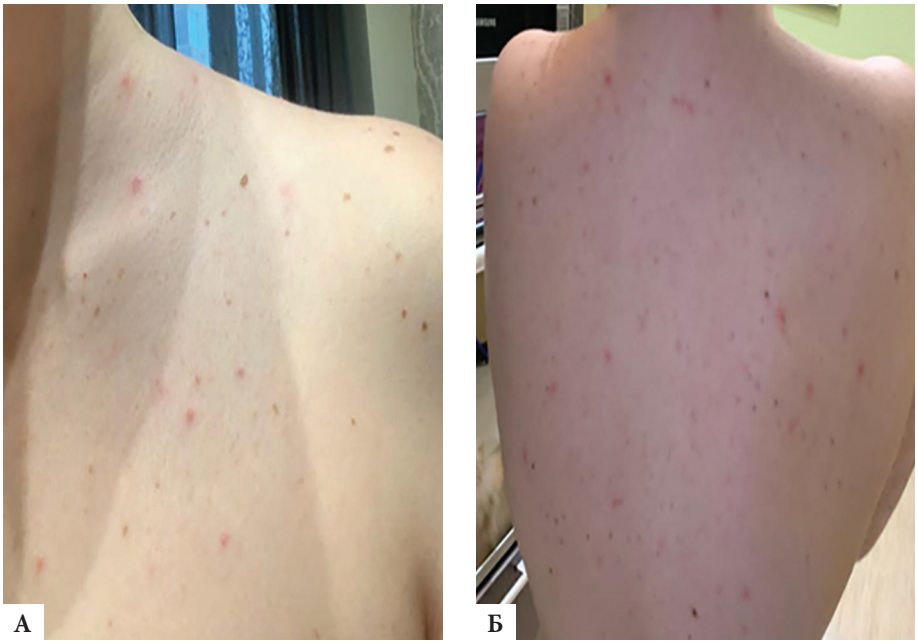

Figure 5. *Patient S., 23 years old. Papulo-vesicular rashes on the skin of A) chest Б) back*

observed mainly on the skin of the back, chest, and—in a lesser extent—abdomen (Fig. 5). The clinical diagnosis of red sweat rash was established (ICD-10: L74.0 Miliaria rubra).

It was recommended to avoid overheating, implement sanitary and hygiene measures (baths with zinc-containing shower gel, ironing underwear and bed linen with a hot iron before use), zinc-containing cream on skin lesions.

Smear from nasal and oropharyngeal mucosa for COVID-19. After receiving positive results that confirmed coronavirus infection, the patient was examined by an infectious disease specialist. The course of infection caused by SARS-CoV-2 was mild; there was no evidence of lung damage. Skin rash regressed after 2 weeks of treatment.

Case Report No. 5

Patient V., male, 48, consulted a dermatologist with complaints of skin rash that developed on Day 4 of low-grade fever accompanied by mild occasional itching. The patient also noted weakness, loss of taste, nasal congestion, and muscle pain. The patient took no treatment on his own.

Life history: The patient has acute respiratory diseases 2-3 times a year; there is no drug intolerance.

Epidemiological history: a week ago, the patient accompanied his relative suspected of COVID-19 to the hospital (coronavirus test results are not known).

Objective status: Clear consciousness, active position. The condition is satisfactory. Body temperature 37.1°C. Regular body type, normosthenic, weight 90 kg, height 168 cm, BMI 31.9 kg/m^2. Mucousa of the oral cavity is pink, no rash, posterior pharyngeal wall is hyperemic, tonsils are not enlarged, no dental caries, and the root of the tongue is coated with yellow plaque. Vesicular breathing, respiratory rate 17/min. Heart rhythm is regular, heart tones are clear, HR 86/min, blood pressure 145/85 mm Hg on both arms, saturation 96%. Abdomen is soft, painless, liver does not protrude below the costal margin. Heavy, bright red teardrop-shaped papules were observed on the skin of the chest, abdomen; more on the back, buttocks, arms; less on legs, 3 to 10 mm in diameter, prone to peripheral growth, covered with delicate scales. Face with no rash, nail plates are not affected. Scraping the papules revealed symptoms typical for psoriasis: "stearic stain", "terminal film," and "bloody dew" (Fig. 6). A clinical diagnosis of guttate psoriasis was established (ICD-10: L40.4 Guttate psoriasis).

CBC on appointment: hemoglobin 140 g/L, RBC 4.2 × 10^{12}/L, color index 1.00, hematocrit 46.0%, WBC 4.0x10^9/L, neutrophils 50.2%, lymphocytes 44.8%, monocytes 8.0%, eosinophils 0.9%, basophils 0.1%, ESR 20 mm/h, platelets 250 × 10^9/L. Blood biochemistry: total protein 79.3 g/L, glucose 5.9 mmol/L, urea 5.1 mmol/L, uric acid 110.0 μmol/L, total bilirubin 18.0 μmol/L, direct bilirubin 2.5 μmol/L, aspartate aminotransferase 35 U/L, alanine aminotransferase 28 U/L, total cholesterol 5.9 mmol/L, C-reactive protein 10 mg/L. Antistreptolysin O 5 IU/mL, microprecipitation reaction negative. Hepatitis B surface antigen (HBsAg) not found, total antibodies to hepatitis C virus (anti-HCV) not found. Common urinalysis within normal range.

Smear from nasal and oropharyngeal mucosa for COVID-19. After receiving positive results that confirmed coronavirus infection, the patient was referred to an infectious disease specialist and hospitalized. According to computed tomography results, lung damage was more than 70%, the course of COVID-19 infection was severe, the patient was on oxygen support.

Topical glucocorticosteroid agents in the form of 0.05% betamethasone cream were added to the

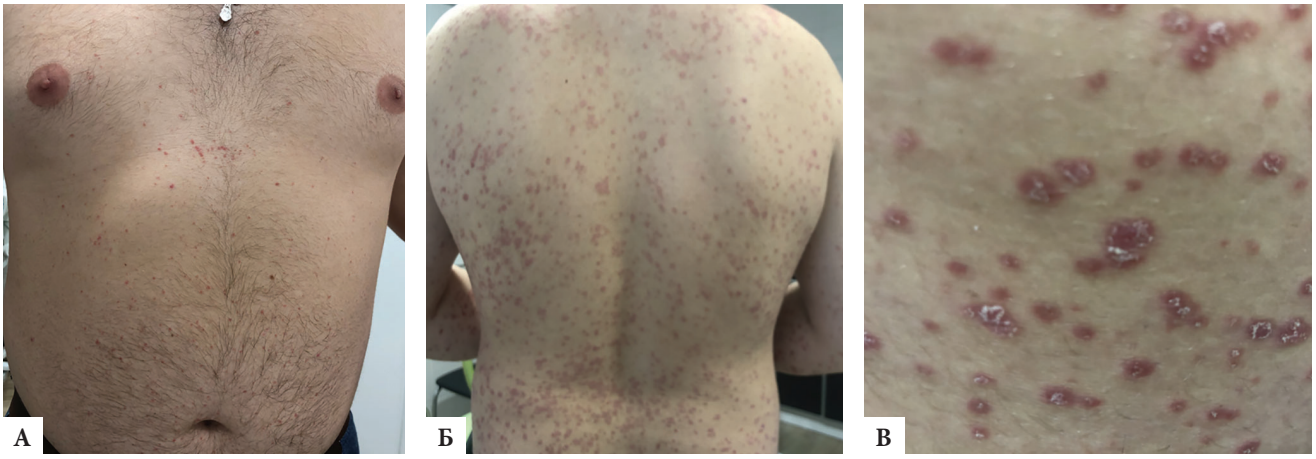

Figure 6. *Patient V., 48 years old. Papulo-squamous rashes on the skin A) abdomen Б) back B) macro photography of elements*

management of underlying disease. In the course of treatment, on Day 15 in hospital, skin symptoms regressed: no new rash appeared; current rash stopped growing, peeled off heavily, its infiltration and brightness decreased.

At the time of discharge from the hospital (Day 40), skin lesions had regressed completely.

Case Report No. 6

Patient M., female, 26, consulted a dermatologist with complaints of skin itching accompanied by bright pink rash. The first elements appeared 11 days ago on the skin of hands. Temperature increased to 37.6°C and there was loss of smell for about a week. The patient thought it was associated with high consumption of chocolate (1 chocolate bar per day). The patient took antihistamines on her own for a week with temporary positive effect.

From life history: The patient has acute respiratory diseases 1-3 times a year; chickenpox—at the age of 2; there is no drug intolerance.

Epidemiological history: her husband was hospitalized with confirmed COVID-19 three weeks ago.

Objective status: Clear consciousness, active position. The condition is satisfactory. Body temperature 37.1°C. Regular body type, normosthenic, weight 65 kg, height 168 cm, BMI 23.0 kg/m^2. Mucousa of the oral cavity is pink, no rash, posterior pharyngeal wall is hyperemic, tonsils are not enlarged, no dental caries, the root of the tongue is coated with yellow plaque. Vesicular breathing, respiratory rate 18/min. Heart rhythm is regular, heart tones are clear, HR 82/min, blood pressure 135/85 mm Hg on both arms, saturation 97%. Abdomen is soft, painless, liver does not protrude below the costal margin. Examination of the skin of the trunk, upper and lower extremities revealed multiple confluent urticaria up to 3 cm in diameter (Fig. 7). A clinical diagnosis of acute idiopathic urticaria was established (ICD-10: L50.1 Idiopathic urticaria).

CBC on appointment: hemoglobin 140 g/L, RBC 4.7×10^{12}/L, WBC 4.6×10^{9}/L, neutrophils 52.2%, lymphocytes 36.8%, monocytes 10.0%, eosinophils 0.9%, basophils 0.1%, ESR 24 mm/h, platelets 270×10^{9}/L. Blood biochemistry: total protein 70.0 g/L, glucose 5.6 mmol/L, serum urea 5.2 mmol/L, uric acid 102.0 μmol/L, total bilirubin 16.0 μmol/L, direct bilirubin 2.0 μmol/L, aspartate aminotransferase 25 U/L, alanine aminotransferase 22 U/L, total cholesterol 4.9 mmol/L, C-reactive protein 12 mg/L. Antistreptolysin O 15 IU/mL.

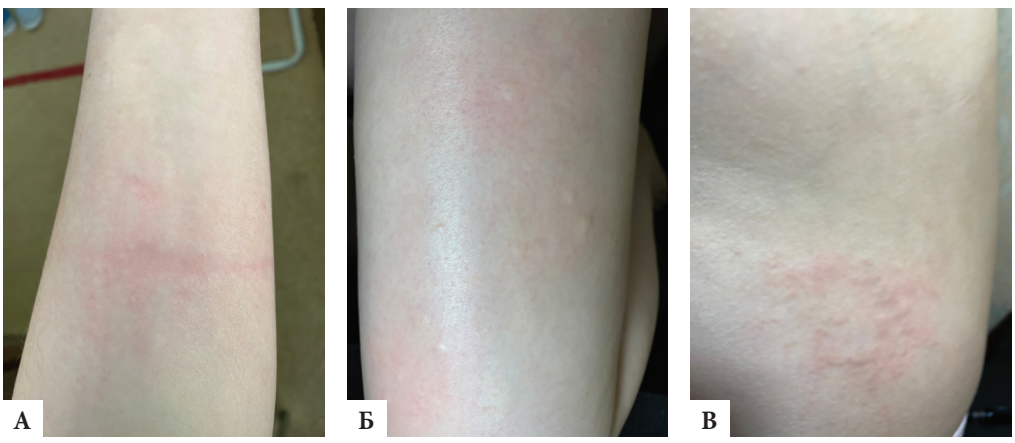

Figure 7. *Patient M., 26 years old. Urticaria. Blisters in the area of A) left forearm Б) right thigh B) torso*

Microprecipitation reaction negative. Hepatitis B surface antigen (HBsAg) not found, total antibodies to hepatitis C virus (anti-HCV) not found. Common urinalysis within normal range.

Smear from nasal and oropharyngeal mucosa for COVID-19. After receiving positive results that confirmed coronavirus infection, the patient was referred to an infectious disease specialist and hospitalized. According to computed tomography results, lung damage was about 40%. The course of COVID-19 infection was assessed as moderate.

In the course of treatment (including systemic glucocorticosteroids), on Day 5 in hospital, urticaria completely regressed.

Discussion

Back in 2004, in their work on the study of ACE2 protein distribution in tissues, which is the functional receptor for SARS coronavirus, Hamming I. et al. wrote that vascular abnormalities and inflammatory changes in various organs, including the skin, may be associated with the systemic toxic effects of immune responses caused by SARS-CoV infection [16].

Today, many authors consider the development of papulosquamous rash as an infectious and allergic skin lesion associated with COVID-19 infection, i.e., paraviral dermatosis. Skin vasculitis is probably directly caused by coronavirus infection, as a result of which the walls of small vessels of the dermis are damaged by immune complexes circulating in the blood [14]. Magro C. et al. (2020) reported an inflammatory thrombogenic vasculopathy with deposition of C5b-9 and C4d complement components in both involved and unchanged skin. Also, co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in interalveolar septa and skin microvasculature was observed in two clinical cases. The authors concluded that a subgroup of patients with severe COVID-19 may have a catastrophic microvascular injury syndrome mediated by the activation of complement pathways and an associated procoagulant state [17]. Potekaev N.N. et al. (2020), based on their experience and analysis of literature data, argue that there is a probable causal relationship between skin vasculitis and COVID-19 infection as a result of damage to small vessels of the dermis by circulating immune complexes, activation of complement pathways and the procoagulant environment [14].

Demopoulos C. et al. (2020) argue that a common pathogenetic link for all clinical varieties of urticaria is the increased vascular permeability of the microvasculature and the development of acute edema around these vessels due to the increased level of histamine and other inflammatory mediators (PAF; cytokines released by activated mast cells) in serum, which leads to vasodilation and plasma extravasation [18]. It was also demonstrated that it was the sharp increase in the level of PAF, the most powerful trigger of platelet activation and thrombus formation, that stimulated perivascular activation of mast cells and caused pneumonia in patients with COVID-19 followed by severe acute respiratory syndrome at the end of the disease [18]. It is probably the sharp increase in the PAF level in several patients with the onset of COVID-19 that induces the development of acute urticaria. Therefore, urticaria-like rash may be the first symptom of COVID-19.

The skin rash described here, which develops at the onset of COVID-19 (in the acute period of the disease before laboratory confirmation of infection and treatment), varied in its clinical presentation and developmental mechanism. However, these skin manifestations have one thing in common—the beginning and the end of these skin processes coincided with the course of SARS-CoV-2 infection. In several cases, sweat rash (associated with high fever and increased sweating for several days) and toxidermia (due to the patient's individual intolerance to acetylsalicylic acid) are not directly related to coronavirus infection. Other clinical cases of skin vasculitis and urticaria described are most likely to be included in the symptom complex of COVID-19. The case of papulosquamous rash is considered an infectious and allergic skin lesion associated with COVID-19. In their article, Gisondi P. et al. (2021) justifiably concluded that the polymorphism of skin manifestations in cases of COVID-19 can be due to a variety of underlying pathogenetic mechanisms [11].

Conclusion

Sharing clinical experience in the analysis of skin manifestations in patients with COVID-19 is extremely relevant during the ongoing pandemic. Evaluation of the accumulated information allows determining the diagnostic and prognostic significance of skin symptoms in patients with COVID-19.

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