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РЕКОМЕНДАЦИИ ПО КОРРЕКЦИИ ПИТАНИЯ В ЛЕЧЕНИИ АТЕРОСКЛЕРОЗА

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Recommendations For Nutritional Correction in The Treatment of Atherosclerosis

Резюме

Коррекция питания является основой российских и зарубежных рекомендаций по лечению атеросклероза, стабильных и нестабильных форм ишемической болезни сердца. Благодаря правильно подобранному сбалансированному рациону возможно достижение целевых показателей липидного профиля. Поэтому назначение диеты является обязательным и самым первым компонентом в лечении любых форм атеросклероза. Анализ научной литературы с использованием библиографических баз NCBI, WoS, Scopus и РИНЦ показал, что наиболее приемлемы в профилактике и лечении атеросклероза вегетарианская и веганская диеты, достоверно снижающие риск развития и прогрессирования атеросклероза, осложнений и смертности. Это связано с тем, что растительные волокна препятствуют всасыванию холестерина и способствуют нормализации микрофлоры кишечника. Содержащиеся в овощах, фруктах, ягодах, чае и зерновых полифенолы препятствуют агрегации тромбоцитов и воспалительным процессам, способствуют улучшению состояния эндотелия и соотношения липопротеинов крови. Антиатерогенными свойствами обладают соевый белок, витамин D, омега-3-жирные кислоты и многие другие описанные в обзоре компоненты. Для всеядных людей необходимо ограничение атерогенных продуктов, богатых холестерином, железом, сахаром, кальцием и фосфатами. Важное значение имеет способ приготовления, поскольку при жарке как растительных, так и животных продуктов образуются атерогенные вещества, способствующие воспалительным процессам в стенках артерий и дислипидемии.

Ключевые слова: *антиатерогенная пища, атеросклероз, вегетарианство, диета, пищевые волокна, растительные продукты*

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Abstract

Nutrition correction is the basis of Russian and foreign recommendations for the treatment of atherosclerosis, stable and unstable forms of ischemic heart disease. A properly selected balanced diet allows achieving target lipid profile indicators. Therefore, the appointment of a diet is a mandatory and the very first component in the treatment of any form of atherosclerosis. Analysis of scientific literature using the bibliographic databases NCBI, WoS, Scopus and RINTS showed that vegetarian and vegan diets are the most acceptable in the prevention and treatment of atherosclerosis, reliably reducing the risk of development and progression of atherosclerosis, complications and mortality. This is due to the fact that plant fibers prevent the absorption of cholesterol and help normalize the intestinal microflora. Polyphenols contained in vegetables, fruits, berries, tea and grains prevent platelet aggregation and inflammatory processes, help improve the condition of the endothelium and the ratio of blood lipoproteins. Soy protein, vitamin D, omega-3 fatty acids and many other components described in the review have anti-atherogenic properties. Omnivores need to limit atherogenic products rich in cholesterol, iron, sugar, calcium and phosphates. The cooking method is important, since frying both plant and animal products produces atherogenic substances that contribute to inflammatory processes in the arterial walls and dyslipidemia.

Key words: *antiatherogenic food, atherosclerosis, vegetarianism, diet, dietary fiber, plant products*

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AS — atherosclerosis, IHD — ischaemic heart disease, HDL — high-density lipoproteins, LDL — low-density lipoproteins, MFC — macrophage foam cell, PSFA — polyunsaturated fatty acids, NFA –unsaturated fatty acids, CVD — cardiovascular disease, IL — interleukin

Introduction

The main strategy to prevent atherosclerosis (AS) is promotion of healthy lifestyles (HLS), quitting bad habits, especially smoking [1]. An important parameter of HLS is the use of special diets, reducing the risk of AS-induced cardiovascular diseases (CVD) [2]. Dietary interventions are the foundation of the Russian and foreign recommendations on the management of AS, stable and unstable ischaemic heart disease. An optimally selected, balanced diet can help in achieving lipid profile targets. In this context, vegan and vegetarian diets are the most efficient. In 2017, a study in 3,696,778 subjects demonstrated reduced risk of AS in individuals who consumed a lot of fruit and vegetables [3]. Meta-analyses conducted in 2023 showed significantly reduced risk of CVD, IHD [4] and AS [4] in vegetarians. The long-term plant-based diet (3.7 years on the average) results not only in slower AS progression, but also firm myocardium reperfusion, as confirmed by PET CT results, and AS regression seen on angiocardiograms [6]. At the same time, unhealthy diets are a leading cause of early death in a majority of countries, mainly deaths of CVD [7]. A meta-analysis conducted in 2024 demonstrated statistically better arterial stiffness and reduced risk of AS in vegetarians vs. general population consuming meat as well [8].

However, alternative diets are required, because not all people can adhere to a strict vegan or vegetarian diet due to individual differences. Since AS pathogenesis is impacted not only by dyslipidaemia [9], which depends on genetic and epigenetic factors [10], but also inflammatory processes [11] and endothelial dysfunctions [12], a Mediterranean diet can be recommended in this case. This diet means limited consumption of sweets and meat, moderate consumption of wine, fermented milk products and seafood, frequent consumption of olive oil, nuts, seeds, grain, vegetables, fruit, and legumes. There are reports of antiatherogenic effects of the Mediterranean diet for inflammation and vascular endothelium dysfunction due to changes in expression of genes *TCF7L2, CETP, APOA2, IL-6, COX-2* involved in this process [13]. The arterial endothelial function (production of VCAM-1, ICAM-1, VEGF molecules) is also normalised with limited consumption of food (small servings) to lose weight [12]. This can be the reason why Okinawa residents, who consume fewer calories, live longer [14].

Antiatherogenic effects of vegan, vegetarian and Mediterranean diet can be a result of a well-balanced ratio of food components, because plant products contain significantly more carbohydrates, less fat and sodium as compared to animal products [15]. According to meta-analyses results, the lowest risk of AS-induced CVD mortality is observed when the carbohydrate ratio is 50 % to 55 % (vs. fats and proteins), whereas a high risk was identified when this ratio decreased or increased. Consumption of plant proteins and fats (vs. animal proteins and fats) reduced the risk of AS mortality and associated CVD [16]. It is also essential to replace products with a high glycaemic load with whole-grain products and cereal with a low glycaemic load; and to consume less salt, red and processed meats [17]. Therefore, according to clinical guidelines of the National Atherosclerosis Society (NAS), Russian Gerontologist and Geriatrician Association, Eurasian Therapeutic Association, Eurasian Cardiology Association, Russian Society of Cardiosomatic Rehabilitation and Secondary Prevention, Russian Scientific Medical Therapeutic Society, a diet involving consumption of a lot of fibre, wholegrain cereals, vegetables, fruit and fat-free dairy products has been proven to be efficient in CVD prevention [18].

Inflammation is a significant factor of AS pathogenesis [11]; therefore, in addition to reduced levels of cholesterol and LDL, it is essential to cut on products with proinflammatory characteristics. Plant products are optimal. A randomised clinical trial in patients with IHD, who were on a vegan diet for 8 weeks, showed significant reduction in high-sensitivity C-reactive protein levels by 32 % vs. the group who were on the diet developed by the American Heart Association [19]. However, even plant products contribute to AS development if cooked incorrectly, because frying with animal or vegetable oils is

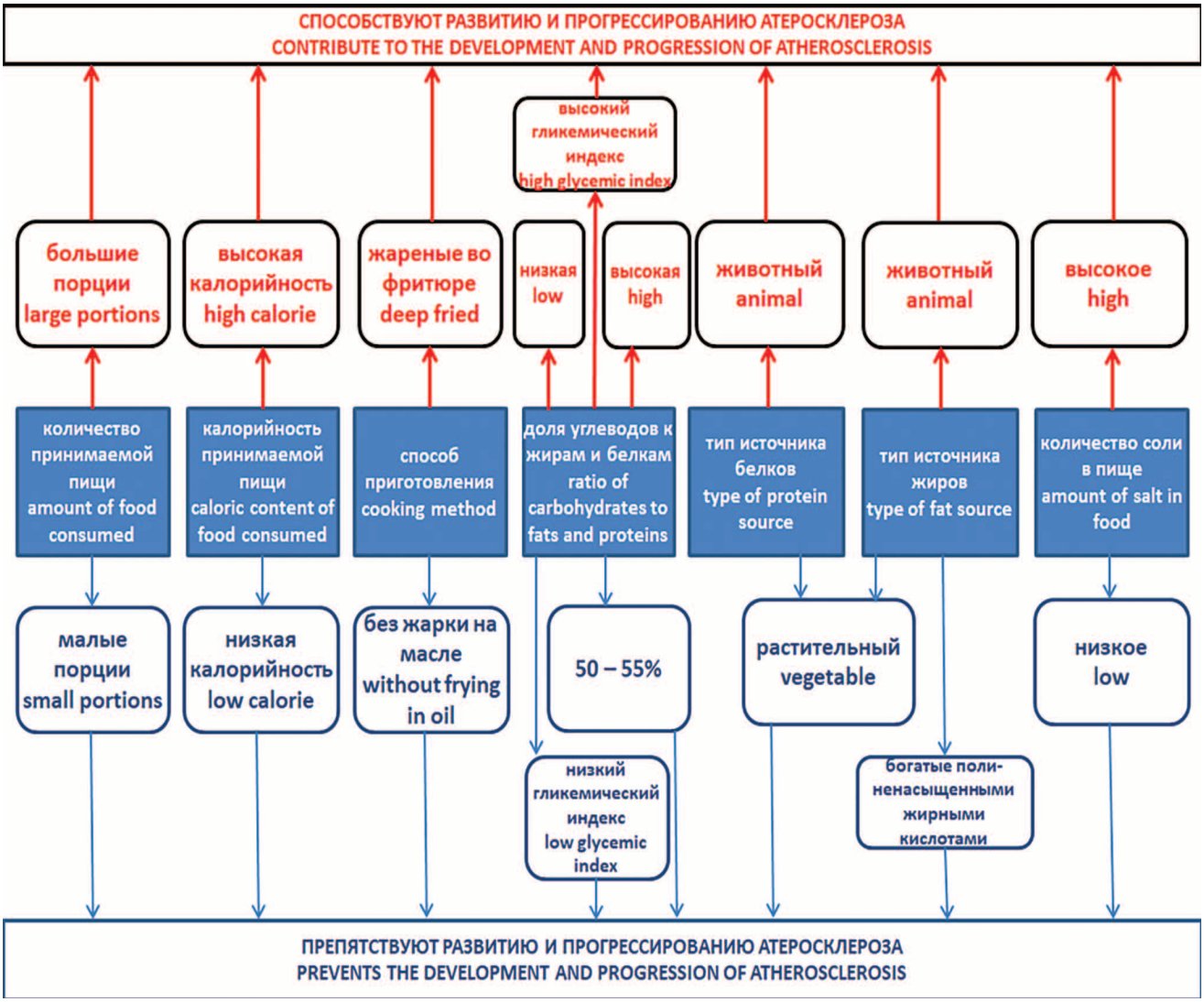

Figure 1. *Scheme of the effect of various components of the diet on the development of AS*

associated with production of oxidised food lipids, which cause vascular wall inflammation and atherogenesis [20]. Therefore, deep-fried potato and banana crisps, savoury snacks contribute to AS [21]. Thus, for AS prevention and management it is essential to consume low-calorie food, to ensure optimal carbohydrate composition and predominant content of plant protein and fat, as well as to limit consumption of salt, animal and deep-fried food (Fig. 1). It is important to consider in detail mechanisms of action of products possessing antiatherogenic effects, which can be recommended to patients with AS.

Effects of plant products on atherosclerosis

One of the mechanisms of favourable effects of vegan and vegetarian diets on AS [3, 4, 6, 8] is regulation of blood cholesterol levels. Up to 80 % of endogenous cholesterol is synthesised in the liver and is excreted with bile as bile acids. However, absorbed bile pool in the ileum contains 2/3 of biliary and 1/3 of endogenous cholesterol [22]. Effects of vegetarian and vegan diets on these processes facilitate reduced cholesterol levels and reduction in atherosclerotic load from atherogenic lipoproteins [5]. This is primarily due to the fact that plant products contain fibres, which are not digested by human gastric enzymes. These can be water-soluble and insoluble (coarse) dietary fibres. Water-soluble fibres contained in barley, oats, legumes, vegetables and fruit include beta-glucans, gums, pectin, slime, stable starches and fructans (inulin, fructo-oligosaccharides). They adsorb and bind cholesterol, reducing its absorption and facilitating its excretion with bile and faecal lipids [23].

Normally, 100 to 300 mg of cholesterol is evacuated by an adult with faeces daily [22]. Nuts, mill offals and wholegrain products contain insoluble dietary fibres (hemicellulose, lignin, cellulose), which reduce the transit time of cholesterol in intestines and its absorption. The recommended daily consumption of dietary fibres is 25 g for women and 38 g for men [23]. Although nuts contain a lot of fats, their consumption reduces total cholesterol and LDL levels, thus reducing the risk of AS [24].

In randomised controlled studies, daily consumption of 3 g of barley [25] and oat [26] beta-glucan, as well as food supplementing with oats fibres [27] facilitated reduction of blood cholesterol levels in subjects.

In addition to the effects of dietary fibres on intestinal cholesterol absorption, plant products contain various substances, possessing other mechanisms of antiatherogenic action. It has been demonstrated that higher consumption of tomatoes, tomato products and lycopene supplements has favourable effects on endothelial function and blood lipids [28]. Plant products contain various polyphenols, which protect against AS; this action is associated with antioxidative and anti-inflammatory action, modulation of lipid metabolism and intestinal microbiota function. Polyphenol-rich products are chocolate, coffee, tea, and fruit in any form [29]. Polyphenols (Fig. 2) include flavonoids (also subclasses of flavonols, flavones, isoflavones, flavanones, anthocyans), stilbenes (resveratrol and benzoic acid), phenolic acids (cinnamic acid), lignans (silimarin). Flavonols include kaempferol, quercetine, myricetin, which have antioxidant effects, stimulate endothelial NO-synthase, reduce VCAM-1 (vascular cell adhesion molecule-1) expression. They can be found in blueberries, merlot, kale, tea, broccoli, onions, and leek [30].

Onions are very rich in quercetine, a polyphenol compound; a clinical study in healthy males show that the daily consumption of quercetine normalises endothelial dysfunction compromised in AS patients [31]. Garlic contains flavonoids myricetin, isoquercitrin and isorhamnetin [32]. Regular consumption of garlic extract by AS patients for a year improved vascular elasticity and restored impaired microvascular perfusion [33]. In a randomised, double-blind, placebo controlled study in patients with a higher risk of CVD, garlic extract was statistically efficient in inhibition of calcification progression in coronary arteries and reduced production of proinflammatory cytokine IL-6 [34]. Flavones found in citrus rind (tangeritin, sinsensetin, nobiletin) inhibit phospholipases PLCγ2 and MAPK in platelets. Soya isoflavones (daidzen, glycitin, genistein) reduce the risk of IHD and myocardial infarction [30].

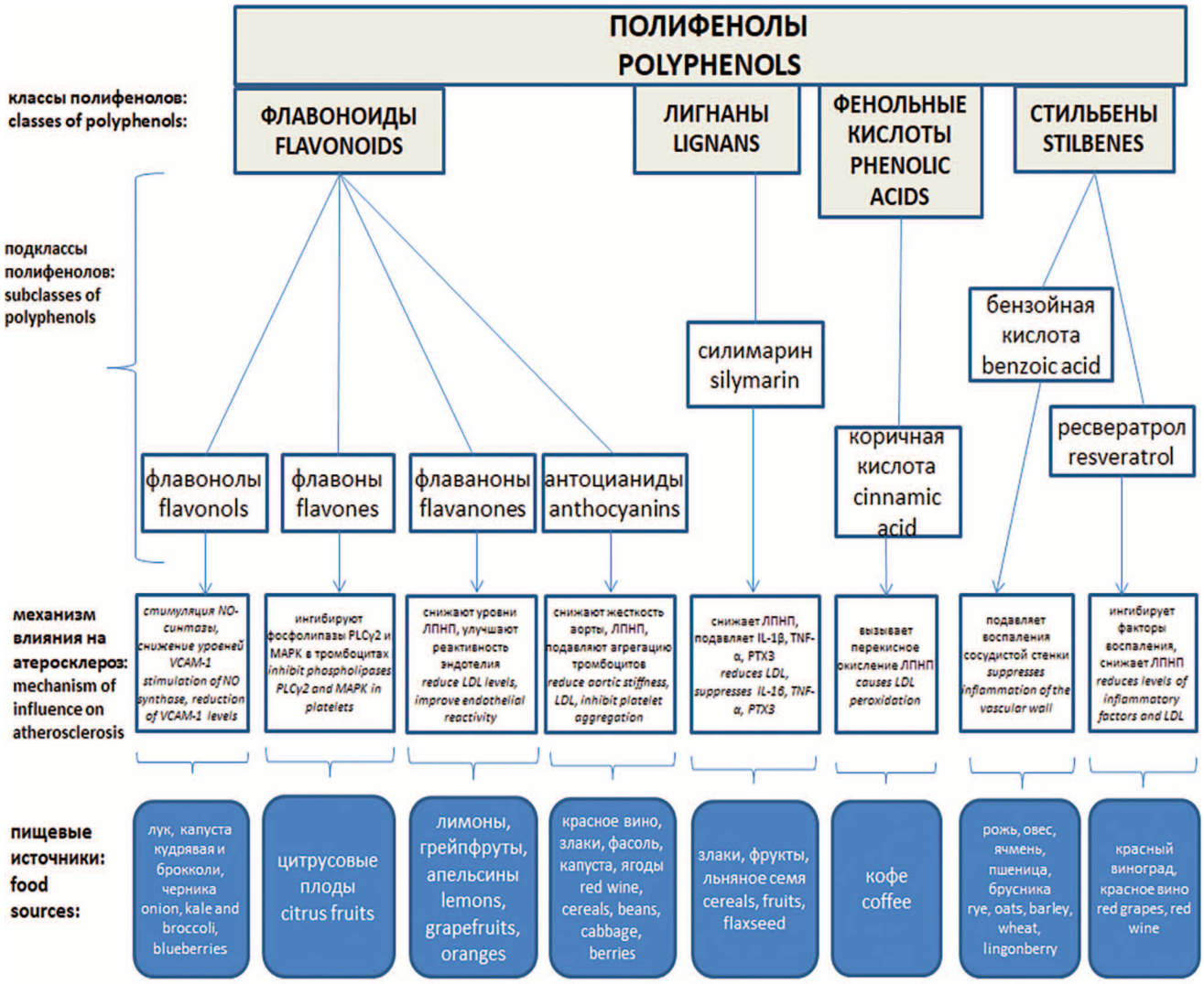

Figure 2. *Polyphenols contained in plant products and their effects on the development of atherosclerosis*

Flavanones eridicitol, hesperetin, naringenin in lemons, oranges and grapefruits reduce atherosclerotic plaque progression, reduce LDL and triglyceride levels, and improve microvascular endothelial reactivity. Anthocyans in blueberries, dewberries, strawberries, cherries, aubergines, opinions, radishes, cabbage, beans, grains, and red wine reduce aorta stiffness, LDL, triglyceride and total cholesterol levels, inhibit platelet aggregation. Resveratrol in grapes and wine inhibits production of nuclear factor NF-κβ and other inflammation factors, reduces LDL and thrombogenic PAI-1 (plasminogen activator inhibitor-1) levels, stimulates expression of *SIRT1* and production of anti-inflammatory adiponectin, and inhibits expression of proinflammatory factors eNOS, NFE2L2, ETI, IL-8 [30]. According to a meta-analysis conducted in 2024, daily consumption of 15 mg of resveratrol by individuals at a risk of IHD reduces TNF-α levels and improves endothelial function due to higher eNOS levels [35]. Benzoic acid in rye, barley, wheat and cowberry has anti-inflammatory and antibacterial effects. Cinnamic acid in coffee beans facilitates cross-oxidation of LDL. Silimarin in grains, fruit, holy thistle and flax seeds also reduces LDL cholesterol and total cholesterol levels, inflammatory biomarkers PTX3, TNF-α, IL-1β [30].

Citrus fruits are a source, that is very rich in flavonoids with anti-inflammatory and antioxidative effects (kaempferol, apigenin, luteolin, rutin, nobiletin, hesperetin, hesperidin, naringenin, naringin, quercetine). These flavonoids modulate adhesion molecules, including ICAM-1, VCAM-1, E-selectin, P-selectin. In preclinical AS models, administration of citrus flavonoids reduced levels of chronic inflammation TNF-α, NF-κB, interleukins, oxidative stress markers (glutathione, superoxide dismutase) [36]. Hesperidin in citrus fruit activates ABCA1 expression 1.8 times and boosts reverse cholesterol transport [37]. Citrus flavonoids naringenin, tangeritin, nobiletin and hesperetin are also potential therapeutic agents for the management of metabolic dysfunction. Epidemiological studies demonstrate positive correlation between consumption of large levels of flavonoids and reduced risk of IHD and stroke. Cell cultures and animal models confirmed lipid-lowering and anti-inflammatory effects of citrus flavonoids [38].

Naringenin and hesperetin in citrus fruit inhibit cholesterol synthesis as a result of 2.4-fold reduction in hydroxy-methyl-glutaryl-CoA-reductase production and can be an alternative to statins [37]. Plant products contain other promising substances, which can be used in production of new AS medications. For instance, curcuma is rich in 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, also known as curcumin, which reduces blood lipid levels and inhibits aortic AS [39]. In a randomised clinical trial, daily consumption of 500 mg of curcumin for 8 weeks contributed to statistically significant reduction in total cholesterol, triglycerides, LDL and TNF-α in patients who underwent elective coronary angioplasty [40]. Dietary supplements with capsaicinoid (found in pimento) reduce cholesterol and LDL levels without any effects on triglycerides HDL [41]. Antiatherosclerotic effects are observed in vegetable protein isolates due to their optimal amino acid composition and presence of residual bioactive plant substances. According to meta-analysis results, daily dietary supplementation with 25 g of soya protein reduces blood LDL levels in individuals with mild hypercholesterolaemia [42].

Results of randomised controlled studies show that replacement of saturated fat in food with linolic acid (omega-6, which is a main component of numerous vegetable oils, including sunflower, soya and corn oils) is efficient in lowering serum cholesterol levels, but does not reduce the risk of death of CVD [43]. Despite the beneficial effects of Mediterranean diet, rich in olive oil [13], literature analysis did not show any randomised clinical trials with statistically significant data on the impact of olive oil or oleic acid on AS development. This can be associated with the fact that, in addition to omega-6, virgin olive oil also contains oleuropein, hydroxytyrosol and tyrosol, which possess cardioprotective effects. There are reports on the inhibiting effect of oleuropein on collagen-induced platelet activation and IL-8 production. In experiments, administration of tyrosol at a dose of 4 mg/kg body weight in the presence of saturated fats and cholesterol reduced AS lesions as compared to animals on the same diet, but without tyrosol. Inhibition of collagen-induced platelet activation under the influence of hydroxytyrosol has been demonstrated. In men with elevated blood pressure, hydroxytyrosol normalised the blood lipid profile. Tyrosol and hydroxytyrosol inhibited phosphorylation of MAPK (mitogen-activated protein kinase, which boosts cell proliferation), production of reactive oxygen intermediates, and secretion of proinflammatory cytokines, including IL-8 [44]. However, a meta-analysis conducted in 2024 showed that consumption of omega-3 (the main component of flaxseed oil) reduces the all-cause mortality, including deaths caused by atherosclerotic cardiovascular diseases. An increase in omega-3 consumption by 1 g/day reduced the risk of death by 3.5 %. Consumption of omega-6 and total polysaturated fatty acids (including oleinic acid) did not demonstrate any significant correlation [45]. Another meta-analysis also confirmed that high doses of omega-3 significantly reduce AS progression [46]. In addition to plants, omega-3 is found in oily fish, consumption of which significantly reduces plasma triglyceride levels and increases the concentration of anti-atherogenic HDL [47]. Also, omega-3 consumption is associated with marked inhibition of platelet aggregation in patients with CVDs vs. healthy controls [48]. These effects were observed when sources of omega-3 were not heat treated (raw flaxseed oil), because aldehydes and epoxy fatty acids produced during frying neutralise favourable effects on AS [20].

Role of vitamins and intestine-active products in the development of atherosclerosis

Reduction in the risk of AS of peripheral arteries with consumption of vitamins A, B6, E, C and folic acid has been demonstrated [49]. It is essential to supplement food with products rich in vitamin B and not dietary supplements containing these vitamins, because a meta-analysis of randomised controlled studies did not show any proofs of the protective effect of vitamins B on AS progression [50]. Since the highest content of vitamins C and E, precursors of vitamin A and folic acid is found in plants, available data are another argument for the use of vegetarian and vegan diets in the prevention and management of AS. Randomised controlled studies using flow-mediated dilatation demonstrated that folic acid restores epithelium damaged by AS [51]. Beta-carotene, riboflavin and niacin affect AS pathogenesis by inflammation inhibition [11]. A meta-analysis showed that niacin also lowers LDL levels [52]. Although vitamin B supplements do not affect AS development, they do not induce disease. Therefore, vitamin supplements are not contraindicated in patients with AS and can be recommended in case of vitamin deficiency.

The main factors of AS pathogenesis are macrophage foam cells (MFC) in atherosclerotic plaques. MFC are dysfunctional for autophagy. Vitamin D3 and its receptor inhibit MFC production and induce autophagy, considerably restoring oxidative lipoprotein autophagy, boosting autophagy-mediated lipid destruction in macrophages, thus preventing macrophage conversion into MFC [53]. In comparative experiments in Yucatan micropigs, which were fed with cholesterol-rich feed for 48 weeks, vitamin D3 deficiency lowered plasma HDL levels and contributed to cholesterol accumulation and AS development. Animals, who received vitamin D3 at a dose of 1,000 IU/day and 3,000 IU/day, did not show such differences. On foam cells isolated from human monocytic macrophages, vitamin D3 contributed to polarisation to M2 macrophages, with reduced expression of pro-inflammatory TNF-α, IL-1β, IL-6, and improved cholesterol outflow [54].

In cell culture experiments, vitamin D3 prevented endothelial cell death by modulating apoptosis and autophagia due to inhibition of superoxide ion production, supporting mitochondrial function and cell viability, kinase activation and NO production induction [55]. In mice experiments, removal of vitamin D3 receptor accelerated AS development due to better adhesion, migration and transfer of MFC cholesterol to atherosclerotic plaques. MFC production was induced by interaction between vitamin D3 receptor with SERCA2b and activation of stress CaMKII-JNKp-PPARγ signalling, stimulation of CD36 and SR-A1 receptors [56]. According to a systemic review of clinical trial results, vitamin D3 deficiency is associated with asymptomatic AS [57]. Blood tests and ultrasonic Doppler vessel examination in Korean adults showed a negative association between vitamin D3 levels and carotid AS [58]. Clinical studies did not demonstrate adverse effects of high doses of vitamin D3 for AS development and progression. Even a single dose of 100,000 IU of vitamin D3 taken by female patients with AS did not affect endothelial function and vessel stiffness, inflammation and coagulation parameters [59]. Meta-analyses made it possible to reliably demonstrate that dietary supplementation with vitamin D3 improves endothelial function [60], significantly reduces the risk of intima-media complex thickening in the carotid [61] and the risk of CVD [62]. Table 1 shows specific food components and their effects on AS progression.

It is worth noting that AS development is affected by gut microflora, which is impacted not only by fermented milk products, containing live bifidus bacteria and lactic bacteria, but also by plant food (Table 2). When consumed with moderation, skimmed and full-fat dairy products do not contribute to the risk of AS, while regular consumption of yoghurt and small amounts of cheese has antiatherogenic effect [17]. This is associated with probiotics blocking development of abnormal gut microflora, which causes inflammation (contributing to AS plaques), with cholesterol and lipid fermentation by microbiota and formation of short-chain fatty acids, which are harmless for vascular walls [63]. Bacteria metabolites, such as trimethylamine N-oxide and bile acids, have protective effects against AS [64]. Antiatherogenic effects of naringenin in citrus fruit are due to induction of bile acid synthesis by gut microflora [37]. Quercetine in onions improves enzyme activity of intestine microbiota and normalises blood lipid profile [65]. The effects of berries and phytochemicals are a result of their ability to modulate gut microbiota, reducing *Firmicutes/Bacteroidetes* ratio and activating beneficial bacteria, such as *Akkermansia muciniphila* [66].

Atherogenic food products

Intake of cholesterols with food has an important role to play in the development of AS [67]. Therefore, animal-derived food rich in cholesterol (especially red and white meat) contributes to higher LDL cholesterol levels [68], higher risk of AS and AS mortality [16]. The development of AS is also facilitated by products, which are associated with inflammatory processes (rich in vitamin B12, cholesterol, fat and carbohydrates, high-calorie products, saturated and trans fats), which increase IL-1β, IL-4, IL-6, IL-10, TNFα, and C-reactive protein levels, involved in disease pathogenesis [69].

Since AS is associated with ageing and telomere shortening [70], irrespective of demographics, lifestyle and consumption of other products and drinks,

Table 1. *Specific food components with anti-atherosclerotic effect and their mechanisms of action*

Name of the substance	Impact effect	Food sources	Author
Lycopene	normalizes endothelial function and blood lipid composition	tomatoes	[28]
Naringenin and Hesperetin	inhibit cholesterol synthesis by inhibiting hydroxymethylglutaryl-CoA reductase	citrus	[37]
Curcumin	reduces levels of total cholesterol, triglycerides, LDL, TNF-α	turmeric	[39, 40]
Capsaicinoids	reduce cholesterol and LDL levels	hot peppers	[41]
Soy protein	reduce LDL level	Soybeans	[42]
Omega-6 fatty acids	reduce cholesterol level	vegetable oils (corn, sunflower, soybean)	[43]
Oleuropein	inhibits IL-8 production and collagen-induced platelet activation	olive oil	[44]
Hydroxytyrosol and Tyrosol	normalize blood lipid profile, inhibit MAPK phosphorylation and secretion of proinflammatory cytokines	olive oil	[44]
Omega-3 fatty acids	reduce triglyceride levels and increase HDL, suppress platelet aggregation, slow atherosclerosis progression	flaxseed oil, fish	[45-48]
Folic acid	restores impaired endothelial function	whole grain bread, legumes, citrus fruits	[51]
Beta-carotene (provitamin A)	suppresses inflammation of the vascular wall	carrots, pumpkin, mushrooms	[22]
Niacin (vitamin PP)	suppresses inflammation of the vascular wall, reduces LDL levels	beans, tomatoes, buckwheat, peanuts, carrots	[22, 52]
Vitamin D3	inhibits the formation of MPC, induces autophagy and lipid breakdown, reduces the synthesis of IL-6, TNF-α, IL-1β in macrophages, prevents the death of endothelial cells and improves their function	mushrooms, fish, yeast, cheese, butter, egg yolk	[53-55, 60]

Table 2. *Foods that inhibit the development of atherosclerosis by affecting the intestines*

Name of the substance	Impact effect	Food sources	Author
Water-soluble dietary fiber (beta-glucans, gums, pectin, mucilage, resistant starches and fructans)	adsorb and bind cholesterol, reducing its absorption and increasing its excretion with bile and fecal lipids	barley, oats, legumes, vegetables, fruits	[23]
Insoluble dietary fiber (hemicellulose, lignin, cellulose)	reduce the transit time of cholesterol through the intestines, thus reducing its absorption	nuts, bran, whole grains	[23]
Lactic acid bacteria (probiotics)	prevent the development of infection that causes inflammation, participate in cholesterol metabolism in the intestine	cheese, yogurt, kefir, cottage cheese	[63]
Naringenin	induces the synthesis of bile acids by intestinal microflora	citrus	[37]
Quercetin	improves the enzymatic activity of intestinal microbiota	onion	[65]
Phytochemicals	activate beneficial bacteria in the gut, promoting cholesterol metabolism	berries	[66]

Table 3. *Food products that promote the development of atherosclerosis*

Food products	Impact effect	Author
Meat, cheese, egg yolk, lard, offal	exogenous cholesterol sources increase LDL levels	[67, 68]
Processed meat	telomere shortening, vascular endothelial aging	[71]
Meat products with phosphates	cause the development of coronary atherosclerosis	[72, 73]
Iron-rich foods (heme meats)	contribute to the progression of atherosclerosis	[74]
Rich in vitamin B12, cholesterol, fats and carbohydrates, high-calorie foods	induce the synthesis of IL-1β, IL-4, IL-6, IL-10, tumor necrosis factor alpha and C-reactive protein, involved in the pathogenesis of AS, promoting inflammation of the vascular wall	[69]
Fried foods in vegetable oil	form high concentrations of genotoxic and cytotoxic lipid oxidation products (epoxy fatty acids and aldehydes)	[20]
Potato chips	increase concentrations of oxidized LDL, IL-6, C-reactive protein	[75]
Products stored in plastic packaging containing phthalates	disrupt lipid metabolism, accelerate the development of atherosclerosis, thicken the intima media	[77]
Products with calcium additives	increase the risk of coronary heart disease	[78]
Drinks with sucrose	increase the risk of coronary heart disease in men	[79]

consumption of processed meat causes telomeres to shorten and facilitates the development of AS [71]. High concentrations of serum phosphate increase the risk of asymptomatic coronary AS and CVD death by 44 % [72]. Since, during processing, phosphates are actively added to raw meat (to improve the water-retaining properties and protein solubility) and meat products, their intake contributes to the development of AS [73]. Experiments in ApoE-/- mice demonstrated the role of iron overload in AS aggravation, as well as better vessel condition with low intakes of iron and chelated iron therapy. Therefore, it is recommended to limit consumption of products rich in iron in patients with AS (red heme meat) [74].

Vegetable fats can also have atherogenic potential when used for frying. When used for frying, cooking oils, which are rich in polyunsaturated fatty acids, produce highly concentrated genotoxic and cytotoxic products of lipid oxidation (including epoxy fatty acids and aldehydes) as a result of oxygen recirculating peroxide outbursts. These toxins are absorbed by intestine and contribute to inflammatory processes in vascular walls, inducing AS [20]. Therefore, in order to prevent AS, vegetarians and vegans are recommended to limit frying using vegetable oils. Daily consumption of potato chips by healthy volunteers for 4 weeks showed significant increase in levels of oxidated LDL, IL-6, C-reactive protein, and blood acrilamide levels. These changes were risk factors for the development of AS [75]. At the same time, elderly individuals with asymptomatic IHD, who ate jacket potato and mashed potato, did not show any effects for the disease progression and coronary artery calcification [76].

Food packaging and plasticisers in PVC materials contain phthalates. As a result of daily use of plastics contacting with food, phthalates inter the body; they interfere with lipid metabolism and speed up AS development. There is positive correlation between the use of phthalates and thickened intima-media complex [77]. According to several meta-analyses, dietary calcium supplements are associated with a higher risk of IHD, whereas consumption of food rich in natural calcium does not contribute to the development of coronary artery AS. Natural means calcium in consumed food (living plant and animal organisms) in the form of various salts as part of cytoplasm and extracellular fluid. Thus, any calcium salts (mainly calcium carbonate and citrate) added artificially are unnatural and contribute to AS [78]. Prospective clinical trials show increased risk of IHD in males who drink drinks sweetened with sugar [79]. Table 3 shows food products and their effects, which should be avoided or limited in order to prevent AS.

Conclusion

The fundamental element of the Russian and foreign guidelines for the prevention and management of atherosclerosis is a balanced diet, which can help in achieving the target blood cholesterol and LDL levels. The literature analysis demonstrated that the optimal diets are

vegetarian, vegan and Mediterranean diets. The effect is a result of antiatherosclerotic action of dietary fibres in plant products, which speed up bowel movements, adsorb and bind cholesterol, thus improving its removal from the body. Also, omega-6 fatty acids, soya protein, curcumin, and capsaicinoids lower blood LDL levels. There are reports of anti-inflammatory effects of beta-carotene, vitamins PP and D3, probiotics in plant products. Licopene, folic acid, vitamin D3 normalise function of vascular endothelium. There are reports on various effects of polyphenols in plant products on pathogenesis of atherosclerosis, as well as the ability of hesperetin and naringenin in citrus fruit to inhibit cholesterol synthesis in the liver due to inhibition of hydroxy-methyl-glutaryl-CoA-reductase. An important method of atherosclerosis prevention and management is avoidance of atherogenic food, frying with vegetable oils (contain aldehydes and epoxy fatty acids), products rich in cholesterol (meat, cheese, egg yolk, by-products), phosphates, iron, saturated and trans fats, with calcium supplements, which are stored in phthalate-containing packaging, sweet drinks. It is also essential to reduce consumption of high-calorie food, limit intake of carbohydrates with a high glycaemic index, crisps, and deep-fried products.

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ВЛИЯНИЕ ИНГИБИТОРОВ НАТРИЙ-ГЛЮКОЗНОГО КОТРАНСПОРТЕРА 2 ТИПА НА РАЗВИТИЕ И ТЕЧЕНИЕ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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Effect of Sodium-Glucose Cotransporter Type 2 Inhibitors on The Development and Course of Atrial Fibrillation

Резюме

Фибрилляция предсердий — одно из самых распространенных нарушений сердечного ритма, связанное с повышенным риском инсульта, смертности от сердечно-сосудистых заболеваний и госпитализаций. На развитие аритмии влияет ряд факторов риска, включая артериальную гипертензию, хроническую сердечную недостаточность, ишемическую болезнь сердца и эндокринные расстройства. Новые рекомендации Европейского общества кардиологов (2024) подчеркивают важность управления факторами риска для повышения эффективности лечения и улучшения прогноза у пациентов с фибрилляцией предсердий. Ингибиторы натрий-глюкозного котранспортера 2 типа (глифлозины), изначально применявшиеся как гипогликемические препараты, сегодня широко используются и для снижения риска неблагоприятных сердечно-сосудистых событий. Однако вопрос о применении этих препаратов с целью снижения риска возникновения и улучшения течения фибрилляции предсердий остается открытым. С целью поиска ответа на него был проведен обзор литературы, который показал, что ингибиторы натрий-глюкозного котранспортера 2 типа теоретически могут обладать антиаритмическим эффектом, реализующимся за счет нескольких механизмов. Анализ научных данных говорит о том, что в большинстве случаев использование ингибиторов натрий-глюкозного котранспортера 2 типа уменьшает риск развития впервые возникшей фибрилляции предсердий, положительно влияет на течение аритмии и снижает риск ее рецидива после аблации. При этом до конца не ясно, являются ли обсуждаемые вопросы класс-эффектом или препараты, входящие в группу глифлозинов, имеют разную эффективность. Обозначенные вопросы обуславливают необходимость проведения дальнейших проспективных исследований для подтверждения антиаритмического эффекта у ингибиторов натрий-глюкозного котранспортера 2 типа.

Ключевые слова: *фибрилляция предсердий, ингибиторы НГЛТ2, глифлозины, сахарный диабет*

Конфликт интересов

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

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Abstract

Atrial fibrillation is one of the most common heart rhythm disorders associated with an increased risk of stroke, cardiovascular mortality and hospitalizations. The development of arrhythmias is influenced by a number of risk factors, including arterial hypertension, chronic heart failure, coronary heart disease and endocrine disorders. New guidelines from the European Society of Cardiology (2024) emphasize the importance of managing risk factors to improve treatment efficacy and prognosis in patients with atrial fibrillation. Sodium-glucose cotransporter type 2 inhibitors (gliflozins), originally used as hypoglycemic drugs, are now also widely used to reduce the risk of adverse cardiovascular events. However, the use of these drugs to reduce the risk of atrial fibrillation and improve the course of atrial fibrillation remains an open question. In order to find an answer to this question, a literature review was conducted, which showed that inhibitors of sodium-glucose cotransporter type 2 can theoretically have an antiarrhythmic effect realized through several mechanisms. Analysis of scientific data suggests that in most cases, the use of sodium-glucose cotransporter type 2 inhibitors reduces the risk of first-time atrial fibrillation, has a positive effect on the course of arrhythmia and reduces the risk of its recurrence after ablation. At the same time, it is not clear to the end whether the discussed issues are class-effect or the drugs belonging to the gliflozin group have different efficacy. The mentioned issues necessitate further prospective studies to confirm the antiarrhythmic effect in sodium-glucose cotransporter type 2 inhibitors.

Key words: *atrial fibrillation, SGLT2 Inhibitors, gliflozins, diabetes mellitus*

Conflict of interests

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AF — atrial fibrillation, CHF — chronic heart failure, DM — diabetes mellitus, SGLT2i — sodium-glucose linked transporter-2 inhibitors, RCS — randomised controlled studies, NHE1 — type 1 Na+/H+ exchanger, ACVD — atherosclerotic cardiovascular diseases, DPP4i — dipeptidyl peptidase-4 inhibitors

Introduction

Atrial fibrillation (AF) is the most common type of rhythm disturbance, which is associated with a higher risk of cardioembolic stroke, cardiovascular deaths, and hospitalisations [1]. The incidence of AF is 2 %. In Russia, the rates are similar [2, 3]. In some cohorts, this value can be even higher. For example, during the first month after the infection, the incidence of atrial arrhythmias among post-COVID patients is 12 times higher than in the general population [4]. Given the longer life expectancy of the population, the incidence of AF is likely to be even higher: over the next 50 years, the incidence of arrhythmias can double [5].

In a majority of cases, the exact aetiology of AF is unknown; however, some clinical conditions are associated with a higher rate of arrhythmia. They include a number of cardiovascular diseases: arterial hypertension, chronic heart failure (CHF), ischaemic heart disease, acquired and congenital heart disorders [6, 7]. In the Framingham Heart Study, CHF increases the risk of AF by 8.5 times in men and by 14 times in women [8]. Common causes are also endocrine disorders, including diabetes mellitus (DM), which increases the risk of AF by 28 % [9]. DM-related factors, not the cardiovascular comorbidity, contribute to the development of arrhythmia: unstable blood glucose level, oxidative stress, and inflammation [10].

The new European Society of Cardiology Guidelines for the Management of AF (ESC, 2024) focus on comorbidities. CARE approach (C — Correction of comorbidities and risk factors; A – Avoidance of stroke and thromboembolism; R — Reducing symptoms by effective use of heart rate and rhythm control; E — Evaluation and follow-up) in comorbid patients involves control of risk factors in order to prevent AF recurrences and progression. It allows boosting treatment efficiency, improving prognosis, and preventing unfavourable outcomes [11].

Recently, sodium-glucose linked transporter-2 inhibitors (SGLT2i, gliflozins) have been widely used in clinical settings. Initially claimed as hypoglycaemic agents, these medications demonstrated the ability to reduce the number of adverse cardiovascular events and lower the risk of hospitalisations for CHF, as well as showed effects on the reduction of the risk of chronic kidney disease progression [12, 13]. Currently, dapa- and empagliflozins are recommended to all patients with CHF irrespective of their ejection fraction, including those with AF [11, 14]. Although SGLT2 inhibitors have proven to be efficient, it is still unclear whether they can be used to reduce the risk of AF and impact the existing arrhythmia.

The objective of this review is to study the ability of SGLT2i to reduce the risk of development and improved course of AF.

Methods of search

A literature search was conducted, which included relevant articles in PubMED, eLIBRARY databases and also at ClinicalTrials, both in Russian and English, over a period from 2016 to 2024. The following keywords and phrases containing such keywords were used in the literature search: SGLT2 inhibitors, gliflozins, atrial fibrillation, diabetes mellitus, antiarrhythmic effect. The search included systemic reviews, meta-analyses, both published and unpublished randomised controlled studies (RCS), and observational studies. The final analysis of publications did not include theses, poster reports, thesis papers, and conference materials. All in all, 130 publications were analysed; the final analysis comprised 18 publications, including five publications discussing possible antiarrhythmic mechanism of action of SGLT2i [19-23], and 13 publications discussing the efficacy of gliflozins in the reduction of risk of AF and impact for existing arrhythmias [24-36].

Mechanisms of antiarrhythmic effects of SGLT2i

To date, a number of pleiotropic effects of gliflozins have been described, which include reduction of albuminuria, blood pressure, body mass, and uric acid levels [15-18]. However, their antiarrhythmic effects are still unclear. At the same time, oxidative stress and energy deficit of cardiac cells, which underlie the AF arrhythmogenesis, are associated with mitochondria dysfunction and impaired sodium and calcium exchange, which can be a point of intervention with gliflozins.

The possible mechanism of antiarrhythmic effects of gliflozins is additional inhibition of type 1 Na+/H+ exchanger (NHE1) [19]. The main cause of excessive NHE1 activation is intracellular acidosis induced by myocardial ischemia [20]. In addition, the experimental model demonstrated that NHE1 is activated also during atrial tachycardia [21]. Later, Chinese authors (2008) reported that NHE1 activity is clearly higher both in ageing atria and in fibrillating atria [22]. Irrespective of the cause of excessive NHE1 activation, it results in cytomatrix overloading with Na+ ions, which alters inversely the function of Na+/Ca2+ exchanger and contributes to cytomatrix overloading with Ca2+ ions. This is associated with the development of cardiac dysfunction, abnormal conductivity and triggered activity, which can add to AF arrhythmogenesis [20, 23]. Simultaneously, Na+/Ca2+ exchanger is activated on the mitochondria membrane, causing higher Ca2+ outflow from the organelle. Reduced intramitochondrial concentration of Ca2+ leads to impairment of a number of essential functions, including ATP synthase dysfunction and excessive synthesis of reactive oxygen intermediates, which results in more significant atrial remodelling, also in patients with existing AF [19]. However, it does not eliminate the contribution of other possible mechanisms in the creation of antiarrhythmic effects of SGLT2i (Fig. 1), given there is no clear answer to the question about the key mechanism.

Role of SGLT2i in the reduction of the risk of AF de novo

A majority of large RCS study the effects of SGLT2i on the incidence of atherosclerotic cardiovascular (ACVD) complications and CHF. One of them, DECLARE-TIMI 58, studied the effects of dapagliflozin on DM patients

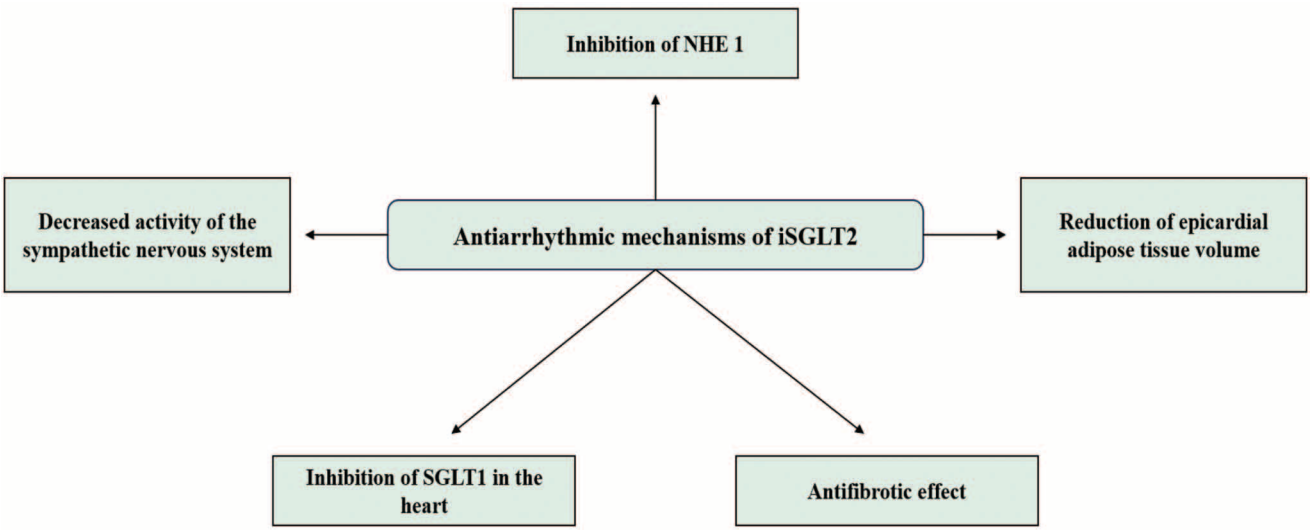

Figure 1. *Mechanisms putatively underlying the antiarrhythmic effect of iSGLT2*
Note. iSGLT2 — sodium-glucose cotransporter type 2 inhibitors, SGLT1 — sodium-glucose cotransporter type 1, NHE1 — Na+/H+ exchanger type 1

with ACVD (n=6,974) or with a high risk of such diseases (n=10,186). Since the authors of the original study did not aim at identifying the ability of SGLT2i to delay the onset of AF, an additional retrospective analysis was conducted in a separate arm (n=1,116), which showed 19 % reduction in the risk of arrhythmia vs. placebo (OR 0.81; 95 % CI: 0.68–0.95; p=0.009). The results did not depend on a history of a specific diagnosis of ACVD or CHF [24].

Alternative results were reported in the DAPA-HF study. Butt J.H. et al. (2022) demonstrated that the use of dapagliflozin did not reduce the risk of AF de novo in patients (n=2,834) with CHF and decreased ejection fraction (OR 0.81; 95 % CI: 0.60–1.22). This can be a result of the study characteristics, which was probably conducted for a shorter period of time than needed to see the antiarrhythmic effects of SGLT2i: the median observation time was 18 months, while in DECLARE-TIMI 58, the observation lasted for 48 months; and the effects for AF were usually seen 24 months after dapagliflozin initiation, however in a completely different patient population. Also, AF monitoring in DAPA-HF was not active enough, which could result in missed episodes of arrhythmia and a low number of patients with AF de novo (n=123; 4.3 %) [25].

It appears that the problem of AF underdiagnosing is present in other large RCS of SGLT2i, because AF recording was not an endpoint and the condition was treated as an adverse event; the disease was often diagnosed only on the basis of the medical history and ECG recording during control visits. For example, in the EMPA-REG OUTCOME study, the incidence of AF de novo was also low and did not differ between placebo (n=106; 1.6 %) and empagliflozin (n=153; 2.3 %) [26].

The favourable effects of SGLT2i in the prevention of AF de novo are supported by the fact that analysis results of DECLARE-TIMI 58 were similar to those of meta-analyses. For example, a meta-analysis of 34 studies (n=63,166, 63 % of males, mean age: 60 years) demonstrated that the use of SGLT2i reduced the risk of any atrial arrhythmias in patients with DM (OR 0.81; 95 % CI: 0.69–0.95; p=0.008) [27]. However, in a larger sample (46 studies, n=101,100) in another meta-analysis, the results differed again: according to the authors, SGLT2i did not reduce the risk of AF irrespective of the follow-up duration, drug type or dose, and patient population [28].

It is likely that the contradictory conclusions can be a result of characteristics of the studies included in the meta-analysis. All studies had significantly differing designs and follow-up duration; none of them had AF as an endpoint, and the history of AF was not taken into account during patient enrolment [29].

SGLT2i and AF progression

Up to date, there are just a few literature reports on the studies, aiming at establishing the relationship between SGLT2i and AF progression in patients with DM and pre-existing AF. In one study, the authors compared the efficacy of SGLT2i and dipeptidyl peptidase-4 inhibitors (DPP4i) during the period from 2014 to 2019 (cohort study). The primary endpoint was AF-associated events: hospitalisation, A&E visits, electrical cardioversion or catheter ablation. Secondary parameters included all-cause mortality, hospitalisation for decompensated CHF, ischaemic stroke or transient ischaemic attack. Among 2,242 patients with DM and AF, who were followed up for an average period of three years, the primary endpoint was recorded in 8.7 % (n=97) of patients in SGLT2i group vs. 10.0 % (n=112) of patients in DPP4i group (OR 0.73; 95 % CI: 0.55–0.96; p=0.03). SGLT2i were associated with significantly reduced all-cause mortality rates and hospitalisations for CHF, but did not show any difference in the risk of ischaemic stroke/transient ischaemic attack [30].

Similar results were obtained in a study by Korean authors (2024), who conducted a retrospective analysis of a database of patients (n=11,012) with DM and AF: the use of SGLT2i resulted in significantly lower all-cause mortality (OR 0.43; 95 % CI: 0.29–0.67) and marked kidney protection, which is also very important: higher blood creatinine levels of over 50 % or dialysis initiation were less common in SGLT2i group (OR 0.50; 95 % CI: 0.38–0.66; p<0.001) [31].

Undoubtedly, a major fault of these studies is their retrospective nature, which has practical limitations for the use of these studies due to the low level of evidence. This problem is being resolved: the EMPA-AF (NCT04583813) and BEYOND (NCT05029115) studies are being currently planned.

SGLT2i and reduction in post-ablation rates of AF

There are a number of articles describing that SGLT2i can reduce the risk of AF recurrences after ablation. One of the major studies in this domain is a study by Abu-Qaoud M.R. et al. (2023) [32]. The study included DM patients, who underwent AF ablation in 2014 to 2021. The patients were divided into two equal arms (n=2,225) depending on SGLT2i status. The primary endpoint was an episode of AF recurrence during the 12-month follow-up. The secondary endpoints were: decompensated CHF, ischaemic stroke, all-cause hospitalisations and death during the same period. The use of SGLT2i was associated with a significantly lower risk of AF recurrence (OR 0.68; 95 % CI: 0.602–

0.776; p<0.0001). Elements of the secondary endpoint were also less common (OR 0.85; 95 % CI: 0.77–0.95; p=0.003); however, the incidence of strokes had only minor differences.

Similar results were reported also by Japanese colleagues (2022), who conducted a prospective randomised study to compare the efficacy of SGLT2i and DPP4i in AF recurrence after ablation. Seventy patients with AF and DM were randomised to tofogliflozin group (n=38) or anagliptin group (n=32); also, patients were stratified depending on the left atrial diameter and AF pattern. The primary endpoint was AF recurrence during 12 months after ablation. In anagliptin group, AF recurrences were more common than in tofogliflozin group (47 % vs. 24 %, p=0.0417) [33].

The limitation of these studies can be inclusion only of DM patients, therefore, the results cannot be extrapolated to all AF patients, and another RCS is required to assess the effects of SGLT2i on AF recurrences after ablation, irrespective of DM status of patients.

Efficacy of specific SGLT2 inhibitors

Are the above issues class effects, or do various gliflozins have various efficacy? The mentioned meta-analysis of 34 studies showed that only dapagliflozin was associated with a significantly reduced risk of atrial arrhythmias in DM patients (OR 0.74; 95 % CI: 0.60–0.91; p=0.005), while canagliflozin showed statistically insignificant results (OR 0.81; 95 % CI: 0.60–1.08; p=0.15), empagliflozin did not affect the risk of AF (OR 1.17; 95 % CI: 0.75–1.82; p=0.49) [27].

Similar results were obtained by investigators in South Korea (2024). In an observational study, conducted in 2016–2018, DM patients (n=137,928, mean age: 55 years old, males: 58 %) were treated with dapa- or empagliflozin. In dapagliflozin group, events of AF were less common (OR 0.89; 95 % CI: 0.79–0.99). It is worth noting that the results were similar both in groups of low and high cardiovascular risk. Age, gender, body mass index, diabetes duration, and renal function did not affect the final result [34].

The fly in the ointment is a retrospective cohort study conducted by Japanese authors (2022), where the national database analysis was used to compare specific SGLT2i and their role in primary prevention of CHF, ischaemic heart disease, stroke and AF in DM patients (n=25,315, mean age: 52 years, 82.5 % of males). The risks of the mentioned cardiovascular events were similar with the use of specific SGLT2 inhibitors. However, the database had a number of significant limitations: there was no preliminary information on DM duration; patients over 75 years old were excluded; there were no data on the socio-economic status of patients [35].

It is important to note that if the antiarrhythmic effect is indeed a result of NHE1 inhibition, then there cannot be a significant difference in the efficacy of various SGLT2 inhibitors, as demonstrated by Uthman L. et al. (2018) in their study in laboratory mice [36].

Conclusion

Thus, there is no clear answer to whether SGLT2i are efficient in reduction of the risk and improvement of existing AF; however, there are abundant facts about the effects of these medications on the reduction of arrhythmia burden, especially in DM patients. This situation necessitates further prospective studies.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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ПРОФИЛАКТИКА ПРОФЕССИОНАЛЬНОГО КОСТНО-МЫШЕЧНОГО ДИСКОМФОРТА У ПРЕДСТАВИТЕЛЕЙ РАЗЛИЧНЫХ ПРОФЕССИЙ С ИСПОЛЬЗОВАНИЕМ ТЕЛЕКОНСУЛЬТАЦИЙ (ОБЗОР ЛИТЕРАТУРНЫХ ИСТОЧНИКОВ)

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Prevention of Work-Related Musculoskeletal Discomforts in Various Occupations using Teleconsultation (Literature Review)

Резюме

Принимая во внимание растущий спрос на услуги онлайн, особенно среди разного рода офисных работников, цель данной работы заключается в том, чтобы проанализировать данные литературных источников касательно телеконсультаций по профилактике профессионального костно-мышечного дискомфорта у офисных работников. Результаты обзора подчеркнули отсутствие надлежащей осведомленности о телеконсультациях среди офисных работников, а также недостаточный уровень знаний об этой технологии. Рекомендуется, чтобы компании отнеслись с должным вниманием к внедрению услуг телеконсультаций для улучшения состояния здоровья и самочувствия своих работников, не забывая при этом о рентабельности.

Ключевые слова: *телеконсультация, гигиена труда, обучение, телемедицина, дистанционная медицина*

Конфликт интересов

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

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Abstract

Given the growing demand worldwide for online services, particularly among individuals engaged in diverse kinds of office work, this paper aims to analyze the literature data on teleconsultation for the prevention of work-related musculoskeletal discomforts among office workers. The findings of this review underscored a notable lack of attention to teleconsultation among office workers, coupled with insufficient education on utilizing this technology. It is recommended that companies prioritize the implementation of teleconsultation services to enhance the health and well-being of their employees, while also considering it as a cost-effective strategy.

Key words: *teleconsultation, occupational health, education, telemedicine, telehealth*

Conflict of interests

The authors declare no conflict of interests

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MSDs — Musculoskeletal Discomforts, GBD — Global Burden of Disease, CBT — Cognitive Behavioral Therapy, MBSR — Mindfulness-Based Stress Reduction, NSAID — Nonsteroidal Anti-Inflammatory Drug, SMD — Standardized Mean Difference, CI — Confidence Interval, AMSTAR — Assessment of Multiple Systematic Reviews

Introduction

Musculoskeletal discomforts (MSDs) are associated with pain and a prevalent issue-affecting worker across various occupations, with implications for their health and work performance. The causes of this pain can appear in various areas of the body and include physical and psychological aspects of working conditions. Effective preventive strategies are essential to reduce the onset and progression of work related musculoskeletal discomforts. Various types of mental and physical counseling are available for individuals with musculoskeletal discomforts, including pharmacological and non-pharmacological methods. Both time and cost savings emerged as crucial factors for individuals across all occupations, especially those occupations that require sitting for long periods of time and working with a laptop, keyboard, and mouse. This highlights the significant need for teleconsultation services.

Teleconsultation, which is a subset of telemedicine, is usually an efficient and acceptable alternative to in-person visits and could be used as a technology-based prevention method. According to the published papers, this literature review is trying to summarize the findings related to prevention of work related musculoskeletal discomforts among office workers, using teleconsultation.

For this purpose, multiple databases including PubMed, Scopus, Embase, Web of Science, and Google Scholar were systematically searched up to January 2024. The selected keywords for the search included “teleconsultation”, “occupations”, “telemedicine”, “office workers”, and “computer based workers”. Additionally, the reference lists of relevant papers were manually checked to ensure comprehensive coverage. The eligible papers, which focused on the use of online platforms for teleconsultation related to the health of office workers, were imported into Mendeley.

Epidemiology

Musculoskeletal discomforts (MSDs) are prevalent issues affecting office workers, with significant implications for their health and work performance. The incidence of MSDs and associated pain has dramatically increased in recent years, resulting in additional costs for healthcare systems [1,2]. Factors such as age, work history, obesity, stress, and prolonged static posture contribute to this pain [3,4]. These factors not only affect individuals’ psychological well-being but also affect their physical performance, often resulting in increased absenteeism and early retirement [5]. MSDs, excluding lower back pain, increased significantly by almost 30.7 % from 1990 to 2019 [2]. It is worth noting that, according to the 2017 Global Burden of Disease (GBD) report, lower back pain ranks as the second-highest cause of disability [6]. These personal risk factors explain the variation in the occurrence of MSDs and related disabilities seen among several nationalities and countries over time [7–9]. It is also important to consider the socio-economic situation of individuals and the provision level, including healthcare security.

High levels of burnout are associated with MSDs, according to Armon et al. (2010), which suggests that stress at work may increase the likelihood of developing these conditions [10]. Research conducted in 2014 found that a large number of employees deal with aches and pains in their muscles and joints. This study found that variables such as age, job satisfaction, company size, and safety climate were associated with the frequency of these symptoms [11]. In low-skill, physically demanding jobs, workers are more likely to experience daily pain, and women are more likely than men to report stressors other than pain [12].

In a recent study conducted in the Netherlands, office workers were found to experience numerous MSDs, not only in the lower back, shoulders, and neck, but also in the forearms, wrists, and knees, which could become chronic in nature [4, 12].

It is interesting to note that the severity of pain in the neck and shoulders is reported to be higher in women compared to men [13]. This difference between genders could be attributed to different anthropometric characteristics, especially in workstations that are typically designed for men [14].

In 2022, Putsa et al. mentioned that the prevalence of MSDs was 37.9 %, with the most common areas of complaint being the neck, shoulders, and back [15]. Ikiz and Ergin concluded that among the participants, 81.7 % experienced pain in at least one area of the body, with

the back being the most frequently reported pain, at a rate of almost 55 % [16].

Among the selected studies in this paper, the prevalence of MSDs ranged from 38 % to 80 % across different countries, with variations in education level, salary, age, and gender. In addition, in all of them, lower back pain, neck pain and shoulder pain were the most frequent areas of pain. Therefore, it is important to note that there would be several causes for MSDs that should be considered.

Etiology

The causes of MSDs can appear in various areas of the body and include physical and psychological aspects of working conditions. MSDs occur more frequently in jobs that require lifting heavy loads or working with arms raised, even after years of exposure [17]. Common complaints among office workers such as healthcare or fields involving frequent job changes or multiple duties, include back, neck, and knee pain [18, 19]. Psychosocial factors such as gender, psychosocial risk, work-life balance, and meaning of work influence MSDs. These factors emerge in different ways in different cultures. For example, women tend to work long hours, value power and promotions, and dislike social support, which increases the risk of MSDs [20]. The high prevalence of somatization in multifocal MSDs suggests that psychological variables rather than physical variables play a more important role in pain control [21].

According to the studies included in this review, the main cause of MSDs is related to long periods of sitting and lack of physical activity among office workers. Discrepancies in working conditions and anatomical and physiological characteristics are other reasons for the variations found in different studies. Diseases of the musculoskeletal system were observed in 15 % of all cases, and psychosomatic causes were estimated to be the leading factor in around 40 % of cases. Information about the main reasons for MSDs among office workers is provided in Table 1.

As shown, in 50 % of the selected papers (among 3048 subjects), lack of physical activity and prolonged sitting are identified as the main causes of MSDs, which

Table 1. *The reasons for MSD among office workers*

No.	Title	Results
1	«Work-related musculoskeletal problems and associated factors among office workers» [19].	Among 359 office workers, 53.8 % were in the category of low risk, and 4.2 % were in the category of high risk for MSDs. Age, body mass index, gender, the amount of work — related effort, and mental demand were listed as symptoms of MSDs.
2	«Factors associated with reduced risk of musculoskeletal disorders among office workers: a cross-sectional study 2017 to 2020» [15].	Among 545 computer-based workers, almost 38 % presented MSDs in the neck and shoulders. Lack of physical activity and long periods of sitting were the main reasons for MSDs.
3	«Occupational and non-occupational risk factors for neck and lower back pain among computer workers: a cross-sectional study» [22].	Among 2000 office workers, 48 % had MSDs in the neck and lower back. Lack of physical activity, job demands, and long-time sitting were the main reasons for MSDs.
4	«Risk Analysis of Musculoskeletal Disorders (MSDs) Among Computer User Workers in Makassar» [23].	Among 72 computer — based workers, work — related posture and ergonomic risk factors were introduced as the main reasons for MSDs.
5	«Analyzing musculoskeletal system discomforts and risk factors in computer-using office workers» [24].	Among 395 office workers, lack of physical activity and longtime sitting were the main reasons for MSDs.
6	«Effects of computer use on upper limb musculoskeletal disorders and function in academicians» [25].	Among 100 academicians, gender and age were presented as the important reasons for MSDs, especially in neck, shoulders and lower back.
7	«Effect of physical activity intervention on the musculoskeletal health of university student computer users during homestay» [26].	Among 40 computer-based students, during Covid-19, lack of physical activity and longtime sitting were the main reasons for MSDs.
8	«Musculoskeletal disorders and associated factors among office workers in an activity-based work environment» [27].	Among 68 office workers, lack of physical activity, working duration, and longtime sitting were the main reasons for MSDs.
9	«Musculoskeletal symptoms and their associated risk factors among Saudi office workers: a cross-sectional study» [28].	Among 451 office workers, almost 55 % of subjects had severe MSDs in lower back area. Age, body mass index were the most important factors for MSDs.
10	«Effects of risk factors related to computer use on musculoskeletal pain in office workers» [29].	Among 362 office workers, almost 60 % presented MSDs. work related posture and ergonomic risk factors were introduced as the main reasons for MSDs.

can occur in various areas of the body. In 30 % of these studies (among 910 subjects), the importance of age and gender in relation to MSDs is emphasized. Finally, in 20 % of the studies (among 434 subjects), the significance of ergonomic factors is highlighted.

According to the sources we analyzed, there is a significant correlation between the risk of MSDs and age and gender. Collins et al. demonstrated that the prevalence of lower back, neck, and shoulder MSDs was similar and above 50 % among 852 subjects. Additionally, there were significant differences in psychosocial exposures between different age groups and genders. However, there was no association between these exposures and the symptoms of MSDs [30]. In a non-randomized controlled study conducted among 252 office workers, it was shown that women are more susceptible to MSDs compared to men, particularly in the neck area (approximately +30 %) [16].

Traditional Prevention

Common MSDs can have a significant impact on a person's quality of life. Effective preventive strategies are essential to reduce the onset and progression of chronic musculoskeletal pain. Multilevel non-pharmacological approaches, such as exercise therapy, cognitive behavioral therapy, and other modalities including taping, and dry needling, are the cornerstone of the treatment of chronic and nonspecific musculoskeletal pain [31–34]. However, studies on the effectiveness of cognitive behavioral therapy (CBT) combined with exercise for the treatment of MSDs yields conflicting results. Some studies found significant improvements, while others found no changes at all [35]. Patients suffering from MSDs pain experience significant improvements in pain, disability, depression, and stress after participating in a new group and individual therapy program that combines psychological documentation with emotional identification and expression [36,37]. Physical exercise therapy alone can result in higher levels of disability, pain intensity, and fear of movement, while individually tailored behavioral medicine interventions that include biopsychosocial factors can lead to higher levels of pain control and self-efficacy [38].

Optimizing pain management in primary services for MSDs is possible by using a pharmacological pain management algorithm, self-management techniques, and cognitive behavioral therapy under the supervision of case management nurses [39]. Factors such as gender, age, education level, employment status, pain intensity, and psychological stress can affect the possibility of visiting a doctor for non-inflammatory musculoskeletal pain. Consulting with a musculoskeletal specialist in the workplace can improve pain relief and overall health, and can also encourage positive health habits, such as reducing NSAID use and increasing participation in physical therapy [40]. Patient-focused counseling for MSDs has been shown to be more effective than standard treatment in reducing psychological distress (anxiety) and the number of pain points [41,42]. Massage has also been shown to be more effective in the short term in treating chronic musculoskeletal pain, while Mindfulness-Based Stress Reduction (MBSR) has long-term positive effects on mood [43].

Technology-based prevention (Teleconsultation)

Various types of mental and physical counseling are available for individuals with MSDs, including pharmacological and non-pharmacological methods [32]. Teleconsultation, which is a subset of telemedicine, is usually an efficient and acceptable alternative to in-person visits. This is because they typically save money and cut down on transportation expenses without significantly impacting patient satisfaction or clinical outcomes [44].

Telemedicine is a broad term that encompasses various services such as diagnosis, consultation, therapy, and monitoring, all delivered through online platforms. Anyone can access this service from anywhere and at any time [45]. Due to these unique circumstances, the use of telemedicine during the pandemic has increased significantly not only among healthcare providers but also among people seeking treatment and advice [46, 47].

Over the years, with the evolution of telemedicine and the improvement of the knowledge of health providers and patients, the outcome measures of patients and their experiences regarding the services received online were considered and reported as well [46]. In addition, it is important to consider real-world factors that could affect the quality and safety of accessing online care. This is mainly because we prioritize factors such as ease of use of the technology and devices used, as well as the accuracy of the program process. Failure to adhere to these parameters can reduce patient engagement and waste patient and government time and money.

Several studies have investigated various types of telemedicine solutions for MSDs, with teleconsultation emerging as a significant tool in healthcare. Teleconsultation leverages communication technology to provide medical services remotely, which is particularly beneficial during times of social distancing or for patients with limited access to in-person consultations. Patients are more likely to adhere to physical therapy treatment plans when using remote counseling. This has several advantages, including ease of practice and regular contact with experts. During the COVID-19 pandemic, patients greatly benefited from telehealth visits, allowing them to continue exercising and stay in touch with physical therapists [48]. There is evidence that telemedicine in orthopedics and neurosurgery improves patient care by reducing the rate of unnecessary patient transfers and increasing the rate of early access to subspecialty care [49, 50].

There is also evidence suggesting that teleconsultation could significantly enhance occupational therapy education and healthcare delivery. However, the effectiveness and sustainability of this approach hinge on the implementation strategy, which should prioritize ongoing learning and adaptation. Unfortunately, teleconsultation remains unexplored among office workers, with insufficient education on its utilization. One significant drawback is the inability of patients to physically attend therapy sessions, rendering the use of therapy equipment impossible [48]. Although telemedicine can help manage physician workload and reduce unnecessary face-to-face consultations, it is not suitable for initial consultations because physical examination is essential for musculoskeletal evaluation [51]. Teleconsultation encounters challenges in terms of technicalities, communication, and the lack of a physical examination. This is especially true for conditions such as spinal cord injuries, where a hands-on approach is frequently required [52].

When dealing with MSDs that occur on the job, this approach is especially helpful because prompt and effective treatment is of the utmost importance. Remote clinical examinations, telerehabilitation, patient prioritization methods, mobile units for prehospital care, videoconferencing, weekly data submissions with video consultations, a variety of medical conditions, and long-term management interventions are all part of telemedicine [53, 54]. By allowing for constant monitoring and frequent consultations, telemedicine interventions boost patient agency and self-management by raising patients' level of understanding and agency over their health situations. According to studies conducted in emergency rooms, telemedicine has the potential to be cost-effective by lowering direct and indirect expenses while keeping staff and patients on board [55].

Remote neurological evaluations and treatment for MSDs can be efficiently provided by telemedicine. In order to make sure that both the doctor and the patient have working telehealth equipment, it is important to plan ahead for the visit so that telemedicine may be used appropriately. Improve the quality of virtual visits by providing patients with detailed instructions on how to position themselves, the camera, and their clothing. A thorough musculoskeletal assessment and in-depth patient history can be accomplished using telemedicine. Doctors can practice clinical examination methods that they would do in person using common household items. For initial management, there are home care instructions and rehabilitation tools available online. When a patient's diagnosis or treatment plan is uncertain, an in-person appointment should be set up [56]. Urgent examination is necessary for patients who may have a deformity or neurovascular impairment. In the event that the patient's condition is improving as anticipated, virtual follow-up can be conducted. An in-office evaluation should be conducted if the patient's condition is not improving or is getting worse and referral to formal physical therapy or specialty services should be considered as necessary.

Prognosis

Despite some limitations in image resolution and the need for a physical examination, teleconsultation using mobile camera phones is a viable option for the early diagnosis and triage of digital soft-tissue injuries. The technology has the potential for future uses in telemedicine and telecare, and it is easy to use, inexpensive, and portable [57]. Asynchronous teleconsultation in orthopedics can effectively manage most patient queries in primary health care, reducing the need for referrals to specialists, demonstrating the potential to improve patient management, and overcoming distance barriers to healthcare access [58]. Teleconsultation methods, including telephone and teleconsultation, are well accepted by patients waiting for outpatient rehabilitation services because teleconsultation provides higher quality human contact and can better meet support needs [59]. A physical activity program delivered by EHealth using physical therapist-led remote counseling resulted in clinically meaningful functional improvements in rural musculoskeletal pain patients compared with usual care [60].

Conclusion and practical recommendations

The use of teleconsultation has the potential to reduce and prevent MSDs in a variety of work environments. This service provides a practical and economical method of healthcare by facilitating continuity of care and reducing the need for in-person visits by specialist physicians. The use of telemedicine in orthopedic care has been shown to reduce the burden on secondary care services, and despite certain limitations such as a lack of physical equipment and the need for a physical examination, patients have demonstrated a high level of satisfaction with the method in some cases [61].

Since the COVID-19 pandemic, telemedicine has been an important resource for treating work-related MSDs. There are advantages and disadvantages to this method in the realm of musculoskeletal health, as it makes use of visual and auditory technologies to deliver remote evaluations and treatment. To aid in the diagnosis of local vs transferred pain, telemedicine can successfully mimic several features of in-person musculoskeletal examinations, such as the patient self-palpation and pointing to painful locations. The convenience of telemedicine may explain why patient satisfaction has remained high despite its limits in physical examination components such as palpation, percussion, and auscultation.

Table 2. *Prospects and limitations of telemedicine in MSDs*

No.	Benefits of telemedicine in MSDs	Limitations of telemedicine in MSDs
1	Early detection and intervention, and also preventing the progression of MSDs.	Lack of in-person assessment may limit the accuracy of diagnosing specific musculoskeletal conditions.
2	Patients can consult with specialists remotely, reducing the need for physical visits.	Access to reliable internet and appropriate devices may be a challenge in certain regions.
3	It enables personalized exercise programs at home, improving patient compliance.	Protecting patient data during virtual consultations is crucial but can be challenging.
4	It reduces travel time and costs for patients and healthcare systems.	Some musculoskeletal conditions require hands-on evaluation, which telemedicine cannot provide.
5	It allows continuous monitoring and follow-up, enhancing patient outcomes.	Motivating patients to actively participate in tele-rehabilitation can be difficult.
6	It provides educational resources for self-management and prevention.	Licensing, reimbursement, and liability issues vary across regions and may hinder telemedicine adoption.

When it comes to measuring things like gait, discomfort, muscle strength, and range of motion, telemedicine tests are reliable and valid. There needs to be a push for standardized measurements and tech upgrades because its validity for orthopedic special testing and neurological disorder assessments is low to moderate. Workplace resistance training exercise programs can aid in the prevention and management of symptoms and illnesses involving the musculoskeletal system in the upper extremities. Workers who are subjected to physically demanding tasks may find relief from musculoskeletal ailments through workplace strength training.

By adhering to a traditional method that incorporates pre-visit planning and clear patient instructions, telemedicine becomes more effective in treating MSDs. Virtual follow-ups are possible if the patient's condition is improving, and common household items can be utilized to mimic clinical examination methods. Virtual follow-ups are possible if the patient's condition is improving, and common household items can be utilized to mimic clinical examination methods. The benefits and limitations of telemedicine are concluded in Table2.

There is a lack of attention to the researches related to telehealth specified for MSDs among office workers, but there are some studies focused on MSDs using different aspects of telehealth such as teleconsultation and telerehabilitation. Therefore, here we have tried to summarize those related papers.

In a recent systematic review, conducted by Amin et al . in 2022, among 15 studies (12341 subjects were included in total), all the subjects were above 18 years old and had work — related MSDs. In all of those studies, the quality of the studies was confirmed using a critical appraisal checklist tool. Subjects were satisfied with both telerehabilitation and face-to-face intervention, but in three studies, it was mentioned that the subjects were more satisfied with telerehabilitation compared to face — to — face intervention [62].

The findings of another systematic review conducted among 13 studies (1520 subjects were included in total), and all the subjects were above 18 years old and had MSDs. The quality of the studies was confirmed using the Downs & Black Checklist. Their findings showed that telerehabilitation is effective in improving physical performance (SMD 1.63, 95 %CI 0.92-2.33, I2=93 %) and is more favorable (SMD 0.44, 95 %CI 0.19-0.69, I2=58 %) compared to face — to — face intervention. It is suggested as a practical and cost — effective method to improve physical performance and reduce pain levels among subjects with MSDs [63].

In an amazing umbrella review that summarized 35 systematic reviews, the quality of the papers was confirmed by AMSTAR 2. Unfortunately, 24 papers were found to have low quality. The final conclusion of this paper suggested that telerehabilitation is a favorable and cost — effective method compared to face — to — face interventions. It is important to note that most of the papers included in this study were of low quality, highlighting the need for further research with higher quality standards [46]. No adverse events were reported in those published papers.

However, the findings of this review underscored a notable lack of attention to teleconsultation among office workers, coupled with insufficient education on utilizing this technology. It is imperative for companies to prioritize the integration of teleconsultation services to enhance the health and well-being of their employees, while also recognizing its potential cost-saving measure. Moreover, ensuring regular educational training on teleconsultation usage is essential and warrants substantial emphasis. Additionally, providing regular educational training on teleconsultation usage is crucial and should be duly emphasized.

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Информация об авторах

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ИЗУЧЕНИЕ РОЛИ ПЭТ-КТ С ФДГ В ВЫЯВЛЕНИИ ВЫСОКОЗЛОКАЧЕСТВЕННОЙ ДИФФУЗНОЙ В-КРУПНОКЛЕТОЧНОЙ ЛИМФОМЫ

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Exploring the Role of FDG PET CT Scan in Detecting High Grade Diffuse Large B-Cell Lymphoma

Резюме

Введение. Диффузная В-крупноклеточная лимфома (ДВККЛ) является наиболее распространенным типом неходжкинской лимфомы. В настоящее время стандартным методом оценки пациентов на ранних стадиях диагностики рака в онкологических центрах г. Мешхед является компьютерная томография (КТ), гистопатологическое исследование образцов ткани, взятие образца костного мозга и цитологические исследования. Все эти исследования требуют времени и значительных финансовых затрат. Следует отметить, что на данный момент наиболее рекомендуемым подходом к определению стадии лимфомы является ПЭТ-КТ с ФДГ, который сочетает в себе использование меченой глюкозы и КТ-сканирования и является более точной альтернативой. Цель настоящего исследования заключается в изучении возможностей ПЭТ-КТ с ФДГ как инструмента диагностики высокозлокачественной лимфомы. **Методы.** В настоящем исследовании оценивали пациентов с различными типами ДВККЛ, которые прошли ПЭТ-КТ-сканирование с ФДГ для определения стадии заболевания в больнице Разави (г. Мешхед, Иран) в период с 2017 по 2021 годы. Собирали необходимую клиническую и параклиническую информацию, включая информацию о стадии заболевания, локализации опухоли на момент постановки диагноза, результатах иммуногистохимического исследования и ответе на лечение. Кроме того, оценивали результаты ПЭТ-сканирования с ФДГ, включая распространенность процесса и метаболическую активность опухоли до начала лечения, патологические характеристики опухоли, клиническое поведение и ответ на лечение: частоту ответа (ЧО), выживаемость без признаков заболевания (ВБЗ) и общую выживаемость (ОВ) пациентов. Степень агрессивности в настоящем исследовании классифицировали по морфологическим характеристикам и результатам иммуногистохимического окрашивания, прогностическим факторам, клинической картине и ответу на лечение. Для анализа данных использовали пакет программ SPSS, а уровень значимости составлял p <0,05. **Результаты.** Результаты сравнения двух групп пациентов с гистологически подтвержденной высокозлокачественной опухолью (n = 12) и неуточненной опухолью (n = 14) показали, что максимальные значения стандартизированного уровня накопления (SUVmax) у пациентов с агрессивной лимфомой составили 27,5 ± 15,6 (медиана: 25,6), а у пациентов с неуточненной лимфомой — 15,4 ± 9,8 (медиана: 14,4) (p = 0,01). Общая выживаемость пациентов с агрессивной формой составила 10 месяцев, а пациентов с неагрессивной формой — 24 месяца (p = 0,002). Кроме того,

значение SUVmax, равное 21,1, имело чувствительность и специфичность 66 % и 72 % соответственно для дифференциации агрессивных и неагрессивных форм опухоли. **Заключение.** Результаты показали, что ПЭТ-КТ и ФДГ может в значительной степени способствовать дифференциации агрессивных и неагрессивных форм лимфомы, поскольку повышение метаболической активности (SUVmax) зачастую свидетельствует об агрессивном процессе.

Ключевые слова: *ДВККЛ, высокозлокачественная В-крупноклеточная лимфома, ПЭТ-КТ-сканирование, агрессивная лимфома, исход*

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Конфликт интересов

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

Информация о финансировании

Настоящее исследование «Изучение роли ПЭТ-КТ с ФДГ в выявлении высокозлокачественной диффузной В-крупноклеточной лимфомы» основано на докторской диссертации в Университете медицинских наук г. Мешхед и получило финансовую поддержку проректора по исследовательской и технологической работе Университета медицинских наук г. Мешхед. Однако университет не принимал участие в разработке, проведении или написании этой статьи.

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Abstract

Introduction. Diffuse B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma. Currently, the standard method for evaluating patients at the initial stages of cancer diagnosis in Mashhad oncology centers involves computed tomography scans (CT scans), histopathological evaluation of tissue, bone marrow sampling, and cytogenetic studies, all of which are time-consuming and costly. It is worth mentioning that at present, the most recommended approach for determining lymphoma staging is the FDG-PET/CT scan, which combines labeled glucose with CT scan and offers a more accurate alternative. The objective of this study is to explore the potential of FDG-PET/CT scan as a tool for detecting high-grade lymphoma. **Methods.** In this study, patients with different types of DLBCL who underwent FDG-PET Scan for staging at Razavi Hospital, Mashhad, Iran between 2017 and 2021 were examined. The necessary clinical and paraclinical information, including the stage of the disease, the involved site at the time of diagnosis, the result of immunohistochemical examination, and the response to treatment were collected. FDG-PET Scan information including the extent of involvement and metabolic activity of the tumor before the start of treatment, pathological characteristics of the tumor, clinical behavior, and response to treatment in the form of response rate (RR), disease-free survival (DFS) and overall survival (OS) of the patients. Was also investigated. Aggressive histology in the present study was classified based on morphological characteristics and immunohistochemical staining, prognostic indicators, clinical behavior and response to treatment. Data were analyzed using SPSS software at a significance level of $p<0.05$. **Results.** Comparing the two groups of patients with high grade histology (n=12) and NOS (n=14), the results showed that SUV max values in patients with aggressive lymphoma were 27.5 ± 15.6 (median 25.6) and in patients with NOS lymphoma was 15.4 ± 9.8 (median 14.4) ($p=0.01$). The overall survival of patients in the aggressive group was 10 months and in the non-aggressive group was 24 months ($p=0.002$). Also, the cut — off -point of 21.1 for SUV max has a sensitivity of 66 % and a specificity of 72 % in differentiating aggressive from non-aggressive types. **Conclusion.** The results revealed that FDG PET CT Scan can provide valuable insights into differentiating lymphomas with a more aggressive type from their usual types, as those with heightened metabolic activity (SUVmax) are often indicative of aggressive behaviors.

Key words: *DLBCL, High-Grade B-Cell Lymphoma, PETCT SCAN, Aggressive Lymphoma, outcome*

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Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

This research has been approved by the Regional Organizational Ethics Committee of Mashhad University of Medical Sciences with code IR.MUMS.MEDICAL.REC.1401.523. Given that only the health data of the patients was utilized in this study and no interventions were administered, the ethics committee exempted the need for written informed consent.

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What is new?

Due to the remarkable superiority of fluorodeoxyglucose (FDG)-positron emission tomography (PET) for its superior sensitivity in diagnosing lymphatic and extra-lymphatic involvements, Lymphoma plays a significant role in staging patients with DLBCL. Histopathological evaluation of the involved tissue and bone marrow as well as cytogenetic evaluations are the conventional approaches in the examination of patients in their early diagnosis. The diagnosis and staging of this disease require a significant amount of time and resources. Moreover, the aggressive nature of these of these methods and the situation in Iran may impose restrictions on their use. Therefore, this study was carried out to examine the potential impact of FDG PET CT Scan in identifying the types of diffuse B-cell lymphoma with a high level of malignancy and differentiating it from less aggressive types. It needs to be kept in mind that the reliability of visual and quantitative response assessment can be impaired by inconsistent PET scanning protocols and image reconstruction methods. Even though standardization is still lacking, quantitative FDG-PET has the potential to substantially improve prognostication in lymphoma. Over recent years, PET using FDG has brought many advances in the diagnosis and treatment of lymphoma patients.

What is important?

The study suggests using FDG PET CT Scan alongside morphological investigations and pathological immunophenotyping during standard staging to identify patients who may benefit from cytogenetic testing. This is particularly important in our country where access to such testing is limited.

FDG — Fluorodeoxyglucose, PET — Positron emission, CT scan — Computed tomography scans, DLBCL — Diffuse large B cell lymphoma, RR — Response rate, DFS — Disease-free survival, OS — Overall survival, CHOP — Chemotherapy regimen used in the treatment of non-Hodgkin lymphoma, IPI — International Prognostic Index, CNS — Central nervous system, SUV — Standardized Uptake Values, DFS — Disease-free survival, BCL2 — B-cell lymphoma 2, BCL6 — B-cell lymphoma 6, BNHL — B-cell non-Hodgkin lymphoma, NCSS — Number Cruncher Statistical Systems, ROC — Receiver operating characteristic, AUC — Area Under the Curve

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma; it accounts for 30-40 % of all newly diagnosed cases [1]. The standard frontline treatment for patients with DLBCL is to use six cycles of chemotherapy regimen that includes cyclophosphamide, doxorubicin, vincristine and prednisone along with the monoclonal antibody rituximab (R-CHOP) [2]. However, unlike the early stages of the disease where treatment could be limited to fewer sessions of chemoimmunotherapy with or without radiotherapy, based on the International Prognostic Index (IPI) definition, high-risk advanced DLBCL, may require intensified treatment including prophylactic treatment of the central nervous system (CNS) [3, 4]. Despite significant advances in the management of this malignancy, the rate of complete recovery is still lower than in Hodgkin's lymphoma, and about one-third of all patients relapse after the first-line treatment [5]. Due to the remarkable superiority of fluorodeoxyglucose (FDG)-positron emission tomography (PET) for its superior sensitivity in diagnosing lymphatic and extra-lymphatic involvements, Lymphoma plays a significant role in staging patients with DLBCL [6]. In addition, several international clinical trials have investigated the role of FDG-PET CT in the early stages of treatment for differentiating patients needing therapy intensification from good responders, i.e., candidates for de-escalation of therapy [7-11]. Histopathological evaluation of the involved tissue and bone marrow as well as cytogenetic evaluations are the conventional approaches in the examination of patients in their early diagnosis.

According to the aforementioned measures, the diagnosis and staging of this disease requires a significant amount of time and resources. Moreover, the aggressive nature of these of these methods and the situation in Iran may impose restrictions on their use. Therefore, this study was carried out to examine the potential impact of FDG PET CT Scan in identifying the types of diffuse B-cell lymphoma with a high level of malignancy and differentiating it from less aggressive types.

Material and Method

This pilot study retrospectively analyzed the files from 2017 to 2021 in the nuclear medicine department of Razavi Hospital in Mashhad, Iran. It was approved by the Regional Ethics Committee of Mashhad University of Medical Sciences with code IR.MUMS.MEDICAL.REC.1401.523. Based on information from the hematology and oncology departments of Qaem and Imam Reza hospitals, as well as private clinics, The files of patients aged 15 to 65 diagnosed with diffuse B cell lymphoma through morphological and immunohistochemical testing were included in the study, all of whom were scheduled to undergo an FDG-PET/CT scan prior to receiving treatment.

Really, in a retrospective study, a sample is selected and the researcher looks back at the history of the members of this sample. Furthermore, in a retrospective study, data is readily available for collection and analysis, requiring a smaller research team and fewer resources. However, this was a limitation of this study mentioned in and future studies are recommended to use prospective approaches.

We conducted the present study to track the survival of patients with diffuse large B-cell lymphoma. For the follow up, the aftercare protocol involved referencing the disease details documented in medical records from clinics and hospitals, along with input from the attending physician which included a period of 4 months to 3 years, they were only contacted solely to ascertain whether they were alive or dead.

Patients were excluded if they had incomplete information, heart failure, poor performance status (ECOG PS >= 2), or a history of other hematological or solid organ malignancies. The response rate was determined by the patient's state of complete response, partial response, stable disease, or progressive disease.

A complete response indicates that treatment has fully resolved the disease and there is no evidence of disease in any of the primary sites on imaging. A partial response is when the affected areas have decreased by over 20 % compared to their original size with the same initial imaging modality. Progressive disease is when new lesions appear or previous lesions increase in size by over 20 %. Stable disease refers to any other condition. If a patient with lymphoma does not achieve a complete response at the end of treatment, it is considered treatment failure and disease resistance, and the next line of treatment should be pursued. PET information, including SUV, is used to evaluate the pathological characteristics of the tumor and treatment responses in terms of primary response, DFS, and OS.

Patients who exhibit early resistance to chemotherapy, experience relapse within six months, or have an advanced and widespread disease that affects non-lymphatic organs such as the central nervous system, liver, or bone marrow, are classified as high-grade B-cell lymphoma. This includes those who were in stage 4 of the disease from the start, had a high proliferation index (Ki67), or had previously expressed *MYC*, *BCL2*, or *BCL6* genes (i.e. double/triple expressors). Their SUV levels were compared to those of other types of DLBCL without aggressive features. High-grade B-cell lymphomas are traditionally composed of Double HIT, Double Expressor, Burkitt, and Burkitt-like lymphomas.

These cases all had similar characteristics, such as a high mitosis rate (Ki67 cell proliferation index above 80-90 %), advanced stage at diagnosis, initial involvement of the central nervous system, rapid progression, numerous clinical symptoms, poor treatment response, quick relapse, and a high mortality rate. These traits distinguish DLBCL-NOS types from high-grade B-cell lymphoma cases in this study.

Recent evidence indicates that double hit and double expressor classifications, along with the previously mentioned pathological and genetic traits, share similar clinical characteristics, including resistance to standard treatment, early recurrence, high mortality, initial 4th stage disease, high risk of central nervous system involvement, and a high proliferation index [12].

In this study, clinical criteria and morphological characteristics in microscopic examination and immunohistochemical staining were used in pathology evaluation as screening criteria for high grade lymphoma. Due to the high costs of gene rearrangement tests, which are not standard practice even for hospitalized patients in our current economic state, they were not included in this study.

The sample size was estimated based on research by Ngeow et al [13], where SUV max measurements from PET scans were used to distinguish between normal B-NHL types and aggressive B-cell lymphoma types. In that study, the area under the curve (AUC) was reported to be 0.81. With alpha at 0.05 and beta at 0.2, and using NCSS (PASS11) software, the minimum sample size was calculated to be 12 people in each group (aggressive and normal).

As this was a pilot study, only a limited number of patients were included. It is north Worthing that the present study is the first step of the entire research protocol and is often a smaller-sized study assisting in planning and modification of the main study. More specifically, in large-scale clinical studies, the pilot or small-scale study often precedes the main trial to analyze its validity. Researchers had a strong desire to include the data collected from the pilot study into the main study because this allows the researchers to reduce both the number of participants required for the study and the duration of the study. However, this is only allowed in an internal pilot study. Finally, this was one of the main limitations of this study that was discussed in the discussion section. Furthermore, another limitation was that Since the number of events in this study did not reach the level required for Cox regression analysis, we did not perform this analysis [14].

The nuclear medicine department at Razavi Hospital being the exclusive provider of FDG-PET/CT scans in the eastern region of Iran, enabled us to attain a sufficient sample size. Consequently, all patients were examined through a census method during the specified time period.

After assessing the normality distribution of the data using the Kolmogorov Smirnov test, we applied the student's t-test (or Mann-Whitney) to compare continuous data, and the Chi-square test (or Fisher's exact test) to analyze qualitative data. Additionally, we examined the survival of patients using the Log Rank Test and Kaplan-Meier estimator.

Using the ROC curve, the cut point for SUV max (obtained from PET scan) was established after segregating patients into two groups based on their pathology data — aggressive and normal. SPSS software was employed to conduct statistical analysis, with a significance level of $p < 0.05$ set for all analyses. It is accepted as a rule of thumb that a minimum of 10 events per variable is needed for Cox regression analysis. As in current research the number of events (mortality) did not reach

the desired level (10 events), we did not perform the Cox regression model.

The interpretation of the ROC curve results is as follows [15]:

AUC equal to 0.5: The approach used cannot distinguish between two groups (i.e., ability to diagnose patients with and without the disease or condition based on the test).

AUC Between 0.7 and 0.8: The approach used demonstrates acceptable validity in distinguishing between two conditions.

AUC Between 0.8 and 0.9: The approach used demonstrates excellent validity in distinguishing between two conditions.

AUC more than 0.9: The approach used demonstrates outstanding validity in distinguishing between two conditions.

Results

Out of 59 patients examined, 26 were eligible for the study. The mean age of the subjects was 55.6 ± 13.6 years, with the youngest aged 26 and the oldest 75. The majority of subjects were male, comprising 19 individuals (73.1 %). Additionally, 34.6 % (9 people) had a history of comorbidity upon diagnosis. The distribution of patients by disease stage was as follows: stage three (10 individuals, 38.5 %), stage two (7 individuals, 26.9 %), stage four (5 individuals, 19.2 %), and stage one (4 individuals, 15.4 %). According to the International Prognostic Index, a significant number of individuals fell into subgroups Low-intermediate risk (10 individuals, 38.5 %), High-intermediate risk (7 individuals, 26.9 %), and stage four (5 individuals, 19.2 %). A non-aggressive disease subgroup was reported in 14 patients (53.8 %), while 12 patients (46.2 %) exhibited aggressive behavior and histology. Recurrence was observed in 1 patient (3.8 %) and 7 patients (26.9 %) experienced death. It is worth noting that all cases of death and recurrence were recorded in the group of patients with aggressive disease (Table 1).

In Figure 1, the SUV_{max} variable with AUC=0.79 (95 % CI 0.61-0.96) demonstrated acceptable validity in distinguishing patients with aggressive lymphoma from NOS subtype (p=0.012). Additionally, the cut point of 21.1 for SUV_{max} yielded a sensitivity of 66 % and a specificity of 72 % in distinguishing aggressive from non-aggressive types.

Comparing patients with the aggressive and NOS subtypes, the results indicated that the mean age of the patients was 60.3 ± 11.1 years (median 60.5 years) and 51.6 ± 14.6 years (median 54 years), respectively. The observed difference was not found to be significant (p=0.1).

The values of SUV_{max} in patients with invasive histology were 27.5 ± 15.6 (mean 25.6) and in patients with NOS histology were 15.4 ± 9.8 (mean 14.4), the observed difference It was statistically significant (p=0.01). (Figure 2).

Based on the data in Figure3, patients in the aggressive group had a median overall survival of 10 months, which was significantly lower than the NOS group's overall survival of 24 months (p=0.002, log-rank test).

Table 1. *Demographic characteristics of patients*

Variable		Frequency	Percentage
Sex	Male	19	73.1
	Female	7	26.9
History of comorbidity**	Yes	17	65.4
	No	9	34.6
Disease Stage	1	4	15.4
	2	7	26.9
	3	10	38.5
	4	5	19.2
International Prognostic Index	Low risk	3	11.5
	Low-intermediate risk	10	38.5
	High-intermediate risk	7	26.9
	High risk	6	23.1
Behavior group	Aggressive	12	46.2
	Non-aggressive	14	53.8

Note. **The current study identified aggressive histology as the diagnosis of Burkitt's lymphoma, unclassifiable Burkitt-like lymphoma with a high mitosis rate (Ki67 cell proliferation index above 80-90 %), advanced stage at diagnosis, CNS involvement from the start, rapid progression, numerous clinical symptoms, poor treatment response, and quick relapse.

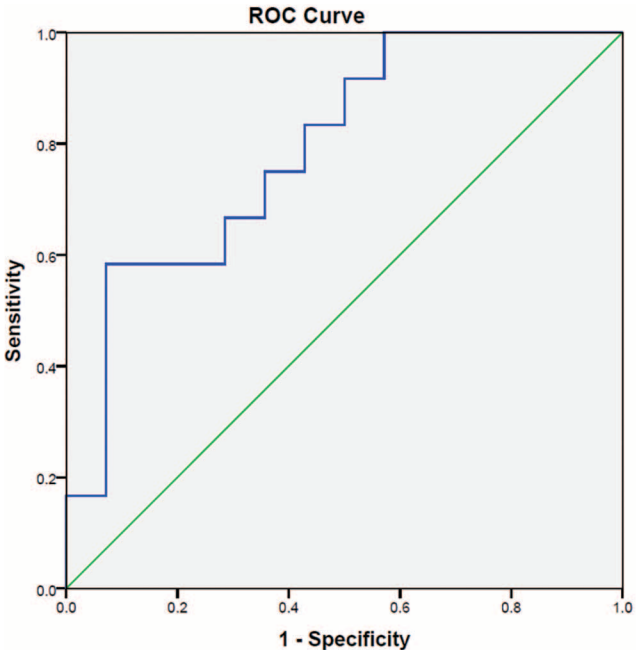

Figure 1. *ROC curve of SUV_{max} value in differentiating aggressive from NOS subtype in DLBCL patients*

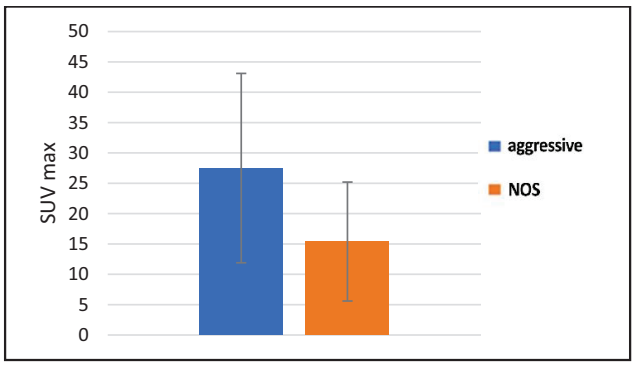

Figure 2. *Comparison of SUV_{max} in DLBCL patients with aggressive and NOS subtype*

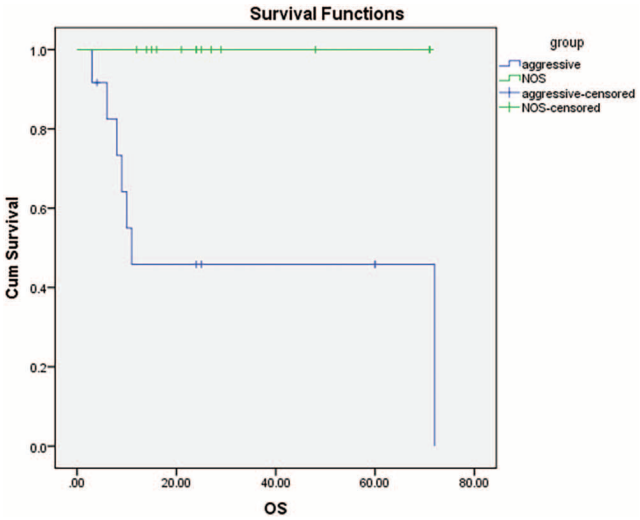

Figure 3. *Comparison of overall survival of DLBCL patients with aggressive and NOS subtype*

Table 2. *Comparison of Mortality Rates in DLBCL patients based on Aggressive and NOS Histology*

		Aggressive	NOS	p-value
Dead		7(58.3)	0	0.001*
Relapsed		1(8.3)	0	0.4*
Disease Stage	1	2(16.7)	2(14.3)	0.4**
	2	2(16.7)	5(35.7)	
	3	5(41.7)	5(35.7)	
	4	3(25)	3(14.3)	
International Prognostic Index	Low risk	0	3(21.4)	0.3**
	Low-intermediate risk	5(41.7)	5(35.7)	
	High-intermediate risk	4(33.3)	3(21.4)	
	High risk	3(25)	3(21.4)	

Note. *Fisher's exact test
** Mann-Whitney

Unfortunately, due to only one recorded case of recurrence, a disease-free survival analysis could not be performed.

This study found a notable disparity in mortality rates between patients with aggressive and NOS histology. The former had a mortality rate of 58.3 %, while the latter had a rate of 0 % (p=0.001) (Table 2).

Overall survival was compared by grouping patients based on their SUV_{max} values (less than 21 vs. equal to or greater than 21.1). The analysis showed no significant difference in survival between the two groups (24 months versus 15 months; log-rank test (p=0.6)). The study's small sample size may have hindered the recognition of a substantial difference, despite the evident contrast in the survival rates between the two groups.

Discussion

Recent cytogenetic studies have shown that diffuse large B cell lymphoma is not a uniform disease, consisting of different subgroups [16, 17]. Aggressive behavior in specific subgroups can lead to the early involvement of non-lymphatic organs in the diagnosis process. The core principle of the cytogenetic investigations mentioned above involves the examination of *MYC*, *BLC6*, and *BLC6* gene rearrangements. As a result, 90 % of B-cell lymphomas are classified as non-germinal center (NGC) or activated B cell (ABC) subtypes, associated with worse outcomes and are rarely DH, while the remaining 10 % are classified as GCB, with better outcomes and include double expressor (DE) and double hit (DH) cases. Despite the unreliability of IHC results for patient classification, access to cytogenetic evaluations in Mashhad is limited due to expensive costs, leading to most patients receiving monotonous treatment without consideration for specific subgroups. Meanwhile, following the European Society of Medical Oncology (ESMO) guideline and with a focus on resource conservation, patients with B-cell lymphoma are first screened with IHC, then their results are confirmed through FISH and NGS. With the increasing use of PET/CT scans for lymphoma patients, this research explores its effectiveness in identifying diverse forms of diffuse large B-cell lymphoma, with higher aggressive behavior compared to conventional ones. Additionally, as a functional imaging method, PET can also show tumoral cell activity.

The study demonstrates that FDG-PET/CT scans effectively distinguish between aggressive and non-aggressive lymphomas. Aggressive lymphomas exhibit higher metabolic activity and SUV_{max}, with a determined cut-off point of 21.1 MBq/g for differentiating aggressive histology from normal histology. Additionally, research by Kuker et al. (2023)[18] and Zhou et al. (2016)[19] supports the prognostic value of FDG-PET/CT scans, particularly in predicting overall and disease-free survival in patients with DLBCL. These findings highlight

the significance of metabolic activity and SUV_{max} as prognostic indicators in lymphoma patients.

Zhao et al. (2021) studied 87 DLBCL patients who had FDG PET/CT scans before treatment. Their findings indicated that increased metabolic activity is linked to worse outcomes for patients treated with the R-CHOP regimen, and tumor metabolic volume independently predicts prognosis in this patient group [20].

Consistent with our findings, other studies, including those by Esfahani et al. (2013) [21], Xie et al. (2016) [22], and Shagera et al. (2019) [23], in various patient populations with lymphoma have reported similar results regarding the relationship between metabolic activity and patient survival. It seems that higher metabolic activity and volume in patients are associated with worse outcomes compared to those with lower levels. Evidence from a meta-analysis of 13 DLBCL studies [24]and a large phase III clinical trial (registration code NCT01287741) in the US Clinical Trials Registry [25] supports this conclusion.

In comparing patients with aggressive and NOS histology, this study found that histology type has no significant relationship with disease stage at diagnosis and IPI. However, patients with aggressive histology experience poorer median survival and higher mortality, consistent with the findings of numerous other studies.

Several investigations have explored the impact of aggressive histologies (double and triple HIT DLBCL) on the prognosis and treatment efficacy of DLBCL patients. Barrans et al. (2010) examined 303 newly diagnosed DLBCL patients, most of whom received R-CHOP therapy. The results revealed that being diagnosed with double-hit or triple-hit DLBCL is associated with a higher likelihood of GCB and a lower survival rate compared to cases without rearrangements but with a higher IPI score [26]. Another study by the British Columbia Cancer Agency (BCCA) followed 135 DLBCL patients treated with R-CHOP, showing poor outcomes in cases with aggressive histologies [27].

Our research supports previous studies and provides strong evidence that DLBCL is not a homogeneous disease, requiring precise cytogenetic and histopathological assessment for accurate diagnosis and treatment. Our study also suggests poorer overall survival in patients with increased metabolic activity, although this was not statistically significant. This study is one of the first to investigate the role of lymphoma metabolic activity in determining the invasion rate of malignant lesions in Iran, with a significant sample size. However, the study had limitations, particularly the retrospective approach. Additionally, the limited availability of complete cytogenetic evaluation, specifically FISH analysis for *MYC*, *BCL2*, and *BCL6* gene rearrangements, was another constraint.

The findings may be less generalizable if there are some double expressors in the less aggressive category, given the clinical criteria used for classification. Moreover, as there was only one recorded case of recurrence, we could not perform DFS analysis.

The population studied in this research was highly heterogeneous, including Burkitt's lymphoma patients and those with double or triple DLBCL, which may lead to varying outcomes. Considering that Diffuse Large B-Cell Lymphoma is a broad subset of non-Hodgkin's lymphoma, here, we made an effort to ensure that every patient belonged to the Diffuse Large B-Cell Lymphoma subgroup, in order for heterogeneity not to negatively impact the interpretation of the results. Really, Heterogeneity can indicate differences within individual samples, between samples, and between experimental results in a meta-analysis.

These patients were diagnosed at a younger age and underwent more intense treatment, potentially skewing the overall results of the study. The SUVmax results were not compared based on cytogenetic evaluation, suggesting that reported SUVmax values may be affected if this evaluation is completed. Future studies should assess the expression levels of MYC proteins, BLC6, and BLC2 in patients to understand their correlation with SUVmax and disease prognosis. Additionally, if financial conditions allow, genetic modifications of these proteins can be assessed using PCR. It is recommended that upcoming research incorporates radiomics into the evaluation of FDG-PET/CT scan images and explores the predictive value of each individual feature.

Conclusion

The study involved 26 patients and found that MBq/g = 21.1 SUV max with (95% CI 0.61 — 0.96) AUC = 0.79 is a valid means of distinguishing between aggressive and less aggressive DLBCL lymphoma (p=0.012). As such, the study suggests using FDG PET CT Scan alongside morphological investigations and pathological immunophenotyping during standard staging to identify patients who may benefit from cytogenetic testing. This is particularly important in our country where access to such testing is limited.

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ОЦЕНКА ВЗАИМОСВЯЗИ КЛИНИЧЕСКИХ И ЛАБОРАТОРНЫХ ПОКАЗАТЕЛЕЙ С ПЕРЕНЕСЕННОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ У ПАЦИЕНТОВ С РЕСТЕНОЗОМ КОРОНАРНЫХ АРТЕРИЙ

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Assessment of the Association Between Clinical and Laboratory Parameters and Past Coronavirus Infection in Patients with Coronary Artery Restenosis

Резюме

Понимание факторов риска рестеноза стента коронарных артерий имеет особую важность в отношении лиц, перенесших коронавирусную инфекцию (КВИ). Такие пациенты требуют тщательного наблюдения, приоритетного лечения и профилактики. **Целью** нашего исследования явилась оценка связи клинических и лабораторных показателей с перенесенной коронавирусной инфекцией у пациентов с рестенозом коронарных артерий. **Материалы и методы.** Проведено поперечное исследование на сплошной выборке пациентов с ИБС (931 пациент), прошедших повторную реваскуляризацию миокарда в период с 2020 г. по 2023 г. 420 пациентов основной группы имели рестеноз стента коронарных артерий, из них 162 (38,5 %) пациентов перенесли в прошлом КВИ. В контрольную группу вошли 511 пациентов с повторной реваскуляризацией миокарда без рестеноза стента, из них 107 (20,9 %) перенесли КВИ. Лабораторные анализы включали тропонин I, D-димер, креатинкиназу (КК), креатинкиназу-МВ (КК-МВ), сывороточный креатинин и глюкозу, С-реактивный белок (СРБ), аланинаминотрансферазу (АЛТ), аспартатаминотрансферазу (АСТ) и фибриноген, антитела IgG и IgM к coronavirus и определение РНК методом полимеразной цепной реакции. Статистические расчеты проводились с использованием программного обеспечения SPSS версии 20.0. **Результаты**. Было установлено наличие статистически значимо более высоких показателей антител IgG к коронавирусу и С-реактивного протеина в основной группе исследования в сравнении с группой контроля. При делении групп исследования на подгруппы пациентов с перенесенной КВИ и без КВИ были установлены статистически значимые различия по уровню тропонина ($p<0,001$), в том числе в группе с рестенозом и КВИ в сравнении с группами без рестеноза с КВИ, с рестенозом без КВИ и в группах с реваскуляризацией без КВИ и с рестенозом без КВИ. Уровни D-димера, КФК, КФК-МВ, СРБ и АЧТВ имели статистически значимые различия в группах с перенесенным КВИ в сравнении с группами без КВИ. Результаты множественного регрессионного анализа свидетельствовали о наличии статистически значимой положительной взаимосвязи в группах исследования между развитием инфаркта миокарда и такими показателями, как СРБ, глюкоза крови, липопротеиды низкой плотности (ЛПНП), перенесенная КВИ, а также отрицательной взаимосвязи с фракцией выброса левого желудочка и липопротеидами высокой плотности (ЛПВП). Роль данных предикторов в развитии инфаркта миокарда была установлена с помощью ROC-анализа. **Заключение.** Результаты нашего исследования свидетельствуют о наличии взаимосвязи перенесенной коронавирусной инфекции с повышением риска развития рестеноза коронарных артерий у лиц с предшествующей реваскуляризацией миокарда.

Ключевые слова: *рестеноз коронарных артерий, коронавирусная инфекция, лабораторные показатели, отношения шансов, реваскуляризация миокарда*

Конфликт интересов

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

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Abstract

Understanding the risk factors for coronary in-stent restenosis is particularly important in patients with coronavirus disease (COVID-19). Such patients require careful monitoring, priority treatment, and prevention. **The aim** of our study was to assess the association between clinical and laboratory parameters and previous coronavirus infection in patients with coronary artery restenosis. **Materials and methods.** A cross-sectional study was conducted on a continuous sample of patients with coronary artery disease who underwent repeated myocardial revascularization in the period from 2020 to 2023 (931 patients). 420 patients in the main group had coronary artery stent restenosis, of which 162 (38.5 %) had suffered from coronavirus infection (CVI). The control group included 511 patients with repeated myocardial revascularization without stent restenosis, of whom 107 (20.9 %) had undergone CVI. Laboratory tests included troponin I, D-dimer, creatine kinase (CK), creatine kinase-MB (CK-MB), serum creatinine and glucose, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and fibrinogen, IgG and IgM antibodies to coronavirus and RNA detection by polymerase chain reaction. Statistical calculations were performed using SPSS version 20.0 software. **Results:** It was established that there were statistically significantly higher levels of IgG antibodies to coronavirus and C-reactive protein in the main study group compared to the control group. When dividing the study groups into subgroups of individuals with and without previous CVI, statistically significant differences in troponin levels were found ($p<0.001$): between the level in the group with restenosis and CVI compared to groups without restenosis with CVI, with restenosis without CVI, and in groups with revascularization without CVI and with restenosis without CVI. The levels of D-dimer, CPK, CPK-MB, CRP, and APTT had statistically significant differences in the groups with previous CVI compared to the groups without CVI. The results of multiple regression analysis indicated a statistically significant positive relationship in the study groups between the development of myocardial infarction and such indicators as CRP, blood glucose, low-density lipoproteins (LDL), previous CVI, as well as a negative relationship with left ventricular ejection fraction and high-density lipoproteins (HDL). The role of these predictors in the development of myocardial infarction was confirmed using ROC analysis. **Conclusion:** The results of our study indicated a relationship between previous coronavirus infection and an increased risk of coronary artery restenosis in patients with previous myocardial revascularization.

Keywords: *coronary artery restenosis, coronavirus infection, laboratory parameters, odds ratios, myocardial revascularization*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The study was approved by the Local Ethics Committee of the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation (extract from the protocol No. 214. January 24, 2022). The study was also approved by the Local Ethics Committee of Semey Medical University, Kazakhstan (extract from the protocol No. 7. March 16, 2022).

Informed consent was obtained from all subjects participating in the study. Written informed consent was also obtained from patients for the publication of this article.

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ALT — alanine aminotransferase; AST — aspartate aminotransferase; APTT — activated partial thromboplastin time; OMB — obtuse marginal branch; DB — diagonal branch; CHD — coronary artery disease; MI — myocardial infarction; CAG — coronary angiography; CVI — coronavirus infection; CK — creatine kinase; CK MB — creatine kinase MB; HDL — high-density lipoprotein; LDL — low-density lipoprotein; INR — International Normalized Ratio;

LC — left circumflex coronary artery; RCA — right coronary artery; LAD — left anterior interventricular branch of the coronary artery; PCR — polymerase chain reaction; RNA — ribonucleic acid; DM — diabetes mellitus; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; LVEF — left ventricular ejection fraction; HR — heart rate; PCI — percutaneous coronary intervention, EchoCG — echocardiography; COVID-19 — new coronavirus infection

Introduction

In recent decades, due to progress in the field of interventional cardiology, there has been a significant increase in cardiac surgery for coronary artery stenosis and thrombosis, which has led to an increase in life expectancy for patients with acute coronary syndrome and an improvement in their quality of life. Thanks to the development of new approaches to stenting and the emergence of new-generation drug-eluting stents, the number of complications of this intervention has been significantly reduced; however, due to numerous reasons, the risk of developing restenosis or thrombosis of the installed stent remains [1].

Restenosis can be defined as an angiographically confirmed narrowing of the lumen of a coronary artery by more than 50 %, localized in the area of a previously implanted stent [2,3]. Most often, restenosis develops within the first three months after previous revascularization. After six months, the risks of restenosis decrease, and the process remains, as a rule, stable, since during this period, stent endothelialization and remodeling of the coronary vessel wall are completed. However, when using drug-eluting stents, the endothelialization process can be delayed for up to 2 years [4]. The mechanism of early restenosis development is associated with trauma to the vascular wall during device implantation, leading to the development of an inflammatory reaction accompanied by the migration of neutrophils, monocytes, and platelets and the release of inflammatory mediators [5]. Subsequently, induction of smooth muscle cell migration into the vascular intima with their accumulation and proliferation of fibroblasts is observed. Increased synthesis of extracellular matrix causes thickening of neoadventitia and neointima, narrowing the lumen of the coronary vessel in the area of the previously implanted stent [6]. Thus, there is a direct relationship between inflammation, the formation of neointima, and the development of restenosis at the site of the implanted stent [7].

At the peak of the COVID-19 pandemic, due to the high burden on the healthcare system and the sharply increased need for resources, the activity of interventional cardiology worldwide significantly decreased, and the number of cardiac catheterization procedures decreased. At the same time, the need for repeated cardiac surgery for coronary restenosis due to coronavirus infection increased [8]. Understanding risk factors for stent thrombosis and restenosis is of particular importance for individuals at risk for adverse outcomes, especially elderly patients with previously revascularized myocardium and associated medical conditions who have had COVID-19. Such patients require close monitoring, priority treatment, and prophylaxis.

It has been established that coronavirus infection promotes thrombus formation in arterial and venous vessels and acts as a provoking factor in the development of acute coronary syndrome (myocardial infarction (MI) or unstable angina). Hypercoagulation risk can lead to the development of stent thrombosis, which progresses in the presence of other risk factors [4].

The aim of our study was to assess the interrelationship between clinical and laboratory parameters and previous coronavirus infection in patients with coronary artery restenosis.

Material and Methods

Characteristics of the study groups

We conducted our study on a continuous sample of patients with coronary artery disease who underwent repeat myocardial revascularization between May 2020 and May 2023. Design of the study is cross-sectional one. A total of 931 patients were included in the study. Inclusion criteria: patients with coronary artery stent restenosis aged 34 to 88 years with full information on clinical signs of myocardial ischemia, laboratory and instrumental examination data. 420 patients included in the main group had coronary artery stent restenosis requiring repeat revascularization, of which 162 (38.5 %) patients had a history of coronavirus infection for one year. The control group included 511 patients with repeated myocardial revascularization without stent restenosis. Of these, 107 (20.9 %) patients had coronavirus infection for the previous year.

The endpoints for the study were cardiovascular mortality, hospital discharge, and the incidence of coronary artery stent restenosis depending on the time of its development.

Exclusion criteria: individuals with autoimmune systemic diseases, oncological and hemato-oncological patients, patients with acute infectious and inflammatory diseases, coagulopathies, pregnancy and the postpartum period, mental illness, as well as individuals who refused to participate in the study.

After risk stratification, all patients underwent coronary angiography (CAG) followed by myocardial

Table 1. *Social-demographic characteristics of patients included in the study (N = 931)*

Indicators		Absolute number	%
Age (years)	<50 years	76	8.17
	51-70 years	592	63.58
	71>	263	28.25
Sex	male	700	75.18
	female	231	24.82
Job status	disabled person	76	8.17
	pensioner	508	54,56
	unemployed	133	14.28
	works	214	22.99
Have been vaccinated against COVID-19		504	54,1
Therapy received prior to hospitalization			
Dual antiplatelet therapy		738	79,2
Triple antiplatelet therapy		193	20,8
Beta Blockers		705	75,7
RAAS Blockers		814	87,4
Statins		837	89,9
Mineralocorticoid receptor antagonists		524	56,2
Arterial hypertension		911	97,9
Diabetes mellitus		191	20,5
Obesity I-III degree		217	23,3
Chronic kidney disease		248	26,6
Chronic heart failure		768	82,5

revascularization with stenting. A study participant card was created for each patient. Patients were informed that they were included in the study and that the results of the study would be published in a scientific journal with confidentiality of information. Written consent to participate in the study was obtained from each patient.

The average age of all patients included in the study was 64.31 ± 8.19 years. For women, this rate was 67.07 ± 10.48 years, for men — 63.39 ± 9.92 years. More than 60 % of patients were in the age stratum of 51-70 years, there was a predominance of males by more than three times. More than 70 % of patients were retired in accordance with age or disabled (Table 1). About half of the patients were vaccinated against COVID-19. The vast majority of patients had concomitant arterial hypertension and chronic heart failure, diabetes mellitus was established in 20.5 %, chronic kidney disease — in 26.6 %, obesity — in 23.3 % of patients.

Collection of clinical and laboratory parameters

Patient clinical data were collected from an electronic medical database, including demographics, clinical data, comorbidities, imaging results, laboratory tests, clinical outcomes, and information on previous myocardial revascularization and coronavirus infection. All registered events were reviewed from hospital electronic records and assessed by two cardiologists by consensus.

The study database included a description of the coronary angiography and coronary artery stenting procedure for each patient. Venous blood samples were collected from all patients within 10 minutes of admission. Laboratory tests included complete blood count, high-sensitivity troponin I, D-dimer, creatine kinase (CK), creatine kinase-MB (CK-MB), serum creatinine and glucose, ESR, C-reactive protein, alanine aminotransferase (ALT), aspartate aminotransferase

(AST), and fibrinogen. Evidence of previous coronavirus infection was provided by anamnesis data, as well as laboratory parameters — IgG and IgM antibodies to Coronavirus (SARS-CoV-2) and the determination of Coronavirus COVID-19 RNA by the polymerase chain reaction (PCR) method.

Methods of statistical analysis

Descriptive statistics were performed during the study. For all continuous variables, the mean value and corresponding confidence intervals were calculated depending on the type of data distribution. For variables with a distribution deviating from normal, the median and interquartile range were determined. Qualitative variables were analyzed by calculating absolute and relative indicators.

For categorical variables, data were presented as absolute and relative numbers. For qualitative data, the significance of differences in groups was determined by performing the Chi-square (χ 2) test. For quantitative data, central tendencies were measured.

Comparison of laboratory parameters between patient groups was performed using the nonparametric Mann-Whitney U test for samples with asymmetric distribution. Nominal variables were compared using the Pearson χ^2 goodness-of-fit test, and rank variables were analyzed using the Tau-s-Kendall test.

The relationship between clinical and laboratory parameters and the probability of MI development was studied using multiple linear regression analysis. Statistical significance was established at $p < 0.05$. ROC curve analysis was used to assess the diagnostic significance of quantitative features in predicting the outcome.

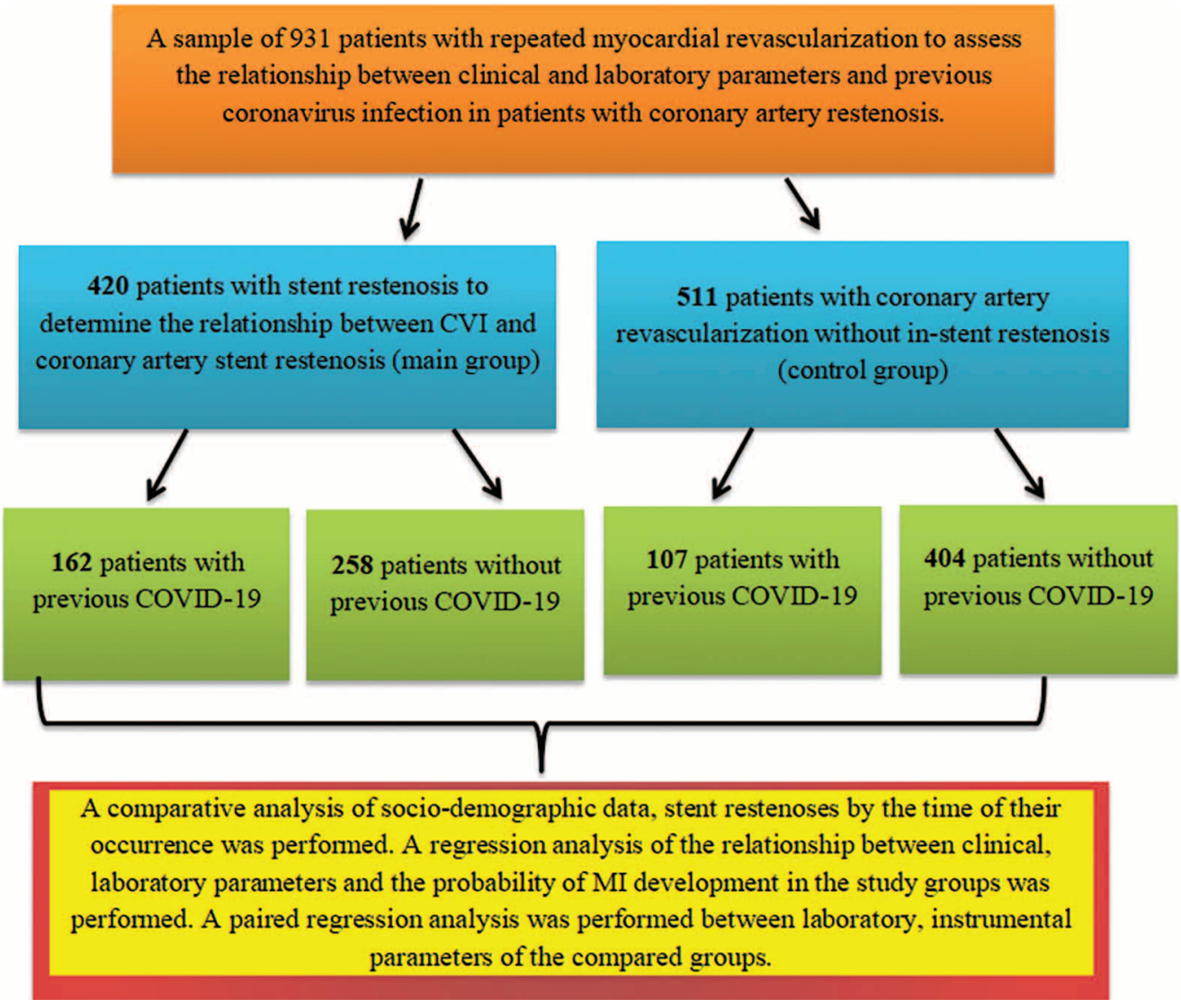

Figure 1. *Study design*
Note: CVI — coronavirus infection; MI — Myocardial infarction

The separating value of the quantitative feature at the cut-off point was determined by the highest value of the Youden index. Differences were considered statistically significant at $p < 0.05$. All statistical calculations were performed using SPSS version 20.0 software (IBM Ireland Product Distribution Limited, Ireland).

The study design is presented in Figure 1. The observation period was 1 year.

Results and discussion

In the main study group, the majority of patients were males — 315 (75 %) people; 25 % (105 people) were women. The control group included 385 (75.3 %) men and 126 (24.7 %) women. No statistically significant differences in gender and social status were found in the study groups. Arterial hypertension was present as a comorbid condition in the vast majority of patients in both study groups. Diabetes mellitus was diagnosed in approximately one-fifth of patients in both study groups, although no statistically significant differences were found between the study groups for these indicators. In the main study group, there were more deceased individuals compared to the control group — 19 (57.6 %) vs. 14 (42.4 %) patients, respectively, but the values did not have statistically significant differences ($\chi 2 = 3.597$; $p = 0.166$) (Table 2). At the same time, in the main group, among deceased individuals, coronavirus infection in the anamnesis was in 13 out of 19 individuals (68.4 %), and in the control group — in 7 patients out of 14 (50 %).

In the main group, at the time of inclusion in the study, more than half of the patients had very late stent restenosis (more than a year after previous stenting): 231 (55.0 %), 152 (36.2 %) patients had late stent restenosis (from one month to one year after stenting), 37 (8.8 %) had subacute stent restenosis (up to one month after previous stenting). In the control group, the structure of restenosis periods was identical; no statistically significant differences were found in the study groups (Table 3).

It was found that in more than half of the cases in both groups, interventions were performed on the anterior interventricular branch of the left coronary artery (LAD) (522 cases or 56.1 %), followed by the right coronary artery (RCA) (268 cases or 28.8 %), then the circumflex branch of the left coronary artery (LC) (121 cases or 12.9 %). No statistically significant differences in the study groups regarding stent localization were found (Table 4). In 326 (33.1 %) of the cases listed in the table, multivessel coronary vascular disease was observed, with two or more stents being implanted.

There were no statistically significant differences in the study groups concerning clinical parameters such as systolic and diastolic blood pressure, heart rate, and left ventricular ejection fraction according to echocardiographic examination. The median values of these parameters in both groups did not exceed normal values.

Analysis of laboratory parameters in patients included in the study groups demonstrated the presence of statistically significantly higher values of IgG antibodies to coronavirus and C-reactive protein in the main study group compared to the control group. No significant differences were found in other laboratory parameters in the study groups (Table 5). Non-zero values of antibodies to IgM and IgG in individuals in the control group can be explained by possible contact with patients with a history of coronavirus infection without any clinical manifestations of the disease or previous vaccination; it should be noted that the average values in the control group were within normal values (<10 for antibodies to IgG and <2 for antibodies to IgM).

It was of considerable interest to us to compare the results of clinical data and laboratory tests in the comparison groups depending on the presence of a history of coronavirus infection. For this purpose, we divided the main and control groups into subgroups of individuals with and without a history of COVID-19: group 1 — individuals with restenosis and COVID-19, group 2 — with restenosis without COVID-19, group 3 — with repeated myocardial revascularization without restenosis with COVID-19, and group 4 — with repeated myocardial revascularization without restenosis without COVID-19. No statistically significant differences were found for parameters such as age, gender, presence of comorbid diseases, and left ventricular ejection fraction according to echocardiography. Regarding laboratory parameters, statistically significant differences were found in troponin levels ($p < 0.001$), including by study group between the level in the group with restenosis and CVI compared with the groups without restenosis with CVI, with restenosis without CVI and in the groups with revascularization without CVI and with restenosis without CVI. The D-dimer level had statistically significant differences in the groups with previous CVI compared to the groups without CVI. The same trend was found for CPK, CPK-MB, and CRP (regarding this indicator, it should be noted that statistically significant differences were established even for the groups with restenosis without CVI compared to the group without restenosis and CVI) and APTT. For such parameters as fibrinogen and AST, statistically significant differences were found only in the main group between the subgroups with a history of CVI compared to patients without CVI. No statistically significant differences were found in the study groups for the other laboratory parameters (Table 6).

Multiple regression analysis was performed to assess the independent relationship between the development

of MI and in-stent restenosis of the infarction-related coronary artery. The results of the analysis are presented in Table 7. Adjusted odds ratios (AOR) indicated a statistically significant positive relationship between the risk of developing myocardial infarction in individuals with previous revascularization and such indicators as blood glucose, CRP, LDL, and previous CVI (1.114; 1.014; 1.199; 1.621, respectively). Left ventricular ejection fraction and HDL were statistically significantly negatively associated with the risk of MI (AOR 0.954; 0.638, respectively).

When assessing the probability of developing MI among the studied patients from the values of laboratory parameters using ROC analysis, the following curves were obtained (Figure 2). The area under the curve (AUC) for LDL was 0.542 (0.504-0.581, p=0.03), for CRP 0.6 (0.562-0.637, p=0.0001), blood glucose 0.649 (0.612-0.685, p=0.0001), and COVID-19 infection 0.558 (0.519-0.596, p=0.003). With an increase in the values of two variables — LVEF and HDL — a decrease in the risk of MI was shown. Thus, the AUC for LVEF was 0.343 (0.308-0.378, p=0.0001), for HDL — 0.46 (0.422-0.498, p=0.038).

It is known that stent restenosis remains a problem for patients with coronary artery disease who have undergone myocardial revascularization using stents, and the risk factors for its occurrence have not yet been fully studied. After stent implantation, restenosis develops mainly within the first three months [9]. Restenosis occurs due to intimal hyperplasia within the stent, which leads to myocardial ischemia. With the introduction of drug-eluting coronary stents, the incidence of restenosis and, consequently, re-interventions has been significantly reduced. The incidence of restenosis after bare metal coronary stent implantation is approximately 20-35 %, while the use of drug-eluting stents has further reduced the incidence of restenosis to 5 %-10 % [2].

Table 2. *Comparative characteristics of social and demographic data in the study groups*

Characteristics of study groups		Study groups				Statistical test for the significance of differences	
		Main group		Control groups			
		n	%	n	%	χ2	p
Outcome	discharged	392	93.3	491	96.1	3.597	0.166
	died	19	4.5	14	2.7		
	transferred	9	2.1	6	1.2		
Sex	male	315	75	385	75.3	0.014	0.904
	female	105	25	126	24.7		
Social status	invalid	30	7.1	46	9.0	3.765	0.288
	pensioner	238	56.7	270	52.8		
	unemployed	52	12.4	81	15.9		
	works	100	23.8	114	22.3		
Diabetes mellitus		91	21.7	100	19.6	0.622	0.430
Arterial hypertension		414	98.6	497	97.3	1.885	0.170

* Discharged after current hospitalization when stent restenosis was diagnosed

Table 3. *Characteristics of stent restenoses depending on the timing of their development*

Timing of restenosis	Studied groups				χ2	p
	Main		Control			
	n	%	n	%		
Subacute	37	8.8	48	9.4	0.187	0.911
Late	152	36.2	179	35.0		
Very late	231	55.0	284	55.6		
Total	420	46.1	511	53.9		

Table 4. *Characteristics of the localization and number of implanted stents*

Localization of stent	Total		n= 420 Main group		n= 511 Control group		p
	n	%	n	%	n	%	
OMB	8	0,9	2	0,5	6	1,2	
RCA	268	28,8	117	27,9	151	29,5	
DB	12	1,3	6	1,4	6	1,2	0,679
Cx	121	12,9	52	12,4	69	13,5	
LAD	522	56,1	243	57,9	279	54,6	
Number of implanted stents							
1	605	64,9	269	64,0	336	65,8	0,587
2 and>	326	33,1	151	36,0	175	34,2	

Note. OMB — obtuse marginal branch; RCA — right coronary artery; DB — diagonal branch; Cx — circumflex branch of the left coronary artery; LAD — left anterior interventricular branch of the left coronary artery

Table 5. *Characteristics of laboratory parameters in patients of study groups*

Rate	Main group		Control group		P
	Me	Q1-Q3	Me	Q1-Q3	
Troponin I mkg/l	0,10	0,1-0,26	0,10	0,1-0,28	0,831
D-dimer ng/ml	452,0	295,0-619,0	437,0	293,5-613,5	0,580
CPK (U/l)	190,0	117,75-289,0	186,0	109,1-304,5	0,816
CPK-MB (U/l)	18,95	15,0-32,78	19,0	15,0-34,4	0,796
Platelets 10^9/l	233,0	197,75-272,0	231,0	193,0-272,0	0,533
Antibodies IgG	8,6	6,5-67,3	6,9	5,4-9,31	0,001
Antibodies IgM	0,9	0,79-1,6	0,90	0,7-1,5	0,084
CRP mg/l	10,7	5,97-17,55	9,06	4,5-17,78	0,003
Fibrinogen g/l	3,18	2,61-3,81	3,20	2,60-3,95	0,661
APTT	29,0	25,4-33,7	29,4	25,42-33,8	0,609
Creatinine mkmol/l	82,25	72,0-102,0	87,0	72,0-102,1	0,794
Urea	5,85	4,8-7,4	5,7	4,75-7,26	0,546
ALT U/l	25,0	17,47-35,95	25,6	18,0-37,9	0,430
AST U/l	23,1	17,38-33,51	23,52	17,36-36,3	0,681
Leucocytes 10^9/l	8,0	6,5-10,11	8,20	6,7-10,68	0,199
Hemoglobin (g/l)	141,0	131,0-153,0	143,0	131,5-153,0	0,528
INR	1,0	0,92-1,09	1,0	0,92-1,10	0,401
Triglycerides mmol/l	1,67	1,17-2,38	1,60	1,12-2,36	0,677
HDL mmol/l	1,00	0,89-1,23	1,02	0,89-1,24	0,527
LDL mmol/l	2,78	2,19-3,45	2,78	2,17-3,49	0,882
Glucose mmol/l	6,10	5,42-7,66	6,01	5,4-7,5	0,583
Neutrophils * %	64,86± 10,61		65,98±10,38		0,106
Lymphocytes * %	25,85±9,33		25,11±9,34		0,229

Note. * The variable has a normal distribution (Cp [SD])
CRP — C-reactive protein; CPK — creatine phosphokinase; HDL — high-density lipoprotein; LDL — low-density lipoprotein; ALT — alanine aminotransferase; AST — aspartate aminotransferase; APTT — activated partial thromboplastin time, INR — International Normalized Ratio

Table 6. *Clinical and laboratory characteristics of patients in the main and control groups depending on the status of the transferred COVID-19*

Rate	Main group (Me, Q1-Q3)		Control group (Me, Q1-Q3)		p*
	CVI+ (group 1)	CVI- (group 2)	CVI+ (group 3)	CVI- (group 4)	
Age	64 (59-70)	63 (57-72.5)	65 (60-69)	64 (57-72)	0.992
Male gender	115 (71.4 %)	200 (77.2 %)	78 (73.6 %)	307 (76.0 %)	0.556
AH	158 (98.1 %)	256 (98.8 %)	105 (99.1 %)	391 (96.8)	0.241**
DM	39 (24.2 %)	52 (20.1 %)	28 (26.4 %)	72 (17.8 %)	0.142**
LVEF	51 (45.0-56.0)	53 (46.0-58.0)	52 (46.0-57.0)	51.5 (45.0-56.0)	0.354
Troponin I mcg/l	0.1 (0.1-3.39)	0.1 (0.1-0.12)	0.1 (0.1-0.62)	0.1 (0.1-0.22)	0.001 P3-1=0.001 P4-1=0.005 P3-2=0.037
d-dimer ng/ml	490.0 (350.6-719.0)	415.0 (287.5-574.0)	489.0 (346.75-694.0)	418.0 (283.75-597.25)	0.001 P2-1=0.005 P4-1=0.006 P3-2=0.02 P4-3=0.021
CPK (U/l)	199.0 (147.0-374.0)	183.0 (102-268.0)	196.5 (158.25-364.0)	183.2 (102.0-284.0)	0.001 P2-1=0.003 P4-1=0.005 P3-2=0.003 P4-3=0.005
CPK -MB (U/l)	22.6 (17.3-48.1)	17.8 (14.1-24.4)	23.65 (16.92-45.75)	18.25 (14.78-29.55)	0.001 P2-1=0.001 P4-1=0.001 P3-2=0.001 P4-2=0.002
Platelets 109/l	237.0 (201.0-272.0)	231.0 (194.0-272.0)	231.5 (195.5-271.0)	230.5 (193.0-272.0)	0.466
CRP mg/l	12.45 (4.8-19.3)	9.8 (4.79-28.3)	10.2 (4.9-21.7)	6.8 (3.5-11.0)	0.001 P2-1=0.001 P3-2<0.001 P4-2=0.001
Fibrinogen g/l	3.32 (2.75-4.18)	3.10 (2.5-3.73)	3.22 (2.71-4.12)	3.18 (2.6-3.8)	0.039 P2-1=0.039
APTT	31.3 (26.76-34.7)	28.0 (24.8-33.0)	31.2 (26.55-34.33)	29.0 (25.3-33.73)	0.001 P2-1=0.003 P3-2=0.026
Creatinine mkmol/l	83.5 (72-103)	86.0 (72-101.0)	79.85 (69.93-95.2)	88.0 (74.0-103.0)	0.055
ALT U/l	27.4 (18.99-37.2)	22.27 (17.0-34.15)	25.05 (17.21-34.0)	25.65 (18.0-38.0)	0.102
AST U/l	25.00 (18.3-39.0)	21.9 (17.0-32.0)	25.45 (18.5-40.5)	23.04 (17.27-35.0)	0.009 P2-1=0.021
Leucocytes 109/l	8.4 (6.5-10.9)	7.87 (6.5-9.9)	8.01 (6.37-9.93)	8.3 (6.73-10.86)	0.132
Hemoglobin (g/l)	141.0 (128.0-152.0)	142.0 (132.0-153.0)	140.0 (128.0-153.5)	143.0 (132.0-153.0)	0.394
INR	1.0 (0.91-1.1)	0.99 (0.92-1.08)	1.0 (0.9-1.13)	1.0 (0.93-1.1)	0.862
Triglycerides mmol/l	1.6 (1.12-2.2)	1.7 (1.2-2.45)	1.60 (1.11-2.40)	1.60 (1.12-2.34)	0.802
HDL mmol/l	0.98 (0.88-1.2)	1.02 (0.9-1.24)	1.0 (0.88-1.25)	1.02 (0.9-1.24)	0.783
Glucose mmol/l	6.18 (5.44-8.51)	6.1 (5.4-7.38)	6.35 (5.42-8.8)	6.01 (5.4-7.37)	0.078
Urea mmol/l	5.9 (4.8-7.5)	5.8 (4.8-7.3)	5.8 (4.7-6.88)	5.8 (4.79-7.3)	0.773
Neutrophils %	65.69 ± 11.1	64.35 ± 10.28	66.09 ± 11.06	65.96 ± 10.22	0.234***
Lymphocytes %	24.4 (19.4-33.3)	25.8 (20.7-31.6)	25.0 (17.55-32.05)	24.25 (19.68-31.6)	0.590
LDL mmol/l	2.85 (2.15-3.4)	2.74 (2.2-3.46)	3.0 (2.22-3.49)	2.7 (2.17-3.48)	0.658

Note. *Kruskal-Wallis test; **Pearson chi-square; ***Fisher F-test
AG — arterial hypertension, DM — diabetes mellitus; CRP — C-reactive protein; LVEF — left ventricular ejection fraction, CPK — creatine phosphokinase; HDL — high-density lipoproteins; LDL — low-density lipoproteins; ALT — alanine aminotransferase; AST — aspartate aminotransferase, APTT — activated partial thromboplastin time, INR — International Normalized Ratio

Table 7. *Characteristics of the relationship between model predictors and the probability of detecting MI*

Rate	Unadjusted indicator		Adjusted indicator	
	OR; 95 % CI	p	AOR; 95 % CI	p
LV ejection fraction, %	0.945; 0.93 –0.960	<0.001*	0.954; 0.938–0.969	<0.001*
Glucose, mmol/l	1.154; 1.099–1.212	<0.001*	1.114; 1.059–1.174	<0.001*
CRP, g/l	1.015; 1.009–1.021	<0.001*	1.014; 1.008–1.019	<0.001*
LDL, mmol/l	1.158; 1.009–1.328	0.036*	1.199; 1.034–1.392	0.017*
HDL, mmol/l	0.599; 0.401–0.896	0.013*	0.638; 0.411–0.989	0.045*
COVID-19	1.742; 1.305–2.326	<0.001*	1.621; 1.189–2.212	0.002*

Note. * — the influence of the predictor is statistically significant (p < 0,05); OR — odds ratio; AOR — adjusted odds ratio. CRP — C-reactive protein; HDL — high-density lipoproteins; LDL — low-density lipoproteins. COVID-19 — new coronavirus infection

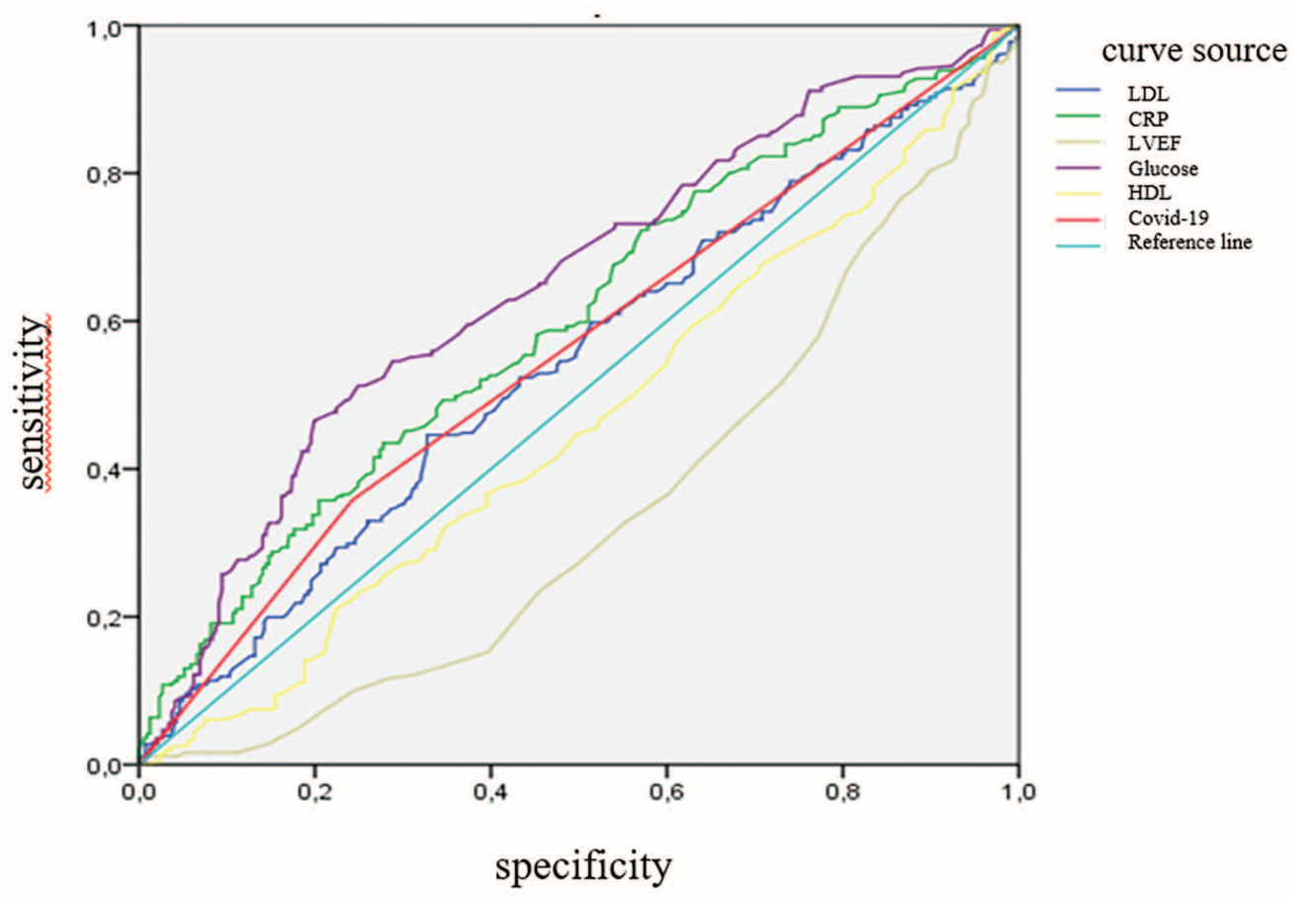

Figure 2. *Estimation of the probability of developing MI using ROC analysis*
Note. CRP — C-reactive protein; LVEF — left ventricular ejection fraction; LDL — low-density lipoproteins; COVID-19 — coronavirus infection

A comparative analysis of the results of our study with the data of other similar studies showed the comparability of the data. Thus, a retrospective study conducted in southern China to assess the incidence and risk factors of coronary artery restenosis included 341 patients with acute coronary syndrome who had previously been implanted with at least one stent. The follow-up was carried out for 3 years. It turned out that 18.2 % of such patients had in-stent restenosis throughout the monitoring period, which could form, on average, over a period of 32 months; the frequency of restenosis for the left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery and the right coronary artery was 6.7 %, 20.9 %, 19.4 %, and 14.4 %, respectively); left ventricular ejection fraction, the number of stents, the type of stent, and antiplatelet therapy made a significant contribution to the development of coronary artery restenosis. Multivariate logistic analysis showed that left ventricular ejection fraction and the number of stents significantly correlated with the incidence of coronary artery restenosis [10]. In our study, very late in-stent restenosis was predominant in both study groups, its proportion was more than 50 %, about a third of patients had late restenosis, and only about 10 % of patients had subacute in-stent restenosis, no statistically significant differences were found in the study groups. In our study, the predominant stent location was also the left LAD, but the second place was the RCA, followed by the left LCA. Multiple coronary vessel lesions were observed in a third of cases. The results of our study similarly indicate the presence of an inverse statistically significant relationship with the risk of myocardial infarction in patients with previous revascularization.

The conducted studies show that patients with previous myocardial revascularization who have had coronavirus infection have a higher risk of developing severe complications [10, 11]. Thus, Polish scientists in their study came to the conclusion that stent thrombosis is more common in patients with multiple comorbidities and in patients with complex atherosclerotic lesions, diabetes mellitus, chronic kidney disease, diffuse and bifurcation lesions of small arteries requiring the installation of more than one stent [11]. During SARS-CoV-2 infection, a cytokine storm occurs 5-10 days after the onset of symptoms, leading to endothelial damage, platelet activation, and the coagulation cascade. The presence of a stent in the coronary artery should be considered a local stasis factor that completes Virchow's triad [11].

According to the results of the study by Giustino G et al., which included 305 patients with previous revascularization who had coronavirus infection, myocardial injury was observed in 190 patients (62.3 %). Compared with patients without myocardial injury, patients with myocardial injury had more electrocardiographic manifestations, higher inflammatory biomarkers, and an increased prevalence of major echocardiographic abnormalities, which included left ventricular wall motion abnormalities, global left ventricular dysfunction, left ventricular diastolic dysfunction and pericardial effusions [12].

Severe coronavirus infection is characterized by an increase in some biochemical parameters responsible for inflammatory reactions (ferritin, C-reactive protein), thrombus formation (D-dimer, fibrinogen, prolongation of PT), and damage to myocardial muscle tissue (troponin, creatine phosphokinase). Thus, serum ferritin levels are important for the immune response, which increases in severe cases of COVID-19, and elevated ferritin levels can cause a cytokine storm, exerting a direct immunosuppressive and proinflammatory effect [13].

According to current guidelines, determination of high-sensitivity troponin I is mandatory in the diagnosis of ischemic cardiac injury, since troponin I is a protein of the heart muscle [14]. The results obtained in our study indicate statistically significant differences in troponin levels ($p < 0.001$) in the study groups after dividing them depending on the previous coronavirus infection in both the main and control groups, whereas no such differences were found when comparing the main and control groups without taking into account the previous COVID-19. In a study conducted on a sample of patients with current COVID-19 in five hospitals in New York, an increase in cardiac troponin concentration was found in 36 % of patients. Troponin I levels in the range of 30–90 ng/L corresponded to an adjusted hazard ratio (HR) of 1.76 (95 % CI: 1.37–2.24), and troponin concentrations >90 ng/L increased the adjusted HR to 3.03 (CI: 2.42–3.80) [15]. However, some authors explain the increase in troponin I levels in COVID-19 not by ischemic injury, but by inflammatory changes in the myocardium [16].

After COVID-19, a common complication is a high prothrombotic status, which contributes to the development of thrombosis, heart attacks or strokes [14]. Elevated D-dimer levels are observed in thrombosis, thromboembolism, heart failure, coronavirus infection, etc. A high concentration of this laboratory indicator is a predictor of death [17]. Initial coagulopathy in patients with COVID-19 is manifested by an increased content of D-dimers. In the late period after coronavirus infection, an increase in prothrombin time and APTT, an increase in platelet and fibrinogen levels

are observed [17]. Assessment of the progression of COVID-19 is carried out, among other things, through regular monitoring of laboratory parameters, including D-dimer and fibrinogen [17]. Regarding the results of our study, it should be noted that statistically significant differences in the D-dimer level were found only when dividing the study groups into subgroups depending on the previous COVID-19, whereas a comparison of the indicator in the main and control groups did not show such differences.

C-reactive protein increases at the onset of COVID-19 [14,18]. There is a direct relationship between C-reactive protein concentration and adverse outcomes according to study results [18]. Patients with coronavirus infection with high levels of D-dimer and C-reactive protein have the highest risk of adverse outcomes [19]. The results of our study are consistent with these data: differences in C-reactive protein levels in the study groups remained statistically significant depending on both the presence of stent restenosis compared to patients with repeat myocardial revascularization without restenosis, and depending on the history of COVID-19.

The causes of elevated liver transaminases in inflammatory processes include impaired cell membrane permeability. In COVID-19 patients, liver lymphocyte infiltration, centrilobular sinusoidal dilation, and focal necrosis could be observed, and SARS-CoV-2 could directly bind to ACE2-expressing cholangiocytes [20,21]. Liver damage can also be drug-induced [22]. IL-6 is a potent cytokine that serves to transmit inflammatory signals. IL-6 production can occur from immune cells, fibroblasts, endothelial cells, and hepatocytes, which causes the acute phase of liver damage [23]. Increased AST and ALT activity are associated with a severe course and worse prognosis, the risk of death in patients with coronavirus infection. Thus, a systematic review with meta-analysis Wang Y et al., 2021 that included 1370 patients with COVID-19 showed a significant relationship between elevated AST levels and an increased risk of mortality in patients with COVID-19 (SMD = 0.75, 95 % CI: 0.33–1.17, p <0.001). The same relationship was found for ALT (SMD = 0.35, 95 % CI: 0.13–0.57, P = 0.002) [24]. The results of our study demonstrate statistically significant differences in the level of liver transaminases when dividing the study groups into subgroups depending on the previous COVID-19.

The results of a systematic review with meta-analysis conducted by Chinese scientists in 2023 showed an increased level of pro-inflammatory biomarkers (CRP, LDH, D-dimer, interleukin-6, leukocytes) for six months after COVID-19 [25], which may explain the results obtained in our study among patients who had COVID-19. A study conducted by Spanish scientists studying patients with myocardial revascularization (stenting) who had COVID-19 described cases of stent thrombosis associated with hypercoagulability due to the COVID-19 virus. In this study, there was an increase in D-dimer (more than 500 mg/l in 100 % of patients), an increase in C-reactive protein (more than 5 mg/l in 100 % of patients), an increase in ferritin (more than 400 ng/ml in 75 % of patients), lymphocytopenia (in 50 % of patients), an increase in troponin in 100 % of patients, and a decrease in the estimated glomerular filtration rate in 75 % of patients [26]. A group of American scientists examined 5,700 patients admitted to infectious disease departments with COVID-19. The following changes in the laboratory tests of patients were noted: lymphopenia (60 % of patients), an increase in D-dimer (56 %), ferritin (76 %), C-reactive protein (79 %), and lactate dehydrogenase (70 %) [27]. In a study from a hospital in Wuhan, China, 187 patients showed leukocytosis, increased neutrophils, and decreased lymphocytes with high troponin T levels [28].

The results of our work when comparing laboratory parameters in the study groups showed statistically significant differences in the C-reactive protein and IgG antibodies to coronavirus, which is probably due to the large proportion of patients who had coronavirus infection in the main group, even in the late period. Of considerable interest is the fact that after dividing the study groups by the presence of coronavirus infection in the anamnesis, statistically significantly higher values were found not only for the C-reactive protein indicator, but also for troponin, CPK, CPK-MB, D-dimer and APTT for individuals who had COVID-19. The results of multiple regression analysis indicate the presence of a statistically significant positive relationship between the likelihood of myocardial infarction in patients with previous revascularization and such laboratory parameters as CRP, blood glucose, LDL, and previous COVID-19.

Conclusions.

The results of our study allow us to conclude that there is a statistically significant positive association between the likelihood of myocardial infarction and previous coronavirus infection, increased levels of C-reactive protein, LDL and glucose in the blood, as well as a decrease in LVEF and HDL. These data allow us to judge the unfavorable role of previous coronavirus infection in the process of formation of coronary artery stent restenosis.

Вклад авторов:

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Батенова Г.Б.: разработка дизайна исследования; организация набора материала, создание базы пациентов, написание текста рукописи и представление результатов

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ ПАЦИЕНТА С ОСТРЫМ ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ ТРИКУСПИДАЛЬНОГО КЛАПАНА И МУЛЬТИПЛЕКСНЫМ ПОДХОДОМ К ОЦЕНКЕ РИСКА ОСЛОЖНЕНИЙ

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Clinical Case of a Patient with Acute Tricuspid Valve Infective Endocarditis and A Multiplex Approach to Evaluation of The Complication Risk

Резюме

Инфекционный эндокардит (ИЭ) отличается трудностью диагностики, лечения и оценки риска неблагоприятного прогноза. На сегодняшний день отсутствуют одобренные для применения шкалы и калькуляторы риска осложнений и летального исхода, помогающие практикующему врачу принимать решения, особенно у пациентов с изолированным правосторонним ИЭ. Для правостороннего ИЭ сроки выполнения успешного хирургического лечения остаются неопределенными. Ранее разработанные калькуляторы риска (итальянский калькулятор Rizzi и французский Hubert) плохо валидированы на широкой популяции пациентов с ИЭ, в особенности для правостороннего ИЭ. Одним из обязательных параметров калькуляторов является определение этиологической принадлежности. Однако при отрицательных результатах микробиологических исследований, достигающих 56-83 %, данный параметр становится неинформативным. Более того существующие инструменты оценки риска не учитывают активность заболевания (в том числе лабораторную), которая интуитивно для каждого врача яв-

ляется важным ориентиром в принятии решений. На данный момент есть большая потребность во внедрении молекулярно-биологических методов для улучшения качества этиологической диагностики и в углубленном изучении возможных биомаркеров от простых (нейтрофильно/лимфоцитарный, тромбоцитарно/лимфоцитарный и системный иммуно-воспалительный индексы) до более сложных (нейтрофильные внеклеточные ловушки, цитокиновый профиль).

Представлено клиническое наблюдение молодого пациента с острым ИЭ трикуспидального клапана с гигантской вегетацией (28 мм), осложненным тяжелой клапанной недостаточностью без признаков сердечной недостаточности, с рецидивирующим эмболическим синдромом в систему легочной артерии с формированием легочной гипертензии, определяющих показания для кардиохирургического лечения. Этиологическая принадлежность ИЭ к *Staphylococcus aureus* установлена только при ПЦР-исследовании. Неотложные сроки вмешательства определены на основании повышения новых маркеров — нейтрофильно/лимфоцитальный индекс ≥20,0, системный иммуновоспалительный индекс ≥2314,0 и нейтрофильные внеклеточные ловушки ≥14,2, свидетельствующих о крайне высоком риске летального исхода. Фундаментальное патогистологическое исследование тканевого материала выявило малое содержание неповрежденных провоспалительных макрофагов CD86+, вероятно связанное с их избыточным разрушением и бесконтрольным выходом обильного количества провоспалительных цитокинов, приведших к быстрому и тяжелому поражению трикуспидального клапана. Таким образом современное ведение пациентов с ИЭ должно быть мультиплексным с применением актуальных методов этиологической и визуализирующей диагностики, и направленным на раннее выявление пациентов неблагоприятного риска для своевременного дифференцированного подхода к консервативной или кардиохирургической тактике лечения.

Ключевые слова: *инфекционный эндокардит, прогноз, трикуспидальный клапан, нейтрофильно-лимфоцитарный индекс, нейтрофильные внеклеточные ловушки, ПЦР*

Конфликт интересов

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

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Abstract

Infective endocarditis (IE) is characterized by the difficulty of diagnosis, treatment and risk assessment of an unfavorable prognosis. Currently there are no approved scales and calculators for the risk of complications and death that help the practitioner make decisions, especially in patients with isolated right-sided IE. For right-sided IE, the timing of successful surgical treatment remains uncertain. Previously developed risk calculators (Italian Rizzi calculator and French Hubert) are poorly validated in a wide population of patients with IE, especially for right-sided IE. One of the required parameters of calculators is the determination of etiological affiliation. However, with negative results of microbiological studies reaching 56-83 %, this parameter becomes uninformative. Moreover, existing risk assessment tools do not take into account the activity of the disease (including laboratory activity), which intuitively is an important guideline for every doctor in decision-making. At the moment, there is a great need for the introduction of molecular biological methods to improve the quality of etiological diagnosis and in-depth study of possible biomarkers from simple (neutrophil/lymphocytic, platelet/lymphocytic and systemic immuno-inflammatory index) to more complex (neutrophil extracellular traps, cytokine profile).

We present a clinical case of a young patient with acute tricuspid valve IE with giant vegetation (28 mm), complicated by severe valvular insufficiency without signs of heart failure, recurrent embolic syndrome in the pulmonary artery system with the formation of pulmonary hypertension, determining indications for cardiac surgical treatment. The etiological affiliation of IE to *Staphylococcus aureus* was established only by PCR. The urgent timing of intervention was determined based on an increase in new markers — neutrophil/lymphocytic index ≥20.0, systemic immuno-inflammatory index ≥2314.0 and neutrophil extracellular traps ≥14.2, indicating an extremely high risk of death. A fundamental pathohistological study of the tissue material revealed a low content of intact CD86+ proinflammatory macrophages, probably associated with their excessive destruction and uncontrolled release of copious amounts of proinflammatory cytokines, which led to rapid and severe damage to the tricuspid valve. Thus, modern management of patients with IE should be multiplex using current methods of etiological and imaging diagnostics, and aimed at early detection of patients at adverse risk for a timely differentiated approach to conservative or cardiac surgical treatment tactics.

Key words: *infective endocarditis, prognosis, tricuspid valve, neutrophil-lymphocyte index, neutrophil extracellular traps, PCR*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

The study was carried out in accordance with the standards of Good Clinical Practice, the principles of the Declaration of Helsinki, and approved by the local ethics committee of the Medical Institute of the Patrice Lumumba Peoples' Friendship University of Russia (protocol No. 27 dated 03/18/2021). All patients signed informed consent for the collection of anonymized medical data.

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IE — infective endocarditis, CD — Cluster of Differentiation, PCR — polymerase chain reaction, TV — tricuspid valve, NLI — neutrophilic/lymphocytic index, TLI — thrombocytic/lymphocytic index, SIMI — system immune-mediated index, BMI — body mass index, RR — respiratory rate, BP — blood pressure, HR — heart rate, CT — computer tomography, AKI — acute kidney injury, CRP – C-reactive protein, CKD-EPI GFR — CKD-EPI glomerular filtration rate, EF — left ventricular ejection fraction, PASYS — pulmonary artery systolic pressure, DNA – deoxyribonucleic acid, *MRSA — methicillin resistant Staphylococcus aureus,* NET – neutrophil extracellular trap, COVID-19 — coronavirus infection 2019

Introduction

Infective endocarditis (IE) is known for its negative trends, associated with higher incidence rates, also due to primary IE, and number of hospitalisations with aggravated clinical forms, making diagnosis and therapy challenging and resulting in negative prognosis [1-5]. The versatile aetiological array of IE is characterised by dangerous trends in higher incidence rates of staphylococcal and enterococcal IE [1-5]. Isolated right-sided IE is rare in individuals, who do not take intravenous psychoactive substances and do not have intracardiac implants; and it obstructs identification of the entry of infection [1, 2, 6]. Microbiological IE pathogen identification is often challenging because of the method limitations and early antibacterial initiation, which affect the reduction in blood pathogen concentrations, especially in right-sided IE [1, 2, 7]. All the above affects timely initiation of etiotropic antibacterial therapy. Therefore, there is much discussion of modifications of the standard algorithm for aetiological diagnosis of IE and introduction of additional methods, such as immunochemistry and biomolecular methods; the latter offering ample opportunities.

Early evaluation of the prognosis and identification of the groups of the highest risk of unfavourable outcomes, primarily embolism and hospital mortality, are not optimal. Despite a series of studies to identify significant predictors of unfavourable outcomes and development of risk calculators, e.g. Rizzi (Italy) and Hubert (France), they are not widely used and are just mentioned in recommendations, without any mandatory use in routine activities [1, 2, 8, 9]. Moreover, a majority of studies included patients with left-sided IE, while right-sided IE is mentioned just in individual local studies [8, 10]. This issue is mentioned in national and European guidelines, where for left-sided IE, indications for surgery and optimal intervention window are specified, depending on the risk of unfavourable outcomes; whereas right-sided IE has only indications stated, without any clear timing for surgery [1, 2]. In general, it is worth mentioning that evaluation of the risk of complications takes into account demographics, presence of complications, aetiology, and echocardiography parameters. The high rates of negative microbiology results offset the significance of the aetiological parameter; besides, disease activity (also laboratory) is often disregarded, which is an important decision-making reference point. Therefore, besides imrpovement in the aetiological diagnosis quality, it is essential to study various biomarkers, both simple ones, which can be used at the point-of-care (neutrophilic/lymphocytic index, thrombocytic/lymphocytic index, and system immune-mediated index), and more sophisticated (neutrophil extracellular traps, cytokine profile), which will expand the capabilities for diagnosis evaluation and determination of the surgery window.

We present a clinical case study of a patient with no bad habits, who has damaged tricuspid valve (TV). The aetiological diagnosis in this patient was based on the use of additional biomolecular methods, while early evaluation of a high risk of unfavourable outcomes was possible due to identification of neutrophil extracellular traps and calculation of inflammation indices (neutrophilic/lymphocytic index (NLI), thrombocytic/lymphocytic index (TLI), system immune-mediated index (SIMI)). Also, unique histopathological changes, associated with the characteristics of tissue macrophages and contributing to the major involvement of the valve apparatus, were identified.

Clinical case study

Patient O, 36 years old, no bad habits and no history of cardiovascular diseases. The acute phase started rapidly with the body temperature of 40°C, dry dough, and chest pain. Outpatient therapy with cefixime 400 mg/day (6 days); no effect (Fig. 1). The patient was hospitalised with suspected pneumonia; TV IE was diagnosed, which was complicated by bilateral multisegmental pneumonia with destruction. With the therapy (vancomycin 2.0 g/day + gentamycine 240 mg/day, 6 days), the patient had persistent fever up to 39.0°C, large vegetations and recurring pulmonary artery embolism; the patient was moved to the cardiac surgery ward.

The patient was admitted to the cardiac surgery ward in moderately severe condition; body mass index (BMI): 24.7 kg/m^2; no oedema or rash; respiratory rate (RR): 22/min, harsh respiration, multiple sonorous wet small bubbling rales in projection of both lungs; blood pressure (BP): 110/70 mm Hg; heart rate (HR): 110 bpm, systolic murmur at the base of the ensisternum, hepatatosplenomegaly.

Initial blood count: WBC 21.8×10^9/L, NEU 20.2×10^9/L, LYM 0.59×10^9/L, RBC 4.33×10^{12}/L, Hb 126 g/L, platelets 157×10^9/L, **NLI 34.2,** TLI 266.1, **SIMI 5,361.9.** Repeated blood count: WBC 13.1×10^9/L, NEU 10.9×10^9/L, LYM 1.7×10^9/L, RBC 3.85×10^{12}/L, Hb 120 g/L, platelets 282×10^9/L, NLI 6.4, TLI 165.9, SIMI 1,808.1.

Blood biochemistry upon admission: creatinine 68.9 μmol/L, estimated glomerular filtration rate ($eGFR_{CKD-EPI}$) 116 mL/min, urea 4.3 mmol/L, total bilirubin 57 g/L, C-reactive protein (CRP) 214.8 mg/mL. Seven days later: creatinine 307.4 μmol/L, $eGFR_{CKD-EPI}$ 21 mL/min (stage 3 acute kidney injury with over 3-fold increase in creatinine levels). Fourteen days later: creatinine 79.5 μmol/L, $eGFR_{CKD-EPI}$ 109 mL/min, CRP 4.8 mg/mL. Coagulation profile: unremarkable. Urinalysis: density 1015, microscopic haematuria (10–15 cells).

Chest CT (upon admission): bilateral polysegmental pneumonia, spreading; aggressive lesions and effusion in pleural cavities.

Transthoracic echocardiography (echoCG) (before surgery): left ventricular ejection fraction (EF) 65 %, vegetation on septal leaf of TV up to 2.8 cm with 3rd degree tricuspid regurgitation, pulmonary artery systolic pressure (PASYS) 33 mm Hg.

Transesophageal echocardiography (before surgery): EF 57 %; left heart is not dilated; right heart is dilated; vegetation on TV leaves up to 2.0 cm, 4th degree tricuspid regurgitation, PASYS 45 mm Hg.

On day 2 of hospitalisation to the cardiac surgery ward, the patient underwent TV replacement with biological prosthesis Biolab No. 33 (Fig. 1, 2).

The post-surgery period was uncomplicated; however, the antibacterial therapy needed replacement because of acute kidney injury (AKI) and allergic reaction: vancomycin 2.0 g/day (19 days, stage 3 AKI) → teicoplanin 400 mg/day (4 days, urticaria) → linezolid 1,200 mg/day (14 days).

Transthoracic echoCG (after surgery): EF 60 %, satisfactory bioprosthesis performance, PASYS 30 mm Hg.

Microbial examination of blood and valve tissue samples did not show any presence of the pathogen.

Blood and TV tissue PCR test showed DNA of *S. aureus MRSA* 5,4×106 copies/mL.

Pathohistological examination of resected TV tissues: purulent inflammation with a large blood clot (vegetation), focal fibrosis, macrophage accumulation (Fig. 2).

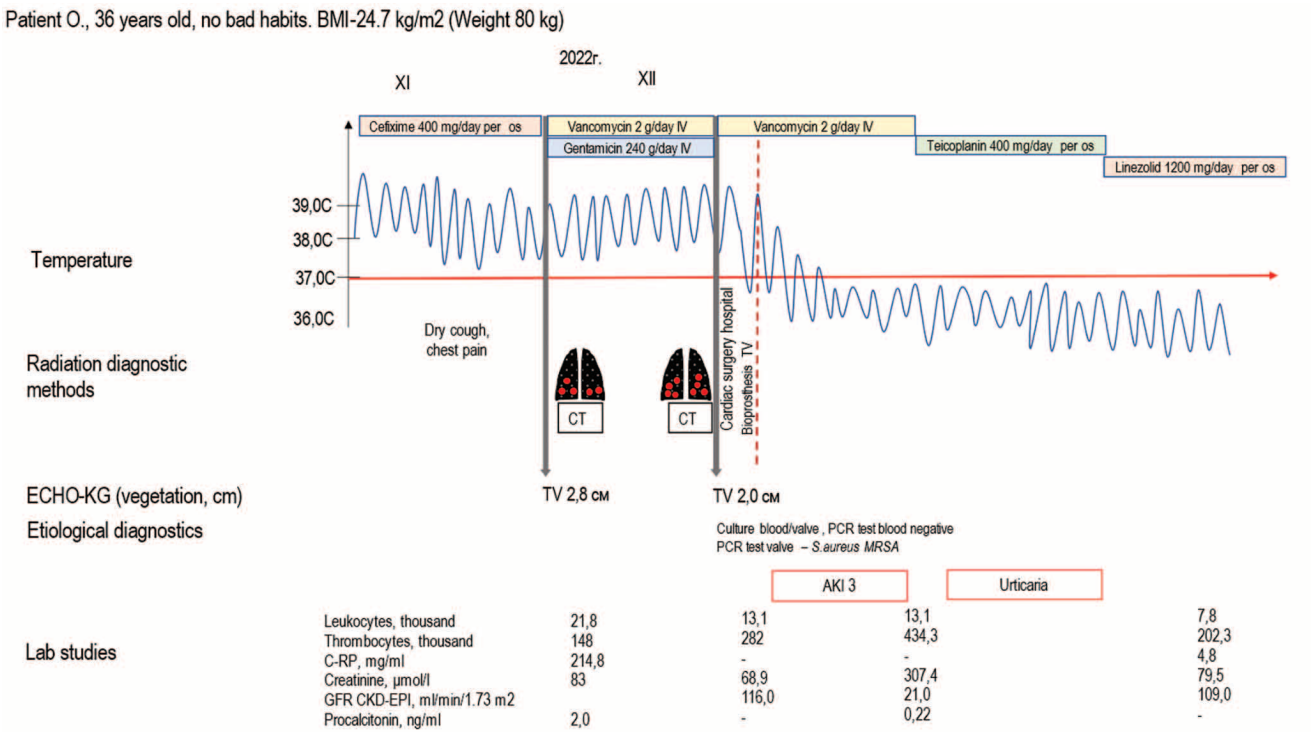

Figure 1. *Patient O. Case history diagram*

Notes: BMI — body mass index, CT — computed tomography, TV — tricuspid valve, PCR — polymerase chain reaction, AKI — acute kidney injury, C-RP — C-reactive protein, GFR CKD-EPI — glomerular filtration rate calculated using the CKD-EPI formula

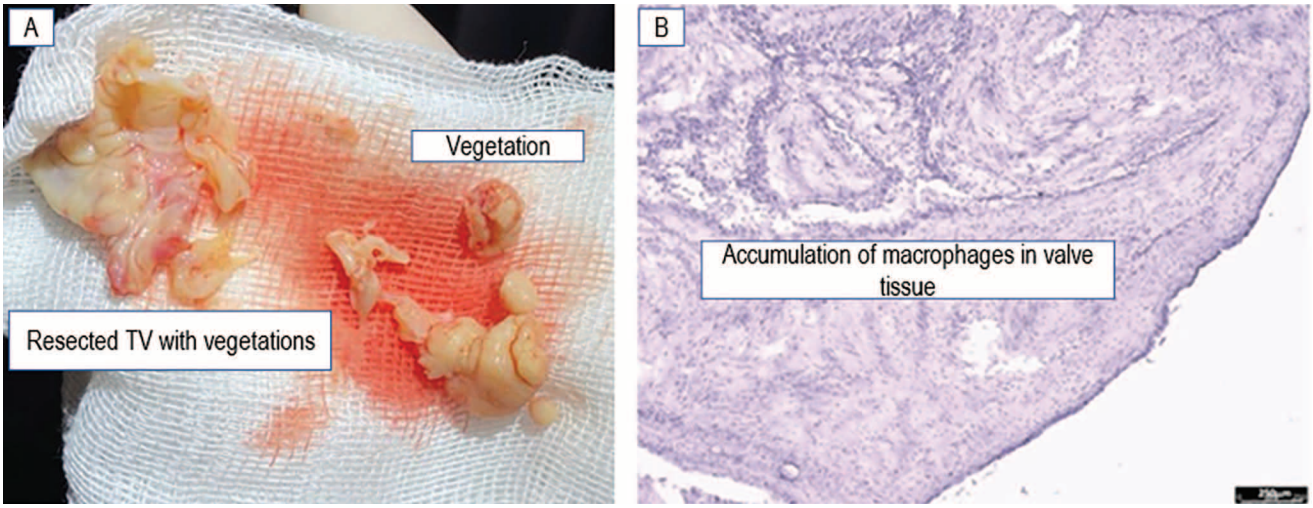

Figure 2. *Tricuspid valve (TV) tissue: A — Surgical material, B — Endocardial sections stained with hematoxylin. Scale bar 250 μm*

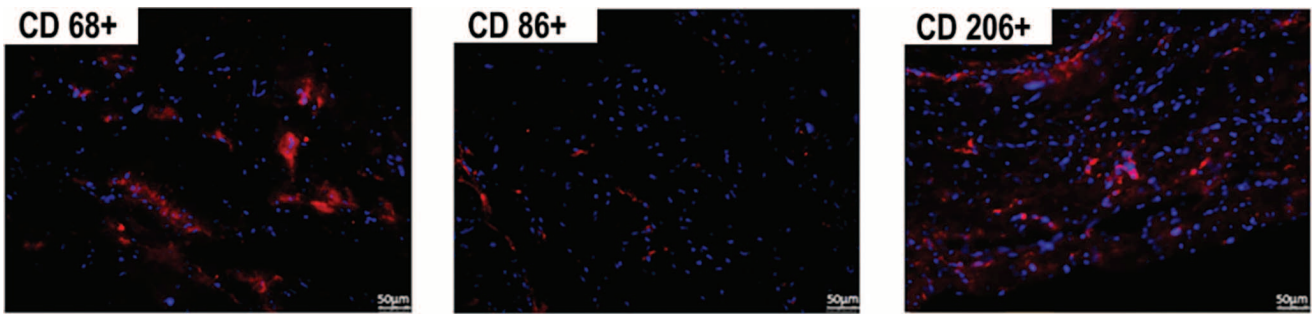

Figure 3. *Immunohistochemical staining of the endocardium of a patient with IE of the TV to detect CD 68+, CD 86+ and CD 206+ cells*

Note: Cluster of Differentiation (CD) 68+ (a common marker of macrophages), a small amount of CD 86+ (a marker of the pro-inflammatory phenotype of macrophages) and a large amount of CD 206+ (a marker of the anti-inflammatory phenotype of macrophages) cells are shown. Scale bar 50 μm. Red glow — expression of markers CD 68+, CD 86+, CD 206+. Blue glow — nuclei staining with DAPI (4',6-diamidino-2-phenylindole)

An immunohistochemical examination of resected valve tissue for the presence of whole macrophages showed CD 68+ (common macrophage marker), small amounts of CD 86+ (proinflammatory macrophage marker) and numerous CD 206+ cells (anti-inflammatory macrophage marker) (Fig. 3).

Also, upon patient admission we examined neutrophil extracellular trap (NET) levels using electron microscopy of monolayer blood smears, with eosin methylene blue and eosin azure blue staining [11]. NET levels (%) in smears (a share of transformed neutrophils in NET) were calculated as NET (%) = N_{NET} / ($N_{neutrophil}$ + $N_{eosinophil}$ + $N_{basophil}$ + N_{NET}), where N_{NET} is the number of neutrophil extracellular traps, $N_{neutrophil}$ is the number of native neutrophils, $N_{eosinophil}$ is the number of native eosinophils, $N_{basophil}$ is the number of native basophils [11]. Patient's NET upon admission was 14.7 %; seven days later, NET was 9.1 % (Fig. 4).

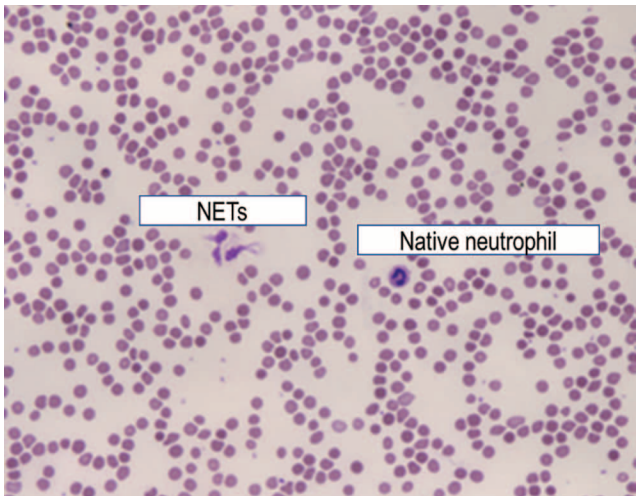

Figure 4. *A smear made as a monolayer to determine NETs in a patient with IE TV*

Note: NETs — neutrophil extracellular traps

Based on the medical record, clinical data, laboratory test and examination results, the following final clinical diagnosis was made for the patient on the first day of hospitalisation:

Diagnosis:

Primary: acute tricuspid valve IE, caused by *S. aureus MRSA*. Severe TV insufficiency. Pulmonary hypertension, degree 1. TV replacement with biological prosthesis Biolab No. 33.

Complications: bilateral polysegmental pneumonia. Bilateral dropsy of chest. Vancomycin-induced AKI, 3rd degree. Allergy reaction (urticaria fever) to teicoplanin.

The patient was discharged on day 35 in satisfactory condition Outpatient follow-up visits in 3 and 6 months: stable condition; normal body temperature; blood and urine test results: unremarkable; transthoracic echoCG: satisfactory prosthesis performance; no extra overlappings are seen.

Discussion

This clinical case study is interesting due to the development of complicated TV IE in a patient without predisposing factors, the key role in the aetiological diagnosis of which was played by PCR testing, allowing initiation of post-surgery etiotropic therapy. Despite obvious indications for heart surgery, the timing of the intervention was not clear, given the patient's haemodynamic stability. Assignment of the patient to the group of the high risk of short-term mortality was possible due to the measurement of blood neutrophil extracellular trap and inflammation indices (neutrophilic/lymphocytic index (NLI), thrombocytic/lymphocytic index (TLI), system immune-mediated index (SIMI)). Also, unique histopathological changes were found, which indicated elevated destruction of tissue macrophages and major damage to the valve apparatus.

IE remains a challenging condition for practitioners, both during diagnosis and selection of an adequate therapy, which is the cause of its unfavourable prognosis [1, 2, 12]. Very often this disease is confused with other pathologies, where false diagnoses are made, and IE diagnosis is delayed [1, 2, 13, 14]. In this clinical case study, first clinical manifestations were disguised as community-acquired pneumonia; however, its nature made it possible to assume an embolic site of infection and diagnose tricuspid valve IE at early stages. The period from first symptoms to IE verification is this patient did not exceed 14 days, meaning early diagnosis.

Native valve involvement in IE is very rare; it is recorded in 2 to 10 cases out of 100,000 person years [1, 2, 15]. Primary IE of the native tricuspid valve, not associated with intracardiac implants, congenital heart disorder or intravenous psychoactive substances, is very uncommon [1, 2]. We have presented a unique clinical case of a patient with IE of native unchanged TV without any predisposing factors. We were unable to identify the source of infection; however, given the disease aetiology, we suspect skin infections, which the patient is likely to have missed.

The aetiological nature of IE is traditionally a decisive factor in disease diagnosis, being both a major and manor Duke criterion, and also a factor for correct etiotropic therapy. Not only the fact of pathogen identification is of importance, but also its etiopathogenetic relation to active IE. The most challenging is high IE incidence with unknown aetiology, which accounts for 56–83 % and is associated not only with the features of bacteraemia, but also known for not only its low blood pathogen concentration (also as a result of early antibacterial therapy), but highly labour-intensive microbiological examination [1, 2, 7]. In this patient, microbiological examinations of blood and resected valve tissues yielded negative results at all stages of examination. We also conducted a PCR test of whole venous blood and resected valve tissue, which demonstrated DNA of methicillin-resistant *S. aureus*. We assume that this is the most probable pathogen, given the clinical manifestations and aggressive disease. Previous examinations and available own data also confirm the high diagnostic efficiency of molecular biological methods in aetiological diagnosis of IE, especially in making decisions whether to continue with antibacterials during the post-surgery period or not [16, 17].

Indications for surgery in right-sided IE are stricter than for the left heart and include the following requirements: right ventricular dysfunction caused by acute severe tricuspid regurgitation; diuretic resistance (class/level I/B); persistent vegetation with respiratory distress requiring artificial lung ventilation after recurrent embolism (I/B); **large residual vegetation on tricuspid valve (> 20 mm) after recurrent septic pulmonary embolism (I/C)**; patients with left heart involvement (I/C) [1, 2]. It is worth emphasising that the specific timing for heart surgery for right-sided IE is the same as for left-sided IE; it is not regulated and is at the doctor's discretion [1, 2]. In this case study, initial size of vegetations was 28 mm; vegetations were associated with embolism in the bed of the pulmonary artery. After the therapy, vegetations shrank to 20 mm, but recurrent embolism, fever and worsening tricuspid regurgitation persisted; they were correctly considered indications for heart surgery; however, the urgency remained unclear.

The pressing need for accurate and practically accessible markers of unfavourable prognosis is a result of high mortality rates in IE [1-6, 15, 18]. The most common

clinical and instrumental predictors of hospital mortality are: cardiac insufficiency, prosthetic cardiac valve, stroke, AKI, large vegetations, high Charlson Comorbidity Index, left heart involvement, *S. aureus*, therapy-induced embolism [1, 2, 19, 20]; and laboratory markers are: CRP, procalcitonin, total counts of WBC, neutrophils, NT pro-BNP, D-dimer [1, 2, 20, 21]. Overall, despite the seeming versatility of clinical, instrumental and laboratory markers, their predicative value is not optimal and is challenging for a medical practitioner. Moreover, the majority of these parameters were aimed at left-sided IE. It is generally worth concluding that to date there is no unique parameter. Of interest are user-friendly practical indices of inflammation — neutrophilic/lymphocytic index, thrombocytic/lymphocytic index and system immune-mediated index (platelets*neutrophilics/lymphocyts) [22, 23]. Bacterial infections, including sepsis and IE, are known to be associated with gradually increasing neutrophil and decreasing lymphocyte levels, and their ratio can be more accurate in indicating disease severity. Besides, clinically, there are often reduced platelet counts along with increased blood infection activity and the correlation between consumption thrombocytopenia and larger vegetations [24]. Therefore, the ratio of platelets and inflammation cells can also be informative (TLI, SIMI). A number of studies in patients with bacteraemia demonstrated that NLI is a more accurate marker of unfavourable outcome as compared to isolated WBC count [22, 23]. Hu W. et al. (2022) noted that with the threshold SIMI ≥ 1,960.9, there is 6.9-fold increase in the risk of embolic events [23], while Agus H.Z. et al. (2020) found out that with SIMI ≥ 2,314.0 (AUC 0.641, p=0.019) the risk of death increases [22]. According to our cohort study, the risk of death at hospital increases at NLI ≥ 20.0, SIMI ≥ 2,314.0, TLI ≤ 82.0 [25]. Upon admission, our patient had **NLI 34.2,** TLI 266.1, **SIMI 5,361.9,** which corresponds to a high risk of hospital death and is an indication for urgent heart surgery. Over time, the values decreased significantly: NLI — to 6.4, TLI — to 165.9, and SIMI — to 1,808.1, indicating stable satisfactory post-surgery period.

Neutrophils and platelets have a vital role to play in immune blood-clotting, including NET formation [26]. The key role of NET is to trap, neutralise and destroy pathogens [26]. NET dysregulation can contribute to pathological processes. Kumar S. et al. (2019) demonstrated the correlation between NET and sepsis severity [27]. A number of studies aimed at identification of a NET threshold value in order to evaluate unfavourable prognosis in various pathologies: NET ≥ 23 % — for sepsis, NET ≥ 16 % — for COVID-19, NET ≥ 12 % — for severe community-acquired pneumonia [28-30]. For IE patients, we had a NET threshold value of ≥ 14.2, i.e. a high risk of hospital death [31]. In this case study, NET upon admission was 14.7 %, indicating uncontrolled excessive inflammation and unfavourable prognosis, also confirming the need for urgent heart surgery.

Also, this clinical case study is unique for its additional analysis of the cellular composition of vegetations and resected valve tissue, in addition to a standard histological examination. The level of whole-cell pro-inflammatory macrophages in the surgical material was surprisingly low. We assume we have witnessed the "macrophage failure" phenomenon [32], resulting from increased macrophage destruction under the influence of NETs and uncontrolled release of pro-inflammatory cytokines, causing severe valve damage and the need for heart surgery.

Challenging management of almost every patient with IE in real-time clinical settings shaped the attitude of the national and international scientific communities of cardiologists in support of a multidisciplinary approach [1, 2]. The positive impact of such an approach for the patient in this case study was obvious; it affected the correct evaluation of indications for surgery and selection of the timing on the basis of comprehensive examination results. During hospitalisation, the patient had problems with antibacterial therapy caused by vancomycin-induced AKI, which required replacement of vancomycin with teicoplanin (complicated by urticaria), then with linezolid. During hospitalisation, the patient's kidney function restored completely, and the outcome of therapy was generally favourable.

Conclusion

The young patient had clinical acute suspected IE of tricuspid valve (one major and two minor Duke criteria — fever and vascular factor) with gigantic vegetation (28 mm), complicated by valve insufficiency, recurrent embolic syndrome in the pulmonary artery with pulmonary hypertension. Histopathological criteria confirmed the diagnosis of IE; however, aetiology was established only on the basis of PCR test results of blood and resected valve tissue. High NET, NLI and SIMI levels corresponded to a very high risk of death and necessitated an urgent surgery. Timely surgery resulted in patient recovery; all calculated inflammation indices and NET value decreased, indicating a low risk of complications. Low levels of undamaged pro-inflammatory CD 86+ macrophages in resected TV tissue is a sign of excessive macrophage destruction with release of numerous pro-inflammatory cytokine, which resulted in rapid and severe TV damage. A multiplex approach was a key to successful therapy and full recovery of the patient. Therefore, state-of-the-art management of IE patients should

be comprehensive, with the use of up-to-date methods of aetiological and imaging diagnostics, and should aim at early identification of patients with unfavourable risks in order to apply an individualised approach to the traditional or cardiac management strategy.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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Pisaryuk A.S.: concept and design of the article, editing the text

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ОПЫТ ДВУХЛЕТНЕГО НАБЛЮДЕНИЯ ПАЦИЕНТА С БОЛЕЗНЬЮ ДЕРКУМА НА ФОНЕ ТЕРАПИИ МЕТОТРЕКСАТОМ

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Experience of Two-Year Observation of a Patient with Dercum Disease During Methotrexate Therapy

Резюме

Болезнь Деркума, также известная как болезненный липоматоз, нейролипоматоз, синдром Андера — редко встречающееся заболевание, главным клиническим проявлением которого является наличие болезненных образований подкожной клетчатки, с локализацией в различных частях тела: на конечностях, туловище, ягодицах. К возможным этиологическим факторам относят генетические мутации, наличие аномальных клеточных белков, эндокринные нарушения, изменения со стороны нервной системы. Чаще это заболевание встречается среди женщин старше 35 лет. Случаи развития болезни Деркума у детей и подростков встречаются редко. Пациенты с этим заболеванием зачастую имеют избыточную массу тела. Выделяют 4 типа болезни Деркума: генерализованная диффузная, генерализованная узловая, локализованная узловая, юкста-артикулярная. В некоторых случаях повышаются островоспалительные маркеры: скорость оседания эритроцитов, С-реактивный белок. В представленном клиническом случае также отмечен высокий уровень фактора некроза опухоли-α со снижением в динамике, что требует дальнейшего изучения прогностических возможностей данного биомаркера в оценке активности заболевания. Гистологические исследования подкожных элементов у пациентов с болезнью Деркума не имеют специфических изменений (морфологическая картина соответствует липоме). В литературе обсуждаются различные методы терапии, включающие липосакцию, массаж, а также нестероидные противовоспалительные препараты, глюкокортикоиды, метотрексат и др. Представленный клинический случай описывает раннюю диагностику болезни Деркума с проведением дифференциальной диагностики с панникулитами другой этиологии и достижение стойкой ремиссии на фоне терапии метотрексатом у пациентки 42 лет с жалобами на наличие болезненных локальных узелковых образований кожи верхних и нижних конечностей разного размера.

Ключевые слова: *болезнь Деркума, липоматоз, метотрексат, панникулит*

Конфликт интересов

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

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Abstract

Dercum disease, also known as painful lipomatosis, neurolipomatosis, Ander's syndrome, is a rare illness. The main clinical manifestation of this disease is the presence of painful formations of subcutaneous tissue, localized in various parts of the body: on the limbs, trunk, buttocks. Possible etiological factors include genetic mutations, the presence of abnormal cellular proteins, endocrine disorders, changes in the nervous system. This disease is more common among women over 35 years old. Cases of Dercum disease in children and adolescents are rare. Patients with this disease are often overweight. There are 4 types of Dercum disease: generalized diffuse, generalized nodular, localized nodular, juxta-articular forms. In some cases, acute inflammatory markers increase: the erythrocyte sedimentation rate, C-reactive protein. A high level of tumor necrosis factor-α with a decrease over time was also noted in the presented clinical case, it requires further study of the prognostic capabilities as a marker of disease activity. Histological examination of subcutaneous elements did not reveal specific changes (the morphological picture corresponds to lipoma). Various methods of therapy are discussed in the literature, including liposuction, massage. Non-steroidal anti-inflammatory drugs, glucocorticoids, methotrexate also may be used. *The clinical case presents a 42-year-old female patient with complaints of the presence of painful local nodular skin lesions of various sizes on the upper and lower extremities. We describe the early diagnosis of Dercum disease with differential diagnosis with panniculitis of other etiologies and the achievement of stable remission against the background of methotrexate therapy.*

Key words: *Dercum disease, lipomatosis, methotrexate, panniculitis*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Experience of Two-Year Observation of a Patient with Dercum Disease During Methotrexate Therapy» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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ANCA — anti-neutrophil cytoplasmic antibodies, DD — Dercum disease, CRP — C-reactive protein, TNO-α –tumour necrosis factor-α

Introduction

Dercum disease (DD), also known as lipomatosis, lipomatosis of the nerve, Ander syndrome, is a rare disease of unknown origin, the main characteristic of which is painful subcutaneous tissue lesions in various locations [1]. The first to describe this pathology was American doctor Francis Xavier Dercum, who in 1888 published two articles and proposed the term "lipomatosis dolorosa" for the disease, which was later named after him [1]. There is no specific genetic basis for DD. However, it is argued that there is family predisposition for "lipomatosis dolorosa"; this condition was described in immediate family members who had liposome proteins of a specific structure. Also, in 1973 Cantu J.M. et al. proposed to characterise DD as an autosomal dominant disease; however, in opposition to this, numerous authors point out the sporadic nature of this pathology [1]. Initially, endocrine disorders (dysfunctional thyroid gland, pancreas, hypophysis) were believed to be the aetiological factor of DD. However, in the first half of the XX century this idea was abandoned because there were no clinically significant laboratory abnormalities of the endocrine system [2-6].

One of the most significant manifestations of the disease is a very intense pain syndrome, which can be associated with higher activity of the sympathic nervous system, resulting from the presence of such provoking factors as hypoxia, production of some substances (protons, serotonin, substance P, etc.), which affect pain receptors, vasospasm, inflammatory reactions, necrosis [7].

Currently, lipid metabolism defects attract attention as an element of DD pathogenesis, but this mechanism is not clear. In their academic paper, Blomstrand R. et al. (1971) described decreased synthesis of monounsaturated fatty acids in affected adipose tissue vs. healthy tissue. However, another study contains opposite results: monounsaturated fatty acid levels were higher in patients with DD (Fagher B. et al., 1991) [2, 8].

There are reports of decreased reaction of the affected adipose tissue to noradrenaline and anti-lipolytic effects of insulin [5, 9].

In periarticular DD, adipose fascia inflammation impairs lymph flows in these areas, causing fluid accumulation in interstitial tissue and fascia induration and development of fibrosis around fat lobules and making them palpable. Pain in these lesions is a result of inflammation in fascia and nerves. It is also believed that development of this disease can be related to poor tissue regeneration following a traumatic injury, which causes chronic inflammation and damage to adjacent structures [10].

The incidence is higher in females at a ratio of 5–30:1 [11]. Disease manifests at the age of 35–50 years old. There are just few reports on DD in children and adolescents [12].

In 1901, J. Roux et al. were the first to propose diagnosis criteria, which included four clinical symptoms:

- Painful subcutaneous lesions;
- Generalised obesity;
- Asthenic syndrome;
- Mental symptoms (depression, dementia, confusion) [13].

Later, these criteria were modified: mental symptoms and asthenia were removed, probably because these symptoms were observed in a majority of patients with DD. In 1910, Stern H. separated two fundamental signs — obesity and painful adipose lesions [14].

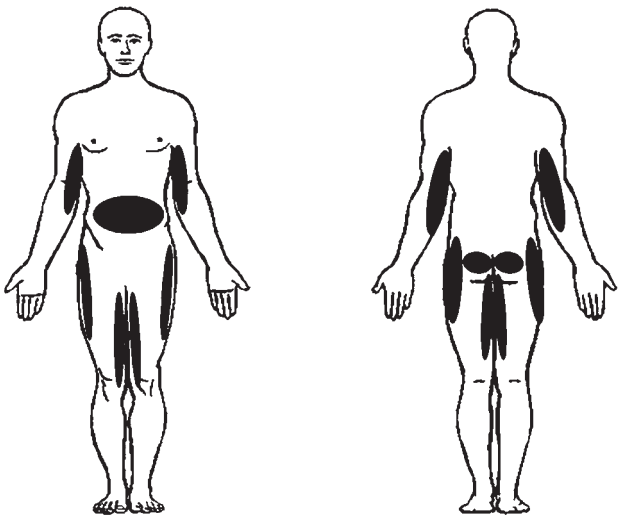

Figure 1A. *The most common localization of the formations in Dercum's disease (cited from [18]).*

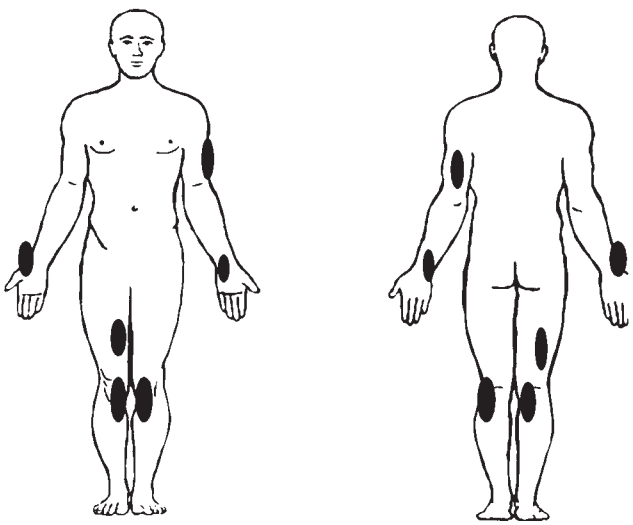

Figure 1Б. *Localization of the formations in the presented patient*

Emotional fluctuations and asthenic syndrome are considered to be sequelae of the existing pain syndrome and obesity, which can cause sleep disturbances and fatigue [15].

DD is associated with severe burning pain; however, some patients experience mild discomfort up to paroxysmal pain episodes. Usually, skin above lesions is normal.

Lesions can be located in any part of the body; gluteal region involvement is reported in 70 % of cases [1]. According to a questionnaire by Herbst K.L. et al. (2007) of over 100 patients with confirmed DD, this disease can affect buttocks, extremities, and trunk (Fig. 1A) [16].

Trentin C. et al. (2008) describe a case where DD caused mastalgia in a patient, who was suffering from multiple painful lesions in her breast [17].

The risk group of this disease includes individuals with various metabolic disorders (overweight, impaired glucose tolerance). In addition to painful lesions in adipose tissue, patients with DD can experience an array of symptoms. These include weakness, bruising, sleep disturbances, shortness of breath, joint pain, nerve and mental symptoms, such as mood swings, depression, epilepsy, disorientation, and dementia [5]. Neurological symptoms are often associated with metabolic disorders in obese patients, e.g. diabetic neuropathy. There is a report of septic shock in a patient with DD caused by lipoma necrosis after lymphatic oedema resulting from constriction of lymph and blood vessels in the affected area [19].

Literature sources contain contradictory information on the role of inflammatory biomarkers in DD diagnosis: increased C-reactive protein (CRP) levels were recorded in 33 % of patients, while erythrocyte sedimentation rate was higher than normal values in 38 %. However, direct correlation between DD and high values of these parameters has not been proven, because some patients participating in the study had autoimmune comorbidities, which could cause higher ESR and CRP values [16].

According to Herbst K.L. et al. (2009), fine-needle aspiration did not show any morphological differences between DD lesions and lipomas. Biopsy samples contained excessive connective tissue [1].

Currently, there is no approved unified classification of DD. Three versions of DD classification are used. The first one is the classification by V. Giudiceandrea (1900), where three types of pathologies were identified (Table 1) [20].

A modification of the mentioned classification is the classification by J. Roux et al. (1901) (Table 2) [13].

The most up-to-date is the classification proposed by E. Hansson as modified by Kosseifi S. et al. (2010) (Table 3).

Table 1. *Classification of Decrum disease types (according to V. Giudiceandrea) [20].*

Type	Description
Type 1. Nodal form	Localization of lipomas of various sizes on the upper and lower extremities, back, chest. Formations can merge with each other
Type 2. Diffuse form	Diffuse pain in adipose tissue of a symmetrical nature
Type 3. Mixed form	The presence of fatty formations and diffusely painful adipose tissue at the same time

Table 2. *Classification of Decrum disease types (according to J. Roux et al.) [13]*

Type	Describtion
Type 1. Nodal form	Many painful lipomas
Type 2. Limited diffuse type	Painful fatty deposits (often on the inside of the knees and/or thighs)
Type 3. Generalized diffuse type	Diffuse pain in adipose tissue (often in the limbs and trunk)

Table 3. *Classification of Decrum disease types (according to E. Hansson et al.) [14]*

Type	Describtion
Type 1. Generalized diffuse form	Painful sensations in adipose tissue, very small fat deposits localized in all areas of the body are determined. Pain can occur in areas without visible compactions
Type 2. Generalized nodular form	Painful sensations at the site of localization of lipomas located in several parts of the body
Type 3. Localized nodular form	Painful lipomas in certain areas of the body
Type 4. Juxta-articular form	Painful folds of fat inside or around large joints (knees, hips or elbows)

DD should be differentiated from fibromyalgia, cellulitis, endocrine disorders, primary mental disorders, multiple symmetrical lipomatosis (Madelung's disease), multiple family lipomatosis, Proteus syndrome and benign adipose tissue tumours [12].

Clear guidelines for the management of DD are not available, and healthcare providers have to select a strategy on their own. In some cases, lipoplasty has favourable effects with pain syndrome regression, confirmed in a study by Hansson E. et al. (2012) [14]. Another non-drug therapy is massage of adipose tissue and fascia, which sometimes also helps to reduce pain syndrome [21].

Given the presence of pain syndrome, drug therapy involves pain management: use of intralesional and intravenous lidocaine, non-steroidal anti-inflammatory drugs. Also, therapy can include pregabalin, interferon α-2b, glucocorticoids, metformin, as well as infliximab and methotrexate [1].

DD is a very rare finding (less than 100 PubMEd publications, access date: August 17, 2024), since there are no large-scale studies of this disease. Available publications are either clinical case studies or literature reviews. In Russian literature, there are just individual clinical cases of this condition [22].

The objective of this clinical case study is to demonstrate the experience with DD diagnosis and successful methotrexate therapy.

Clinical case study

On May 04, 2022, a female patient, 42 years old, visited MEDSI Medical Centre in Michurinskiy Avenue (Moscow) and complained of painful subcutaneous lesions in her right knee and proximal phalanges of her right hand, low-grade fever for a month, episodes of significant weakness, and pain in her both feet. She was examined by a surgeon, thyroid specialist, rheumatologist. Subcutaneous lesions appeared within the past month. Also, the patient reported short-term painful episodes of weakness with fever up to 37.0 °C.

According to the medical record, the patient has degree 1 obesity (158 cm, 75 kg, BMI 30 kg/m^2), insulin resistance, hypothyroidism caused by chronic autoimmune thyroiditis. She takes L-thyroxine prescribed by the thyroid specialist.

The patient used unprescribed non-steroidal anti-inflammatory gels; no favourable effect. Initial examination: satisfactory condition; clear skin and visible mucosa; joints: unremarkable. Blood pressure: 132/65 mm Hg, heart rate: 78 bpm. Respiratory and GI systems: unremarkable. As for the objective status, the patient had oedema of both shanks (up to the lower third), palpable local nodular lesions of the skin of upper and lower extremities (various diameter, the largest measuring up to 3 cm), moderately painful (Fig. 1B). Calcaneal region allodynia was diagnosed. Additional examinations were performed.

Complete blood count and urinalysis results were normal. Blood biochemistry demonstrated 3-fold increase in CRP values to 16.39 (reference values are provided in brackets: 0–5) mg/L (Table 4), uric acid to 454.6 (142–340) μmol/L. Tumour necrosis factor-α (TNF-α) of 12 (0–6) pg/mL was recorded. Creatinine, liver enzymes and glucose levels were normal.

An ultrasound examination of soft tissue of the knee showed irregular areas of lower echogenicity, measuring 30x9x36 mm, 2 mm deep from the skin surface. An ultrasound examination of the proximal phalanges of the third finger of the right hand (dorsal surface) and second finger of the right hand (palmar surface) showed similar changes, measuring 5×4×3 mm. Colour Doppler visualisation: unremarkable. The patient did not have synovitis of the knee and proximal phalanges of the second and third fingers of the right hand.

Right knee CT: clinically unremarkable.

During outpatient follow-up for two months, the patient had increasing pain in individual lesions on her fingers, neuropathic pain in heel region (Table 5), significant weakness lasting for over two hours, which prevented the patient from doing household chores. The patient managed weakness on her own.

When the clinical representation of the disease was analysed, episodes of asthenic, pain syndrome, painful subcutaneous lesions (panniculitis syndrome) were noted. Differential diagnoses ruled out TB, parasitic infections, sarcoidosis, upper and lower extremity panniculitis.

Abdominal ultrasound revealed gallbladder polyps. Mammography, gastroscopy and colonoscopy, as well as skeletal examination to rule out rare bone conditions did not show any pathologies.

There were no markers of autoimmune pathology (anti-neutrophil cytoplasmic antibodies (ANCA), cyclic citrullinated peptide antibodies, antinuclear antibodies, HEp-2 cell antinuclear antibodies).

Based on the medical record, physical examination results, DD was added to differential diagnosis.

Based on the clinical, laboratory and instrumental data obtained during the two months after the initial visit, the final diagnosis was made: Dercum disease of the upper and lower extremities (onset in April 2022), periarticular form, associated with psychopathic pain syndrome and moderate inflammation (high CRP levels). Primary hypothyroidism due to chronic autoimmune thyroiditis, medically compensated. Degree 1 obesity.

Methotrexate therapy was initiated: 15 mg SC once a week, then the dose was increased in 5 mg increments once every three weeks to 25 mg. L-thyroxine was continued under supervision of a thyroid specialist. Three months later, favourable effects were observed: clinical signs disappeared, CRP levels normalised, and TNO-α decreased to 8 ng/mL.

In this clinical case study, methotrexate was discontinued after stable remission for one year. The patient was in remission for six months without GC therapy.

The patient is followed up by a rheumatologist and undergoes follow-up laboratory blood tests (complete

Table 4. *Investigations*

Test, units of measurement	The first visit	The second visit (in 1 month)	Reference values
C-reactive protein, mg/l	25,7	7,4	0-5,0
Antibodies to complement factor C1q, U/ml	0,84		0-10,0
C3 complement component, g/l	1,7		0,9-1,8
C4 complement component, g/l	0,46		0,1-0,4
Interleukin-1 beta, pg/ml		<5,00	<5,00
Interleukin-6, pg/ml		2,0	0-5,9

Table 5. *Diagnostic criteria for chronic neuropathic pain (cited from [23])*

	Diagnosis points	What the patient had
A.	A.1. History of disease or injury to the somatosensory nervous system. A.2. Neuroanatomically logical (dermatomal) distribution of pain.	-
B.	The pain is accompanied by the presence of sensory symptoms with neuroanatomical distribution.	-
C.	Additional diagnostic tests may confirm damage or disease of the somatosensory nervous system that explains the pain.	-
D.	The pain is not explained by another medical condition that causes chronic pain.	+

Diagnostic criteria:
Presence of persistent or recurrent pain lasting ≥3 months and presence of at least points A and D.
The presence of points B and C increases the likelihood of the diagnosis.

blood count, CRP, alanine aminotransferase, aspartate aminotransferase, creatinine, glucose, glicated hemoglobin, thyrotropic hormone, urinalysis) once every three months; the results are within the normal range. In this case, the prognosis is favourable due to the early diagnosis, timely therapy initiation and good response to treatment.

Discussion

DD is a diagnosis by exclusion, an important aspect of which is differential diagnosis with numerous conditions. First of all, these are a group of panniculitis conditions [23]. In general, panniculitis is an inflammatory disease with extensive subcutaneous tissue involvement; also, the process can affect internal organs and locomotor system [24]. The distinguishing characteristic of DD is that the skin in visually unchanged, as opposed to erythema nodosum in sarcoidosis; also, there are no discharges on the skin, as in Weber-Christian disease (Table 6). Patients with DD do not show inflammatory changes in lesions on imaging (ultrasound, MRI).

To diagnose DD (criteria by Stern H., 1910), two symptoms must be present: generalised overweight or obesity and chronic pain in adipose tissue lasting for over three months. Both characteristics were present in this clinical case study, and the patient was diagnosed with the condition after a comprehensive differential diagnostic search.

DD is a diagnosis by exclusion, because the combination of symptoms described in this clinical case study is unique and extremely rare.

There are no specific laboratory tests to suspect DD. This patient had elevated TNO-α levels. Currently, there is no information on the pathogenetic correlation between TNO-α and DD. This can be an area of studies as a marker of this disease. The patient in this case study had a high CRP level, which normalised with the therapy; however, not all patients with DD have elevated CRP values [16].

Therefore, DD can be diagnosed in obese patients suffering from chronic pain in the adipose tissue, provided any other aetiology of changes is ruled out.

Table 6. *Diagnostic criteria for Weber-Christian panniculitis [25]*

Criteria		What the patient had
fever 38–39°C	1	–
the presence of dense painful formations mainly on the trunk, buttocks, thighs and limbs	1	+
joint pain	1	+
joint swelling	1	–
fatigue, weakness	1	+
headache	1	–
nausea	1	–
diarrhea	1	–

Diagnosis: triad — the presence of painful subcutaneous formations, fever, constant recurrence of these symptoms

Conclusion

Thus, a combination of panniculitis syndrome and significant asthenia and neuropathic pain is a specific manifestation of DD. DD should be differentiated from rheumatologic conditions, sarcoidosis, panniculitis of other origin. Awareness of healthcare providers of DD will ensure timely diagnosis and patient referral to a specialist for titration of therapy.

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ГИПЕРОСМОЛЯРНАЯ КОМА: ДИАГНОСТИЧЕСКИЕ СЛОЖНОСТИ НА КЛИНИЧЕСКОМ ПРИМЕРЕ

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Hyperosmolar Coma: Diagnostic Difficulties on the Clinical Example

Резюме

Гиперосмолярное гипергликемическое состояние является острым осложнением сахарного диабета, летальность при котором достигает 50 %. Одна из причин неблагоприятного исхода — несвоевременная диагностика, которая нередко обусловлена недостаточной осведомленностью врачей в отношении особенностей клинических и лабораторных проявлений данного диабетического осложнения. Гиперосмолярное состояние чаще развивается у пациентов старшего возраста с полиморбидностью, а в клинической картине преобладают неврологические симптомы, что также вносит сложности в диагностику и становится причиной диагностических заблуждений. В статье представлен клинический случай гиперосмолярного гипергликемического состояния, диагностика которого вызвала трудности на всех этапах, включая посмертное патологоанатомическое исследование. Первоначально предполагалось острое нарушение мозгового кровообращения, затем тяжелое состояние пациентки связали с острым инфарктом миокарда, а по результатам патологоанатомического исследования было сделано заключение о сепсисе и септическом шоке. Рецензирование истории болезни пациентки показало, что наиболее вероятным диагнозом было гиперосмолярное состояние вследствие декомпенсации сахарного диабета на фоне воспалительного процесса. Выраженная дегидратация пациентки, как причина ее сопорозного состояния, подтверждалась данными осмотра и лабораторно-инструментального исследования: сухость кожи и слизистых, малое количество мочи, признаки сгущения крови и преренальная острая почечная недостаточность. Вместе с тем отсутствие явных очаговых неврологических нарушений, клинически значимых изменений со стороны сердечно-сосудистой системы, лихорадки и нарушений гемодинамики не позволяли, на наш взгляд, связать тяжелое состояние пациентки с инсультом, инфарктом миокарда или септическим шоком. Дегидратация осложнилась развитием синдрома диссеминированного внутрисосудистого свертывания, желудочно-кишечным кровотечением и геморрагическим шоком с летальным исходом. Данный клинический случай свидетельствует о том, что в дифференциальной диагностике заболеваний ключевым подходом является анализ клинической картины с точки зрения патогенеза нарушений. Разбор подобных клинических ситуаций может служить для врачей подспорьем в вопросах диагностики гиперосмолярного состояния.

Ключевые слова: *гиперосмолярная кома, гиперосмолярное состояние, острая декомпенсация сахарного диабета*

Конфликт интересов

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

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Abstract

Hyperosmolar hyperglycemic state is an acute complication of diabetes mellitus, the mortality rate of which reaches 50 %. One of the reasons for the unfavorable outcome is untimely diagnosis, which is often due to insufficient awareness of doctors regarding the features of clinical and laboratory manifestations of this diabetic complication. Hyperosmolar state often develops in older patients with polymorbidity, and neurological symptoms predominate in the clinical picture, which also complicates diagnosis and causes diagnostic errors. The article presents a clinical case of hyperosmolar hyperglycemic state, the diagnosis of which caused difficulties at all stages, including postmortem pathological examination. Initially, acute cerebrovascular accident was assumed, then the patient's severe condition was associated with acute myocardial infarction, and based on the results of the pathological examination, a conclusion was made about sepsis and septic shock. Review of the patient's medical history showed that the most probable diagnosis was hyperosmolar state, which developed as a result of decompensation of diabetes mellitus against the background of the inflammatory process. Severe dehydration of the patient, as the cause of her soporous state, was confirmed by the data of examination and laboratory and instrumental examination:

dry skin and mucous membranes, small amount of urine, signs of blood thickening and prerenal acute renal failure. At the same time, the absence of obvious focal neurological disorders, clinically significant changes in the cardiovascular system, fever and hemodynamic disturbances did not allow, in our opinion, to associate the patient's severe condition with acute cerebrovascular accident, myocardial infarction or septic shock. Dehydration was complicated by the development of disseminated vascular coagulation syndrome, gastrointestinal bleeding and hemorrhagic shock with a fatal outcome. This clinical case demonstrates that in differential diagnostics of diseases a more reliable approach is the analysis of the clinical picture from the point of view of the pathogenesis of disorders. Analysis of such clinical situations can serve as an aid for doctors in diagnosing hyperosmolar state.

Key words: *hyperosmolar coma, hyperosmolar state, acute decompensation of diabetes mellitus*

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BP — blood pressure, APTT — activated partial thromboplastin time, BBC — blood biochemistry, DIC — disseminated intravascular coagulation, CT — computer tomography, INR — international normalised ratio, MRI — magnetic resonance imaging, CBC — complete blood count, ACVA — acute cerebrovascular accident, CRP — C-reactive protein, EGDS — esophagogastroduodenoscopy, RR – respiratory rate, HR — heart rate, ECG — electrocardiography, echoCG — echocardiography

Hyperosmolar hyperglycaemic state is an acute complication of diabetes mellitus, which manifests with marked hyperglycaemia and associated dehydration and altered state of consciousness. Unlike ketoacidotic hyperglycemic coma, this condition is approximately 10 times less common; at the same time, it is associated with high mortality rates, which can be as high as 50 %. One of the reasons is poor awareness of healthcare providers, making timely diagnosis challenging. Unfortunately, there are just a few articles and clinical case studies on this topic.

Hyperosmolar coma develops in type 2 diabetes mellitus, which is associated with partially preserved insulin secretion, therefore no ketones are present. It is induced by factors contributing to dehydration: acute GIT pathology associated with vomiting and diarrhoea, severe inflammation with fever, restricted fluid intake, and a number of other factors. Hyperglycaemia can be more severe than in ketoacidotic coma, and the values can reach 60–80 mmol/L, because in the presence of ketones, the patient does not have vomiting or nausea, which would make them seek medical attention sooner. It results in more severe dehydration, and fluid deficiency can exceed 10 litres.

Patients in hyperosmolar state are usually elderly, which is partially a result of age-related changes in water-electrolyte metabolism regulation, predisposing them to dehydration: reduced thirst and poorer renal concentrating ability. In the first instance, severe rehydration affects the brain, that is why clinical symptoms are dominated by neurological signs, which are often mistakenly interpreted as cerebrovascular events. A typical sign is altered state of consciousness, spanning from confusion and disorientation to coma, transient focal symptoms — facial asymmetry (downturning mouth), hemianopsia, hemiparesis, hemiplegia, etc.; seizures are also possible. At the same time, nervous system involvement is usually beyond the clear focal syndrome; cerebral damage is more pronounced than local signs; clinical manifestations are unstable and resolve as soon as hyperosmolarity is treated. Brain computer tomography is advisable if neurological symptoms persist despite improvement in hyperosmolarity [1].

Diagnosis of hyperosmolar hyperglycaemic state should take into account clinical and laboratory signs of dehydration: dry skin and mucosa, reduced diuresis and dark. concentrated urine. Complete blood count shows elevated haematocrit and RBC levels. Blood biochemistry results show hyperazotaemia resulting from acute renal failure, in addition to hyperglycaemia. Blood sodium levels are also elevated; test results should be adjusted for hyperglycaemia, because higher blood glucose levels results in higher natriemia values.

The following formula is used to evaluate adjusted sodium levels:

Adjusted sodium levels = measured sodium+1.6 (glucose mmol/L–5.5)/5.5.

Blood biochemistry results and adjusted sodium levels can indicate plasma osmolarity, with the normal values being 285–295 mOsm/L; while in hyperosmolar state, they can be as high as 330 mOsm/L and above.

Plasma osmolarity = 2 (sodium mmol/L+potassium mmol/L)+glucose mmol/L.

Unlike ketoacidotic coma, hyperosmolar state is not associated with metabolic acidosis; however, in some cases, mild acidosis can be possible because of lactic acid accumulation, resulting from impaired microcirculation and tissue hypoxia.

Severe dehydration with pronounced microcirculation impairment causes disseminated intravascular coagulation (DIC) syndrome, which is seen in coagulation profile. DIC leads in gut ulceration, which can be complicated by bleeding.

Usually the cause of death is acute circulatory collapse; postmortem examination often shows advanced thrombosis resulting from disseminated intravascular coagulation.

The key therapeutic strategies are fluid replacement, insulin therapy and potassium level adjustment. Fluid replacement starts with administration of 1 litre of normal saline solution (0.9 %), then adjusted sodium levels are evaluated. If the results exceed 165 mmol/L, then 2.5 % glucose solution is used. Where sodium concentrations are 145–165 mmol/L, it is recommended to initiate infusion therapy with hypotonic (0.45 %) NaCl solution. Once adjusted sodium levels reach 145 mmol/L, saline administration continues. Taken high insulin sensitivity in DM2, insulin therapy should be low-dose (0.5–2 U/h). The target blood glucose level is 13.9–16.7 mmol/L, i.e. higher than in diabetic ketoacidotic coma, where day 1 glycaemic target is 13–15 mmol/L due to a higher risk of cerebral oedema in case of hyperosmolarity. Protection against cerebral oedema is also taken into account in recommendations on the rate of glycaemia reduction: 4 mmol/L/h, plasma osmolarity: 3–5 mOsm/L/h; and sodium levels: 10 mmol/L/day.

Potassium deficiency is usually more pronounced than in ketoacidotic coma because of more severe osmotic diuresis. Potassium deficiency is corrected with blood potassium testing. Recommended concomitant treatment includes broad-spectrum antibiotics due to a high risk of infection, as well as low molecular heparins due to a high risk of blood-clotting [2, 3].

Case study

Female patient R., 74 years old, brought in by the ambulance on August 28, 2021 in semicoma. Her condition had been deteriorating for the past 7–10 days, with increasing atony and lethargy, up to no reactions, which was the reason to call the ambulance. According to the patient's daughter, the patient had had type 2 diabetes mellitus for 25 years, arterial hypertension — for 10 years; four and two years before admission, she was diagnosed with dementia and arrhythmia, respectively. During the past two years, blood sugar levels were corrected with basal-bolus insulin therapy; for the cardiovascular condition, the patient was taking angiotensin-converting enzyme inhibitor (lisinopril), beta blocker (bisoprolol) and antiplatelet (acetylsalicylic acid); for dementia — neurotropic drug (memantine). For the past year, the patient had a medical attendant caring for her.

Upon admission, the condition was severe; level of consciousness — semicoma. Examination revealed dry skin and tongue, reduced skin tightness. Blood pressure (BP) was 100/75 mm Hg; heart rate (HR) — 65 bpm; respiratory rate (RR) — 17/min; O2 saturation — 96 % (with oxygen support); body temperature: 36.4 °C.

Complete blood count (CBC) showed elevated RBC count of 6.34×10^{12}/L (up to 4.7×10^{12}/L; reference values are given in brackets), Hb — 177 g/L (up to 140), hematocrit — 52.4 % (up to 42), WBC — 22.8×10^{9} (up to 8.5), and low platelets count — 154×10^{9}/L (from 200). Blood biochemistry (BBC) showed elevated blood glucose levels — 55.96 mmol/L (up to 5.9), creatinine — 244 μmol/L (up to 84), urea — 29.64 mmol/L (up to 6.7), sodium — 151 mmol/L (up to 145), C-reactive protein (CRP) — 98.07 mg/L (up to 5), lactic dehydrogenase — 453.1 IU/L (up to 230), aspartate aminotransferase — 81.6 U/L (up to 35), creatine phosphokinase — 394.8 IU/L (up to 170). Coagulation profile showed elevated activated partial thromboplastin time (APTT) — 48.4 s (up to 37), APPT index — 1.51 (up to 1.2) and international normalised ratio (INR) — 1.25 (up to 1.2). Urinalysis results: dark urine, glucosuria up to 20 mmol/L, protein traces — 0.033 g/L, no acetone.

Electrocardiography (ECG) showed atrial fibrillation 85–180 per minute without any signs of damage. An ultrasound examination revealed multiple stones in gall bladder opening, elevated echogenicity and diffuse structural inhomogeneity of pancreas, uneven kidney contour, uneven renal parenchyma and diffuse echogenicity heterogeneity. Small amount of urine in bladder. Brain and chest computer tomography (CT): unremarkable.

A preliminary diagnosis was made on the basis of examination and test results. Primary diagnosis: Complex origin encephalopathy (dysmetabolic, residual) with moderate cognitive damage, social and domestic maladaptation, decreased level of consciousness (semicoma). Acute cerebrovascular accident (ACVA) cannot be ruled out. Secondary diagnosis: Stage III hypertensive disease, risk 4. Type 2 diabetes mellitus, insulin therapy. Chronic kidney disease C4. Ischaemic heart disease with rhythm disturbances. Tachysystole atrial fibrillation. Complications: Chronic heart failure 2A.

Based on the diagnosis, intensive care was initiated in ICU.

Next day (August 29, 2021) the patient had black faeces; she was examined by the on-call surgeon and underwent esophagogastroduodenoscopy (EGDS), which showed acute erosive esophagitis and recent bleeding. Antiulcer and anticoagulation reversal therapy was recommended.

It is worth noting that despite recent bleeding, blood draws dated August 29, 2021 and August 30, 2021 showed

persistently high levels of RBC, Hb and haematocrit. WBC levels remained high as well, while platelet count decreased to 80×10^9/L (should be at least 200). Blood biochemistry still showed hyperazotaemia, hyperenzymemia, and high CRP levels. Blood sodium concentration was 158 mmol/L (up to 145). Troponin I test came back positive.

On hospitalisation day three (August 30, 2021), neurological symptoms included restricted active movements, more in the right arm. Ischaemic ACVA of the left carotid pool was diagnosed. In order to confirm the diagnosis, magnetic resonance imaging (MRI) and echocardiography (echoCG) were performed. MRI results showed individual subcortical ischaemia foci in the right occipital and parietal lobes (infarctions). Atrophic changes in cerebral hemispheres. EchoCG results: induration of ascending aorta, coronary tendons and aortic and mitral valve cusps with calcifications. Dilated left atrium. Left ventricle myocardial hypertrophy. Left ventricle diastolic dysfunction.

Based on the clinical symptoms and changes seen on MRI scans, the diagnosis was corrected; primary diagnosis: ischaemic ACVA of both carotid pools, cardioembolic subtype, with right-sided hemiparesis, motor aphasia, pseudobulbar syndrome.

The patient was treated with infusion therapy (sterofundin), antihyperglycemic drugs (insulin), diuretics (furosemide), antimicrobials (moxifloxacin, cefotaxime), metabolic therapy (mexidol, ceraxon), lipid-lowering drugs (atorvastatin), proton pump inhibitor (omez), anticoagulants (heparine), beta blocker (metoprolol), and received enteral feeding (Nutricomp, water). Infusion therapy amounted to 1,500 to 2,150 mL/day.

Follow-up CBC dated August 31 and September 01, 2021: elevated RBC and WBC levels and low platelet count. BBC results: persisting values of nitrogenous waste, enzymes, CRP and sodium, the concentration of which was 150 to 163 mmol/L (up to 145). Coagulation profile: even worse coagulation system impairment — APTT was 116.5–168 s (up to 37), APTT index — 3.6–5.3 (up to 1.2), INR — 2.6 (up to 1.2), Quick's value — 38 % (NLT 75).

At 08.00 a.m. on hospitalisation day five (September 02, 2021), the patient had loose stool with haemorrhagic contents; body temperature rose to 37°C, RR — to 20 per minute, and HR — to 90 bpm; BP dropped to 88/59 mm Hg. Pressor agent dopamine 10 μg/kg/min was started for haemodynamic support. EGDS was performed, which showed coffee grouts-like stomach contents (up to 20 mL); no active bleeding was observed during examination; conclusion: erosive haemorrhagic esophagitis, atrophic hyperplastic gastritis. The patient was examined by a surgeon, who diagnosed acute erosive esophagitis with recent bleeding. At 08.45 a.m., clinical death and asystole were recorded; resuscitation was ineffective. The patient was pronounced dead at 09.15 a.m.

In the postmortem report, the primary diagnose was revised and changed to ischaemic heart disease, acute myocardial infarction of unknown location dated September 02, 2021, complicated by cardiogenic shock. Concurrent diagnosis: erosive haemorrhagic esophagitis with gastrointestinal haemorrhage of unknown origin and grade III haemorrhagic shock.

Postmortem examination showed multiple apical abscesses of maxilla and mandible, as well as numerous organ damage: necrotising nephrosis, centrolobular haemorrhage in the liver, acute erosive ulcerative gastroenteritis, gastrointestinal haemorrhage (approximately 300 mL of blood clots in intestine postmortem), subpleural bleeding in the lungs, myocardial necrosis area on the posterior left ventricle wall (type 2), 3.5×2 cm, 3–5 days old, liquid blood in heart cavities and large vessels, haemorrhage in cortex of kidneys, focal haemorrhage in adrenals, acute general congestion, pulmonary oedema, cerebral oedema.

Discrepancy between the clinical and postmortem diagnosis was recorded. According to medical examiners, the primary diagnosis was acute purulent periodontitis with odontogenic sepsis, systemic inflammatory response syndrome (WBC dated September 02, 2021 — 22.8×109/L), multiple organ damage, disseminated coagulation syndrome in hypocoagulation phase, pulmonary and cerebral oedema; cause of death: septic shock.

The final diagnoses, both clinical and postmortem, require revision.

Discussion

In this clinical case study, the clinical manifestations in the patient were mostly cerebral, whereas signs of focal damage appeared on hospitalisation day three and did not correspond to the degree of impairment of consciousness; that is why ACVE was unlikely, which was confirmed with CT, MRI and postmortem examination results. The severity of the patient's condition could not be a result of myocardial infarction, taken preserved haemodynamics, no ECG and echoCG signs of myocardial damage up to day 5 of follow-up, when the patient died. These findings necessitated the search for metabolic causes of the severe condition of the patient.

The diagnosis "odontogenic sepsis with septic shock" as the primary cause of the disease is also plausible, given the lack of fever and impaired haemodynamics in the patient in semicoma. As far as leukocytosis is concerned, its bacterial origin is inconclusive because of the lack of inflammatory changes seen in complete blood count results (elevated erythrocyte sedimentation rate and left deviation).

The concurrent diagnosis stated in postmortem report needs attention: "erosive haemorrhagic esophagitis with gastrointestinal haemorrhage of unknown origin and grade III haemorrhagic shock". As a matter of fact, haemorrhagic contents of faeces with drop in BP is a sign of massive blood loss. The consecutive asystole implies that the haemorrhagic shock was the cause of death. It is likely that gastrointestinal haemorrhage was caused by DIC syndrome.

The following sequence of events can be suggested.

Acute purulent periodontitis resulted in diabetes mellitus decompensation and marked hyperglycaemia. Apparently, late call for medical assistance was caused by cognitive disorders in the patient, her sensory diabetic neuropathy after 25 years of diabetes mellitus, which disguised the pain syndrome, and by probable misjudgement of the patient's health condition by caregivers. Severe hyperglycaemia up to 55.96 mmol/L was the cause of severe dehydration and hyperosmolar state. Dehydration was confirmed during examination: dry skin with decreased tightness, dry tongue, dark urine, as well as laboratory and instrumental test results — high RBC count, high levels of nitrogenous waste, enzymes, sodium; small amount of urine in the bladder.

High WBC count could also be caused by dehydration and tissue damage resulting from impaired microcirculation. Besides, high WBC values could be induced by blood loss, which could also happen before hospitalisation, confirmed by black faeces on hospitalisation day two and finding ulcerative damage to esophagus mucous seen during EGDS. Blood loss worsened dehydration, and RBC counts remained high because of severe dehydration.

Using the above formulae, adjusted sodium levels upon admission were 160.8 mmol/L, whereas the upper limit of normal is 145; plasma osmolarity was 389.52 mOsm/L, with the reference value being up to 295. Significantly higher osmolarity resulted in severe brain tissue dehydration and semicoma, as well as in impaired microcirculation and DIC syndrome with blood clots, consumption thrombocytopenia, and poor coagulation profile. These damages caused areas of infarction in the brain, myocardium and erosive ulcerative damage to GIT with haemorrhagic shock. Although the postmortem examination showed approximately 300 mL of blood, which is not a fatal blood loss, the severe condition of the patient as well as her elderly age can make her highly susceptible to less blood loss.

This clinical case demonstrates challenging diagnosis of hyperosmolar state, despite involvement of various specialists and advanced laboratory and instrumental capacities. We believe that this is an example of the significance of clinical interpretation taking into account pathological mechanisms [4, 5]. Understanding the clinical symptoms makes it possible to avoid both overestimation and underestimation of laboratory and instrumental results, as well as diagnostic misconceptions, including hyperosmolar state.

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