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МОНОКЛОНАЛЬНАЯ ГАММАПАТИЯ РЕНАЛЬНОГО ЗНАЧЕНИЯ: МОРФОЛОГИЧЕСКИЕ ВАРИАНТЫ ПОРАЖЕНИЯ

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Monoclonal Gammapathy of Renal Significance: Morphological Variants of Lesion

Резюме

В статье рассматривается понятие моноклональная гаммапатия ренального значения, которое объединяет различные почечные заболевания, вызванные отложением моноклонального иммуноглобулина и/или их компонентов в клубочках и тубулоинтерстиции. Данная нозологическая группа была выделена из группы моноклональная гаммапатия неопределенного значения (в 2012 году). Представлены данные по изучению морфологического поражения почек, ассоциированного с моноклональной гаммапатией ренального значения. Спектр почечных заболеваний при моноклональной гаммапатии ренального значения разнообразен, и его классификация основана на локализации почечных поражений в клубочках, канальцах, интерстиции сосудов и стромы, а также особенностью отложения иммуноглобулинов (организованные и неорганизованные). Биопсия почки показана в большинстве случаев для определения локализации поражения, оценки его тяжести и прогноза выживаемости для пациента. Диагностика требует интеграции морфологических изменений с помощью световой микроскопии, иммунофлуоресценции, электронной микроскопии, а в некоторых случаях применяют окрашивание моноклонального белка на изотипы Ig (окраска гематоксилином/эозином, реакция Шиффа (PAS-реакция), серебрение по Джонсу, окраска по конго-рот, трихромальная окраска по Массону). Ранняя диагностика и своевременное назначение гематологом и/или гематоонкологом клон-ориентированной терапии позволяет остановить прогрессирование злокачественного процесса и снижения функции почек. В свою очередь, нефролог, взаимодействуя с гематологом и/или гематоонкологом, ведет наблюдение за пациентом.

Ключевые слова: *моноклональная гаммапатия неопределенного значения, моноклональная гаммапатия ренального значения, моноклональный белок, нефробиопсия*

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Abstract

The article discusses the concept of monoclonal renal gammopathy, which combines various renal diseases caused by the deposition of monoclonal immunoglobulin and / or their components in the glomeruli and tubulointerstitium. This nosological group was identified within the group

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of monoclonal gammopathies of undetermined significance (in 2012). The data on the study of morphological kidney damage associated with monoclonal renal gammopathy are presented. The spectrum of renal diseases in monoclonal renal gammopathy is diverse, and its classification is based on the localization of renal lesions in the glomeruli, tubules, vascular interstitium and stroma, as well as the peculiarity of the deposition of immunoglobulins (organized and unorganized). Kidney biopsy is required in most cases to locate the lesion, assess its severity, and predict patient survival. Diagnostics requires the integration of morphological changes using light microscopy, immunofluorescence, electron microscopy, and in some cases, staining of monoclonal protein for Ig isotypes is used (staining with hematoxylin / eosin, Schiff stain (PAS reaction), Jones stain, Congo Red stain, Masson's trichromal stain). Early diagnosis and timely prescription of clone-oriented therapy by a hematologist and / or a hemato-oncologist can stop the progression of the malignant process and kidney malfunction. A nephrologist should monitor the patient, interacting with the hematologist.

Key words: *gammopathies of undetermined significance, monoclonal gammopathy of renal significance, monoclonal protein, nephrobiopsy, light microscopy, immunofluorescence microscopy, electron microscopy*

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AH — heavy chains, AHL — light and heavy chains, AL — light chains, C3GP — C3-glomerulopathy associated with monoclonal gammopathy, CKD — chronic kidney disease, CSH — crystal storing histiocytosis, GBM — glomerular basement membrane, HCDD — heavy chain deposition on disease, Ig — immunoglobulin, LCDD — light chain deposition on disease, LCPT — light-chain proximal tubulopathy, LHCDD — light and heavy chain deposition on disease, MGRS — monoclonal gammopathy of renal significance, MGUS — monoclonal gammopathy of undetermined significance, MIDD — monoclonal immunoglobulin deposition disease, MM — multiple myeloma, RRT — renal replacement therapy, TMA — thrombotic microangiopathy associated with monoclonal gammopathy, PGNMID — proliferative glomerulonephritis with monoclonal immunoglobulin deposits, TBM — tubular basement membrane

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) includes a number of diseases resulting from the malfunction of B-lymphocytes, leading to persistent pathological secretions of one clone of immunoglobulins or their constituent chains [1–7]. The term "monoclonal gammopathy of undetermined significance" (MGUS) was first used by R. Kyle et al. in 1978. MGUS is an asymptomatic pre-malignant clonal plasma cell proliferative disease. In some patients, this disorder remains benign for a long time; it is a precursor to multiple myeloma (MM) and other B-lymphocytic tumors. In 40% of patients with MGUS, the disease is benign for a long time; 50% of patients at different times have malignant progression; and 10% of patients develop diseases of a non-tumor nature due to the tissue and toxic effect of M-protein. Therefore, upon detection of paraproteinemia, it is hard to say whether or not it will transform into hemoblastosis over time [1–8]. Among other terms previously used to describe MGUS in practical medicine were idiopathic, non-myelomatous, discrete, cryptogenic and rudimentary monoclonal gammopathy, disimmunoglobulinemia, idiopathic paraproteinemia and asymptomatic paraimmunoglobulinemia [6, 7]. Until 2012, the term MGUS was widely used in the medical literature. N. Leung et al. found that some patients with MGUS may have clinical and morphological damage to the renal parenchyma with M-component. Following this discovery, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) proposed a new nosological group in modern nephrology and hematology: monoclonal gammopathy of renal significance (MGRS). The introduction of this term made it possible to differentiate the concept of MGUS and bring a number of clinical cases out of the "undetermined" group [1–8].

MGRS suggests a pathological condition with the characteristic features of the proliferation of a clone of B-cells or plasma cells producing nephrotoxic monoclonal immunoglobulin or its fragments (only a light chain and/or only a heavy chain) [9]. According to the diagnostic parameters, this group of patients cannot be classified as patients with multiple myeloma since this group is characterized by average plasma cells of the bone marrow (BM) — 2.2%, and M-protein level — 1.1 g/l [2–5]. A clone is a population of cells that arose from a single progenitor cell. It inherits all properties, including the ability to actively produce a monoclonal paraprotein (M-protein, monoclonal protein) or its part (only a light chain or only a heavy chain). The result of the effect of monoclonal protein on renal parenchyma is the steady progression of renal dysfunction up to the loss of organ function and a deterioration in the patient's life prognosis [1-9]. Kidney diseases associated with MGRS vary, and their number continues to rise. Therefore, the problem of MGRS remains extremely relevant for physicians of any specialty and is partly due to the lack of knowledge among professionals. A multidisciplinary approach is required to solve this

problem since this problem is most often between two specialties — hematology and nephrology [1–5].

Epidemiology

It has been proven that MGUS is detected in 4.2% in a group of people aged over 50; 5.3% — over 70, and up to 8% in men over 80. MGUS prevalence in African Americans is two to three times higher than in white people from the same population [7, 10]. The incidence of chronic kidney disease (CKD) also increases after the age of 60 [7, 11, 12]. Due to the rising age of the population, CKD development is based on progressive chronic diseases with the formation of nephrosclerosis (diabetes mellitus, arterial hypertension, and others). MGUS gradually results in CKD. Consequently, the same patient may have both manifestations of MGUS and CKD that are not associated pathogenetically [7].

Renal damage due to monoclonal paraprotein is a rare abnormality in the structure of kidney diseases. The prevalence of kidney pathology associated with any variant of monoclonal gammopathy is 7.5% among all patients who underwent diagnostic nephrobiopsy. MGRS was found in only 4% [2–5, 7]. Considering that this disease can only be confirmed via morphological verification of the diagnosis, MGRS is an orphan disease (10.2 cases per 100 thousand adults per year) [7].

Mechanisms and Structure of Kidney Damage in Monoclonal Renal Gammopathy

Pathogenetic mechanisms of the effect of paraprotein on the renal parenchyma vary and have not yet been fully studied. The pathogenesis of this process is due to the structural features and changes in the physicochemical properties of the paraprotein molecule itself and the action of abnormal monoclonal immunoglobulins or its fragments (only the light chain and/or only the heavy chain) (Fig. 1) [1, 4–5, 7].

The range of kidney damage associated with monoclonal gammopathy of renal significance is wide enough to include damage to different nephron sites: glomerulus, tubules; interstitium and vessels. Therefore, there is a variety of clinical manifestations of MGRS in the form of isolated syndrome or combination (arterial hypertension, nephrotic, etc.) [1–7]. Without additional examination methods, clinical and morphological damage in MGRS is difficult to distinguish from other renal pathologies not associated with monoclonal gammopathy. The type of kidney damage is determined by the innate structural characteristics and physicochemical properties of monoclonal immunoglobulin and not by the characteristics of the clone that produces it [1–7].

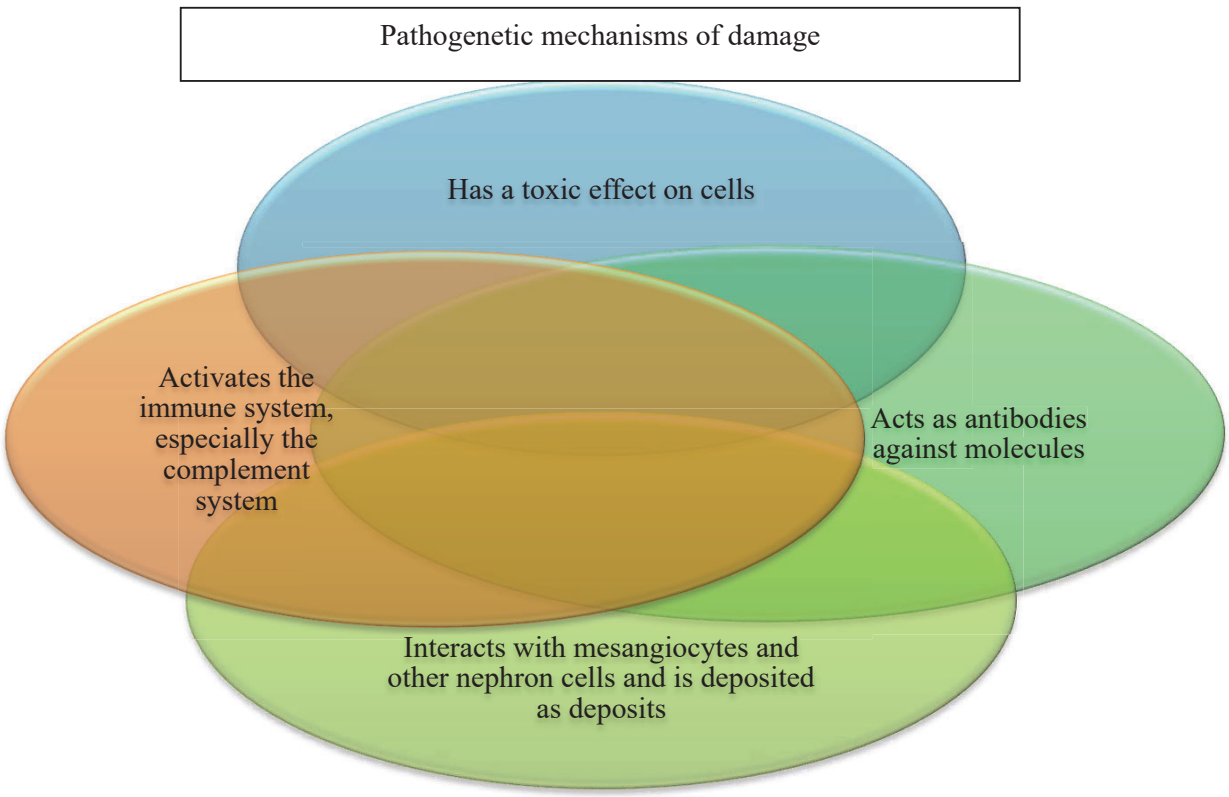

Figure 1. *Pathogenetic mechanisms of damage to the renal parenchyma by paraprotein*

Diagnosis of Monoclonal Gammopathy of Renal Significance (MGRS)

The establishment of the diagnosis of MGRS requires determining the specificity of kidney damage arising from the action of the monoclonal protein produced by the clone. Considering the significant variety of possible kidney damage, the morphological examination of renal tissue remains the main diagnostic method for MGRS (tab. 1) [1, 4, 6, 7].

The morphological analysis result emphasizes the specific features of the MGRS lesion in each case, and also provides information regarding the renal prognosis [1, 4, 6, 7].

In 2017, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) introduced a new classification for MGRS-associated kidney damage based on morphological results of studies (light microscopy, immunofluorescence studies with a full set of antibodies and electron microscopy). Kidney deposits were

Table 1. *Morphological diagnosis of monoclonal gammopathy of renal significance (MGRS)*

Light-optical research
Application of the following stains: · Hematoxylin/eosin · Schiff (PAS reaction) · Jones stain · Congo Red · Masson's trichrome stain
Immunofluorescence study
· Detection of deposits in the kidney parenchyma monoclonal immunoglobulin molecules (panel of antibodies to IgA, IgM, IgG (typing IgG), IgD, λ и κ chains, C3, C1q). · For the purpose of differential diagnosis of fibrillary glomerulonephritis which deposits may be congophilic, a DNAJB9 study is used. DNAJB9 is a protein of the chaperone family specific for this type.
Microscopic examination (ultrastructural)
Allows to assess the degree of damage and the nature of the deposits formed by the monoclonal protein (organized / non-organized).

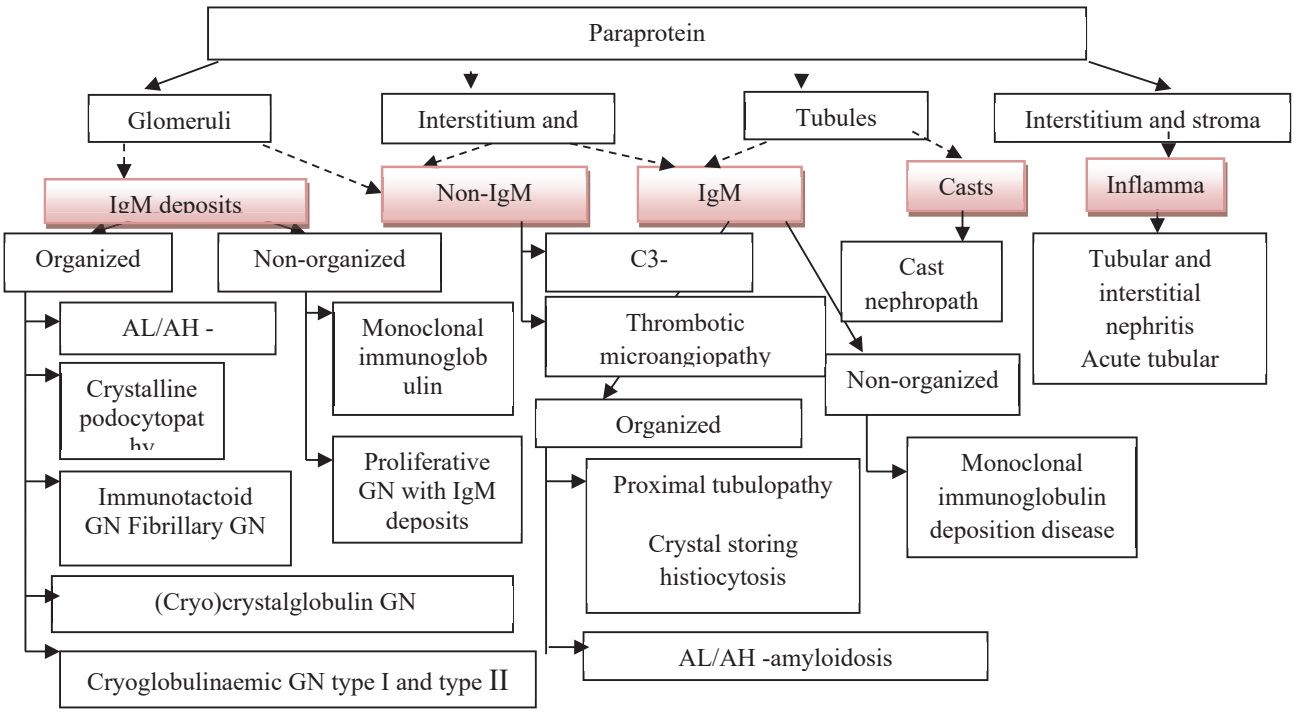

Figure 2. *Pathological variants of renal damage due to paraprotein (adapted from Smirnov A.V., Afanasyev B.V., Poddubnaya I.V. et al., 2020)*

originally classified into the following categories: organized, unorganized and non-immunoglobulin gammopathies [4, 6, 7, 13, 14]. Two additional subcategories were added to the 2017 classification [13]. The subcategory of thrombotic microangiopathy (TMA) and the subcategory of pathological deposits that are ultrastructurally similar to monoclonal gammopathies, but are not always them, have been added to the category of non-immunoglobulin gammopathies (Fig. 2) [7, 14].

Damage with Organized IgM Deposits

Organized deposits of monoclonal immunoglobulins are divided into fibrillar (in amyloidosis), microtubular (in cryoglobulinemic and immunotactoid nephritis), crystalline and/or inclusive forms in proximal light chain tubulopathy, with or without Fanconi syndrome, and with CHS [4, 6, 7]. This pathology is detected via nephrobiopsy. The leading diagnostic method is light, immunofluorescence, and electron microscopy. The primary method for verifying the structure and type of organized deposition is staining monoclonal immunoglobulin and/or its fragments in different ways: hematoxylin/eosin, Schiff reaction (PAS reaction), Jones stain, Congo-red stain, Masson's trichrome stain [4, 6, 7].

Fibrillar Forms of Monoclonal Immunoglobulin Deposition

Fibrillar forms include amyloidosis, which includes subtypes with the deposition of light chain (AL), heavy chain (AH), and heavy and light chains (AHL). For a long time, this condition remained the only one in the group of fibrillar deposits. However, monoclonal fibrillary glomerulonephritis was recently discovered [7, 15–19].

Amyloid fibrils are more likely to affect glomeruli and blood vessels as well as the interstitium (in 60% of patients). Intratubular cytoplasmic amyloidosis is rare [20]. In most cases, M-protein-associated amyloidosis develops from fragments of monoclonal light chains (AL) that are more often of the λ isotype than the κ isotype, and in rare cases — from fragments of intact immunoglobulin (Ig) or only heavy chains (AH) [6, 7, 20]. During light microscopy, amyloid fibrils look like continuous unbranched and randomly arranged deposits with a diameter of 7–12 nm. Staining with hematoxylin/eosin reveals pale eosinophilic inclusions; staining with Schiff's reagent (PAS-reaction) gives a negative or weakly positive reaction; interaction with trichrome (Masson's stain) gives a blue or silver color (negative). Congo red stain (with distinctive bright green refraction in polarized light) remains the indispensable gold standard for amyloid detection for more than 50 years. Immunofluorescence microscopy demonstrates monotypic staining of amyloid deposits. Electron microscopy shows amyloid deposits in the kidneys that look like unbranched fibrils, which are randomly arranged and visible in the mesangium, glomeruli or tubules, interstitium and vessels [6, 7].

Amyloidosis is a systemic disease, and in most patients, not only renal tissue but also other organs are involved in the pathological process (subcutaneous fat, gastrointestinal tract, bone marrow) [6, 7, 20]. A small group of patients (7–17%) with fibrillary glomerulonephritis (monoclonal fibrillary glomerulonephritis) clinically meets the criteria for monoclonal gammopathy. The formation of "fibrillar" deposits (IgG deposits limited by light chain) is found in 3–15% of this group of patients [6, 7, 15, 16, 18, 21, 22].

In fibrillary glomerulonephritis, fibrils are arranged randomly and are on average twice thicker (10–30 nm) than those observed in amyloidosis and usually do not stain with Congo red. Light microscopy can help confirm fibrillary glomerulonephritis by staining the glomeruli for a homologue DnaJ Heat Shock Protein Family (Hsp40) Member B9, which is a reliable marker of the disease. Immunofluorescence assay is not specific (IgG staining: mostly IgG4, less often IgG1 and C3 complement components) [6, 7, 18, 21].

These differences can be used to distinguish monoclonal glomerulonephritis from the subtypes of heavy chain (AH) or heavy and light chain (AHL) deposition [6, 7, 23, 24].

Microtubular Forms of Monoclonal Immunoglobulin Deposition

Immunotactoid glomerulonephritis and cryoglobulinaemic glomerulonephritis are two diseases characterized by immunoglobulin deposits in the form of microtubules. Microtubules can be distinguished from fibrils by their hollow center and large diameter (17–90 nm) [6, 7, 21, 22]. There are three types of cryoglobulinemia. Type I (simple cryoglobulins) includes monoclonal immunoglobulins of the same class (A, G or M), less often — monoclonal light chains of immunoglobulins. Type II (mixed cryoglobulins) includes one monoclonal immunoglobulin in the role of an antibody (usually IgM, less often IgA or G) combined with polyclonal IgG. Type III (mixed cryoglobulins) includes several classes of polyclonal immunoglobulins and sometimes non-immunoglobulin molecules (fibronectin, lipoproteins, C3-component of complement) [1, 4, 6, 7, 21, 25].

Therefore, monoclonal renal gammopathies (MGRS) include type I and type II cryoglobulinemia since type III cryoglobulinemia is associated exclusively with polyclonal immunoglobulins [1, 4, 7, 21].

Type I cryoglobulinemia is characterized by loss of M-protein at temperatures below 37 °C and dissolution when serum is heated. This can cause glomerulonephritis associated with cryoglobulinemia (20–30%), and systemic manifestations (vasculitic eruptions, peripheral neuropathy — Raynaud's syndrome and arthralgia). The most common cause of type II cryoglobulinemia is hepatitis C infection. Only about 10–30% of cases are associated with B-cell lymphoproliferation [1, 4, 7, 21]. A typical sign of cryoglobulinemia during light microscopy is membranoproliferative glomerulonephritis with endocapillary proliferation. Moreover, numerous WBC with intracapillary infiltration are found, and Schiff's reagent (PAS reaction) reveals huge PAS-positive intraluminal immune deposits (protein hyaline thrombi). Immunofluorescence microscopy shows intraluminal Ig and deposits of C3, C4, C1q complement components. Electron microscopy reveals the substructures of microtubules, fibrils and deposits in the form of "fingerprints" [1, 4, 6, 7, 21]. Immunotactoid glomerulonephritis is often monoclonal, in contrast to fibrillar glomerulonephritis. More often it is a renal-limited disease and, unlike cryoglobulinemia, it does not show typical signs of cryoglobulinemic glomerulonephritis (formation of glomerular protein thrombi, vasculitis of arteries and/or arterioles) [1, 6, 7, 21].

Glomerular deposits in immunotactoid glomerulonephritis are uniformly composed of microtubules (with limited λ or κ isotypes) and are more often arranged in parallel rows with predominantly subepithelial and subendothelial localization [6, 7, 21, 26, 25, 27]. Congo red stain gives a negative result (no dichroism detected: reddish and green-yellow glow).

Immunofluorescence microscopy shows distinct hollow centers and staining of C3 complement component. During electron microscopy, focal parallel arrays 30–90 nm in diameter are determined [6, 7, 21].

Crystalline and/or Inclusive Forms of Deposition of Monoclonal Immunoglobulins

Light-chain proximal tubulopathy (LCPT), crystal storing histiocytosis (CSH), and (cryo) crystalglobulin glomerulonephritis are diseases characterized by immunoglobulin deposits in the form of crystals and/or inclusions. Proximal tubulopathy has crystalline and non-crystalline variants. In the crystalline version of LCPT, numerous crystals of light chains of various shapes are found inside the cells of proximal tubules, inside lysosomes, or are freely located in the cytoplasm. This version is primarily associated with the deposition of the κ-light chain and is clinically manifested by complete or partial Fanconi syndrome that develops in young patients [6, 7, 28–32]. During light microscopy, *κ* light chains have a rod or rhomboid shape. They are hypereosinophilic and do not stain when exposed to Schiff reagent (PAS reaction). Pronase (a biochemical mixture of proteinases isolated from the extracellular fluid of Streptomyces griseus) is used to render a crystalline inclusion during immunofluorescence microscopy of proximal tubule cells. Electron-dense intracytoplasmic inclusions are rendered during electron microscopy [6, 7, 28–30].

In cases of the non-crystalline version of LCPT, cells of proximal tubules are stretched and damaged due to the accumulation of numerous non-crystalline inclusions of light chains in lysosomes. This type is usually associated with the deposition of λ light chains. Fanconi syndrome is rarely manifested. The type is favorable compared to the crystalline variant of kidney damage. The non-crystalline variant of LCPT can sometimes look like acute tubular necrosis or acute interstitial nephritis [6, 7, 28, 30, 33].

In patients with CSH, light chain crystals, predominantly of *κ* chains, are often found in renal histiocytes and cells of proximal tubules; they can have a wide extrarenal distribution, including the bone marrow, lymph nodes, lungs, thyroid gland, parotid gland, cornea, synovium, skin, subcutaneous fat, stomach, liver and brain [6, 7, 34–37].

Infiltration by histiocytes and deposition of light chain crystals (more often *κ*) lead to interstitial fibrosis and tubular atrophy. Diagnosis of crystal storing histiocytosis (CSH) can be challenging since crystalline inclusions cannot always be identified by immunofluorescence microscopy. Therefore, the use of the pronase or immunoperoxidase method may be required [6, 7]. Crystal storing histiocytosis (CSH) can develop concurrently with proximal light chain tubulopathy. In this case, organized cytoplasmic inclusions — needle- or oval-shaped crystals in proximal tubular cells — are visible with the help of electron microscopy [6, 7, 34, 35]. (Cryo) crystalglobulin glomerulonephritis is a rare monoclonal gammopathy characterized by immunoglobulin thrombi in the arterioles and capillaries of glomeruli [6, 7, 39].

These thrombi have a crystalline structure; in some patients, the crystallization process is accelerated by exposure to cold — this is cryocrystalline globulinemia [6, 7, 32, 39, 40].

Renal biopsy specimens from patients with cryocrystalline globulinemia show large extracellular crystals in the capillaries and arterioles of glomeruli that are

often associated with fibrin thrombi and inflammation. Mesangial and endocapillary hypercellularity is often absent during microscopic investigation. As with cryoglobulinemia, intravascular deposition of crystals leads to the occlusion of small vessels, thrombosis and/or inflammatory vasculitis [6, 7].

Damage with Unorganized IgM Deposits

Unorganized deposits of monoclonal immunoglobulins are observed in patients with monoclonal immunoglobulin deposition disease (MIDD) and in patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits — PGNMID) [4, 6, 7].

Monoclonal immunoglobulin deposition disease (MIDD) includes three subtypes that are characterized by light chain deposition on disease or both light and heavy chain deposition on disease [6, 7, 21, 22]. Light chain deposition disease (LCDD) is the most common subtype (isotype κ). Kidneys are almost always affected; extrarenal lesions are common in the heart, liver, and lungs. During light microscopy, nodular glomerulosclerosis and nodular mesangial enlargement are visible along with the thickening of the glomerular and tubular basement membranes (GBM and TBM). Non-specific manifestations are as follows: varying degrees of tubular atrophy, interstitial fibrosis and inflammation. Immunofluorescence microscopy demonstrates monotypic, linear and amorphous light chains that are deposited in the mesangium and along the glomerular and tubular basement membranes (GBM and TBM) [6, 7, 21, 22]. With light and heavy chain deposition disease (LHCDD) and heavy chain deposition disease (HCDD), light microscopy shows linear deposits. Monotypic γ, α, or μ light chains are visible along the glomerular and tubular basement membranes (GBM and TBM). During electron microscopy, granular deposits look non-fibrillar, electron-dense, and are located in glomeruli subendothelially, in the mesangium, and on the outer side of the tubular basement membrane [6, 7, 21, 22].

On the contrary, in cases of proliferative glomerulonephritis with monoclonal immunoglobulins deposition (PGNMID), deposits of intact monoclonal IgG, rarely IgA or IgM, occur in glomeruli [6, 7, 22, 41]. Light microscopy shows predominantly endocapillary proliferation and/or membranoproliferative glomerulonephritis (MPGN) or without morphological changes. According to immunofluorescence microscopy, IgG deposits are limited to glomeruli and include one isotype of a light chain and one isotype of a heavy chain, most often IgG3κ [6, 7, 22, 41, 42]. Positive staining for C3 and C1q indicates the activation of the complement system. During electron microscopy, granular and disorganized deposits are limited to glomeruli, where they are located in the mesangium and subendothelial space, less often — in the subepithelial space [6, 7].

Non-Immunoglobulin Gammopathies

Not all kidney damage associated with monoclonal gammopathy of renal significance (MGRS) includes deposits of monoclonal immunoglobulins. A common form of MGRS-related disorder with no such deposits is C3-glomerulopathy associated with monoclonal gammopathy, C3GP, which is detected in about 30% of patients [6, 7, 43]. C3-glomerulopathy associated with monoclonal gammopathy leads to kidney dysfunction via an indirect mechanism. This mechanism is a process when M-protein acts as an autoantibody to C3-convertase, or as an autoantibody to other regulating proteins for complement; this leads to the dysregulation of the alternative complement pathway [6, 7, 43–45]. Light microscopy shows mesangial proliferative, membranoproliferative, or endocapillary proliferative glomerulonephritis. It looks like large subepithelial deposits — in the form of a "hump". C3GP is characterized by the deposition of a fragment of the C3 component of the complement system in the glomeruli, at least twice as intense as any combination of IgG, IgM, IgA and C1q [6, 7, 31, 44, 46]. Immunofluorescence microscopy in 5–10% of patients reveals membranoproliferative glomerulonephritis with masked monoclonal deposits. These patients require additional immunofluorescence tests: use of proteases to identify monoclonal immunoglobulin in deposits [6, 7, 31, 46]. Electron microscopy reveals electron-dense mesangial, subepithelial and subendothelial deposits [6, 7]. The group of non-immunoglobulin gammopathies also includes thrombotic microangiopathy associated with monoclonal gammopathy (TMA), which is characterized in some patients by microangiopathic hemolytic anemia. TMA can occur simultaneously in patients with monoclonal gammopathies, including MM and Waldenstrom macroglobulinemia (WM) [6, 7, 47]. This disease is relatively rare and new, with a few cases described in the literature. Ravindarn et al. established a connection between gammopathy, TMA and a high level of monoclonal immunoglobulins in 21% of patients aged 50 and over [6, 7, 48]. The pathophysiology of these disorders is not always well understood, but it may be associated with monoclonal immunoglobulin that acts as an autoantibody against the regulatory complement of protein.

Kidney damage due to TMA is characterized by the formation of blood clots in the capillaries of glomeruli, swelling of the endothelium, mesangiolysis with microaneurysms and the formation of a double contour

of the walls of the capillaries of the glomeruli. Therefore, the process is based on acute tubular damage with varying degrees of tubulointerstitial scarring [6, 7, 49, 50].

New Approaches in the Diagnosis and Administration of Monoclonal Gammapathies of Renal Significance

Until now, monoclonal gammopathies were diagnosed through the quantitative determination of circulating abnormal protein: serum protein electrophoresis with the determination of the M-gradient level, immunofixation of proteins with the determination of their type, electrophoresis and immunofixation of proteins in daily urine. A new method for determining free light chains in blood serum — Freelite — emerged in the early 2000s; it is based on the interaction of type λ and κ light chains with highly specific antisera. The proliferation marker is impaired κ/ λ ratio (normal range 0.26–1.65).

The attention of a hematologist and/or hematooncologist should be focused on the identification of the clone, since any detected variant of damage in MGRS requires the timely initiation of clone-oriented therapy, which allows preserving kidney function and preventing uncontrolled progression of the malignant process by reducing the accelerated secretion of abnormal immunoglobulin and/or its chains. In the diagnosis and treatment of this disease, a nephrologist plays an important role; he/she works with a hematologist and/or hematooncologist. First of all, the nephrologist should correct the prescribed clone-oriented therapy considering the nephrotoxicity of chemotherapeutic agents and assess the renal response to the hematological treatment taking into account the glomerular filtration rate. With the progression of the pathological process and deterioration of renal function, the nephrologist decides on the prescription of renal replacement therapy (RRT) methods since these methods allow the removal of abnormal immunoglobulins and/or its chains from the body, thus reducing their toxic effect on kidney parenchyma. With the development of terminal stage chronic kidney disease (CKD S5) and when constant RRT is required, the nephrologist puts the patient on the waiting list and prepares the patient for kidney allotransplantation [1–8].

Conclusion

MGRS is a new group of diseases based on the hyperproduction of nephrotoxic monoclonal immunoglobulin (M-protein, paraprotein) and/or their MGRS-constituent chains. The discovery of the pathogenetic mechanisms of renal tissue damage (pathological activation of the complement system, toxic effect of a cell clone, interaction of antibodies with glomerular antigens of nephron cells). It was this discovery that made it possible to classify MGRS as a separate nosological unit. Renal tissue damage associated with MGRS has a specific morphological pattern associated with the deposition of monoclonal immunoglobulins. Monoclonal immunoglobulin detected in serum and/or urine should be identical to that detected in nephrobiopsy.

Timely initiation of clone-oriented therapy allows preserving kidney function and preventing uncontrolled progression of the malignant process by reducing the secretion of abnormal immunoglobulin and/or its chains.

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Список литературы / References:

1. Козловская Л.В., Рамеев В.В., Когарко И.Н. и др. Поражения почек, ассоциированные с моноклональной гаммапатией неопределенного значения: клинические формы, механизмы развития, подходы к лечению. Клиническая медицина. 2016; 94 (12): 892-901. DOI: http://dx.doi.org/10.18821/0023-2149-2016-94-12-892-901
Kozlovskaya L.V., Rameev V.V., Kogarko I.N., et al. Renal lesions associated with monoclonal gammopathies of undetermined significance : clinical forms, mechanisms of development, approaches to treatment. Klin. med. 2016; 94(12): 892-901. DOI: http://dx.doi.org/10.18821/0023-2149-2016-94-12-892-901 [In Russian]
2. Смирнов А.В., Добронравов В.А., Храброва М.С. и др. Междисциплинарный подход в практике врача-терапевта: фокус на моноклональную гаммапатию ренального значения (сокращенная версия Консенсуса гематологов и нефрологов России по введению нозологии, диагностике и обоснованности клон-ориентированной терапии). Терапия. 2020; 2(36): 22-33. DOI: https://dx.doi.org/10.18565/therapy.2020.2.22-33
Smirnov A.V., Dobronravov V.A., Khrabrova M.S. et al. An interdisciplinary approach in the practice of general physician: a focus on monoclonal gammopathy of renal significance (shot version of the Consensus of hematologists and nephrologists of Russia on the establishment of nosology, diagnostic approach and rationale for clone specific treatment). Therapy. 2020; 2(36): 22-33. DOI: https://dx.doi.org/10.18565/therapy.2020.2.22-33 [In Russian]

3. Смирнов А.В., Афанасьев Б.В., Поддубная И.В. и др. Моноклональная гаммапатия ренального значения: консенсус гематологов и нефрологов России по введению нозологии, диагностике и обоснованности клон-ориентированной терапии. Архивъ внутренней медицины. 2020; 10(2): 102-118. DOI: 10.20514/2226-6704-2020-10-2-102-118
Smirnov A.V., Afanasyev B.V., Poddubnaya I.V. et al. Monoclonal Gammopathy of Renal Significance: Consensus of Hematologists and Nephrologists of Russia on the Establishment of Nosology, Diagnostic Approach and Rationale for Clone Specific Treatment. The Russian Archives of Internal Medicine. 2020; 10(2): 102-118. DOI: 10.20514/2226-6704-2020-10-2-102-118 [In Russian]
4. Смирнов А.В., Добронравов В.А., Храброва М.С. и др. Поражение почек при моноклональной гаммапатии: мультидисциплинарный подход в онкогематологии и нефрологии. Онкогематология. 2020; 15(2): 49–60. doi: 10.17650/1818-8346-2020-15-2-49-60
Smirnov A.V., Dobronravov V.A., Khrabrova M.S. et al. Kidney involvement in monoclonal gammopathies: multidisciplinary approach in oncohematology and nephrology. Onkogematologiya. 2020; 15(2): 49–60. DOI: 10.17650/1818-8346-2020-15-2-49-60 [In Russian]
5. Храброва М.С, Добронравов В.А, Смирнов А.В. Поражения почек, ассоциированные с моноклональными гаммапатиями: одноцентровое исследование. Нефрология. 2018; 22(6): 38–46. DOI: 10.24884/1561-6274-2018-22-6-38-46
Khrabrova M.S, Dobronravov V.A, Smirnov A.V. Kidney disease associated with monoclonal gammopathies: single-center study. Nephrology (Saint-Petersburg). 2018; 22(6): 38–46. DOI: 10.24884/1561-6274-2018-22-6-38-46 [In Russian]
6. Amaador K, Peeters H, Minnema MC, et al. Monoclonal gammopathy of renal significance (MGRS) histopathologic classification, diagnostic workup, and therapeutic options. Neth J Med. 2019; 77(7): 243-254.
7. Leung N, Bridoux F, Batuman V., et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group [published correction appears in Nat Rev Nephrol. 2019 Feb; 15(2): 121]. Nat Rev Nephrol. 2019; 15(1):45-59. DOI:10.1038/s41581-018-0077-4
8. Fermand JP, Bridoux F, Dispenzieri A., et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood. 2018; 132(14): 1478–1485. DOI: 10.1182/blood-2018-04-839480
9. Leung N, Bridoux F, Hutchison CA., et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012; 120(22): 4292–4295. DOI: 10.1182/blood-2012-07-445304
10. Kyle RA, Therneau TM, Rajkumar SV., et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006; 354(13): 1362-1369. DOI:10.1056/NEJMoa054494
11. Delanaye P, Glassock RJ, Pottel H., et al. An Age-Calibrated Definition of Chronic Kidney Disease: Rationale and Benefits. Clin Biochem Rev. 2016; 37(1): 17-26.
12. Swaminathan S, Leung N, Lager DJ., et al. Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study. Clin J Am Soc Nephrol. 2006; 1(3): 483-487. DOI:10.2215/CJN.00710805
13. Bridoux F, Leung N, Hutchison CA., et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int. 2015; 87(4): 698–711. DOI: 10.1038/ki.2014.408
14. Fermand JP, Bridoux F, Kyle RA., et al. How I treat monoclonal gammopathy of renal significance (MGRS). Blood. 2013; 122(22):3583-3590. DOI:10.1182/blood-2013-05-495929
15. Nasr SH, Valeri AM, Cornell LD., et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. Clin J Am Soc Nephrol. 2011; 6(4): 775-784. DOI:10.2215/CJN.08300910
16. Nasr SH, Valeri AM, Cornell LD., et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. Clin J Am Soc Nephrol. 2011; 6(4): 775-784. DOI:10.2215/CJN.08300910
17. Nasr SH, Markowitz GS, Stokes MB., et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004; 65(1): 85-96. DOI:10.1111/j.1523-1755.2004.00365.x
18. Nasr SH, Vrana JA, Dasari S., et al. DNAJB9 Is a Specific Immunohistochemical Marker for Fibrillary Glomerulonephritis. Kidney Int Rep 2017; 3(1): 56–64. DOI: 10.1016/j.ekir.2017.07.017
19. Said SM, Sethi S, Valeri AM., et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. Clin J Am Soc Nephrol. 2013; 8(9): 1515-1523. DOI:10.2215/CJN.10491012
20. Gibier JB, Gnemmi V, Glowacki F., et al. Intratubular amyloid in light chain cast nephropathy is a risk factor for systemic light chain amyloidosis. Mod Pathol. 2018; 31(3): 452-462. DOI:10.1038/modpathol.2017.124
21. Bridoux F, Javaugue V, Bender S., et al. Unravelling the immunopathological mechanisms of heavy chain deposition disease with implications for clinical management. Kidney Int. 2017; 91(2): 423-434. DOI:10.1016/j.kint.2016.09.004
22. Nasr SH, Valeri AM, Cornell LD., et al. Renal monoclonal immunoglobulin deposition disease: a report of 64 patients from a single institution. Clin J Am Soc Nephrol. 2012; 7(2): 231-239. DOI:10.2215/CJN.08640811
23. Alexander MP, Dasari S, Vrana JA., et al. Congophilic Fibrillary Glomerulonephritis: A Case Series. Am J Kidney Dis. 2018; 72(3): 325-336. DOI:10.1053/j.ajkd.2018.03.017
24. Dasari S, Alexander MP, Vrana JA., et al. DnaJ Heat Shock Protein Family B Member 9 Is a Novel Biomarker for Fibrillary GN. J Am Soc Nephrol. 2018; 29(1): 51-56. DOI:10.1681/ASN.2017030306
25. Ojemakinde K, Turbat-Herrera EA, Zeng X., et al. The many faces of cryoglobulinemic nephropathy: a clinico-pathologic study of 47 cases with emphasis on the value of electron microscopy. Ultrastruct Pathol. 2014; 38(6): 367-376. DOI:10.3109/01913123.2014.952803
26. Heher EC, Rennke HG, Laubach JP., et al. Kidney disease and multiple myeloma. Clin J Am Soc Nephrol. 2013; 8(11): 2007-2017. DOI:10.2215/CJN.12231212
27. Karras A, Noël LH, Droz D., et al. Renal involvement in monoclonal (type I) cryoglobulinemia: two cases associated with IgG3 kappa cryoglobulin. Am J Kidney Dis. 2002; 40(5): 1091-1096. DOI:10.1053/ajkd.2002.36350
28. Kapur U, Barton K, Fresco R., et al. Expanding the pathologic spectrum of immunoglobulin light chain proximal tubulopathy [published correction appears in Arch Pathol Lab Med. 2008 Jan; 132(1): 13. Leehy, David J [corrected to Leehey, David J]]. Arch Pathol Lab Med. 2007; 131(9): 1368-1372. DOI:10.1043/1543-2165(2007)131[1368:ETPSOI]2.0.CO;2
29. Stokes MB, Valeri AM, Herlitz L., et al. Light Chain Proximal Tubulopathy: Clinical and Pathologic Characteristics in the Modern Treatment Era. J Am Soc Nephrol. 2016; 27(5): 1555-1565. DOI:10.1681/ASN.2015020185
30. Herrera GA. Proximal tubulopathies associated with monoclonal light chains: the spectrum of clinicopathologic manifestations and molecular pathogenesis. Arch Pathol Lab Med. 2014; 138(10): 1365-1380. DOI:10.5858/arpa.2013-0493-OA

31. Larsen CP, Messias NC, Walker PD., et al. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. Kidney Int. 2015; 88(4): 867-873. DOI:10.1038/ki.2015.195
32. Leung N, Buadi FK, Song KW., et al. A case of bilateral renal arterial thrombosis associated with cryocrystalglobulinaemia. NDT Plus. 2010; 3(1): 74-77. DOI:10.1093/ndtplus/sfp140
33. Larsen CP, Bell JM, Harris AA., et al. The morphologic spectrum and clinical significance of light chain proximal tubulopathy with and without crystal formation. Mod Pathol. 2011; 24(11): 1462-1469. DOI:10.1038/modpathol.2011.104
34. de Alba Campomanes AG, Rutar T, Crawford JB., et al. Crystal-storing histiocytosis and crystalline keratopathy caused by monoclonal gammopathy of undetermined significance. Cornea. 2009; 28(9): 1081-1084. DOI:10.1097/ICO.0b013e318199f73b
35. Dogan S, Barnes L, Cruz-Vetrano WP. Crystal-storing histiocytosis: report of a case, review of the literature (80 cases) and a proposed classification. Head Neck Pathol. 2012; 6(1): 111-120. doi:10.1007/s12105-011-0326-3
36. El Hamel C, Thierry A, Trouillas P., et al. Crystal-storing histiocytosis with renal Fanconi syndrome: pathological and molecular characteristics compared with classical myeloma-associated Fanconi syndrome. Nephrol Dial Transplant. 2010; 25(9): 2982-2990. DOI:10.1093/ndt/gfq129
37. Kanagal-Shamanna R, Xu-Monette ZY, Miranda RN., et al. Crystal-storing histiocytosis: a clinicopathological study of 13 cases. Histopathology. 2016; 68(4): 482-491. DOI:10.1111/his.12768
38. Koo H, Oh DH, Chun YS., et al. A case of crystalline keratopathy in monoclonal gammopathy of undetermined significance (MGUS). Korean J Ophthalmol. 2011; 25(3): 202-205. DOI:10.3341/kjo.2011.25.3.202
39. Gupta V, El Ters M, Kashani K., et al. Crystalglobulin-induced nephropathy. J Am Soc Nephrol. 2015; 26(3): 525-529. DOI:10.1681/ASN.2014050509
40. Leung N, Barnidge DR, Hutchison CA. Laboratory testing in monoclonal gammopathy of renal significance (MGRS). Clin Chem Lab Med. 2016 Jun 1; 54(6): 929-37. DOI: 10.1515/cclm-2015-0994.
41. Bhutani G, Nasr SH, Said SM., et al. Hematologic characteristics of proliferative glomerulonephritides with nonorganized monoclonal immunoglobulin deposits. Mayo Clin Proc. 2015; 90(5): 587-596. DOI:10.1016/j.mayocp.2015.01.024
42. Vignon M, Cohen C, Faguer S., et al. The clinicopathologic characteristics of kidney diseases related to monotypic IgA deposits. Kidney Int. 2017; 91(3): 720-728. DOI:10.1016/j.kint.2016.10.026
43. Sethi S, Rajkumar SV. Monoclonal gammopathy-associated proliferative glomerulonephritis. Mayo Clin Proc. 2013; 88(11): 1284-1293. DOI:10.1016/j.mayocp.2013.08.002
44. Czarnecki PG, Lager DJ, Leung N., et al. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposits. Kidney Int. 2009; 75(4): 420-427. DOI:10.1038/ki.2008.577
45. Zand L, Kattah A, Fervenza FC., et al. C3 glomerulonephritis associated with monoclonal gammopathy: a case series. Am J Kidney Dis. 2013; 62(3): 506-514. DOI:10.1053/j.ajkd.2013.02.370
46. Lloyd IE, Khalighi MA. Glomerulonephritis with Masked Monotypic Immunoglobulin Deposits and Concurrent Lymphomatous Infiltration. Am J Kidney Dis. 2016; 68(4): 640-644. DOI:10.1053/j.ajkd.2016.05.012
47. Vos JM, Gustine J, Rennke HG., et al. Renal disease related to Waldenström macroglobulinaemia: incidence, pathology and clinical outcomes. Br J Haematol. 2016; 175(4): 623-630. doi:10.1111/bjh.14279
48. Ravindran A, Go RS, Fervenza FC., et al. Thrombotic microangiopathy associated with monoclonal gammopathy. Kidney Int. 2017; 91(3): 691-698. DOI:10.1016/j.kint.2016.09.045
49. Blanc C, Togarsimalemath SK, Chauvet S., et al. Anti-factor H autoantibodies in C3 glomerulopathies and in atypical hemolytic uremic syndrome: one target, two diseases. J Immunol. 2015; 194(11): 5129-5138. DOI:10.4049/jimmunol.1402770
50. Mahmood U, Isbel N, Mollee P., et al. Monoclonal gammopathy of renal significance triggering atypical haemolytic uraemic syndrome. Nephrology (Carlton). 2017; 22 Suppl 1: 15-17. DOI:10.1111/nep.12934

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ИНФЕКЦИОННЫЙ ЭНДОКАРДИТ У ПАЦИЕНТОВ С ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ

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Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

Резюме

Представлен обзор литературы, отражающий частоту возникновения, особенности этиологии, гемодинамики, локализации, клинических проявлений, исходов и лечения инфекционного эндокардита (ИЭ) у пациентов с гипертрофической кардиомиопатией (ГКМП). Несмотря на относительную редкость возникновения ИЭ у больных ГКМП, сочетание этих патологий характеризуется взаимным отягощением и неблагоприятным прогнозом. У больных с обструктивными формами ГКМП присоединение ИЭ усугубляет расстройства кровообращения и повышает вероятность неконтролируемого сепсиса и эмболий, увеличивая тем самым риск летального исхода. Консервативное лечение ИЭ у больных с ГКМП не отличается от такового без ГКМП. Необходимо междисциплинарное взаимодействие при ведении пациентов с ИЭ на фоне ГКМП в определении показаний к кардиохирургическому лечению и выборе оптимального метода. Антибактериальная профилактика ИЭ перед инвазивными медицинскими манипуляциями у пациентов с ГКМП не рекомендуется действующими согласительными документами, однако решение для каждого больного должно приниматься индивидуально с обязательной оценкой риска возникновения ИЭ, тяжести гемодинамических нарушений и прогноза.

Ключевые слова: *инфекционный эндокардит, гипертрофическая кардиомиопатия*

Конфликт интересов

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

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Abstract

A literature review is presented, reflecting the incidence, etiology, hemodynamics, localization, clinical manifestations, outcomes and treatment of infective endocarditis (IE) in patients with hypertrophic cardiomyopathy (HCM). Despite the relative rarity of IE in patients with HCM, the

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combination of these pathologies is characterized by mutual aggravation and poor prognosis. The addition of IE increases the risk of death in patients with obstructive HCM, deteriorating circulatory disorders, increasing the likelihood of uncontrolled sepsis and embolism. Conservative treatment of IE in patients with HCM does not differ from that without HCM. Interdisciplinary interaction is needed in the management of patients with IE against the background of HCM in determining the indications for cardiac surgery and choosing the optimal method. Antibacterial prophylaxis of IE before invasive medical manipulations in patients with HCM is not recommended by the current consensus documents, however, the decision for each patient should be made individually, with a mandatory assessment of the risk of IE, the severity of hemodynamic disorders and prognosis.

Key words: *infective endocarditis, hypertrophic cardiomyopathy*

Conflict of interests

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AH — arterial hypertension, AV — aortic valve, SCD — sudden cardiac death, AF — atrial fibrillation, CI — confidence interval, CT — computed tomography, HCM — hypertrophic cardiomyopathy, HF — heart failure, IE — infectious endocarditis, IVS — interventricular septum, LA — left atrium, LV — left ventricle, LVOT — left ventricular outflow tract, MRI — magnetic resonance imaging, MV — mitral valve, OR — odds ratio, TTE — transthoracic echocardiography

Introduction

Despite significant progress in diagnosis and management, infective endocarditis (IE) has shown no decrease in morbidity for at least 30 years [1, 2] and is characterized by a serious prognosis and high mortality [1, 3]. The diagnosis of IE is often established late [4]. This is largely due to a significant variety of the onset and course of the disease, leading to diagnostic errors [1, 5]. Specific features of the IE course can be due to the etiological factor, conditions of development, previous heart damage, as well as extracardiac manifestations [3, 6]. Initial cardiac damage that results in IE is often caused by congenital or acquired valvular defects [6]. Much less often, such an unfavorable intracardiac background for IE is hypertrophic cardiomyopathy (HCM), which is also a pressing challenge facing cardiology today [7, 8]. Despite the relative rarity of IE in patients with HCM [7, 9], the combination of these pathologies is characterized by mutual complication and poor prognosis [9].

The rare development of IE in patients with HCM is why the combination of these diseases is presented primarily as a description of individual cases [10–13] and small serial observations in the literature [14]. There are not enough extensive retrospective and prospective studies on this issue [9, 15]. An analysis of literature data on this problem was published by one of the co-authors of this paper in 2013 [16]. During this time, new versions of consensus papers were published and implemented both for IE [1, 17, 18] and HCMP [7, 19, 20]. Changes in the study of the combination of these pathologies over the past decade are of interest, particularly treatment approaches, including cardiac surgery and the prevention of IE in patients with HCM.

When preparing this review, literature sources on Pubmed, MEDLINE, Embase, Cochrane, Scopus, Web of Science databases were analyzed. They include consensus papers, case series descriptions and individual observations, guidelines and monographs published over the past ten years. Several fundamental sources on this issue that were written earlier were also included. The search keywords were “infective endocarditis” and “hypertrophic cardiomyopathy” in the title or abstract.

Brief Description of Hypertrophic Cardiomyopathy: Definition, Clinical Picture, Diagnostic Methods, Complications, Treatment

HCM is a genetic disease (usually autosomal dominant, less often due to mutations *de novo*, and in some cases, an autosomal recessive disease). It is characterized by massive (> 15 mm) myocardial hypertrophy, predominantly of the left ventricle (LV), more often of an asymmetric nature due to the thickening of the interventricular septum (IVS), sometimes with the development of obstruction (systolic pressure gradient) of LV outflow tract (LVOT), in the absence of reasons that can cause such severe hypertrophy [7, 19–22].

Causes of HCM include mutations in genes that encode regulatory, contractile and structural proteins of cardiac sarcomeres [19, 23]. Today, HCM is found in about one out of 200–500 people [24]. The disease is characterized by severe hypertrophy of various parts of the LV, most often IVS, which creates an obstacle to blood ejection from LV (obstructive form of HCM) along with

the systolic displacement of the anterior mitral valve (MV) [7, 19].

Clinical manifestations of HCM primarily accompany obstructive forms of the disease [19, 25]. In patients with HCM, chest pains of ischemic origin occur due to a decrease in coronary blood flow (hemodynamic angina) [7, 19]. LVOT obstruction may cause fainting, especially after exercise. Pre- and syncope conditions develop as a result of LVOT obstruction, disturbances in the mechanisms of vascular regulation that lead to episodes of arterial hypotension due to inadequate vasodilation or diastolic dysfunction, as well as various disturbances in rhythm and conduction [19, 24–26]. Heart failure (HF) (dyspnea, cardiac asthma, orthopnea) gradually occurs and progresses due to progressive diastolic dysfunction with preserved or increased ejection fraction [25]; systolic dysfunction develops only in the later stages of this disease [7, 19].

HCM is diagnosed using imaging techniques (echocardiography, magnetic resonance imaging (MRI) of the heart) that reveal maximum end-diastolic wall thickness of ≥ 15 mm anywhere in the LV in the absence of another cause of hypertrophy of this degree [20]. Although HCM in most patients can be associated with a normal life expectancy without limiting its quality and/or the need for cardiac surgery, 30–40% of patients may experience serious consequences associated with the disease [7, 20]. The causes of death in HCM cases are: progressive circulatory failure, life-threatening tachyarrhythmias, including ventricular fibrillation, sudden cardiac death (SCD), embolism of systemic circulation, mainly cerebral vessels [27]. Atrial fibrillation (AF) with HCM occurs in 14–28% of patients. It is poorly tolerated, difficult to treat [28], and is associated with an increased risk of thromboembolic complications (AF increases the risk of ischemic stroke eightfold (!)), HF, SCD and death from all causes [29, 30]. HCM can be combined with another cardiovascular pathology (coronary heart disease, AH, diabetes mellitus) [31], especially with the increasing age of patients [32].

The treatment of HCM patients consists in using drugs with a negative inotropic effect (β-blockers and calcium channel blockers), correction of rhythm disorders (disopyramide, amiodarone) and HF [7, 19, 25, 28]. Treatment with nitrates, diuretics and angiotensin-converting enzyme inhibitors should be avoided since vasodilation mediated by these drugs or the decreased volume of circulating blood leads to increased obstruction in LVOT [19, 24, 25]. A cardioverter-defibrillator is implanted in case of syncope, sudden cardiac arrest, confirmed life-threatening arrhythmias [19, 28, 33]. The possibility of implanting cardioverter-defibrillators for the primary prevention of SCD (based on effective risk stratification) reduces mortality in patients with HCM to 0.5% per year [27]. Based on the corresponding indications (symptoms of LVOT obstruction with pressure gradient of ≥ 50 mm Hg, ineffectiveness of drug therapy), cardiac surgery is used: mainly septal myectomy and percutaneous catheter alcohol septal ablation [7, 24, 34].

Incidence, Hemodynamic Conditions and Localization of Valvular Lesions in Infective Endocarditis with Underlying Hypertrophic Cardiomyopathy

According to the most complete, albeit relatively old study (1999) that included 810 patients with HCM, including 681 patients with long-term (over 55 months) follow-up, the incidence of IE was 1.4 per 1,000 person-years [35]. In individuals with LVOT obstruction, the incidence of IE increased to 3.8 per 1,000 person-years, and with dilatation of the left atrium (LA) over 50 mm, the incidence of IE reached 9.2 per 1,000 person-years [35]. In a recently published large single-center study with extensive patient coverage over 12 years of follow-up, the percentage of patients with HCM with IE was 0.19%, with an estimated frequency of 0.15/1,000 person-years among patients with HCM [36]. In another study with 640 patients with HCM who were followed up over a ten-year period, only three patients had IE (IE incidence of 0.5%) [9]. Therefore, IE is a relatively rare disease in patients with HCM, even in the presence of LVOT obstruction [35, 36]. Most researchers cite IE mostly in patients with obstructive HCM [10, 11, 35, 36]; some sources indicate a similar incidence of IE in both obstructive and non-obstructive forms of the disease [15, 37]. The development of left-sided IE in HCM, especially in its obstructive form, is facilitated by hemodynamic disorders typical for this pathology. Hypertrophied IVS with repeated abnormal systolic movement of the anterior cusp of the mitral valve (MV) [7, 19], aortic regurgitation in some patients, and the centrifugal effect of turbulent blood flow in LVOT cause permanent microtraumatization (erosion) of the endocardium [12, 35, 38], which, under conditions of bacteremia, facilitates the fixation of microorganisms and the formation of microbial vegetations — an indispensable morphological attribute of IE and its "major" diagnostic criterion [1, 3, 4, 6]. As a result, in cases of HCM, IE is predominantly of mitral localization and parietal endocardium of IVS [11, 16, 39]. Other hemodynamic prerequisites for IE in obstructive HCM are elevated intracardiac pressure, lengthening of MV cusps [15], abnormal attachment of papillary muscles, as well as thinning of the myocardium, dilatation of LA and LV (sometimes with aneurysmal dilation of the heart apex), which is observed at the late stage of HCM [35]. All

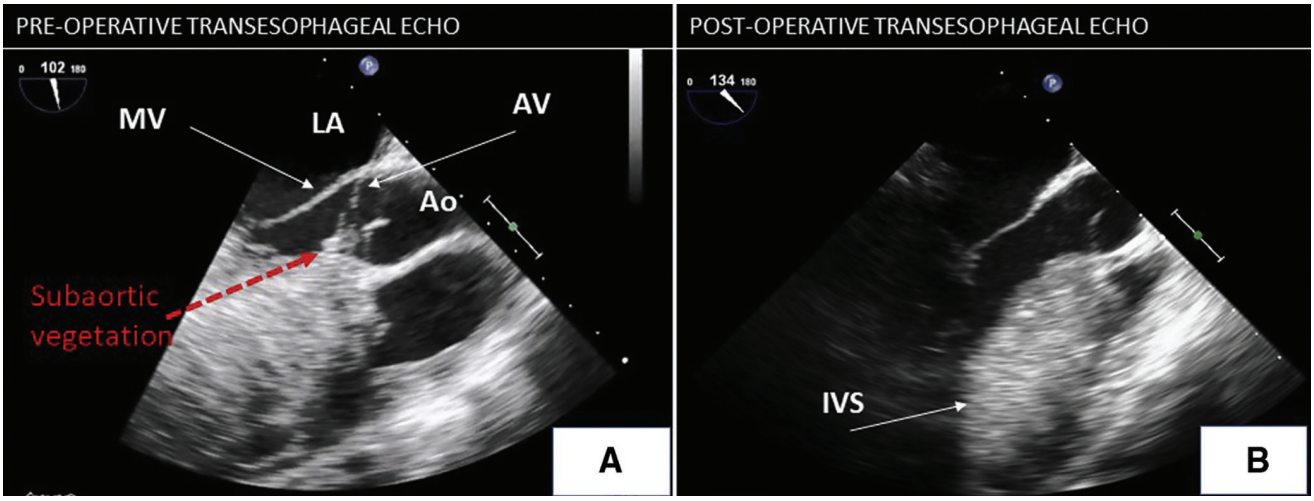

Figure. *Image of a vegetation in infective endocarditis in a patient with hypertrophic cardiomyopathy during transesophageal echocardiography*

Description: A. Preoperative echocardiography shows a subaortic vegetation (indicated by the dashed red line) and marked septal (IVS) hypertrophy. B. On the postoperative image, the vegetation was removed, the patency of the left ventricle outflow tract was improved, severity of IVS hypertrophy after septal myectomy became less significant. MV — mitral valve; LA — left atrium; AV — aortic valve; Ao — aorta. The picture was kindly provided by Madonna Lee (Congenital Cardiac Surgery Department, Seattle Children's Hospital, WA, USA) [13] and permitted for reproduction on conditions of the licence Creative Commons CC-BY-NC-ND

these conditions contribute to permanent hemodynamic damage to the MV valve, the formation of loose and fragile vegetations, and, consequently, embolism and HF progression [11, 16, 35, 39]. Predominant localization of microbial vegetations in patients with HCM is observed on the ventricular side of the anterior MV cusp [35] and on the parietal endocardium of IVS, mainly in its upper third (Fig.) [13]. According to the study by F. Dominguez et al. [15] that included 34 patients with HCM complicated by IE, the incidence of aortic and MV lesions was 71% and 35%, respectively, while in two cases, there was combined damage of two valves. J. R. Sims et al. [37] found a comparable incidence of aortic and MV damage among 30 examined patients with HCM: 47% and 53%, respectively, while there was no effect of LVOT obstruction on the localization of endocarditis. Combined lesions of ≥ 2 valves in IE are not uncommon [15, 37]. There is a report [40] about a severe course of IE with damage to all four valves in a patient with HCM. It should be noted that when performing transthoracic echocardiography (TTE), new valve regurgitation or vegetation on any of the valves could not be detected. Transesophageal echocardiography demonstrated vegetations on four valves and atrial septal defect.

Etiology, Clinical Picture, Diagnosis of Infective Endocarditis in Hypertrophic Cardiomyopathy

Analysis of literature data does not allow to identify significant features that distinguish IE in HCM from other types of this disease in the etiological aspect. Therefore, the most common causative agents of IE in patients with HCM are gram-positive cocci: staphylococci, streptococci and enterococci are etiological agents typical for IE in general [1, 41], much less often — other types of microorganisms [16, 37]. The etiological role of Staphylococcus aureus in IE is associated with a poor prognosis [3].

Analysis of papers published in the late 20th century suggested IE with underlying HCM as a disease of primarily young people. The average age of patients with IE with this pathology in the previously mentioned multicenter study by P. Spirito et al. was 39 years old [35]. However, the average age of patients with IE tends to increase in almost all categories of patients with this disease [1, 3, 4]. This is also true for patients with IE with underlying HCM because the life expectancy of persons with HCM also gradually increases [7, 32]. The combination of HCM and IE in young and middle-aged patients is more common in men [12, 15, 35, 37].

IE with underlying HCM demonstrates all the clinical features inherent in IE of native valves of left-sided localization [10–12, 25, 35]. Besides febrile wave-like or persistent fever with chills, intoxication and blood systemic inflammatory reaction syndrome, patients experience a rapid formation of a defect of insufficiency type (mitral or aortic), left ventricular circulatory failure, systemic embolism, and with a longer course of IE — visceral lesions of immunocomplex origin [1, 3–5]. In the above descriptions of IE cases in patients with HCM, cardioembolic strokes are often cited, which is associated with an unfavorable outcome [11, 12, 25]. Mutual aggravation of these diseases is manifested by the rapid development and progression of HF, and

arrhythmias [15, 16, 39]. Also, among the consequences of IE in patients with HCM, uncontrolled sepsis is more often observed [15], which is associated with persistent hemodynamic damage to MV cusps and resistance to antibiotic therapy.

TTE remains the basic method for diagnosing IE with underlying HCM. It allows detecting vegetations on valve structures and parietal endocardium, destruction of valves, perivalvular changes, and the formation of regurgitation [1, 4, 6]. Using TTE, structural and hemodynamic features caused by HCM are also revealed: wall thickness of the right and left ventricle (including IVS), MV features, pressure gradient in the middle and LVOT, diastolic dysfunction, LA size [7, 19] are signs that have prognostic value in both diseases in the case of IE with underlying HCM [35, 37]. Since its introduction into clinical practice, high diagnostic capabilities of transesophageal echocardiography were identified due to the proximity of the ultrasound sensor to the heart and the ability to obtain high-quality images due to the use of high-frequency sensors. Other modern methods of cardiac imaging in IE (single-photon emission and positron-emission computed tomography (CT), cardiac MRI, etc.) used in the diagnostic process have not been sufficiently studied in IE with underlying HCM, although, undoubtedly, they should be applied where possible and for corresponding indications.

Another "major" diagnostic criterion for IE that is critical for the choice of antibiotic therapy is the isolation of the pathogen from blood [1, 3, 41]. Results of routine laboratory and instrumental studies usually indicate a systemic inflammatory reaction (leukocytosis with a neutrophilic shift, increased level of C-reactive protein, procalcitonin and other markers of inflammation), immune shifts (rheumatoid factor, circulating immune complexes), as well as the presence of visceral lesions that are typical for IE (nephropathy, splenomegaly, etc.) [1, 4, 5]. To detect embolic events, primarily of cerebral vessels, including asymptomatic ones, brain MRI or CT is indicated. Thromboembolism develops in 2–9% of patients with HCM in the absence of IE [7], accounting for 2–11% of death causes for patients with HCM [27]. AF in patients with HCM is associated with a significant risk of cardioembolic stroke [20, 28–31]. With IE with underlying HCM, such a complication can develop along with sinus rhythm [11]. Thromboembolism in HCM can be caused by intracardiac thrombi localized on the thickened endocardium of IVS at the point of contact with the anterior cusp of MV, in the dilated LA [7, 27], and in cases of IE — fragments of microbial vegetations of the valves of the left heart [1, 12, 25, 35]. When describing cases of IE with underlying HCM, clinical signs of circulatory failure are often reported [12, 15, 35]. The addition of left-sided IE to HCM either causes valvular regurgitation or makes the existing one worse [16], leading to the development of HF in patients with previously asymptomatic forms of the disease [42].

Management of infective endocarditis in the presence of hypertrophic cardiomyopathy

is carried out in accordance with the general principles articulated in modern consensus recommendations on IE [1, 43]. Antibiotic therapy is carried out depending on the established or suspected pathogen [1, 3, 41]. Cardiac surgery for IE is used in the presence of conventional indications: progressive HF, uncontrolled infection (including intracardiac abscesses) and for the prevention of embolism [1, 3, 6]. A specific feature of cardiac surgical tactics in IE with underlying HCM is, besides the prosthetics of MV or AV, the possibility of simultaneous Morrow myectomy [9, 10, 15, 37, 44]. Successful transcatheter aspiration of a septic embolus of a coronary artery with subsequent surgical replacement of MV and septal myectomy was described [45]. Such interventions require certain experience and conditions; otherwise, the procedure is associated with a high risk of death [37]. There are isolated cases of IE after alcoholic septal ablation — one of the methods of surgical treatment of HCM today [46]. After successful cardiac surgery, not only foci of valvular infection are eliminated but also LVOT obstruction, which is manifested by an improvement in well-being and hemodynamic parameters (disappearance of fainting, dyspnea, etc.) [9, 15, 36]. Therefore, some researchers prefer cardiac surgical treatment of IE in patients with HCM [9, 10, 36, 47]. The advantages of using cardiac surgery are the possibility of simultaneous sanitation of valve infection and the correction of hemodynamic defect, a decrease in the incidence of thromboembolism, HF, sepsis, and decreased mortality. Interdisciplinary interaction between professionals is crucial when selecting the optimal treatment strategy for patients with IE and HCM, especially in the presence of indications for cardiac surgery [1].

Implantation of intracardiac devices (cardioverter-defibrillators) for the management of rhythm disturbances in patients with HCM is an additional factor that increases the risk of IE associated with intracardiac devices [47]. In terms of incidence, this type of IE is only slightly inferior to the left-sided IE of native valves in patients with HCM. It occurs in cases of the obstructive form, and management strategy requires the mandatory removal of the implanted intracardiac device [47] in accordance with consensus papers [1]. A major British study [48] that assessed the risk of IE in persons with

predisposing cardiac factors showed a significant risk of IE in patients with HCM. Among 4,418 patients with HCM, there were 37 hospitalizations due to IE; odds ratio (OR) 32.8, 95% confidence interval (CI) 23.3–44.6, $p < 0.0001$. The risk of an unfavorable outcome (mortality) was low: among 37 cases of IE in patients with HCM, one death was reported (OR 4.0, 95% CI 0.2–17.5, $p = 0.17$). The presence of implanted cardioverter pacemakers in HCM patients was associated with both a significant risk of IE (OR 9.7, 95% CI 9.0–10.6, $p < 0.0001$), and death associated with IE (OR 10.1, 95% CI 8.6–11.7, $p < 0.001$) [48].

Antibacterial Prophylaxis of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

When it comes to the preventive prescription of antibiotics before invasive procedures to prevent IE, there is some contradiction between consensus papers approved at different times. When assessing the need for antibacterial prophylaxis of this disease, previous recommendations on IE assign patients with HCM to the group of intermediate or moderate risk of developing IE. However, the revision of some provisions on the antibacterial prophylaxis of IE in the latest editions by experts at the European Heart Society [1] and the American College of Cardiology/American Heart Association [18], suggests the use of antibacterial prophylaxis only in patients with a very high cardiogenic risk of developing IE; HCM does not apply here. According to researchers who have been studying the problem for many years, the "softening" of the stance on preventive antibacterial prophylaxis of IE and its optionality before invasive procedures in patients outside the high-risk group of IE should not apply to patients with HCM [9, 35, 49]. Undoubtedly, good oral hygiene and regular dental check-ups, as well as avoidance of intravenous drug use, piercings, tattoos, etc., play a critical role in the prevention of episodes of bacteremia and reducing the likelihood of IE in patients with cardiogenic risk factors [1, 48], including patients with HCM. However, in some clinical situations (severe obstruction of LVOT, symptoms of circulatory failure), when IE, in addition to obstructive HCM, can seriously worsen the patient's prognosis, patients with HCM should still be assigned to a high-risk group [25]. Therefore, for such patients, antibacterial prophylaxis of IE is required, and its potential benefit (prevention of IE) exceeds the risk of developing adverse events (anaphylactic shock, resistance to antibiotic therapy, etc.) [49, 50]. IE is a life-threatening condition [1, 4, 6], and its prevention is preferable to its subsequent management.

Outcomes and Prognosis of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

According to studies dating back to the 1980s, IE was the cause of death in about 5–7% of patients with HCM [37, 51]. With the improvement of the quality of diagnosis and treatment of such patients, mortality from IE with underlying HCM has decreased, which is confirmed by studies today [37]. IE is inferior in the incidence of such causes of death in patients with HCM as SCD and embolism. However, the comorbidity of IE is certainly a factor that worsens the condition and prognosis of patients with HCM [15].

Our Data on the Incidence of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy

When analyzing the observations of 340 patients with IE admitted to the Saratov Regional Clinical Hospital from 2006 to 2019, we recorded three cases of IE in patients with obstructive HCM (incidence of IE with underlying HCM among all patients with IE was 0.8%). During this period, we observed 136 patients with HCM, 61 of them with an obstructive form of the disease; therefore, according to our observations, the incidence of IE among patients with HCM was 2.2%. Two observations were described earlier [12]. In one case of IE with underlying HCM, the course of this disease was complicated by cerebral embolism with the development of stroke. HCM was diagnosed for the first time during hospitalization of the patient, simultaneously with IE. As a result of antibiotic therapy in the hospital, body temperature returned to normal, HF manifestations decreased, and neurological functions were partially restored. Second observation: IE of mitral and aortic valves in a 33-year-old patient with obstructive HCM was diagnosed five years earlier, with underlying intravenous drug addiction and HIV infection, stage IVB (AIDS) with a fatal outcome. The third patient, male, 57, with mitral IE and obstructive HCM, successfully received surgical treatment (septal myectomy and MV prosthetics), but there was no further information on him after changing his place of residence.

Among 278 patients with HCM admitted to the cardiology departments of Donetsk Clinical Territorial Medical Association, Central Clinical Hospital No. 1, State Clinical Hospital No. 2 and the State Institution "V. K. Gussak Institute of Emergency and Reconstructive Surgery", Donetsk, from 2001 to April 2021, 68 (25%) of these patients had an obstructive form at rest, and two patients reliably had IE (0.72%). IE of MV developed in

one patient, IE of MV and AV — in the second patient who was referred for cardiac surgery. Along with prosthetics of AV and MV, surgical myectomy was performed, which made it possible to reduce LVOT gradient twofold (from 40 to 20 mm Hg).

Conclusion

IE with underlying HCM, even in its obstructive form, is a relatively rare disease. In turn, HCM cannot be considered a frequent factor of cardiogenic risk of IE among others. However, due to the peculiarities of hemodynamics, the comorbidity of IE significantly increases the risk of complications and death in patients with HCM, mainly its obstructive form, due to the aggravation of circulatory disorders and increased likelihood of uncontrolled sepsis and fatal embolisms. In this regard, early diagnosis of IE in patients with HCM is required, as well as interdisciplinary interaction in the management of these patients, timely determination of indications for cardiac surgery and the choice of an optimal method. The decision on antibacterial prophylaxis of IE before invasive medical procedures in patients with HCM should be made on a case-by-case basis, with a mandatory assessment of the risk of IE and the severity of hemodynamic disorders and prognosis.

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Список литературы/ References:

1. Habib G., Lancellotti P., Antunes M.J. et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015; 36(44): 3075-128. doi:10.1093/eurheartj/ehv319.
2. Duval X, Leport C. Prophylaxis of infective endocarditis: current tendencies, continuing controversies. Lancet Infect Dis. 2008 Apr; 8(4): 225-32. doi: 10.1016/S1473-3099(08)70064-1.
3. Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. J Am Coll Cardiol. 2017 Jan 24; 69(3): 325-344. doi: 10.1016/j.jacc.2016.10.066. PMID: 28104075.
4. Тюрин В.П. Инфекционные эндокардиты. 2-е издание, дополненное и переработанное. М.: «ГЭОТАР-Медиа», 2013; 368с.
Tyurin V.P. Infective endocarditis. 2nd edition, supplemented and revised. M.: «GEOTAR-Media», 2013; 368 [In Russian].
5. Чипигина Н.С., Карпова Н.Ю., Белова М.В., Савилов Н.П. Инфекционный эндокардит: трудности диагностики. Клиницист. 2020; 14(1-2): 82-90.
Chipigina N.S., Karpova N.Yu., Belova M.V., Savilov N.P. Infective endocarditis: diagnostic difficulties. Klinitsist. 2020; 14(1-2): 82-90 [In Russian].
6. Шевченко Ю.Л. Хирургия инфекционного эндокардита (40-летний опыт лечения). Клиническая медицина. 2020; 98(8): 600-605. doi: 10.30629 /0023-2149-2020-98-8-600-605 Shevchenko Yu.L. Surgery of infectious endocarditis (40 years of treatment experience). Clinical Medicine (Russian Journal). 2020; 98(8): 600-605 [In Russian].
7. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014 Oct 14; 35(39): 2733-79. doi: 10.1093/eurheartj/ehu284.
8. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. N Engl J Med. 2018 Aug 16; 379(7): 655-668. doi: 10.1056/NEJMra1710575.
9. Wu ZW, Yan H. Infective endocarditis in obstructive hypertrophic cardiomyopathy: a case series and literature review. Chin Med J (Engl). 2020 Dec 14; 134(9): 1125-1126. doi: 10.1097/CM9.0000000000001265.
10. Taguchi H, Nakaji S, Tasaki Y, et al. Mitral endocarditis in hypertrophic obstructive cardiomyopathy with leaflet perforation. Gen Thorac Cardiovasc Surg. 2021 Jun; 69(6): 1000-1003. doi: 10.1007/s11748-021-01592-7.
11. Bhandari A, Shah B, Mahaseth A, et al. Stroke in young secondary to infective endocarditis complicating hypertrophic cardiomyopathy. A case report. NJH 2019; 16(1): 57-9. doi: 10.3126/njh.v16i1.23904.
12. Пономарева Е.Ю., Никитина Н.М., Ландфанг С.В. Инфекционный эндокардит на фоне гипертрофической кардиомиопатии: клинические наблюдения. Клиницист. 2014; 8(1): 53-57. doi:10.17650/1818-8338-2014-1-53-57.
Ponomareva Y.Yu., Nikitina N.M., Landfang S.V. Infective endocarditis in the presence of hypertrophic cardiomyopathy: clinical cases. The Clinician. 2014; 8(1): 53-57. [In Russian].
13. Lee ME, Kemna M, Schultz AH, et al. A rare pediatric case of left ventricular outflow tract infective endocarditis in hypertrophic cardiomyopathy. JTCVS Techniques. 2020; 4: 281-282. doi: 10.1016/j.xjtc.2020.09.019.
14. Guo HC, Li JH, Jiang TY, et al. Comparison of clinical effects between percutaneous transluminal septal myocardial ablation and modified morrow septal myectomy on patients with hypertrophic cardiomyopathy. Chin Med J. 2018; 131: 527–531. doi: 10.4103/0366-6999.226075.

15. Dominguez F, Ramos A, Bouza E, et al. Infective endocarditis in hypertrophic cardiomyopathy: A multicenter, prospective, cohort study. Medicine (Baltimore). 2016 Jun; 95(26): e4008. doi: 10.1097/MD.0000000000004008.
16. Пономарева Е.Ю. Инфекционный эндокардит на фоне гипертрофической кардиомиопатии. Клиницист. 2013; 7 (3-4): 9-13. doi: 10.17650/1818-8338-2013-3-4-9-13.
Ponomareva E.Yu. Infective endocarditis in the presence of hypertrophic cardiomiopathy. The Clinician. 2013; 7 (3-4): 9-13 [In Russian].
17. Инфекционный эндокардит. Клинические рекомендации М3 Российской Федерации. 2016: 34.
Infective endocarditis. Clinical guidelines of the Ministry of Health of the Russian Federation. 2016: 34 [In Russian].
18. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul; 148(1): e1-e132. doi: 10.1016/j.jtcvs.2014.05.014.
19. Гипертрофическая кардиомиопатия. Клинические рекомендации М3 Российской Федерации. Москва. 2020: 151.
Hypertrophic cardiomyopathy. Clinical guidelines of the Ministry of Health of the Russian Federation. Moscow. 2020: 151. [In Russian].
20. Ommen S.R., Mital S., Burke M.A. et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2020; 76(25): e159-e240. doi:10.1016/j.jacc.2020.08.045.
21. Gersh BJ, Maron BJ, Bonow RO, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011 Dec 13; 124(24): 2761-96. doi: 10.1161/CIR.0b013e318223e230.
22. Sabater-Molina M, Pérez-Sánchez I, Hernández Del Rincón JP, et al. Genetics of hypertrophic cardiomyopathy: A review of current state. Clin Genet. 2018 Jan; 93(1): 3-14. doi: 10.1111/cge.13027.
23. Ватутин Н.Т., Тарадин Г.Г., Марон М.С. Гипертрофическая кардиомиопатия: генетические изменения, патогенез и патофизиология. Российский кардиологический журнал. 2014; (5): 35-42. doi: 10.15829/1560-4071-2014-5-35-42.
Vatutin N.T., Taradin G.G., Maron M.S. Hypertrophic cardiomyopathy: genetic alterations, pathogenesis and pathophysiology. Russian Journal of Cardiology. 2014; (5): 35-42 [In Russian].
24. Semsarian C, Davis L. The Wait is Over: The 2020 American Heart Association/American College of Cardiology (AHA/ACC) hypertrophic cardiomyopathy guidelines have arrived. Heart Lung Circ. 2021 Apr; 30(4): 465-468. doi: 10.1016/j.hlc.2021.02.002.
25. Bazan SGZ, Oliveira GO, Silveira CFDSMPD, et al. Hypertrophic cardiomyopathy: a review. Arq Bras Cardiol. 2020 Nov; 115(5): 927-935. doi: 10.36660/abc.20190802.
26. Williams L, Frenneaux M. Syncope in hypertrophic cardiomyopathy: mechanisms and consequences for treatment. Europace. 2007 Sep; 9 (9): 817-22. doi: 10.1093/europace/eum093.
27. Maron BJ, Rowin EJ, Casey SA, et al. What do patients with hypertrophic cardiomyopathy die from? Am J Cardiol. 2016; 117 (3): 434-5. doi: 10.1016/j.amjcard.2015.11.013.
28. Miller C.A. S., Maron M.S., Estes N.A. M III. et al. Safety, side effects and relative efficacy of medications for rhythm control of atrial fibrillation in hypertrophic cardiomyopathy. Am J Cardiol. 2019; 123 (11): 1859-1862. doi: 10.1016/j.amjcard.2019.02.051.
29. Alphonse P., Virk S., Collins J. et al. Prognostic impact of atrial fibrillation in hypertrophic cardiomyopathy: a systematic review. Clin Res Cardiol. 2021 Apr; 110(4): 544-554. doi: 10.1007/s00392-020-01730-w.
30. Игнатенко Г.А., Тарадин Г.Г., Ватутин Н.Т. и др. Фибрилляция предсердий при гипертрофической кардиомиопатии. Архивъ внутренней медицины. 2021; 11 (3): 173-185. doi:10.20514/2226-6704-2021-11-3-173-185.
Ignatenko G.A., Taradin G.G., Vatutin N.T., et al. Atrial fibrillation in hypertrophic cardiomyopathy. The Russian Archives of Internal Medicine. 2021; 11 (3): 173-185 [In Russian].
31. Mizia-Stec K., Caforio A.L. P., Charron P. et al. Atrial fibrillation, anticoagulation management and risk of stroke in the Cardiomyopathy/ Myocarditis registry of the EURObservational Research Programme of the European Society of Cardiology. ESC Heart Fail. 2020; 7 (6): 3601-9. doi: 10.1002/ehf2.12854.
32. Чумакова О.С. Гипертрофическая кардиомиопатия у пожилых: причины, диагностика, лечение. Терапевтический архив. 2020; 92 (9): 63-69. doi: 10.26442/00403660.2020.09.000558
Chumakova O.S. Hypertrophic cardiomyopathy in the elderly: causes, diagnosis, treatment. Terapevticheskij arhiv. 2020; 92 (9): 63–69 [In Russian].
33. Ватутин Н.Т., Тарадин Г.Г., Марон М.С. и др. Внезапная сердечная смерть у больных гипертрофической кардиомиопатией. Кардиология. 2016; 56 (1): 56-65.
Vatutin N.T., Taradin G.G., Maron M.S., et al. Sudden cardiac death in patients with hypertrophic cardiomyopathy. Kardiologiia. 2016 Jan; 56 (1): 56-65. doi: 10.18565/cardio.2016.1.56-65 [In Russian].
34. Collis R, Watkinson O, O'Mahony C, et al. Long-term outcomes for different surgical strategies to treat left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Eur J Heart Fail. 2018; 20: 398–405. doi: 10.1002/ejhf.1038.
35. Spirito P., Rapezzi C., Bellone P. et al. Infective endocarditis in hypertrophic cardiomyopathy: prevalence, incidence, and indications for antibiotic prophylaxis. Circulation. 1999 Apr 27; 99 (16): 2132-7. doi: 10.1161/01.cir.99.16.2132.
36. Wang P, Song L, Gao XJ, et al. [Clinical analysis of 14 infective endocarditis in patients with obstructive hypertrophic cardiomyopathy]. Zhonghua Nei Ke Za Zhi. 2020 Dec 1; 59 (12): 982-986. Chinese. doi: 10.3760/cma.j.cn112138-20200104-00003.
37. Sims JR, Anavekar NS, Bhatia S et al. Clinical, radiographic, and microbiologic features of infective endocarditis in patients with hypertrophic cardiomyopathy. Am J Cardiol 2018; 121: 480-484. doi: 10.1016/j.amjcard.2017.11.010.
38. Carrel T. Commentary: Endocarditis in hypertrophic cardiomyopathy: A reason to strengthen the guidelines? JTCVS Techniques 2020; 4: 286-7. doi: 10.1016/j.xjtc.2020.10.046.
39. Guler A, Aung SM, Cakal B, et al. Infective endocarditis complicating hypertrophic obstructive cardiomyopathy: is antibiotic prophylaxis

really unnecessary? Curr Cardiol Rev. 2013 Nov; 9 (4): 308-9. doi: 10.2174/1573403x09666131202142312.
40. Kumar M, Anstadt EJ, Lopetegui Lia N, et al. Streptococcus viridans endocarditis affecting all four valves. Cureus. 2019 May 10; 11 (5): e4635. doi: 10.7759/cureus.4635.
41. Данилов А.И., Козлов Р.С., Козлов С.Н. и др. Практика ведения пациентов с инфекционным эндокардитом в Российской Федерации. Антибиотики и химиотерапия 2017; 62 (1-2): 7-11. Danilov AI, Kozlov RS, Kozlov SN, Dekhnich AV. Real-life management of patients with infective endocarditis in the Russian Federation. Antibiotiki i himioterapiya 2017; 62 (1-2): 7-11 [In Russian].
42. Pachirat O, Klungboonkrong V, Tantisirin C. Infective endocarditis in hypertrophic cardiomyopathy — mural and aortic valve vegetations: a case report. J Med Assoc Thai. 2006 Apr; 89 (4): 522-6. PMID: 16696400.
43. Baddour LM, Wilson WR, Bayer AS, et al.; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015 Oct 13; 132 (15): 1435-86. doi: 10.1161/CIR.0000000000000296.
44. Jorge VC, Araújo AC, Grilo A, et al. Actinobacillus endocarditis associated with hypertrophic cardiomyopathy. BMJ Case Rep. 2012 Aug 13; 2012: bcr0420114140. doi: 10.1136/bcr.04.2011.4140.
45. Bitay M, Varga S, Babik B, et al. Infective endocarditis complicated with coronary artery septic embolization: is it worth to be mentioned? Case presentation and review of the literature. Rev Cardiovasc Med. 2019 Mar 30; 20 (1): 35-39. doi: 10.31083/j.rcm.2019.01.4241.
46. Zemanek D, Veselka J, Chmelova R. Infective endocarditis after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Int Heart J. 2008 May; 49 (3): 371-5. doi: 10.1536/ihj.49.371.
47. Casabé J, Fernández A, Renedo MF, et al. Infective endocarditis in hypertrophic cardiomyopathy. Rev Argent Cardiol 2015; 83 (4): 335-338.
48. Thornhill MH, Jones S, Prendergast B, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. Eur Heart J. 2018 Feb 14; 39 (7): 586-595. doi: 10.1093/eurheartj/ehx655.
49. Maron BJ, Lever H. In defense of antimicrobial prophylaxis for prevention of infective endocarditis in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009 Dec 8; 54 (24): 2339-40; author reply 2340. doi: 10.1016/j.jacc.2009.07.050.
50. Noel N, Naheed Z. Hypertrophic cardiomyopathy: role of current recommendations by the american heart association for infective endocarditis. Pediatr Cardiol. 2013 Mar; 34 (3): 709-11. doi: 10.1007/s00246-012-0324-6.
51. Hubers SA, DeSimone DC, Gersh BJ, et al. Infective endocarditis: a contemporary review. Mayo Clin Proc. 2020 May; 95 (5): 982-997. doi: 10.1016/j.mayocp.2019.12.008.

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ЛЕКАРСТВЕННАЯ СОВМЕСТИМОСТЬ В ЛЕЧЕНИИ ХРОНИЧЕСКИХ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ

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Drug Compatibility in Treatment of Chronic Infectious Diseases

Резюме

В статье рассматриваются вопросы особенностей фармакотерапии у коморбидных пациентов с хроническими инфекционными заболеваниями и сопутствующей соматической патологией в условиях полипрагмазии, принципы метаболизма лекарственных препаратов, варианты нежелательных явлений и межлекарственного взаимодействия, возможностей эффективного комбинирования лекарственных средств. Цель: обосновать возможность и подчеркнуть актуальность дополнительного поиска и создания наиболее оптимальных комбинаций лекарственных средств в условиях длительной и массивной фармакотерапии, которые смогли бы, за счет выигрышного межлекарственного взаимодействия, оптимизации режима, способа введения препаратов и полиморбидности терапевтического эффекта, уменьшить фармакологическую нагрузку при сохранении эффективности лечения, повысить приверженность пациентов к лекарственной терапии.

Ключевые слова: *лекарственная совместимость, межлекарственное взаимодействие, фармакотерапия, полипрагмазия, хронические инфекционные болезни, ВИЧ-инфекция, антиретровирусная терапия, туберкулез, коморбидность*

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Abstract

The article considers the features of pharmacotherapy of patients with chronic infectious diseases and co-morbidities in conditions of polypharmacy, the principles of drug metabolism, variants of adverse effects and drug-drug interactions, the possibilities of effective drug combinations. The purpose is to substantiate the possibility and emphasize the relevance of the additional search of the creation of the most optimal combinations of drugs for long-term and massive pharmacotherapy, that could be due to a beneficial drug-drug interaction, optimization of the regimen, route of drug administration and multitarget of the therapeutic effect, reduce the pharmacological load while maintaining the effectiveness of the treatment, increase patient adherence to drug therapy.

Key words: *drug compatibility, drug-drug interactions, pharmacotherapy, polypharmacy, chronic infectious diseases, HIV infection, anti-retroviral therapy, tuberculosis, comorbidity*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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ADR — adverse drug reaction, AE — adverse event, ART — antiretroviral therapy, CHB — chronic hepatitis B, CHC — chronic hepatitis C, CHD — chronic hepatitis D, HIV — human immunodeficiency virus, MP — medicinal product, NADPH — reduced form of nicotinamide adenine dinucleotide phosphate, NAT — N-acetyltransferase, PT — pharmacogenetic testing, TI — therapeutic index

Introduction

Since the time of Hippocrates, medicine has followed this principle: treat the patient, not just the disease. This means that treatment always requires a personal approach and comprehensive strategy. In the case of chronic disease, pharmacotherapy ranks top alongside non-drug methods, regimen and surgical treatment. In very rare cases, a patient is going to take only one agent. Therapy usually includes 3 to 5–6 or more drug products that are well-established in clinical practice due to their effect on different pathogenetic mechanisms.

Using effective, tolerable and pharmacologically compatible drug products combinations is of particular importance.

Some cases require optimization of the drug administration route aimed either at providing a prolonged effect or better delivery to the epicenter of the pathological process. With regard to antimicrobial resistance, the development of fixed-dose drug combinations with maximum effectiveness and potentiating effect is of special importance. In such cases, effectiveness in relation to an infectious agent should be combined with a minimum effect on the macroorganism, if possible.

Adverse Drug Events

When a relationship is found between an adverse event (AE) and the intake of a medicinal product (MP), it is considered an adverse drug reaction (ADR), that is, a pathological reaction that develops when using conventional doses of medications. The reliability of the association of AEs with a particular drug is assessed by the sum of points calculated using the Naranjo Algorithm [1].

ADRs are classified by type, etiopathogenetic principle, the severity of the clinical course, clinical outcomes, incidence, reliability grade, and pattern of development (Table 1).

The development of prescription patterns for the management of tuberculosis, HIV, viral hepatitides and secondary infectious and non-infectious diseases that imply a high pharmacological load is extremely significant. A specific feature of chronic infectious disease is the duration of drug administration. With the average treatment period of 8–12 weeks, chronic hepatitis C (CHC) is a good example in that context. However, the average intensive phase of tuberculosis treatment is six months. Human immunodeficiency virus (HIV) infection should be managed for life; no elimination strategies have been invented. In most cases, chronic hepatitis B (CHB) should be managed for life as well. Recent studies of the bulevirtide agent used in chronic hepatitis D (CHD) treatment revealed that the suppression of the viral agent also requires a very long, possibly lifelong administration of the drug that causes tolerance issues [6].

Table 1. Classification of adverse drug reactions

Classification	Adverse drug reactions
According to the type [2]	Type A — predictable Type B — unpredictable Type C — with long-term use (dependence, withdrawal syndrome) Type D — delayed (carcinogenicity, teratogenicity, etc.)
According to the etiopathogenetic principle [3]	Toxic reactions Effects due to the pharmacological features of drugs True allergic reactions Pseudoallergic reaction Idiosyncrasy — genetically determined perverted pharmacological response to the first taking of drugs Psychogenic adverse reactions Iatrogenic adverse effects
According to the severity of the clinical course [4]	Light Moderate severity Severe (requiring withdrawal of drugs, additional treatment, and increased hospitalization time)
According to clinical outcomes [4]	Serious (resulting in the death of the patient, life-threatening conditions, the need for emergency hospitalization or the increase of the time of hospitalization. the development of genetic disorders, developmental defects, malignant and benign formations, decrease in vital activity for a period of 3 months or more, disability of the patient) Not serious
According to the frequency of occurrence [5]	Very frequent — occur in more than 10% of patients taking drugs Frequent — develop in 1-10% of patients Less frequent-develop in 0.1-1% of patients Rare — develop in 0.01-0.1% of cases Very rare — develop in less than 0,01% of cases
According to the accuracy (Naranjo scale) [1]	>9 — definite connection of the development of adverse reaction with drug intake 5-8 — probable connection 1-4 — possible connection

Perfect MP should have a wide therapeutic range; maximum efficiency preferably confirmed by the patient's self-assessment; minimal impact on the patient's lifestyle as well as a comfortable administration schedule; it also should not affect basic physiological functions (appetite, physical activity, circadian rhythms, sexual function, weight gain and loss, including abnormal one, i.e., lipodystrophy); such MP should be characterized by a good drug interaction profile, controlled metabolism, optimal elimination rate.

Metabolism of Medicinal Products

Metabolism, regardless of its mechanism, aims to facilitate the MP elimination process. The main goal of metabolism is the inactivation of the MP. However, several metabolites are pharmacologically active, in some cases — more active than the parent compound. In terms of stable pharmacokinetics, drug elimination is as important as absorption, release, and delivery.

Pro-drug is a drug that has little or no intrinsic pharmacological activity but has active metabolites that can provide more efficient delivery of the active ingredient.

MP metabolism can be performed by oxidation, reduction, hydrolysis, hydration, conjugation, or isomerization. Enzymes involved in metabolism are present in many tissues. However, they are mainly concentrated in the liver.

Metabolic reactions can be divided into two types, which can usually be combined in two consecutive phases. Phase I reactions are non-synthetic and involve the formation of new functional groups, or the modification of existing ones, or molecule cleavage (by oxidation, reduction, or hydrolysis). Phase II reactions are synthetic

and involve conjugation with endogenous substances (e.g. glucuronic acid, sulfate, glycine). Metabolites formed as a result of synthetic reactions have more ionized groups (polarity) and are excreted by kidneys (with urine) and the liver (with bile) more easily than metabolites formed during non-synthetic reactions. Some MPs undergo reactions of only one phase (I or II).

The most important enzymatic system of phase I metabolism is the microsomal oxidation system, which includes Cytochrome P-450, a family of microsomal isoenzymes that catalyze the oxidation of most MPs. The source of required electrons, in this case, is NADPH-cytochrome P450 reductase, a flavoprotein that transfers electrons from NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) to cytochrome P450.

Isoenzymes of the cytochrome P450 family are represented by 17 families; the most common isoforms are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4; they can be induced and inhibited by many agents and substances, as well as food components, which explains the mechanism of many drug interactions when one agent increases the toxicity or reduces the therapeutic effect of another [7, 8].

Conjugation makes most medications more soluble, facilitating their elimination by the kidneys. Glucuronidation is the most common way of conjugation and the only synthetic reaction that occurs in the system of liver microsomal enzymes. Hence, it changes with age. Glucuronides are secreted into bile and are also eliminated with urine.

Conjugation with glutamine or glycine leads to products that are easily eliminated with urine and are secreted into bile only in small amounts. Conjugation by acetylation or sulfonation is also possible. Sulfated esters are also polar and are easily eliminated with urine. The intensity of these processes is no longer dependent on age.

The higher the concentration of MP, the more intense its elimination. However, the process has a saturation limit in the form of certain renal or hepatic clearance, which can lead to toxic effects.

The metabolic rate of MP varies depending on genetic factors, comorbidities, age, and drug interactions. A decreased metabolic rate increases the toxicity of drugs, and fast metabolism decreases their effectiveness.

The effect of age on the functional activity of the liver is inconclusive. Drug substances metabolized by the microsomal enzyme system, characterized by decreasing effectiveness with age, reach higher concentrations in elderly patients and have a long half-life. In newborns, the liver microsomal enzyme system is not yet developed, so the metabolism of many MPs also becomes difficult. The process of glucuronide formation is slower in newborns, which can cause serious adverse effects, for example, in the case of chloramphenicol use [9].

MP metabolism can have significant individual differences associated with the polymorphism of genes that encode enzyme systems — and this fact should also be considered when choosing a therapy. Point mutations, i.e., single nucleotide polymorphisms, are very diverse. They can affect the aspects of pharmacokinetics, pharmacodynamics, interfere with the structure of genes responsible for encoding enzymes in both biotransformation phase I (cytochrome P450 isoenzymes, butyrylcholinesterase, paraoxonase) and phase II (N-acetyl transferase, thiopurine methyltransferase epoxide hydrolase).

For example, several MPs, like other exogenous substances, are metabolized with the help of isoenzymes arylamine-N-acetyltransferases: NAT1 and NAT2. The activity of each of them is genetically programmed and determines the rate of acetylation of a particular substance; depending on this rate, fast and slow acetylators are released. Acetylator status can greatly affect the pharmacokinetics of drugs.

The effect of genotype on the development of AEs when using the anti-tuberculosis drug isoniazid is well known. Even when using average therapeutic daily doses, individuals with slow acetylation phenotype have numerous adverse reactions in the form of peripheral neuritis [10], while fast acetylators, on the other hand, have a low response to isoniazid therapy. Most of the results demonstrated that individuals with slow acetylation phenotype are more prone to hepatotoxicity when taking this agent [11].

Pharmacogenetic Testing

Pharmacogenetic testing (PT) helps to identify specific genetic features of individual drug efficacy and, ideally, should precede any pharmacological exposure. The range of studied genes is constantly expanding. There is a great need for algorithms and clinical guidelines on this issue [12].

PT is especially important when one requires a therapy with oral anticoagulants (warfarin, acenocoumarol, phenylin) or prolonged use of antipsychotics, voriconazole, abacavir, hormonal contraceptives, azathioprine, irinotecan; and for the study of hepato- and

neurotoxicity of anti-tuberculosis agents (isoniazid, pyrazinamide, rifampicin) [13]. The ineffectiveness of clopidogrel can become critical in the management of acute myocardial ischemia, and using anticoagulants in almost 30% of cases causes bleeding. PT revealed that sensitivity to warfarin and clopidogrel in a fairly large percentage of cases significantly differs from the general population: in particular, in the study cohort, 22% of patients were resistant to clopidogrel and 21% were highly sensitive to warfarin. A personalized approach to warfarin dosing using a special PT-based algorithm reduces the frequency of bleeding by 4.5 times [14]. PT in relation to clopidogrel is of particular importance in terms of the management of the post-COVID syndrome.

Monitoring drug concentration in blood and studying concentration in other biological substrates can help obtain important information as part of set tasks. Work in this area is vital [15–17]. Studying drug concentration in blood by liquid chromatography and mass spectrometry is an integral part of assessing the individual tolerance of MP.

Along with PT, high-potential areas of personalized medicine include pharmaco-transcriptomic tests and sequencing (determination of the primary nucleotide sequence) of an infectious agent [18].

Doses of Medicinal Products

The classical therapeutic school allows for varying doses of medicinal products depending on the severity of the clinical presentation, the localization of the process (for example, local infection, sepsis, meningitis); the dosage of MP can vary depending on the function of the kidneys or liver.

In case of mass therapeutic interventions (treatment program for the management of HIV and the elimination of hepatitis C), fixed-dose combinations (FCD) are crucial. Fixed-dose combinations are also effective for non-infectious diseases: combined pain relievers, agents for managing hypertension, diabetes mellitus, bronchial asthma, which reduce the number of tablets by 2–3 times.

The demand for such drugs is due to the decreased frequency of administration, decreased total effective dosages and increased compliance. Using combined drugs also demonstrates greater clinical efficacy than separate administration of agents, which is confirmed by clinical trials [19].

Dose, frequency of administration, and therapeutic index (TI) are determined based on the dose-response relationship. TI is the ratio of the maximum dose of a drug with no toxicity to the dose that produces the required effect. It allows assessing the effectiveness and safety of a drug. If a combination of drugs has a potentiating effect, the drug can be used in lower dosing, which increases the TI.

Agents for managing infectious diseases (HIV, viral hepatitides, other infectious diseases) are not used in subtherapeutic concentrations. This is due to the potential variability of pathogens, namely, the development of drug resistance mutations. In these conditions, a decrease in MP concentration below a certain level is dangerous.

Concentration of MP in various media is also of interest. For example, the penetration of antiretroviral therapy (ART) components into different matrices is always analyzed based on the changes in clinical manifestations of HIV; its possible effect on virus reservoirs in various tissues is being studied. Clinical polymorphism and the precedence of affecting certain targets (lymph nodes, central nervous system, internal organs) should also be investigated, including in relation to possible drug exposure. For example, the severity of HIV-associated lymphadenopathy and its response to antiviral treatment is believed to be associated with variability in the penetration of ART components into lymph node tissues, which impacts the overall effectiveness of treatment.

Genetic differences in the pharmacokinetics of drug metabolism may influence the dosage of the drug. For example, isoniazid doses are selected depending on the acetylation level [20].

Due to the age-related features of pharmacokinetics, doses of several agents should also be changed [21].

Microbial translocation with the development of systemic inflammation [22], bacterial overgrowth syndrome, enteropathy, impaired microbiota that leads to inflammatory changes in the intestinal wall [23], and specific intestinal damage by MAC infection can lead to a significantly decreased concentration of drugs in the blood due to impaired diffusion processes and active transport in the intestines [24–26]. At the same time, medicinal products themselves can affect intestinal microbiota, altering drug absorption and closing the vicious circle [27].

In phthisiatric practice, the transition from intensive treatment to a continuation phase has been used for a long time. However, in the management of HIV, treatment phases represent a new direction. The transition from triple regimens to dual regimens, especially with tenofovir withdrawal, ensures complete safety while

maintaining effectiveness (G. D. Kaminsky et al., 2020). However, co-infection of hepatitis B virus does not allow using treatment regimens without tenofovir.

Drug-Drug Interactions

The range of drug interactions is very wide; it is determined by both pharmacokinetic and pharmacodynamic mechanisms that can lead to synergy, or can be neutral, or, on the contrary, lead to mutual suppression. Possible development of additional side effects of varying severity, up to fatal ones, cannot be excluded. When analyzing an agent before its release into clinical practice, maximum attention is paid to drug incompatibility.

There are many examples of successful combinations that have proven to be effective within the established treatment regimens. These include ART, anti-tuberculosis therapy (ATT), combined antihypertensive therapy, combinations of agents in anesthesiology; all these have undeniably proven their advantage over monotherapy.

Possible positive aspects of the combination of drugs with multidirectional effects stay in the background. There is virtually no information in literature sources that is confirmed by clinical trials of the mutual efficacy of ART and ATT drugs, pharmacotherapy of opportunistic infections, and somatic comorbidities. Evaluation of drug combinations always implies just the assessment of incompatibility; in this regard, public databases such as the Liverpool sites are used. www.hiv-druginteractions.org [28], www.hep-druginteractions.org [29]. Compatibility and potentiation stay in the background. This cohort of patients is exposed to one of the most extensive and prolonged pharmacological interventions; the list of medications sometimes includes ten items or more, and their combination is usually not evaluated from a positive perspective.

Winning combinations are possible. One agent can have several practical targets. For example, nucleotide and nucleoside analogs (tenofovir) affect the replication of both HIV and hepatitis B viruses. Dapagliflozin, which is used to manage diabetes mellitus, has been shown to be effective in reducing mortality in cases of heart failure with reduced ejection fraction in the absence of diabetes [30] due to its diuretic and hypotensive effect.

All pharmacokinetic and pharmacodynamic factors that can be analyzed should be considered and compared: drug metabolism pathways, association with groups with the specific features of drug metabolism, specificity of transport, permeability to substrates and distribution, way and rate of elimination, also considering comorbidities that change the elimination rate, the mechanism of the action itself.

Today, HIV and hepatitides are often managed by internists. Considering the universal availability of treatment and required global coverage, an internist will become the primary physician in this area in the future.

When treating patients with HIV, attention is paid to comorbidities that reduce the life expectancy of this cohort due to dyslipidemia, insulin resistance, disorders of bone tissue metabolism induced by the virus and medications, as well as immune complex kidney disease, thrombocytopenia, and encephalopathy of mixed complex origin.

Due to active measures to detect and manage HIV, the life expectancy of individuals with HIV is progressively increasing, and with high compliance, it approaches the life expectancy in the general population. As a result, the average age in this cohort is increasing, and the proportion of elderly patients receiving ART is growing. Therefore, the prevalence of chronic comorbidities and metabolic disorders is increasing, and drug therapy issues in gerontological practice are becoming relevant, complicating the choice of a treatment regimen [31, 32]. Special features of pharmacokinetics (absorption, distribution, metabolism, elimination) in elderly and senile patients increase the frequency of adverse drug reactions by 2–3 times and raise the need for more careful monitoring of treatment tolerance.

Careful attention is focused on gerontological problems, the significance and prevalence of metabolic disorders in the HIV-infected cohort, namely dyslipidemia, lipodystrophy, impaired mineral metabolism, insulin resistance [31–33].

The peculiarities of liver pathomorphology of a polyetiological nature in comorbid patients have high requirements for the choice of medications [34, 35]. Despite that timely and rational ART has demonstrated its hepatological safety and even some antifibrotic effect in cases of concomitant viral hepatitis [36], such a comorbid background significantly increases the incidence of toxic and drug hepatitides in the treatment of tuberculosis, especially generalized drug-resistant forms.

The number of medicinal products that should be taken constantly, together with AEs, leads to depression in patients and adversely affect their compliance. The fact that the patient is already taking many MPs further reduces his/her willingness to take concomitant glucose-lowering, antihypertensive, hypurcemic, lipid-lowering therapy.

Table 2. *Drug interactions between anti–TB and antiretroviral drugs*

	ATV/r	DRV/r	LPV/r	SQV	RTV	DOR	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	ABC	FTC и 3TC	F/TAF	TDF	ZDV
Рифампицин Rifampicin	–⇓72%	–⇓57%	–⇓75%	–⇓	–	–⇓82%	**Н**⇓26%	–⇓	–⇓58%	–⇓80%	**С**⇓q	**С**⇓54%[r]	–⇓	–⇓	**С**⇓40%	+↔	+↔	С⇓p	+⇓12%	**С**⇓47%
Рифапентин Rifapentine	–⇓	–⇓	С⇓	С⇓	С	–⇓	Н⇓	–⇓	С⇓	–⇓	**С**⇓q	**С**⇓s	–⇓	–⇓	С⇓	+↔	+↔	С⇓p	+↔	+↔
Рифабутин Rifabutin	С↑	С↑⇑50%	С↑	С⇓	С	**С**⇓50%[l]	С↓38%	**С**⇓37%	Н↑17%	**С**⇓42%[m]	Сn	+↔	С↑⇓	С↑⇓	+⇑19%	+↔	+↔	С⇓p	+↔	+↔
Изониазид Isoniazid	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Пиразинамид Pyrazinamid	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Этамбутол Ethambutol	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Стрептомицин Streptomycin	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	С↔[a]	+↔	+↔	+↔	+↔	С↔[a]	+↔
Амикацин Amikacin	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	С↔[a]	+↔	+↔	+↔	+↔	С↔[a]	+↔
Канамицин Kanamycin	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	С↔[a]	+↔	+↔	+↔	+↔	С↔[a]	+↔
Капреомицин	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	Н↑[c]	Н↑⇑[b]	С↑⇑[a,d]	+↔	+↔	Н↑⇑[e]	Н↑⇑[b]	С↑⇑[a]	+↔
Офлоксацин Ofloxacin	С♥	+	С♥	–♥	+	+	+	+	+	Н♥	+	+	+	+	+	+	+	+	+	+
Левофлоксацин Levofloxacin	С♥	+	С♥	–♥	+	+	+	+	+	С♥	+	+	+	+	+	+	+	+	+	+
Моксифлоксацин Moxifloxacin	С↓♥	С↓	С↓♥	–♥	С	+↔	С↓	С↓	+↔	С↔♥	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Бедаквилин Bedaquilin	С↑♥	С↑	С↑62%♥	–♥	С	+↔	С↓18%	С↓	+↑3%	Н↔♥	+↔	+↔	С↑	С↑	+↔	+↔	+↔	+↔	+↔	+↔
Циклосерин Cycloserine	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Этионамид Etionamid	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
ПАСК PAS	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	Н↑	Н↑⇑[i]	Н↑⇑[j]	+↔	Н⇓	Н↑⇑[k]	Н↑⇑[i]	Н↑⇑	+↔
Линезолид Linezolid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Меропенем Meropenem	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

	ATV/r	DRV/r	LPV/r	SQV	RTV	DOR	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	ABC	FTC и 3TC	F/TAF	TDF	ZDV
Имипенем + циластатин Imipinem + cylastatin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Амоксициллин + клавулановая кислота Amoxicillin + clavulanic acid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Условные обозначения:

The power and significance of drug–drug interactions:

+ No clinically significant interactions are expected

– The combination of drugs is not recommended

H Potential low-intensity interaction: the combination of drugs is possible, monitoring is necessary, but dose correction is probably not required.

C Potential interaction: the combination of drugs is possible; however, the dose correction or constant monitoring of efficiency and safety is necessary

Comments:

↑ The enhancing of the effect of anti–TB drugs is possible

↓ The weakening of the effect of anti–TB drugs is possible

↔ No significant influence on the drug effect is expected

⇑ The increase of the ART effect is possible

⇓ The weakening of the effect of ART is possible

♥ The increase of the cardiotoxicity (one or both drugs may cause prolongation of the QT and/or PR interval). The ECG monitoring is recommended, according to the combination of the drug with ATV or LPV

% The figures shown in the table express the increase or decrease in AUC observed in studies of drug–drug interactions.

a Drug combinations should be avoided due to the increased risk of nephrotoxicity. If co–prescription of drugs is unavoidable, careful monitoring of kidney function is necessary.

b Co–prescription of drugs may increase the concentration of capreomycin and emtricitabine. The intensity of monitoring of kidney function is determined by the clinical situation.

c The risk of nephrotoxicity of aminoglycosides depends on the dose and duration of administration. The intensity of monitoring of kidney function and the need for dos correction of antiretroviral drugs is determined by the clinical situation.

d Co–prescription may increase concentrations of capreomycin, emtricitabine, and tenofovir. The intensity of monitoring of kidney function is determined by the clinical situation.

e Co-prescription may increase concentrations of capreomycin, emtricitabine or lamivudine. The intensity of monitoring of kidney function is determined by the clinical situation.

i Co–prescription may increase the concentration of PAS and emtricitabine in the blood.

j Co–prescription may increase concentrations of PAS, emtricitabine and tenofovir in the blood.

k Co–prescription may increase concentration of PAS and emtricitabine or lamivudine in the blood.

l In the instructions for DOR, it is recommended to increase the dose of this drug to 100 mg 2 times a day when it is assigned together with rifabutin. DOR 100 mg twice a day should be continued for at least 2 weeks after discontinuation of rifabutin due to ongoing induction of cytochrome P450.

m The dose of rilpivirin should be increased to 50 mg 1 time a day when using the drug in combination with rifabutin. After discontinuation of rifabutin, the dose of rilpivirine should be reduced to 25 mg, but not earlier than 2 weeks later (due to the ongoing induction of cytochrome P450).

n Without protease inhibitors in the treatment regimen, there is no need to correct the dose of MVC. In combination with protease inhibitors (except TPV/ r, FPV/r), it is necessary to prescribe MVC at a dose of 150 mg 2 times a day.

p Co–prescription may decrease the effect of tenofovir alafenamide; no significant influence on emtricitabine effect is expected.

q It is necessary to prescribe MVC at a dose of 600 mg 2 times a day.

r Patients who have not previously taken integrase inhibitors should be prescribed dolutegravir at a dose of 50 mg 2 times a day. In cases of proven or suspected by clinical data resistance to integrase inhibitors, an alternative to the use of rifampicin should be sought, if possible.

s Taking into account the results of studying the interaction of dolutegravir with rifabutin and rifampicin, it is necessary to consider the possibility of increasing the dose of dolutegravir to 50 mg 2 times a day when it is prescribed with rifapentine.

Infectious and phthisiatric patients that are interested in their health are compliant and disciplined with regard to the adherence to their treatment regimen: such patients give special attention to compliance, and most of them understand its significance for the prognosis.

The issue of a patient's self-assessment of drug effectiveness is very relevant; it motivates the patient to undergo treatment and increases compliance. A combination of infectious disease, tuberculosis and chronic somatic diseases raises the issue of minimizing drug exposure. The number of dosage forms taken, in addition to their effectiveness, cost, and frequency of administration, is one of the most important factors of compliance that makes the development of combined agents very promising and desirable.

A rational combination of MPs should be confirmed clinically.

Such combinations can be made considering various criteria available for assessment: pharmacokinetic factors — positive effect on the bioavailability of components, mutual change in metabolism or elimination that allows reducing the dosage of components; pharmacodynamic benefits — mutual potentiation due to the effect on different links of the pathological process, therapeutic value for the treatment of comorbidities, mutual offsetting of side effects with an increase in TI of components and, finally, optimization of the administration regimen.

When choosing treatment regimens, infectious disease experts are usually guided by the summary tables of drug interactions. Careful consideration of the interaction mechanism can help to find different options. So, using the example of the interaction of ART and antituberculosis agents, combinations were found, where the concentration of a particular drug increases or decreases, or additional side effects arise in the form of increased cardio- or nephrotoxicity (Table 2). This should be considered when choosing a therapy.

When treating patients with HIV complicated by secondary diseases, tuberculosis, hepatitides, a wide range of somatotropic pharmacological agents should be added to etiotropic therapy (Table 3).

Let us analyze a case. The patient is taking a first-line scheme for the management of HIV: efavirenz, tenofovir, and lamivudine. He is also receiving a fixed combination of amlodipine, indapamide and perindopril for the management of hypertension (essential arterial hypertension). The patient started complaining of fatigue, low mood, insomnia that prevented him from driving the car he had just purchased. In order to prevent possible undesirable effects of efavirenz on the central nervous system and as a "reward therapy" after taking three tablets for many years, the patient is prescribed FDC elvitegravir / cobicistat / emtricitabine / tenofovir / alafenamide. According to the physician, such a regimen will eliminate the long-term osteorenal toxicity of tenofovir (replaced with tenofovir alafenamide) and enhance the effectiveness of suppressing the virus: viral replication inhibition index of emtricitabine is higher than that of lamivudine. Is the physician doing the right thing? No. Because amlodipine is metabolized by CYP3A4, prescribing a drug with a cobicistat booster will increase amlodipine concentration twofold. Indapamide is metabolized by cytochrome P450, and the cobicistat booster also potentially increases indapamide concentration. This can result in critical hypotension and deterioration of the patient's condition. In this case, one should either consider an alternative agent for managing HIV or adjust hypertension therapy to achieve total pharmacological compatibility. It is also possible to change both drug schemes.

The use of these drugs is determined by the need to manage the main diseases and their complications, the need to correct AEs of etiotropic treatment regimens, and the required symptomatic treatment. The presence and aggravation of somatic comorbidities require the involvement of specialists in various areas: therapist, cardiologist, gastroenterologist, pulmonologist, neurologist, ophthalmologist, urologist; they should also know the peculiarities of interaction of special agents with basic therapy.

Here is an example of the interaction of antihypertensive and antiretroviral agents (Table 4). It should be noted that only four ART agents have no drug interactions with antihypertensive drugs. Other combinations require careful attention due to the mutual effect on the concentration level. Two antihypertensive drugs — lercanidipine and aliskiren — require special attention, up to the avoidance of these combinations, due to a very significant increase in their concentrations. The rest should be monitored by the clinician during dosage selection in relation to the severity of clinical effect and AE. Antiretroviral drugs can affect the concentration of antihypertensive drugs in both directions. However, the most commonly used antihypertensive drugs have less effect — in some cases, they only increase the concentration of antiretroviral drugs.

Table 3. The most commonly used drugs in the treatment of patients with chronic infectious diseases

ATC-Classification System of Drugs	Subgroup	Examples of drugs
Digestive tract and metabolism	Proton pump inhibitors	Omeprazole, rabeprazole
	Antiemetics	Ondansetron
	Motility stimulants	Metoclopramide, trimebutine
	Gastroprotectors	Bismuth preparations
	Hepatoprotectors	Ademetionine, UDCH, phospholipids, milk thistle preparations
	Enzymes	Pancreatin
	Laxatives	Lactulose, sodium picosulfate
	Carminative	Simethicone
	Antispasmodics	Drotaverine, mebeverin
Hematopoiesis and blood	Stimulants of hematopoiesis	Iron preparations, erythropoietin
	Hemostatic drugs	Eltrombopag
The cardiovascular system	ACE inhibitor, Angiotensin II receptor blockers	Enalapril, perindopril, losartan, amlodipine
	Calcium channel blockers	Amlodipin
	Beta-blockers	Bisoprolol, metoprolol
	Hypolipidemic drug/	Atorvastatin, fenofibrate
	Diuretics	Furosemide, torasemide, indapamid
Hormones for systemic use	Systemic corticosteroids	Dexamethasone, prednisone
Antimicrobials for systemic use	Penicillins	Amoxicillin/clavulanate
	Macrolides	Clarithromycin, Azithromycin
	Aminoglycosides	Amikacin
	Cephalosprorins	Ceftriaxone
	Fluoroquinolones	Levofloxacin, Moxifloxacin
	Sulfonamides	Sulfamethoxazole + Trimethoprim
	Antimycotics	Fluconazole, voriconazole
Antineoplastic and immunomodulating agents	Antineoplastic antibiotics	Doxorubicin
	Colony-stimulating factors	Filgrastim
Musculoskeletal system	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Diclofenac, Ibuprofen, Ketoprofen
	Antigout Agents	Allopurinol, febuxostat
Nervous system	Analgesics	Tramadol, paracetamol, acetylsalicylic acid
	Anticonvulsants	Carbamazepine, gabapentin
	Benzodiazepines	Bromodihydrochlorophenylbenzodiazepine
	Antidepressant	Amitriptilline, escitalopram, sertraline
Respiratory system	Mucolytics	Ambroxol, acetylcysteine
	Antitussives	Butamirat
	Antihistamines	Chloropyramine, cetirizine, Loratadine / Desloratadine

Note: *ATC — classification of drugs — anatomical-therapeutic-chemical classification of drugs

Table 4. *Interactions between ARVT and hypotensive therapy*

АРТ/ ARVT	АГП/ AHD	иАПФ/ ACE inhibitors	БРА/ Angiotensin II receptor blockers					БКК/ Calcium channel blockers					Диуретики/ Diuretics						β-блокаторы/ β-blockers				Агонисты I_1- рецепторов/ I_1 receptor agonists		Другие/ Other		
		Каптоприл Рамиприл Эналаприл Периндоприл	Лозартан	Ирбесартан	Телмисартан	Валсартан	Азилсартан	Нифедипин	Амлодипин	Дилтиазем	Лерканидипин	Верапамил	Фуросемид	Торасемид	Индапамид	Гидрохлортиазид	Хлорталидон	Спиронолактон	Атенолол	Бисопролол	Метопролол	Небиволол	Моксонидин	Рилменидин	Доксазозин	Сакубитрил	Алискирен
НИОТ NRTI	3TC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↑E	-	-	-	-	-	-	-	-
	ABC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	TDF	-	-	-	-	-	-	-	-	-	-	E	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	TAF	-	-	-	-	-	-	-	-	-	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FTC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ННИОТ NNRTI	NVP	-	-	-	-	-	-	↓	↓	↓	↓	↓	-	-	-	↓	-	-	-	-	-	-	-	-	↓	-	-
	EFV	-	↑	↑	-	-	-	↓	↓	↓	↓	↓	-	↑	↓	↓	-	-	-	-	-	-	-	-	↓	-	-
	ETV	-	↑	↑	-	-	-	↓	↓	↓E	↓	↓	-	↑	-	↓	-	-	-	-	-	-	-	-	↓	-	↑
	RPV	-	-	-	-	-	-	↓	↓	E	↓	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	DOR	-	-	-	-	-	-	-	-	E	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ИП PI	ATV	-	↓	↓	-	↑	-	↑	↑	↑		↑	-	↓	↑	↑	-	-	↑	↑	↑	-	-	-	↑	↑	□
	LPV/r	-	↓	↓	-	↑	-	↑	↑	↑	□	↑	-	-	↑	↑	-	-	↑	↑	↑	↑	-	-	↑	↑	□
	DRV/r	-	↓	↓	-	↑	-	↑	↑	↑	□	↑	-	↓	-	↑	-	-	↑	-	↑	-	-	-	↑	↑	-
	FPV	-	-	-	-	↑	-	↑	↑	↑	↑	↑	-	-	-	↑	-	-	-	-	↑	-	-	-	↑	↑	-
	RTV		-	-	-	-	-	-	-	-	□	-	-	-	-	-	-	-	-	-							□
ИИ II	RAL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	DTG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↑	-	-	-	-	-	-	-	-
	EVG/c	-	↓	↓	-	-	-	↑	↑	↑	□	↑	-	↓	↑	↑	-	-	↑	↑	↑	↑	-	-	↑	-	□
	BIC	-	-	-	-	-	-	-	-	E	-	E	-	-	-	-	-	-	↑	-	-	-	-	-	-	-	-
ИРП PRI	MVC	-	-	-	-	-	-	-	-	E	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	E	-

Symbols:

↑	Increased concentration of AHD (antihypertensive drug)
□	Significant increase in concentration AHD, incompatibility
↓	Increase in concentration AHD
E	Increase in concentration ARVT
↑E, ↓E	Simultaneous concentration change AHD and ARVT
АГП (AHD)	Antihypertensive drug
НИОТ(NRTI)	Nucleoside reverse transcriptase inhibitors
ННИОТ (NNRTI)	Non-nucleoside reverse transcriptase inhibitors
ИРП (PRI)	Penetration receptor inhibitors
NVP	Nevirapine
EFV	Efavirenz
ETV	Etravirine
RPV	Rilpivirine
ИП (PI)	Protease inhibitors
ATV	Atazanavir
LPV/r	Lopinavir / ritonavir
RTV	Ritonavir
SQV-inv	Saquinavir
FPV	Fosamprenavir
DRV	Darunavir
II	Integrase inhibitors
RAL	Raltegravir
DTG	Dolutegravir
EVG/c	Elvitegravir/cobicistat
BIC	Bictegravir
MVC	Maraviroc
ENF	Enfuvirtide

Clinicians have accumulated valuable empirical evidence in the combined use of drugs, which could lead to widespread implementation when objectified using informative research tools, clinical and observational studies.

Therefore, the analysis of drug combinations from the perspective of their favorable effects is a promising area in medicine and an important object of research interest; available tools can help provide an objective presentation that will comply with the concept of evidence-based medicine.

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Список литературы / References:

1. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin.Pharmacol.Ther. 1981; 30(2): 239-245. doi: 10.1038/clpt.1981.154
2. Rawlins M, Thompson W. Mechanisms of adverse drug reactions. Textbook of adverse drug reactions, ed. Davies D.M. New York. Oxford University Press. 1991; 18–45.
3. Edwards I.R, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000 Oct 7; 356(9237): 1255-9. doi: 10.1016/S0140-6736(00)02799-9.
4. Drug and Therapeutics Committee Training Course. Session 4. Assessing and Managing Medicine Safety Trainer's Guide. WHO [Electronic resource]. URL: https://www.who.int/medicines/technical_briefing/tbs/04-PG_Dug-Safety_final-08.pdf?ua=1#:~:text=Adverse%20drug%20reaction%20(ADR)%E2%80%94,the%20modification%20of%20physiological%20function.%E2%80%9D (date of application: 26.05.2021).
5. Defenitions, WHO [Electronic resource]. URL:https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf (date of application: 26.05.2021).
6. Caviglia G.P, Rizzetto M. Treatment of hepatitis D: an unmet medical need. Clin.Microbiol Infect. 2020; 26(7): 824-827. doi: 10.1016/j.cmi.2020.02.031
7. Кирилюк А.А., Петрище Т.Л. Особенности влияния пищевых продуктов и их компонентов на фармакологическую активность лекарственных средств. Современные проблемы здравоохранения и медицинской статистики. 2017; 1: 51-64. Kiriljuk A.A., Petrishche T.L. Features of the influence of food products and their components on the pharmacological activity of drugs. Current problems of health care and medical statistics. 2017; 1: 51-64. [In Russian].
8. Дурнев А.Д. Пище-лекарственные взаимодействия: генотоксикологические аспекты. Фармакокинетика и фармакодинамика. 2016; 2: 4-9. Durnev A.D. Food-drug interactions: genotoxicological aspects. Farmakokinetika i farmakodinamika. 2016; 2: 4-9. [In Russian].
9. Lietman PS. Chloramphenicol and the neonate--1979 view. Clin. Perinatol. 1979; 6(1): 151-162.
10. Snider, D.E. Jr. Pyridoxine supplementation during isoniazid therapy. Tubercle. 1980; 61(4): 191-196. doi:10.1016/0041-3879(80)90038-0
11. Сатырова Т.В. Ацетиляторный статус: современный взгляд на проблему. Проблемы здоровья и экологии. 2009. 4(22): 31-36. Satyrova T.V. The acetylated status: present-day point of view on the subject. Health and ecology issues. 2009. 4(22): 31-36. [In Russian].
12. Сычев Д.А., Кукес В.Г., Ташенова А.И. Фармакогенетическое тестирование — новая медицинская технология. Медицинские технологии. Оценка и выбор. 2010; 1(75): 51-58. Sychev D.A., Kukes V.G., Tashenova A.I. Pharmacogenetic Testing: A New Medical Technology. Medical Technologies. Assessment and Choice. 2010; 1(75): 51-58. [In Russian].

13. Sychev D., Antonov I., Ignatev I., et al. Advantages of pharmacogenetic approach (polimorphisms of genes CYP2C9 and VKORC1 study) to warfarin dosing, against the standard method for Russian patients with contestant form atrial fibrilation. J Basic Clin.Pharmacol 2009; 105: 73-74.
14. Сычев Д.А., Антонов И.М., Загребин С.В., и др. Алгоритмы дозирования варфарина, основанные на результатах фармакогенетического тестирования: реальная возможность оптимизации фармакотерапии. Рациональная фармакотерапия в кардиологии. 2007; 3(2): 59-66.
Sychev D.A., Antonov I.M., Zagrebin S.V., et al. Algorithms for dosing warfarin based on the results of pharmacogenetic testing: a real opportunity of optimizing pharmacotherapy. Rational pharmacother.Card. 2007; 3(2): 59-66. [In Russian].
15. Wu L., Ye Z., Liu H., et al. Rapid and highly sensitive quantification of the anti-tuberculosis agents isoniazid, ethambutol, pyrazinamide, rifampicin and rifabutin in human plasma by UPLC-MS/MS. J Pharm Biomed Anal. 2020; 180: 113076. doi: 10.1016/j.jpba.2019.11307
16. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002; 62(15): 2169-2183. doi: 10.2165/00003495-200262150-0000
17. Meloni M., Corti N., Müller D., et al. Cure of tuberculosis despite serum concentrations of antituberculosis drugs below published reference ranges. Swiss Med Wkly. 2015; 145:w14223. doi: 10.4414/smw.2015.14223
18. Parikh UM, McCormick K, van Zyl G, et al. Future technologies for monitoring HIV drug resistance and cure. Curr.Opin HIV AIDS. 2017; 12(2):182-189. doi: 10.1097/COH.0000000000000344
19. Lai J.M. L, Yang S.L, Avoi R. Treating More with Less: Effectiveness and Event Outcomes of Antituberculosis Fixed-dose Combination Drug versus Separate-drug Formulation (Ethambutol, Isoniazid, Rifampicin and Pyrazinamide) for Pulmonary Tuberculosis Patients in Real-world Clinical Practice. J Glob.Infect.Dis. 2019; 11(1): 2-6. doi: 10.4103/jgid.jgid_50_18
20. Mukherjee A., Lodha R., Kabra SK. Pharmacokinetics of First-Line Anti-Tubercular Drugs. Indian J Pediatr. 2019; 86(5): 468-478. doi: 10.1007/s12098-019-02911-w
21. Ших Е.В., Исмагилов А.Д., Сизова Ж.М., и др. Безопасность комбинированной фармакотерапии у пациентов пожилого возраста. Ведомости Научного центра экспертизы средств медицинского применения. 2017; 7(1): 47-54.
Shikh E.V., Ismagilov A.D., Sizova Zh.M., et al. Safety of combination pharmacotherapy in elderly patients. The Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products. 2017; 7(1):47-54. [In Russian].
22. Шмагель Н.Г., Шмагель К.В., Королевская Л.Б., и др. Системное воспаление и повреждение кишечного барьера при эффективном лечении ВИЧ-инфекции. Клиническая медицина. 2016; 94(1): 47-51. doi: 10.18821/0023-2149-2016-94-1-47-51
Shmagel' N.G., Shmagel' Konstantin V., Korolevskaya L.B., et al. Systemic inflammation and compromised intestinal barrier during successful treatment of HIV infection. Clinical medicine. 2016; 94(1): 47-51. doi: 10.18821/0023-2149-2016-94-1-47-51 [In Russian].
23. Bandera A., De Benedetto I., Bozzi G, et al. Altered gut microbiome composition in HIV infection: causes, effects and potential intervention. Curr.Opin HIV AIDS. 2018; 13(1): 73-80. doi: 10.1097/COH.0000000000000429
24. Кондратенко С.Н., Стародубцев А.К. Особенности всасывания некоторых лекарственных средств у больных с различными заболеваниями желудочно-кишечного тракта. Биомедицина. 2006; 5: 29-30.
Condratenko S.N., Starodubtsev A.K. Features of the absorption of certain drugs in patients with various diseases of the gastrointestinal tract. Journal Biomed. 2006; 5: 29-30. [In Russian].
25. Хасанова Г.М., Урунова Д.М., Ахмеджанова З.И., и др. Поражение желудочно-кишечного тракта при ВИЧ-инфекции. Тихоокеанский Мед. Журн. 2019; 3(77): 24-28. doi: 10.17238/PmJ1609-1175.2019.3.24-28
Khasanova G.M., Urunova D.M., Akhmedzhanova Z.I., et al. Defeat of the gastrointestinal tract in hiv infection. Pacific Medical Journal. 2019; (3): 24-28. https://doi.org/10.17238/PmJ1609-1175.2019.3.24-28 [In Russian].
26. Iacob S., Iacob D.G. Infectious Threats, the Intestinal Barrier, and Its Trojan Horse: Dysbiosis. Front.Microbiol. 2019; 10: 1676. doi: 10.3389/fmicb.2019.01676
27. Pinto-Cardoso S., Klatt N.R., Reyes-Terán G. Impact of antiretroviral drugs on the microbiome: unknown answers to important questions. Curr.Opin HIV AIDS. 2018 Jan; 13(1): 53-60. doi: 10.1097/COH.0000000000000428
28. The Liverpool HIV-Drug Interactions website by the University of Liverpool. 2021. [Electronic resource]. URL: https://www.hiv-druginteractions.org/checker (date of application: 26.05.2021).
29. The Liverpool Drug Interactions website by the University of Liverpool. 2021. [Electronic resource]. URL: https://www.hep-druginteractions.org/checker (date of application: 26.05.2021).
30. McMurray J.J. V., Solomon S.D., Inzucchi S.E., et al. Dapagliflozinin Patients with Heart Failure and Reduced Ejection Fraction. NEJM. 2019; 381(21):1995-2008. doi: 10.1056/NEJMoa1911303
31. Guaraldi G., Milic J., Mussini C. et al. Aging with HIV. Curr HIV/AIDS Rep. 2019; 16(6):475-481. doi: 10.1007/s11904-019-00464-3
32. McGettrick P., Barco E.A., Mallon P.W. G. Ageing with HIV. Healthcare (Basel). 2018; 6(1):17. doi: 10.3390/healthcare6010017
33. Lundgren J.D., Battegay M., Behrens G., et al. EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines on

the prevention and management of metabolic diseases in HIV. HIV Med. 2008; 9(2):72-81. doi: 10.1111/j.1468-1293.2007.00534.x

34. Матиевская Н.В., Прокопчик Н.И., Цыркунов В.М. Патоморфологические особенности поражения печени при коинфекции туберкулез/ВИЧ. Журнал ГрГМУ. 2012; 1(37): 66-69.
Matiyevskaya N.V., Prokopchik N.I., Tsyrkunov V.M. Pathomorphological features of liver injury in tuberculosis/HIV coinfection. Journal of the Grodno Stste Medical University. 2012; 1(37): 66-69. [In Russian].
35. Байкова И.Е., Никитин И.Г. Лекарственное поражение печени. РМЖ. 2009; 1:1
Baikova I.E., Nikitin I.G. Drug liver damage. Russian Medical Journal. 2009; 1: 1 [In Russian].
36. Ситдиков И.И., Москалева А.В., Власова Т.И. Гепатотоксические эффекты антиретровирусной терапии — миф или реальность. Вестник СМУС74. 2017; 419:50-55.
Sitdikov I.I., Moskaleva A.V., Vlasova T.I. Hepatotoxic effects of antiretroviral therapy — myth or reality. Vestnik SMUS74. 2017; 419: 50-55. [In Russian].

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ВОЗДЕЙСТВИЕ КОМБИНИРОВАННОЙ ТЕРАПИИ С МЕЛАТОНИНОМ НА ФЕРМЕНТАТИВНОЕ ЗВЕНО ГЛУТАТИОНОВОЙ СИСТЕМЫ И УРОВЕНЬ ТРАНСФОРМИРУЮЩЕГО ФАКТОРА РОСТА-β1 У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА И ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК

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The Effect of Combination Therapy with Melatonin on the Enzymes of Glutathione System and the Level of Transforming Growth Factor- β1 in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease

Резюме

Цель работы. Целью работы являлась оценка воздействия комбинированной терапии с мелатонином на клинико-биохимические показатели развития хронической болезни почек (ХБП) и сахарного диабета (СД) 2 типа, функционирование ферментативного звена

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глутатионовой антиоксидантной системы и активность ферментов — поставщиков NADPH, а также уровень трансформирующего фактора роста-β1 и липидный профиль пациентов. **Материалы и методы.** В исследовании принимало участие 60 пациентов (19 мужчин и 41 женщина, средний возраст — 65,6±9,3 года) с ХБП и СД 2 типа. Пациенты были разделены на 2 группы. Первая группа пациентов находилась на базисном лечении (n=30, 8 мужчин и 22 женщины, средний возраст — 64,1±7,9 года); вторая группа участников (n=30, 11 мужчин и 19 женщин, средний возраст — 69,0±10,5 года) дополнительно к базисной терапии получала 2 мг мелатонина. Контрольную группу составили 65 практически здоровых лиц (30 мужчин и 35 женщин, средний возраст — 42,3±17,7 года) с нормальными показателями общего и биохимического анализов крови. В ходе работы был осуществлен анализ клинико-биохимических показателей и липидного профиля в сыворотке крови, уровня трансформирующего фактора роста-β1 методом иммуноферментного анализа, активности ферментов глутатионовой антиоксидантной системы и NADPH-генерирующих ферментов спектрофотометрическим методом. **Результаты.** Применение мелатонина на фоне базисного лечения по сравнению со стандартной терапией способствовало снижению протеинурии (p=0,01), гипергликемии (p=0,019), концентрации мочевины (p=0,043), гликированного гемоглобина (p=0,045) и трансформирующего фактора роста-β1 (p=0,020) у пациентов с ХБП. Кроме того, использование данного препарата оказывало воздействие на липидный профиль и приводило к возрастанию активности ферментов глутатионовой антиоксидантной системы, ферментов — поставщиков NADPH, что отражает эффективность формирования компенсаторного ответа в условиях активации свободнорадикального окисления на фоне гипергликемии. **Заключение.** Наблюдаемые в ходе исследования различия, очевидно, были вызваны действием мелатонина, для которого характерен нефропротекторный и гипогликемический эффекты, способность нейтрализовывать свободные радикалы и активизировать функционирование компонентов антиоксидантной системы.

Ключевые слова: *хроническая болезнь почек, сахарный диабет 2 типа, окислительный стресс, антиоксидантная система, мелатонин, трансформирующий фактор роста — в1*

Конфликт интересов

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

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Abstract

Aim. The aim of the work was to assess the effect of combination therapy with melatonin on the clinical and biochemical parameters of chronic kidney disease (CKD) and type 2 diabetes mellitus (DM), the level of transforming growth factor-β1, lipid profile, activity of the glutathione antioxidant system enzymes and the activity of NADPH-generating enzymes in patients. **Materials and methods.** The study involved 60 people (19 men and 41 women, average age 65.6 ± 9.3 years) with chronic kidney disease associated with type 2 diabetes. The patients were divided into 2 groups. The first group of patients received basic treatment (n = 30, 8 men and 22 women, mean age 64.1 ± 7.9 years); the second group of participants (n = 30, 11 men and 19 women, mean age 69.0 ± 10.5 years) received 2 mg of melatonin in addition to the basic therapy. The control group consisted of 65 apparently healthy individuals (30 men and 35 women, average age 42.3±17.7 years) with normal indicators of general and biochemical blood tests. In the course of the work, the analysis of clinical and biochemical indicators and lipid profile in blood serum, the level of transforming growth factor-β1 by enzyme immunoassay, the activity of enzymes of the glutathione antioxidant system and NADPH-generating enzymes by the spectrophotometric method were carried out. **Results.** The use of melatonin additionally with basic treatment compared with standard therapy led to a decrease in proteinuria (p=0.010), hyperglycemia (p=0.019), urea concentration (p=0.043), glycated hemoglobin (p=0.045) and transforming growth factor-β1 levels (p=0.020) in patients with CKD. In addition, the use of this drug led to a changing of the lipid profile, and the activity of glutathione antioxidant system enzymes and NADPH-generating enzymes. **Conclusion.** The differences observed during the study were apparently caused by the action of melatonin, which has nephroprotective and hypoglycemic properties, the ability to neutralize reactive oxygen species and activate the antioxidant system functioning.

Key words: *chronic kidney disease, type 2 diabetes mellitus, oxidative stress, antioxidant system, melatonin, transforming growth factor-β1*

Conflict of interests

The authors declare no conflict of interests

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AI — atherogenic index, CKD — chronic kidney disease, DM — diabetes mellitus, G6FDG — glucose-6-phosphate dehydrogenase, GFR — glomerular filtration rate, GP — glutathione peroxidase, GSH — reduced glutathione, GR — glutathione reductase, GT — glutathione transferase, HDL — high density lipoprotein cholesterol, LDL — low density lipoprotein cholesterol, NADP-IDG — NADP-dependent isocitrate dehydrogenase, TC — total cholesterol, TGF-β1 — transforming growth factor β1

Introduction

It is known that the main etiological factors in the development of chronic kidney disease (CKD) include diabetes mellitus (DM) and arterial hypertension [1]. Proteinuria is an important predictor of progressive kidney damage, which leads to tubulointerstitial kidney tissue damage and, as a result, a decrease in glomerular filtration rate, resulting in end-stage renal failure. The kidney is a metabolic organ where mitochondrial oxidation reactions take place. According to studies, increased production of reactive oxygen species and a weakening of the body's antioxidant defense have an adverse effect on the course of CKD [2].

Oxidative stress activates mitogen-activated protein kinases, various cytokines and transcription factors, which ultimately leads to fibrosis and end-stage renal failure. One of the factors activated due to proteinuria and oxidative stress is transforming growth factor β1 (TGF-β1), which is an important mediator of many processes in renal glomeruli and tubules. Also, high glucose concentration increases mRNA and TGF-β1 protein levels in cultured proximal tubular cells, epithelial and mesangial cells of renal glomeruli [3]. Numerous studies have shown that TGF-β1 plays a central role in the development of fibrosis. TGF-β1 increases mitochondrial production of reactive oxygen species in various cell types that mediate TGF-β-induced apoptosis, as well as many of the TGF-β-induced pro- and fibrotic effects [4].

The pathogenic action of free radicals is opposed by the antioxidant system, which is aimed at suppressing free radical oxidation processes. One of the main links of antioxidant defense is the glutathione system, which includes enzymes glutathione peroxidase (GP), glutathione reductase (GR), glutathione transferase (GT) and glutathione tripeptide, which plays the role of a reducing cofactor in glutathione peroxidase reaction. GP is a key enzyme that utilizes reactive oxygen species and lipid peroxidation products. GR facilitates the reduction of glutathione oxidized during glutathione peroxidase reaction without increasing its synthesis *de novo*. GT detoxifies lipid peroxidation products generated during the metabolism of xenobiotics in the endoplasmic reticulum. The glutathione antioxidant system requires a constant supply of the NADPH coenzyme to function. The primary sources of this compound are enzymes glucose-6-phosphate dehydrogenase (G6PDH) and NADP-dependent isocitrate dehydrogenase (NADP-IDH) [5].

Clinical guidelines for the management of CKD include the control of blood pressure, glycemia, lipid metabolism, and nephroprotective therapy [6]. In this regard, it seems appropriate to study the natural metabolites of the body that have a nephroprotective effect and are aimed at suppressing oxidative stress and TGF-β1. One of these metabolites is the hormone melatonin [7]. It is known that melatonin binds free radicals while simultaneously inducing the body's natural antioxidant defense system.

Therefore, the purpose of this work was to assess the clinical and biochemical parameters of CKD, lipid profile, TGF-β1 level, the activity of the glutathione antioxidant system and NADPH-generating enzymes in patients with CKD and type 2 DM during basic treatment and combination therapy with melatonin.

Experimental Part

This clinical study was a randomized, open-label, controlled trial. The study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Burdenko Voronezh State Medical University", extract of minutes No. 4 dated 09/29/2016. All patients signed informed consent to participate in the study. This clinical study was carried out in the endocrinology departments of the Voronezh Regional Clinical Center for Specialized Types of Medical Care and the Voronezh City Clinical Emergency Hospital No. 10. The study included 60 patients (29 males, mean age (65.6 ± 9.3) years) with type 2 DM and CKD. History of CKD was (13.2 ± 6.3) years. Stage 2 CKD was observed in 6 (10%) patients, stage 3a — in 42 (70%), stage 3b — in 12 (20%) patients. The diagnosis of CKD was established according to clinical guidelines [8]. Among comorbidities (Table 1), arterial hypertension (100%), diabetic retinopathy (100%), obesity (69%), chronic heart failure (66%) were the most common. The study had the following exclusion criteria: type 1 DM, viral hepatitis, acute infectious diseases, acute myocardial infarction, malignant neoplasms, acute cerebrovascular accident. After admission to the hospital, all patients underwent therapy adjustment. Group 1 (n = 30, 8 males and 22 females, mean age — (64.1 ± 7.9) years) received basic treatment. Group 2 (n = 30, 11 males and 19 women, mean age — (69.0 ± 10.5) years). In addition to similar basic therapy, they received an agent containing 2 mg of melatonin (Table 2). All patients of group 2 who were on inpatient

treatment had complaints of sleep disturbance. Therefore, with the exception of the administration of melatonin, there were no differences in the treatment of participants in groups 1 and 2. The duration of basic therapy and combined treatment with melatonin carried out in the hospital was two weeks. Clinical and biochemical parameters of the lipid profile, TGF-β1 level, the activity of the glutathione antioxidant system and NADPH-generating enzymes were analyzed upon admission to the hospital and before discharge. The control group included 65 apparently healthy individuals (30 males and 35 females, mean age — (42.3 ± 17.7) years) with normal values of general and biochemical blood tests, who underwent a planned preventive medical examination at the Voronezh City Polyclinic No. 10.

The glomerular filtration rate (GFR) was calculated using the CKD-EPI (2011) formula Daily proteinuria in urine was determined by a photocolorimetric method with pyrogallol red dye and the Brandberg — Roberts — Stolnikov method.

Fasting glucose and postprandial glucose were assessed by the hexokinase enzymatic method and using a Satellite Plus glucometer (ELTA, Russia). To assess lipid metabolism, the concentration of total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol in serum was determined using reagent kits (Bio-La-Test) using an enzymatic photocolorimetric method on a Klima 15MC biochemical analyzer (Spain). The atherogenic index (AI) was defined as the ratio of the difference between total cholesterol and HDL to HDL [AI = (TC – HDL) / HDL], which should normally be ≤ 3.

Glycated hemoglobin parameters were calculated using the reference method using a D 10 analyzer manufactured by Bio-Rad (USA).

Urea and creatinine concentration was analyzed using diagnostic kits manufactured by Olvex (Russia).

The content of melatonin sulfate in the urine of patients was measured by enzyme immunoassay using a kit manufactured by Buhlmann (Germany).

The activity of the studied enzymes was determined on a Hitachi U-1900 spectrophotometer (Japan). HP activity was measured in a spectrophotometric medium of the following composition: 50 mM potassium phosphate buffer (pH 7.4) containing 1.0 mM EDTA, 0.12 mM NADPH (AppliChem, Germany), 0.85 mM reduced glutathione (GSH) (AppliChem, Germany), 0.37 mM H_2O_2, 1 U/ml GR (Sigma Aldrich, USA). The control sample did not contain GSH [9]. GR activity was assessed in 50 mM potassium phosphate buffer (pH 7.4) containing 1.0 mM EDTA, 0.16 mM NADPH, and 0.8 mM GSH [9].

Table 1. *Comorbidities of study participants who received basic treatment (group 1, n=30) and patients who received melatonin in addition to basic therapy (group 2, n=30)*

Comorbidities, n (%)	Group 1, n=30	Group 2, n=30
Arterial hypertension	30(100)	30(100)
Diabetic retinopathy	30(100)	30(100)
Obesity	21(70)	20(67)
Chronic heart failure	22(73)	18(60)
Coronary artery disease	13 (43)	13 (43)
Acute disorders of cerebral circulation	5 (17)	4 (13)
Myocardial infarction	5 (17)	4 (13)
Chronic obstructive pulmonary disease	-	2 (7)
Peripheral artery disease	6 (20)	8 (27)

Table 2. *Prescribed drugs to study participants*

Prescribed drugs	Group 1	Group 2
Oral hypoglycemic drugs	Biguanides (metformin — 500-1500 mg once in the evening) Sulfonylurea preparations (Gliclazide — 30-90 mg once a day) Inhibitors of dipeptidyl peptidase-4 (Vildagliptin — 50-100 mg 1-2 times a day, Alogliptin — 12.5-25 mg once a day)	Biguanides (metformin — 500-1500 mg once in the evening) Sulfonylurea preparations (Gliclazide — 30-90 mg once a day) Inhibitors of dipeptidyl peptidase-4 (Vildagliptin — 50-100 mg 1-2 times a day, Alogliptin — 12.5-25 mg once a day)
Antihypertensive drugs	ACE blockers (Enalapril -5-20 mg 1-2 times a day, Lisinopril 5-20 mg once a day), B-blockers (Bisoprolol — 2.5-10 mg 1 once a day, Metoprolol succinate — 50-100 mg once a day)	ACE blockers (Enalapril -5-20 mg 1-2 times a day, Lisinopril 5-20 mg once a day), B-blockers (Bisoprolol — 2.5-10 mg 1 once a day, Metoprolol succinate — 50-100 mg once a day)
Lipid-lowering drugs	Statins (Atorvastatin — 20-40 mg once a day)	Statins (Atorvastatin — 20-40 mg once a day)
Diuretics	Thiazide diuretics (Indapamide 2.5 mg once a day)	Thiazide diuretics (Indapamide 2.5 mg once a day)
Melatonin	-	2 mg orally, 1 tablet once a day, after meals, in the evening, 1-2 hours before bedtime

GT activity was measured in 0.1 M potassium phosphate buffer (pH 7.4) containing 1.0 mM EDTA, 1.0 mM 1-chloro-2,4-dinitrobenzene, 5.0 mM GSH [10]. G6PDH activity was measured in 50 mM Tris-HCl buffer (pH 7.8) containing 3.0 mM glucose-6-phosphate (Sigma Aldrich, USA), 0.25 mM NADP (AppliChem, Germany), 1.0 mM $MnCl_2$ [11]. NADP-IDH activity was assessed in 50 mM Tris-HCl buffer (pH 7.8) containing 1.5 mM isocitrate (Sigma Aldrich, USA), 2.0 mM $MnCl_2$, 0.4 mM NADP [11]. The rate of the enzymatic reaction was judged by the change in optical density at 340 nm. The unit of enzymatic activity (E) was defined as the amount of enzyme catalyzing the formation of 1 μmol of the reaction product in 1 min at 25 °C. Enzyme activity was expressed in enzymatic units per ml of serum. GSH concentration was determined using a reaction with 5,5-dithiobis-(2-nitrobenzoic) acid (Sigma Aldrich, USA) [11]. Protein concentration in blood serum was assessed by the biuret method.

The level of TGF-β1 in blood serum was measured by enzyme immunoassay using a kit manufactured by Ray-Biotech (USA).

Statistical processing of the material was carried out using SPSS 23.0 software and standard methods of variation statistics (calculation of mean values, standard error of the mean, standard deviation, median values and interquartile range). Normality of distribution in groups was assessed using the Kolmogorov — Smirnov test. The significance of differences was analyzed using Student's t-test and the nonparametric Mann — Whitney test. The Pearson or Spearman rank correlation coefficient was used to identify correlations between the studied parameters depending on the distribution. This paper gives the values of average (0.30–0.69) and strong (> 0.70) correlation. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Baseline clinical and laboratory characteristics of patients are presented in Table 3.

Biochemical parameters, TGF-β1 level and lipid profile of the study participants are presented in Table 4.

The daily proteinuria level in groups 1 and 2 before therapy was 0.540 and 0.781 g/day, respectively. After treatment, this parameter decreased in both groups. However, combination therapy with melatonin more significantly reduced the proteinuria level ($p = 0.010$). Also, combined treatment with melatonin led to a decrease in fasting glucose concentration, postprandial hyperglycemia ($p < 0.001$) and the level of glycated hemoglobin ($p = 0.010$) relative to pre-treatment values. An assessment of melatonin sulfate level in urine confirmed that the level of this hormone increased during therapy in patients of group 2 ($p = 0.010$). As is known, melatonin has a protective effect on organs and tissues during hyperglycemia, which is due to its antioxidant, anti-inflammatory and antiapoptotic effects. This hormone has a positive effect on carbohydrate metabolism due to the ability to inhibit gluconeogenesis in the liver, increase insulin secretion and tissue sensitivity to it, as well as restore mitochondrial dysfunction in diabetes mellitus [12].

Table 3. *Baseline clinical characteristics of patients*

Indicator	Control group, n=65	Group 1, n=30	Group 2, n=30
Sex, m/f, n (%)	30/35 (46% мужчин)	8/22 (27% мужчин)	11/19 (37% мужчин)
Age, years	42,0 (27,5-51,0)	63,0 (59,0-69,0)*	69,0 (59,0-74,5)*
Average duration of diabetes mellitus, years	-	9,2 (7,8-10,9)	10,1 (8,3-11,7)
BMI	26,0 (23,5-27,4)	31,3 (26,4-34,4)	30,5 (26,0-35,6)
BP systolic mm Hg	115,0 (109,0-124,0)	160,0 (155,0-165,0)*	160,0 (151,3-170)*
BP diastolic mm Hg	71,0 (68,0-73,0)	90,0 (85,0-90,0)*	90,0 (85,0-95,0)*
Heart rate beats / min	71,0 (66,0-73,0)	78,0 (75,0-80,0)*	82,0 (76,5-87,5)*
Stages of CKD G2, n/% G3a, n/% G3b, n/%	-	 3 (10%) 20 (67%) 7 (23%)	 3 (10%) 22 (73%) 5 (17%)
GFR, ml / min	102,0 (95,7-108,3)	53,5 (45,8-58,0)*	54,0 (47,0-57,0)*
Concentration of creatinine, μM	87,3 (79,2-90,1)	114,0 (98,3-120,8)*	104,5 (94,5-124,8)*
Concentration of urea, mM	5,2 (4,6-5,5)	6,5 (5,4-8,4)*	7,7 (5,7-10,4)*
Daily proteinuria level, g / day	0,01 (0,007-0,015)	0,40 (0,24-0,65)*	0,54 (0,31-1,18)*
Glycated hemoglobin level, %	5,0 (4,6-5,5)	8,0 (6,8-9,7)*	8,4 (7,0-9,8)*
Fasting glucose concentration, mM	4,8 (3,5-5,2)	9,9 (7,9-12,2)*	10,4 (9,7-12,6)*
Postprandial glucose concentration, mM	5,5 (4,1-6,2)	12,3 (8,9-14,5)*	12,3 (8,9-14,5)*

Note: BMI — Body mass index, BP — Blood pressure, CKD — Chronic kidney disease
Data are presented as median value (Q1-Q3); * — differences from the control group, $p < 0.05$.

Also, an experiment on animals showed that melatonin normalizes the shape and organization of mitochondrial cristae in metabolic dysfunction of renal tubules and reduces the number of cells with an increased index of apoptosis in proximal tubules [13]. Therefore, the antioxidant and antiapoptotic effects typical for melatonin apparently contributed to a more pronounced change in glycemia and proteinuria parameters in patients compared with standard treatment. Among other things, combination treatment with melatonin reduced the level of TGF-β1 compared with standard therapy (p = 0.001). Lately, TGF-β1 is considered a multifunctional cytokine involved in cell growth, differentiation and migration, the formation and degradation of extracellular matrix components, chemotactic processes and apoptosis, as well as immune regulation. TGF-β1 is a key mediator of renal fibrosis [14]. Maintaining the physiological level of TGF-β is necessary for the normal functioning of most tissues and maintenance of organs. Increased expression of TGF-β1 is associated with pathological changes in tissues in various diseases such as pulmonary fibrosis, spinal muscular atrophy and kidney disease [15]. The concentration of TGF-β1 is high in the blood serum of patients with pathologies such as diabetic nephropathy, immunoglobulin A-nephropathy, focal segmental glomerulosclerosis, rapidly progressive glomerulonephritis and lupus nephritis. TGF-β1 also mediates kidney disease by inducing an epithelial-mesenchymal transition involving tubular epithelial cells that are believed to contribute to the pathogenesis of tubular atrophy [15].

Table 4. *Clinical and biochemical parameters and the level of TGF-β1 of the examined patients*

Indicator	Control group	Group 1, n=30			Group 2, n=30			p_2
		Before treatment	After treatment	p_1	Before treatment	After treatment	p_1	
Fasting glucose concentration, mM	4,8 (3,5-5,2)	9,9 (7,9-12,2)*	7,5 (6,6-8,8)	<0,0001	10,4 (9,7-12,6)*	6,8 (5,3-7,9)	<0,0001	0,019
Postprandial glucose concentration, mM	5,5 (4,1-6,2)	12,3 (8,9-14,5)*	8,9 (7,2-10,4)	0,002	12,3 (8,9-14,5)*	7,9 (6,5-9,3)	<0,0001	0,939
Glycated hemoglobin level, %	5,0 (4,6-5,5)	8,0 (6,8-9,7)*	6,70 (5,7-7,1)	0,020	8,4 (7,0-9,8)*	6,0 (5,2-6,2)	0,010	0,005
Daily proteinuria level, g / day	0,01 (0,007-0,015)	0,40 (0,24-0,65)*	0,14 (0,09-0,29)	<0,0001	0,54 (0,31-1,18)*	0,13 (0,08-0,48)	<0,0001	0,010
Concentration of urea, mM	5,2 (4,6-5,5)	6,5 (5,4-8,4)**	5,8 (4,8-7,9)	0,052	7,7 (5,7-10,4)*	6,5 (5,1-9,1)	0,043	0,301
Concentration of creatinine, μM	87,3 (79,2-90,1)	114,0 (98,3-120,8)*	98,0 (86,5-114,8)	0,021	104,5 (94,5-124,8)*	97,0 (81,5-105,5)	0,024	0,254
GFR, ml / min	102,0 (95,7-108,3)	53,5 (45,8-58,0)*	60,0 (55,0-63,8)	0,072	54 (47,0-57,0)*	63,0 (55-67,8)	0,159	0,034
Total cholesterol, mmol/l	4,1 (3,3-4,6)	6,4 (5,1-6,8)*	5,0 (4,4-5,6)	0,008	5,8 (5,1-6,7)*	4,6 (3,9-5,2)	<0,0001	0,321
Triglycerides, mmol/l	1,2 (0,8-1,4)	2,0 (1,4-2,5)*	1,7 (1,2-2,1)	0,29	2,7 (1,4-3,0)*	1,1 (0,9-1,8)	<0,0001	0,005
LDL, mmol/l	2,2 (1,8-2,4)	2,7 (2,2-3,3)*	1,8 (1,5-2,2)	<0,0001	2,6 (2,1-3,4)*	1,8 (1,5-2,2)	<0,0001	0,633
HDL, mmol/l	2,4 (2,2-2,7)	1,06 (0,75-1,20)*	1,10 (1,01-1,20)	0,114	1,02 (0,86-1,27)*	1,24 (1,10-1,35)	0,003	0,203
Atherogenic index	0,70 (0,4-1,0)	5,0 (4,1-5,7)*	3,5 (2,8-4,1)	0,001	5,0 (4,2-5,7)*	2,6 (2,1-3,2)	<0,0001	0,408
TGF-β1, ng/ml	21,0 (17,3-24,8)	128,0 (100,1-151,7)*	98,0 (80,1-115,2)	0,010	130,5 (108,2-153,6)*	80,0 (64,3-97,7)	<0,0001	0,001
Concentration of melatonin sulfate in urine, ng/ml	9,0 (8,1-9,8)	7,0 (6,0-7,8)*	7,5 (6,7-7,9)	0,326	7,1 (6,3-7,7)*	8,8 (8,0-9,5)	0,010	0,001
BP systolic mm Hg	115,0 (109,0-124,0)	160,0 (155-165,0)*	130,0 (121,3-130)	<0,0001	160,0 (151,3-170,0)*	125,0 (120-130,0)	<0,0001	0,592
BP diastolic mm Hg	71,0 (68,0-73,0)	90,0 (85,0-90,0)*	80,0 (80,0-80,0)	<0,0001	90,0 (85,0-95,0)*	80,0 (70,0-80,0)	<0,0001	0,309
Heart rate beats / min	71,0 (66,0-73,0)	78,0 (75,0-80,0)*	70,0 (66,0-70,0)	<0,0001	82,0 (76,5-87,5)*	66,0 (62,5-68,0)	<0,0001	0,611

Note: GFR — Glomerular filtration rate, LDL — Low density lipoproteins, HDL — High density lipoproteins, TGF-β1 — Трансформирующий фактор роста-β1, Transforming Growth Factor-β1, BP — Blood pressure, ЧСС — Частота сердечных сокращений
Data are presented as median value (Q1-Q3); * — differences from the control group, p <0.05

During treatment, the patients in our study showed positive changes in the lipid profile parameters in blood serum. There was a decrease in the concentration of cholesterol, LDL, and atherogenic index ($p < 0.05$) in both groups of patients. Also, in patients who received additional melatonin, the concentration of triglycerides significantly decreased ($p < 0.001$) and HDL level increased ($p = 0.003$). As is known from the literature, daily administration of melatonin helps reduce excess body weight. In addition, the ratio of the concentration of melatonin to insulin in blood negatively correlates with the LDL level and positively with the concentration of HDL [16]. Vasoregulatory effects of melatonin are complex and may involve both central and peripheral mechanisms. Melatonin receptors MT1 are responsible for vasoconstriction, and MT2 — for vasodilation, and depend on circadian time, duration and mode of exposure to endogenous or exogenous melatonin, as well as the functional sensitivity of receptors [17].

The study also showed that combined treatment with melatonin promoted an increase in the activity of antioxidant enzymes of the glutathione unit towards control values, which had a more pronounced trend compared with the corresponding changes with underlying basic therapy. In particular, the use of melatonin contributed to a more significant increase in the activity of GR ($p = 0.031$, compared with basic treatment) and GT ($p < 0.0001$, compared with basic treatment), as well as an increase in the activity of GH ($p < 0.0001$), while in patients in group 1, the activity of this enzyme decreased during treatment ($p = 0.034$) (Fig. 1). Antioxidant activity of melatonin contributes to a more significant increase in the activity of the glutathione system, which plays a key role in the compensatory response to oxidative stress induced under conditions of hyperglycemia [18]. It is known that the dysfunction of antioxidant system components is an important factor in the development of complications in a wide range of diseases, including type 2 DM. In particular, it was shown that the level of oxidative stress markers increases in the kidneys in diabetes, and in mice lacking the main cytosolic and mitochondrial antioxidant enzyme GP 1, the modeling of diabetes leads to a more significant increase in oxidative stress and the progression of kidney disease [19]. Changes in the specific activity of enzymes of the glutathione antioxidant system were of a similar nature (see Fig. 1).

With underlying combination therapy with melatonin, there was also an increase in the activity of NADP-IDG in blood serum compared with pre-treatment parameters ($p < 0.0001$), while with underlying basic therapy, there were no significant differences in this parameter (Fig. 2). Apparently, the increase in NADP-IDG activity is associated with an increase in the need for NADPH of the glutathione antioxidant system under conditions of its activation. Another supplier of NADPH is the pentose phosphate pathway. The key enzyme here is glucose-6-phosphate dehydrogenase (G6PDH). However, as the study shows, both basic treatment and combination therapy with melatonin led to a multidirectional change in the activity of this enzyme in patients. In particular, after using melatonin, 10 (33.3%) patients saw a decrease in the activity of G6PDH in blood serum, and 20 (66.7%) — an increase in comparison with pre-treatment parameters. There is evidence that during oxidative stress, an important mechanism of protection against the action of reactive oxygen species is the interaction in the nucleus of hemoxygenase-1 with the transcription factor Nrf2, which contributes to the enhancement of the expression of the second phase detoxification enzymes, which also include G6PDH [20]. Apparently, the intake of melatonin contributed to an increase in the content of transcription factor Nrf2 in the nuclear fraction and increased the expression of hemoxygenase-1 in patients with CKD, which, as was shown, can reduce oxidative stress [21]. In patients who were characterized by a decrease in G6PDH activity, the inhibition of the functioning of the pentose phosphate pathway was probably observed, and melatonin doses taken were not enough to change this parameter upward. Suppression of this enzyme can occur under conditions of DM with underlying inhibition of glucokinase synthesis and induction of glucose-6-phosphatase in the liver, reducing the availability of glucose-6-phosphate for G6PDH [22].

An analysis of the relationships between biomarkers of CKD, type 2 DM and indicators of the functioning of glutathione antioxidant protection components in the groups is presented in Table 5. Results showed that in patients of group 1, there was a negative correlation between the change in postprandial glucose concentration and shifts in NADP-IDG activity during treatment. This correlation confirms that the degree of oxidative stress caused by chronic hyperglycemia in CKD correlates with the degree of depletion of the GSH pool and the inhibition of the activity of one of the most important suppliers of NADPH for its restoration — NADP-IDG. Also, patients of group 1 were characterized by a positive correlation of changes in GP activity with changes in the concentration of urea and creatinine, as well as a negative correlation with changes in the glomerular filtration rate. The observed negative phenomenon could be due to a tendency towards a decrease in GP activity during standard treatment. For patients of group 2, there were no reliably significant relationships between shifts in the analyzed parameters.

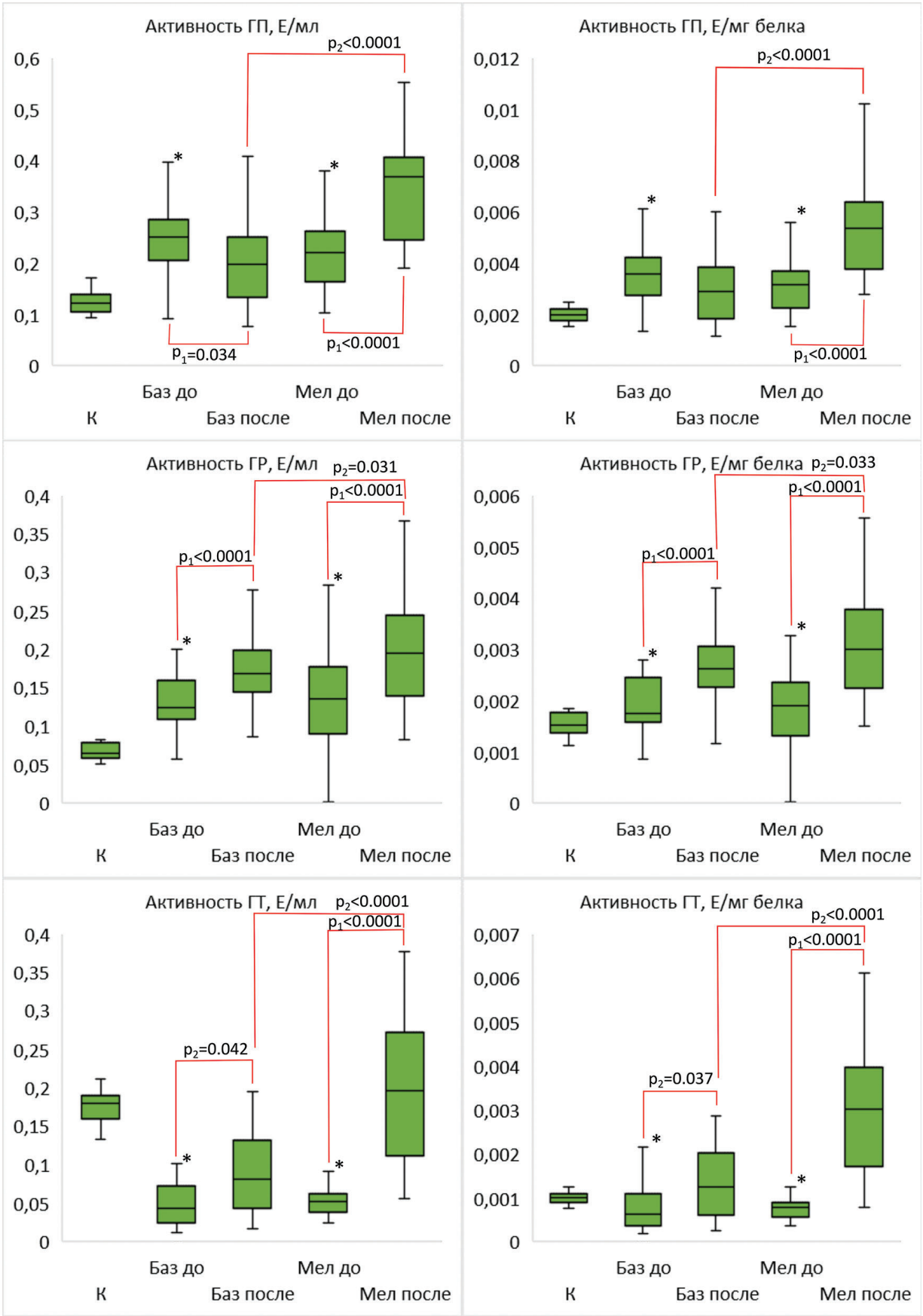

Figure 1. *Activity of glutathione peroxidase (GP), glutathione reductase (GR) and glutathione transferase (GT) in people of the control group (C), patients receiving basic therapy (Bas after) against the indicators before treatment (Bas before), as well as patients receiving combination therapy with melatonin (Mel after) against the indicators before treatment (Mel before)*

Note: * — differences from the control group are significant, p <0.05; p1 — the level of significance of differences between the indicators before and after treatment in groups; p2 — the level of significance of the differences between the changes in indicators that occurred during treatment in the second group compared to the first group

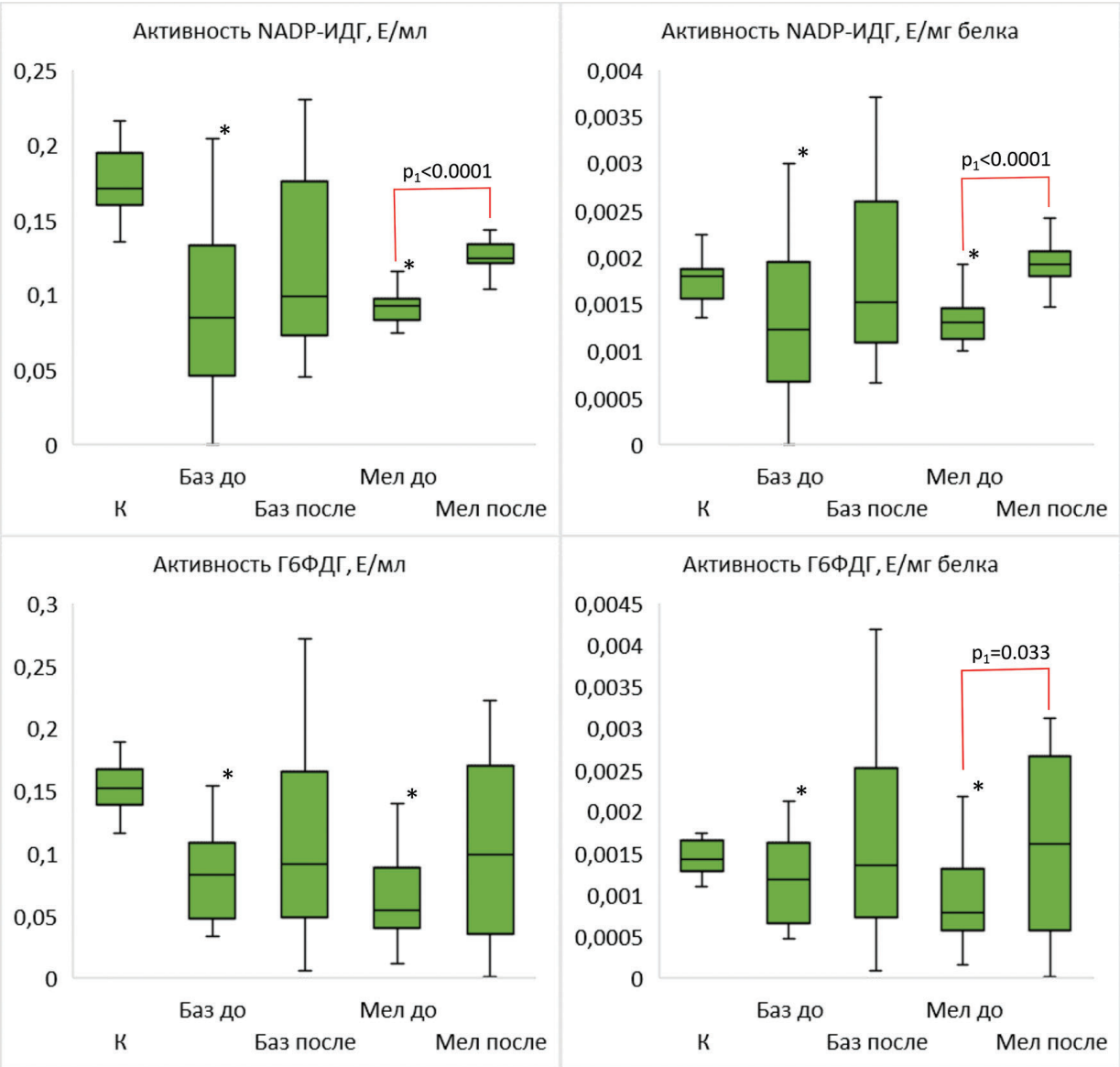

Figure 2. *Activity of NADP-dependent isocitrate dehydrogenase (NADP-IDH) and glucose-6-phosphate dehydrogenase (G6PDH) in people of the control group (C), patients receiving basic therapy (Bas after) against the indicators before treatment (Bas before), and also patients receiving combination therapy with melatonin (Mel after) against the indicators before treatment (Mel before)*

Note: * — differences from the control group are significant, p <0.05; p1 — the level of significance of differences between the indicators before and after treatment in groups; p2 — the level of significance of the differences between the changes in indicators that occurred during treatment in the second group compared to the first group

Table 5. Correlation between changes (Δ) of the studied parameters during treatment in groups of participants

Members of the first group	
Δ postprandial glucose concentration	Δ NADP-ИДГ Δ NADP-IDH r=-0,390 p=0,033
Δ urea concentration	Δ ГП Δ GP r=0,476 p=0,029
Δ creatinine concentration	Δ ГП Δ GP r=0,548 p=0,007
Δ glomerular filtration rate	Δ ГП Δ GP r=-0,571 p=0,004

Apparently, this is due to the more pronounced activating effect of combination therapy with melatonin on the activity of the components of the glutathione antioxidant system, which provides a more effective compensatory response in CKD.

The TGF-β1 level positively correlated with the parameters of proteinuria ($r = 0.800$, $p < 0.0001$), fasting glucose concentration ($r = 0.532$, $p < 0.0001$) and total cholesterol ($r = 0.681$, $p < 0.0001$).

Therefore, the positive effects of melatonin implemented in the treatment regimen for patients with type 2 DM and CKD contributed to an improvement in the oxidative status in the serum of patients. This was reflected in a more significant change in most clinical and biochemical parameters, the level of TGF-β1 and lipid profile compared with participants who received basic treatment.

Conclusion

The data obtained suggest that, compared with basic treatment, combination therapy with melatonin provides a more pronounced antioxidant, hypoglycemic and hypolipidemic effect that is apparently linked with the nephroprotective effect of this hormone. Melatonin promotes the triggering of a compensatory response to oxidative stress, which is one of the key factors in the pathogenesis of complications in type 2 DM. The use of melatonin led to a more significant increase in the activity of glutathione antioxidant system enzymes, as well as the activity of NADP-IDG, one of the main suppliers of NADPH. The observed differences in the effectiveness of the analyzed therapeutic approaches are due to the hypoglycemic activity and direct antioxidant effect of melatonin, as well as its ability to maintain and induce the functional activity of other antioxidants.

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Список литературы/ References:

1. Hwang S.J., Tsai J.C., Chen H.C. Epidemiology, impact and preventive care of chronic kidney disease in Taiwan. Nephrology (Carlton). 2010; 15(S2): 3-9. doi: 10.1111/j.1440-1797.2010.01304.x.
2. Chawla L.S., Bellomo R., Bihorac A. et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol. 2017; 13(4): 241-257. doi: 10.1038/nrneph.2017.2.
3. Chang A.S., Hathaway C.K., Smithies O. et al. Transforming growth factor-β1 and diabetic nephropathy. Am J Physiol Renal Physiol. 2016; 310(8): F689-F696. doi: 10.1152/ajprenal.00502.2015.
4. Chung A.C. K., Dong Y., Yang W. et al. Smad7 suppresses renal fibrosis via altering expression of TGF-β/Smad3-regulated microRNAs. Mol Ther. 2013; 21(2): 388-398. doi: 10.1038/mt.2012.251.
5. Крыльский Е.Д., Попова Т.Н., Кирилова Е.М. Активность глутатионовой антиоксидантной системы и NADPH-генерирующих ферментов при экспериментальном ревматоидном артрите у крыс. Бюллетень экспериментальной биологии и медицины. 2015; 160(7): 30-33. doi: 10.1007/s10517-015-3089-0.
Kryl'skii E.D., Popova T.N., Kirilova E.M. Activity of Glutathione Antioxidant System and NADPH-Generating Enzymes in Rats with Experimental Rheumatoid Arthritis. Bull Exp Biol Med. 2015; 160(1): 24-27. doi: 10.1007/s10517-015-3089-0 [in Russian].

6. Ruiz-Ortega M., Rayego-Mateos S., Lamaset S. et al. Targeting the progression of chronic kidney disease. Nature Reviews Nephrology. 2020; 16: 269–288. doi: 10.1038/s41581-019-0248-y
7. Горбенко М.В., Попова Т.Н., Шульгин К.К., и др. Влияние мелаксена и вальдоксана на активность глутатионовой антиоксидантной системы и НАДФН-генерирующих ферментов в сердце крыс при экспериментальном гипертиреозе. Экспериментальная и клиническая фармакология. 2013; 76(10): 12-15. doi: 10.30906/0869-2092-2013-76-10-12-15.
Gorbenko M.V., Popova T.N., Shul'gin K.K., et al. Effects of melaxen and valdoxan on the activity of glutathione antioxidant system and NADPH-producing enzymes in rat heart under experimental hyperthyroidism conditions. Eksp Klin Farmakol. 2013; 76(10): 12-15. doi: 10.30906/0869-2092-2013-76-10-12-15 [in Russian].
8. Ассоциация нефрологов. Клинические рекомендации «Хроническая болезнь почек». 2019; 169 с.
Association of Nephrologists. Clinical guidelines «Chronic kidney disease». 2019; 169 p. [In Russian].
9. Kryl'skii E.D., Popova T.N., Safonova O.A. et al. Transcriptional Regulation of Antioxidant Enzymes Activity and Modulation of Oxidative Stress by Melatonin in Rats Under Cerebral Ischemia / Reperfusion Conditions. Neuroscience. 2019; 406: 653-666. doi: 10.1016/j.neuroscience.2019.01.046.
10. Iskusnykh I.Y., Kryl'skii E.D., Brazhnikova D.A. et al. Novel Antioxidant, Deethylated Ethoxyquin, Protects against Carbon Tetrachloride Induced Hepatotoxicity in Rats by Inhibiting NLRP3 Inflammasome Activation and Apoptosis. Antioxidants. 2021; 10(1): 122. doi: 10.3390/antiox10010122.
11. Popov S.S., Shulgin K.K., Popova T.N. et al. Effects of Melatonin-Aided Therapy on the Glutathione Antioxidant System Activity and Liver Protection. Journal of Biochemical and Molecular Toxicology. 2015; 29(10): 449-457. doi: 10.1002/jbt.21705.
12. Meng X., Li Y., Li S. et al. Dietary Sources and Bioactivities of Melatonin. Nutrients. 2017; 9(4): E367. doi: 10.3390/nu9040367.
13. Stacchiotti A., Favero G., Giugno L. et al. Mitochondrial and Metabolic Dysfunction in Renal Convoluted Tubules of Obese Mice: Protective Role of Melatonin. PLoS One. 2014;9(10): e111141. doi: 10.1371/journal.pone.0111141.
14. Xavier S., Vasko R., Matsumoto K. et al. Curtailing Endothelial TGF-β Signaling Is Sufficient to Reduce Endothelial-Mesenchymal Transition and Fibrosis in CKD. Journal of the American Society of Nephrology. 2015;26(4):817-829. doi: 10.1681/ASN.2013101137.
15. Gu Y.Y., Liu X.S., Huang X.R. et al. Diverse Role of TGF-β in Kidney Disease. Front Cell Dev Biol. 2020; 8: 123. doi: 10.3389/fcell.2020.00123.
16. Obayashi K., Saeki K., Iwamoto J. et al. Exposure to Light at Night, Nocturnal Urinary Melatonin Excretion, and Obesity/Dyslipidemia in the Elderly: A Cross-Sectional Analysis of the HEIJO-KYO Study. The Journal of Clinical Endocrinology & Metabolism. 2013; 98(1): 337–344. doi: 10.1210/jc.2012-2874.
17. Pandi-Perumal S.R., BaHammam A.S., Ojike N.I. et al. Melatonin and Human Cardiovascular Disease. J Cardiovasc Pharmacol Ther. 2017; 22(2): 122-132. doi: 10.1177/1074248416660622.
18. Lindblom R., Higgins G., Coughlan M. et al. Targeting Mitochondria and Reactive Oxygen Species-Driven Pathogenesis in Diabetic Nephropathy. Rev Diabet Stud. 2015; 12(1-2): 134-156. doi: 10.1900/RDS.2015.12.134.
19. Huang J.Q., Zhou J.C., Wu Y.Y. et al. Role of glutathione peroxidase 1 in glucose and lipid metabolism-related diseases. Free Radical Biology and Medicine. 2018; 127: 108-115. doi: 10.1016/j.freeradbiomed.2018.05.077.
20. Biswas C., Shah N., Muthu M. et al. Nuclear heme oxygenase-1 (HO-1) modulates subcellular distribution and activation of Nrf2, impacting metabolic and anti-oxidant defenses. J Biol Chem. 2014; 189(39): 26882-26894. doi: 10.1074/jbc.M114.567685.
21. Kilic U., Kilic E., Tuzcu Z. et al. Melatonin suppresses cisplatin-induced nephrotoxicity via activation of Nrf-2/HO-1 pathway. Nutr Metab (Lond). 2013; 10(1): 7. doi: 10.1186/1743-7075-10-7.
22. Haeusler R.A., Camastra S., Astiarraga B. et al. Decreased expression of hepatic glucokinase in type 2 diabetes. Molecular Metabolism. 2015; 4(3): 222-226. doi: 10.1016/j.molmet.2014.12.007.

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РОЛЬ УРЕМИЧЕСКОЙ ИНТОКСИКАЦИИ В РАЗВИТИИ СЕРДЕЧНО-СОСУДИСТОГО РЕМОДЕЛИРОВАНИЯ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК 3А-5Д СТАДИЙ

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The Role of Uremic Intoxication in the Development of Cardiovascular Remodeling in Patients with Chronic Kidney Disease Stages 3a-5d

Резюме

В последние десятилетия распространенность хронической болезни почек (ХБП) в популяции имеет отчетливую тенденцию к росту. Это связано, прежде всего, с увеличением частоты встречаемости главных факторов, приводящих к ее развитию: сахарного диабета и артериальной гипертензии. Прогрессирование ХБП на фоне действия обозначенных факторов приводит к неуклонной потере почками их фильтрационной способности и развитию осложнений, связанных с этим процессом. К ним относятся, прежде всего, метаболические нарушения, расстройства кислотно-основного равновесия, дизэлектролитемии, уремическая интоксикация, гипергидратация, белково-энергетическая недостаточность, саркопения. Большинство из них участвует в развитии эндотелиальной дисфункции и формировании сердечно-сосудистого ремоделирования (ССР), как ключевого компонента кардиоренального континуума. При этом наблюдается взаимное негативное влияние патологии сердечно-сосудистой системы на функцию почек и проявлений ХБП на сердечно-сосудистую гемодинамику. Этот «порочный круг» приводит к развитию терминальной почечной недостаточности и повышению сердечно-сосудистого риска и смертности от болезней системы кровообращения пациентов на поздних стадиях ХБП. В связи с чем настоящая работа посвящена изучению роли уремической интоксикации и, в частности, индоксил сульфата, в развитии ССР у пациентов с ХБП на разных стадиях болезни.

Ключевые слова: *сердечно-сосудистое ремоделирование, кардиоренальный континуум, хроническая болезнь почек, индоксил сульфат*

Конфликт интересов

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

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Abstract

In recent decades, the prevalence of chronic kidney disease (CKD) in the population has a clear upward trend. This is due, first of all, to an increase in the frequency of occurrence of the main factors leading to its development: diabetes mellitus and arterial hypertension. The progression of CKD against the background of the action of these factors leads to a steady loss of the kidneys of their filtration capacity and the development of complications associated with this process. These include, first of all, metabolic and acid-base disorders, electrolyte abnormalities, uremic intoxication, overhydration, protein-energy wasting, sarcopenia and others. Most of them are involved in the development of endothelial dysfunction and the formation of cardiovascular remodeling (CVR), as a key component of the cardiorenal continuum. At the same time, there is a mutual negative influence of pathology of the cardiovascular system on renal function and manifestations of CKD on cardiovascular hemodynamics. This "vicious circle" leads to the development of end-stage renal disease and an increase in cardiovascular risk and mortality from diseases of the circulatory system in patients with advanced stages of CKD. In this connection, this work is devoted to the study of the role of uremic intoxication and, in particular, indoxyl sulfate, in the development of CVR in patients with CKD at different stages of the disease.

***Key words**: cardiovascular remodeling, cardiorenal syndrome, chronic kidney disease, Indoxyl sulfate*

Conflict of interests

The authors declare no conflict of interests

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CCA — common carotid artery, CI — confidence interval, CKD — chronic kidney disease, CVR — cardiovascular remodeling, DM — diabetes mellitus, ESRD — end-stage renal failure, GFR — glomerular filtration rate, HD — hemodialysis, IHD — ischemic heart disease, IS — indoxyl sulfate, LBFV — linear blood flow velocity

Introduction

Today, there is a definite trend towards an increase in the number of patients with chronic kidney disease (CKD) with a heterogeneous etiological structure. Some patients develop end-stage renal failure (ESRD) as the disease progresses [1]. On the one hand, CKD aggravates the course of arterial hypertension, coronary heart disease, cerebrovascular disease, as well as microvascular disorders in diabetes mellitus (DM). This causes hemodynamic and metabolic disorders and significantly increases the cardiovascular risk and mortality of patients from circulatory system diseases, including at the early stages of the disease [2]. According to the SPRINT study, the presence of CKD significantly increased the incidence of adverse cardiovascular events (2.84%/year versus 1.55%/year, $p < 0.001$) [3]. On the other hand, diabetes mellitus, arterial hypertension and other cardiovascular diseases accelerate renal function loss, closing the vicious circle and contributing to cardiovascular mortality [4, 5]. In this connection, CKD is not only a nephrological issue but a multidisciplinary problem. Significant efforts are required for a more detailed study of the pathogenetic mechanisms of the development of cardiorenal syndrome.

In this aspect, the progression of cardiovascular remodeling (CVR) plays a key role in the development of cardiovascular pathology in CKD [6]. CVR is associated with a wide range of metabolic and hemodynamic disorders, with uremic intoxication, electrolyte disorders, systemic inflammation, arterial hypertension, vascular calcification, hyperphosphatemia, proteinuria, and anemia contributing the most. These factors and their high prevalence in patients with CKD form the basis of the cardiorenal continuum [7, 8].

Uremic toxins that accumulate in the body during CKD exhibit biological activity and cause toxic effects. The classification of the European Working Group on Uremic Toxins EUTox (2012) identifies free water-soluble low molecular weight compounds (0.5 kDa), medium molecular weight molecules (0.5–60.0 kDa) and protein-bound compounds depending on the size and binding properties [9]. Their content in patients with CKD significantly exceeds that in the group of healthy individuals and is directly linked to uremia symptoms. Albumin-associated indoxyl sulfate (IS) is of particular interest for our study as a key marker of uremic intoxication in the discussed cohort of patients. Its concentration in blood increases in conditions of impaired

kidney filtration capacity. IS plays an important role in the progression of CVR, especially in the group of dialysis patients, since it does not completely penetrate the dialysis membrane and accumulates in the body and causes complications [10, 11]. The wide range of the biological effects of IS, such as potentiation of systemic inflammation, activation of inflammatory response and oxidative stress, vascular wall calcification, effect on adipocytes and immune cells, and stimulation proliferation of endothelial cells, can lead to endothelial dysfunction and the progression of CVR [12–15]. Also, IS can realize its profibrotic effect by influencing the differentiation of smooth muscle and epithelial cells of the proximal tubules of kidneys [16].

Despite the progress achieved in the study of the pathophysiological mechanisms of the effect of uremic toxins on CVR processes, we did not find any work on the comparative assessment of IS levels and indices of morphometry of vascular wall and blood flow velocity. However, it is of research interest. This paper intends to assess the role of uremic intoxication in CVR and the importance of IS as a promising molecular marker of this pathological process.

The purpose of this study was to investigate the role of uremic intoxication and, particularly IS, in CVR in patients with CKD at different stages of the disease.

The inclusion criteria were: CKD stages 3A-5D, use of long-term hemodialysis in patients with CKD stage 5D. The study had the following exclusion criteria: acute or exacerbation of a chronic infection requiring active treatment, alcoholism, drug addiction, as well as mental disorders, pregnancy, breastfeeding, immunosuppressive therapy currently or in the past three months, hereditary metabolic diseases and lack of consent to participate in the study.

We carried out a one-stage cross-sectional study. At the first stage, clinical and anamnestic, and anthropometric data were collected from all patients, and concomitant diseases were identified. Next, laboratory and instrumental examination was carried out: CBC (Sysmex XT 2000i analyzer, Japan), CU (Dirui H-1000 urine analyzer), blood biochemistry (ARCHITECT CI8200 analyzer, USA), as well as ultrasound (basins of brachial, carotid and renal arteries), EchoCG (on Toshiba Aplio 300 machine, Japan), test with endothelium-dependent vasodilation, determination of the concentration of indoxyl sulfate (IS) in blood serum (Luminex MAGPIX machine (USA), "Indoxyl sulfate" laboratory kit BlueGene Corp, (USA)) by ELISA (measurement range — 1–25 ng/ml, sensitivity of the method is 0.1 ng/ml).

At the second stage, a statistical analysis of the data obtained was carried out to study the role of IS in CVR. In order to determine intergroup differences, we divided all patients into two groups: Group 1 — patients with CKD 5D receiving treatment with programmed hemodialysis, group 2 — patients with CKD 3A-5.

Statistical processing of the results was carried out using Statistica 10.0 and IBM SPSS Statistics 25 software. The nature of the distribution of quantitative parameters was determined via the Kolmogorov — Smirnov test with Lilliefors correction, as well as the Shapiro — Wilk test with a sample size of less than 30, with an additional assessment of kurtosis and asymmetry. Quantitative parameters with a normal distribution of samples were represented by the mean and standard error of the mean, and with a distribution different from normal, by the median (Me) and the 25th and 75th percentiles. The reliability of differences between qualitative parameters was determined using the nonparametric criterion χ^2, between quantitative parameters in groups — using the Mann — Whitney test. The Kruskal — Wallis test was used when there were more than two groups. Correlation analysis was carried out using the Spearman test, while the strength of the connection was determined using the Chaddock scale. The critical level of statistical significance when testing null hypotheses is $p < 0.05$. In order to determine the quality of the diagnostic criteria developed by us, we used ROC analysis (Receiver Operating Characteristic curve) with the analysis of AUC (area under the curve).

Materials and Methods

We examined 70 patients with CKD stages 3A-5D. The average age of the patients was 59.3 ± 12.5; there was no significant difference between the groups (group 1 — (58.72 ± 12.50) years, group 2 — (59.91 ± 12.67) years, p_{1-2}= 0.74. The average age of the patients depending on the stage of CKD was: Stage 3A — (63.20 ± 11.78) years, Stage 3B — (59.27 ± 13.70) years, Stage 4 — (55.86 ± 13.80) years, Stage 5 — (62.5 ± 4.9) years, Stage 5D — (58.72 ± 12.50) years, p_{3A-5D} = 0.81). The sample included 30 men (42.3%) and 40 women (57.7%); there was no statistically significant difference between the groups for this parameter (p_{1-2} = 0.089, p_{3A-5D} = 0.17). The etiological structure of CKD in patients was quite diverse and was determined as follows: the most frequently diagnosed: chronic tubulointerstitial nephritis (22 patients — 31%), hypertensive nephropathy (25 patients — 35.2%), as well as diabetic nephropathy (15 patients — 21.1%) and chronic glomerulonephritis (15 patients — 21.1%). It should be noted that the overwhelming majority of patients had arterial hypertension

Table 1. Laboratory serum counts of patients of the 1st and 2nd groups

Indicator	1st group	2nd group	p
	Me[Q1;Q3]		
*Creatinine, μmol / l	810,35 [671,7;949,1]	146,0 [113,0;174,0]	<0,001
*Urea, mmol / l	20,25 [16,99;23,61]	9,9 [7,9;12,6]	<0,001
*GFR, ml / min / 1.73m^2	5,0 [4,0;5,5]	37,5[29,0;45,0]	<0,001
Uric acid, μmol / l	404,26 [363,55;441,8]	391,5 [308,0;446,0]	0,3
*Sodium, mmol / l	137,6 [135,0; 139,55]	139,45 [138,2;141,2]	0,01
*Potassium, mmol / l	5,76 [4,93;6,23]	4,64 [4,34;4,98]	<0,001
*Calcium, mmol / l	1,1 [1,08;1,23]	1,08 [1,01;1,14]	0,008
*Chloride, mmol / l	101,5 [99,0;103,0]	104,0 [102,0;105,0]	0,002

Note: * — the levels are statistically significant based on the Mann-Whitney U test

Table 2. Laboratory serum counts in patients ranked by stage of CKD

Indicator	CKD G3a	CKD G3b	CKD G4	CKD G5	CKD G5D	p
	Me[Q1;Q3]	Me[Q1;Q3]	Me[Q1;Q3]	Me[Q1;Q3]	Me[Q1;Q3]	
*Creatinine, μmol / l	107,0 [104,0;123,0]	146,0 [129,5;153,0]	177,0 [171,0;200,5]	411,0 [331,0;491,0]	810,4 [671,7;949,1]	<0,001
*Urea, mmol / l	7,6 [5,7;9,9]	9,5 [8,95;12,4]	12,4 [10,8;15,0]	16,9 [15,6;18,2]	20,25 [16,99;23,61]	<0,001
*GFR, ml / min / 1.73m^2	51,0 [47,0;55,0]	37,0 [34,0;39,5]	28,0 [25,0;28,5]	11,0 [10,0;12,0]	5,0 [4,0;5,5]	<0,001
Uric acid, μmol / l	400,5 [324,0; 443,0]	420,0 [307,0;479,5]	358,0 [319,0;392,0]	348,0 [250,0;446,0]	404,3 [363,6;441,8]	0,78
Sodium, mmol / l	139,9 [138,5;141,4]	139,4 [138,2;141,1]	139,7 [138,4;140,6]	137,3 [136,9;137,7]	137,6 [135,0;139,6]	0,51
*Potassium, mmol / l	4,6 [4,3;4,9]	4,6 [4,4;4,9]	5,0 [4,4;5,0]	4,8 [4,8;4,8]	5,8 [4,9;6,2]	0,001
*Calcium, mmol / l	1,0 [1,0;1,1]	1,1 [1,0;1,1]	1,1 [1,1;1,2]	1,1 [1,1;1,2]	1,1 [1,1;1,2]	0,02
*Chloride, mmol / l	103,5 [102,0;107,0]	104,0 [103,0;105,0]	105,0 [103,0;106,0]	102,5 [99,0; 106,0]	101,5 [99,0;103,0]	0,03

Note: * — the levels are statistically significant based on the Mann-Whitney U test

(61 patients — 85.9%), while 46.5% had stage III, 42.3% had stage II, and 1.4% of patients had stage I. Comorbidities pathogenetically associated with CKD included the following: diabetes mellitus (DM) — 19 patients — 26.8%, obesity (23 patients — 32.4%), urolithiasis (15 patients — 21.1%), ischemic heart disease (IHD) — 27 patients — 38.0%). The history of CKD averaged (9.24 ± 9.70) years [5; 37].

The number of patients with CKD on long-term HD was 36 (50.7%); 34 subjects (47.9%) were not receiving HD. The distribution of patients by CKD stages was as follows: Stage 3A — 10 patients (14.3%), 3B — 15 (21.4%), 4 — 7 (10%), 5 — 2 (2.9%), 5D — 36 (51.4%).

The group of dialysis patients was found to have a statistically significant increase in the concentration of routine markers of impaired renal filtration capacity, urea and creatinine, as well as a significant difference in the levels of potassium, calcium and chlorine (Table 1). Laboratory characteristics of patients according to CKD stages are shown in Table 2.

Results and Discussion

Analysis of the data obtained showed that the median IS concentration was 5.65 [4.33; 7.12] ng/ml, while significant differences were observed between the comparison groups — the highest concentration was found in the dialysis group compared to the pre-dialysis group: 6.17 [4.62;8.28] ng/ml and 5.3 [4.2;6.28] ng/m, respectively ($p_{1-2} = 0.009$). The level of IS also tended to increase with the progression of CKD (Kruskal — Wallis test, $p._{3A-5D} = 0.05$), respectively in stages: 3A — 4.6 [4.1;6.6] ng/ml, 3B — 5.3 [4.3;5.9] ng/ml, 4 — 5.5 [4.4;6.5] ng/ml and 5 — 6.1 [6.0;6.3] ng/ml. We discovered a moderate negative correlation between the level of GFR and IS ($r = -0.33$) (Fig. 1).

An increase in IS levels with a decrease in GFR indicates increasing uremic intoxication with CKD progression. The data obtained are confirmed by an increase in such known parameters of renal dysfunction as creatinine and urea against the background of disease progression (Tables 1, 2). It should be noted that IS is not only

presented as a byproduct but is also a key regulator of muscle tissue metabolism, endothelial function, oxidative stress, and other processes in the discussed cohort of patients, which needs further investigation.

In order to assess intracardiac hemodynamics and CVR, all patients underwent echocardiography, as well as ultrasound of renal, carotid and brachial arteries.

Due to the pronounced effect of endogenous uremia on the endocardium, we analyzed the state of heart valves: the greatest changes in the form of insufficiency were determined for mitral and tricuspid valves (Fig. 2, 3). It should be noted that tricuspid valve insufficiency was detected statistically significantly more often in the group of patients receiving HD treatment (p_{1-2} = 0.008). Based on the Kendall — Tau test, a significant difference in the frequency of this parameter was revealed depending on the CKD stage (Ƭ = 0.23, p_{3A-5D} = 0.021).

Valvular dysfunction in patients indirectly demonstrates adaptive processes occurring in the cardiovascular system of patients with CKD in response to impaired homeostasis and changes in hemodynamics that are manifested, among other things, by hyperhydration and increased pre- and afterload. Such changes are especially pronounced in patients receiving HD treatment due to the presence and functioning of vascular access and regular HD procedures.

We found a statistically significant difference in the diameter of the aorta in the area of the sinus of Valsalva between groups 1 and 2 (p_{1-2} = 0.005) (Table 3). Also, there was a tendency towards a decrease in the diameter of the aorta in the sinotubular junction for patients receiving HD compared with the pre-dialysis group (p_{1-2} = 0.038) (Table 3). However, an analysis (performed using Kruskal — Wallis test) of echocardiography in the groups of patients ranked by CKD stages showed statistically significant differences only in the aortic diameter in the area of the sinus of Valsalva (p_{3A-5D} = 0.02). In the follow-up group, myocardial hypertrophy was observed significantly more often, in particular, of the interventricular septum (p_{1-2} = 0.007), as well as the posterior wall of the left ventricle (p_{1-2} = 0.011) (Table 3). The discussed changes demonstrate cardiovascular remodeling mainly in the group of dialysis patients, probably due to the peculiarities of the redistribution of fluid in the body, as well as endothelial dysfunction.

The E/a index is a component of the comprehensive assessment of left ventricular diastolic function. It was lower than 1.0 in both groups and significantly lower in the group of patients receiving treatment with long-term HD (p_{1-2} = 0.05), which corresponded to diastolic dysfunction and indicated more pronounced disorders of intracardiac hemodynamics in group 1.

When assessing hemodynamics in the brachial artery system, a significant increase in linear blood flow velocity was found in the group of patients on long-term HD, and a moderate negative correlation (r = –0.42) of this parameter with the CKD stage was found (Table 4). The greatest differences in blood flow velocity were determined in systole (p_{1-2} = 0.008) compared with diastole (p_{1-2} = 0.011), as well as in the systolic-diastolic

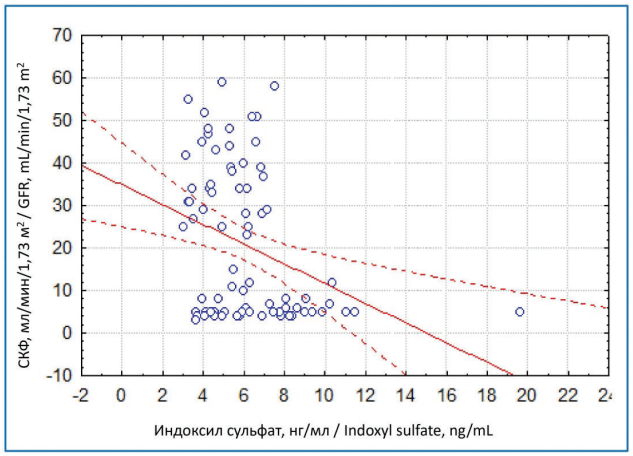

Figure 1. *Correlation between the level of IS and GFR in the general cohort of patients*

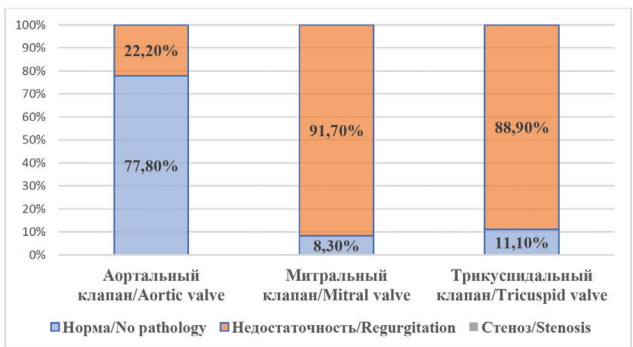

Figure 2. *Features of changes in the heart valve apparatus in patients with CKD5D*

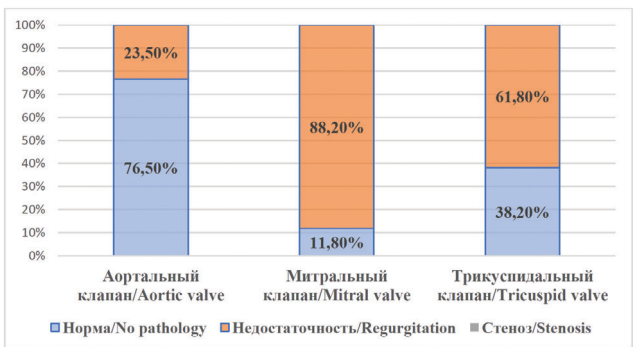

Figure 3. *Changes in the heart valve apparatus in patients with CKD stages 3A-5*

Table 3. *Echocardiography parameters in patients of the 1st and 2nd groups*

Indicator	1st group	2nd group	p
	Me[Q1;Q3])		
*Aortic diameter (Valsalva sinus), mm	31,5 [28,0;33,0]	33,0 [32,0;34,0]	0,005
*Aortic diameter (sinotubular junction), mm	32,0 [30,0;34,0]	33,0 [32,0;34,0]	0,038
EF, %	58,5 [53,5;64,0]	60,0[56,0;63,0]	0,4
CO, L/min	5,5 [4,2;6,5]	4,5 [4,1;5,3]	0,07
*IVST, mm	12,5 [12,0;13,4]	12,0 [11,2;12,3]	0,007
*LVPWT, mm	12,4 [12,0;13,5]	12,0 [11,2;12,3]	0,011
E/A ratio	0,7 [0,7;0,8]	0,8 [0,7;0,9]	0,05

Note: * — the levels are statistically significant based on the Mann-Whitney U test; EF — ejection fraction, CO — cardiac output, IVST — interventricular septum thickness, LVPWT — left ventricular posterior wall thickness, E/A ratio — the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)

Table 4. *Indicators of blood flow in the brachial artery in patients of the 1st and 2nd groups*

Indicator	1st group	2nd group	p
	Me[Q1;Q3])		
*Blood flow velocity along the brachial artery in systole, cm/s	4,6 [4,1;5,3]	4,1[3,7;4,7]	0,008
*Blood flow velocity along the brachial artery in diastole, cm/s	4,2 [3,9;4,9]	3,9[3,5;4,5]	0,011
* Difference in linear velocities of blood flow along the brachial artery in systole and diastole, cm/s	47,5[35,0;59,0]	56,0 [48,0;69,0]	0,015
*Diameter of the brachial artery in systole, mm	63,0 [47,5;77,0]	76,0 [67,0;83,0]	0,008
Diameter of the brachial artery in diastole, mm	16,5 [11,0;21,5]	18,0 [17,0;20,0]	0,057
Resistance index of the brachial artery	0,8 [0,7;0,8]	0,8 [0,7;0,8]	0,6

Note: * — the levels are statistically significant based on the Mann-Whitney U test

difference (p_{1-2} = 0.015). Also, lower values of the diameter of the brachial artery in systole were found in patients of group 1 (p_{1-2} = 0.008). Apparently, this is due to more pronounced vascular stiffness in patients receiving HD treatment with underlying hypercholesterolemia, generalized atherosclerosis and vascular calcification.

In groups 1 and 2, significant changes in renal blood flow were found as CKD progressed. A decrease in blood flow velocity was observed at all levels of the architectonics of renal arteries: in the mouth, hilum, in segmental and interlobar arteries, primarily in group 1 compared to group 2 (Table 5). Maximum changes were observed in the area of segmental and interlobar arteries, on both the right and the left, and the values of these parameters were significantly lower in dialysis patients (Table 5). The distribution of patients in the entire cohort by CKD stages showed statistically significant differences in renal blood flow parameters using the Kruskal — Wallis test: (p_{RI} = 0.24, $p_{Vmax\ mouth}$ = 0.035, $p_{Vmaxseg}$ = 0.016, $p_{Vmin\ segm}$ = 0.007, $p_{Vmin\ inter}$ = 0.02) and left ($p_{Vmax\ mouth}$ = 0.025, $p_{Vmin\ mouth}$ = 0.011, p_{Vmax} = 0.011, $p_{Vminhil}$ = 0.004, $p_{Vmaxseg}$ = 0.015, $p_{Vminseg}$ = 0.001, $p_{Vmaxinter}$ = 0.004, $p_{Vmininter}$ = 0.001).

The obtained data paint the picture of intrarenal hemodynamics in patients with CKD and the severity of renal blood flow disorders, especially in group 1. The reasons for this can be both nephrosclerosis, which develops with underlying uncontrolled hyperglycemia or high blood pressure, and other reasons, including uremic intoxication that potentiates endothelial dysfunction and subsequent vascular remodeling. These processes accelerate CKD progression and worsen the prognosis of the disease.

Blood flow in the systems of common, internal, and external carotid arteries, as well as in the brachiocephalic trunk, was investigated to assess the hemodynamics in cerebral arteries. The greatest intergroup differences were determined in terms of the linear velocity of blood flow into systole in the common carotid artery (p_{1-2} = 0.03) (Fig. 4) and external carotid artery (p_{1-2} = 0.04) (Fig. 5). There was no significant difference in linear blood flow velocity (LBFV) in the carotid system depending on the stage of CKD. There was a decrease in LBFV in the common and external carotid arteries in group 1 compared to group 2, which is probably due to the peculiarities of cardiac remodeling in the group of dialysis patients (myocardial hypertrophy, diastolic dysfunction, valvular pathology are more common), an increase in MVC, loss of kidney filtration capacity and other reasons. Apparently, this outweighs the contribution of endothelial dysfunction of the main arteries with underlying uremic intoxication to the disbalance of vascular resistance and effect on central hemodynamics. However, this issue requires further study.

Table 5. *Renal blood flow parameters in patients of the 1st and 2nd groups*

Indicator	1st group	2nd group	P
	Me[Q1;Q3]		
V_{max} in the proximal right main renal artery, cm/s	54,0[52,5;57,5]	74,5 [61,0;85,0]	0,002
V_{min} in the proximal right main renal artery, cm/s	21,0 [21,0;23,5]	24,5 [21,0;29,0]	0,4
Resistance index in the main proximal renal artery on the right	0,6 [0,6;0,6]	0,6 [0,6;0,7]	0,13
V_{max} in the distal right main renal artery, cm/s	55,0 [49,5; 57,5]	67,5 [54,0;78,0]	0,07
V_{min} in the distal right main renal artery, cm/s	22,0 [17,0;23,0]	30,0 [21,0; 32,0]	0,03
V_{max} in the right segmental arteries, cm/s	22,0 [21,0; 32,5]	50,0 [36,0;54,0]	0,001
V_{min} in the right segmental arteries, cm/s	9,0 [9,0;10,5]	19,0 [13,0;20,0]	0,001
V_{max} in the right interlobar arteries, cm/s	13,0 [13,0;17,0]	22,0 [20,0;26,0]	0,008
V_{min} in the right interlobar arteries, cm/s	6,0 [5,0;6,5]	11,0 [10,0;11,0]	<0,001
V_{max} in the proximal left main renal artery, cm/s	59,0 [50,5;59,0]	75,0 [67,0;89,0]	0,001
V_{min} in the proximal left main renal artery, cm/s	23,0 [21,5;24,0]	32,5 [23,0;33,0]	0,03
Resistance index in the main proximal renal artery on the left	0,6 [0,6;0,6]	0,7 [0,6;0,7]	0,021
V_{max} in the distal left main renal artery, cm/s	51,0[49,0;57,0]	77,0 [57,0;87,0]	0,014
V_{min} in the distal left main renal artery, cm/s	23,0[16,0;25,0]	31,0[21,0;31,0]	0,021
V_{max} in the left segmental arteries, cm/s	23,0[23,0;28,0]	53,0[40,0;53,0]	0,006
V_{min} in the left segmental arteries, cm/s	8,0[7,5;10,0]	19,0[12,0;19,0]	0,003
V_{max} in the left interlobar arteries, cm/s	14,0[14,0;18,0]	23,0[23,0;31,0]	<0,001
V_{min} in the left interlobar arteries, cm/s	5,0[4,5;5,0]	11,0[11,0;12,0]	<0,001

Note: * — the levels are statistically significant based on the Mann-Whitney U test; Vmax — maximum blood flow velocity, Vmin — minimum blood flow velocity; RI — resistance index

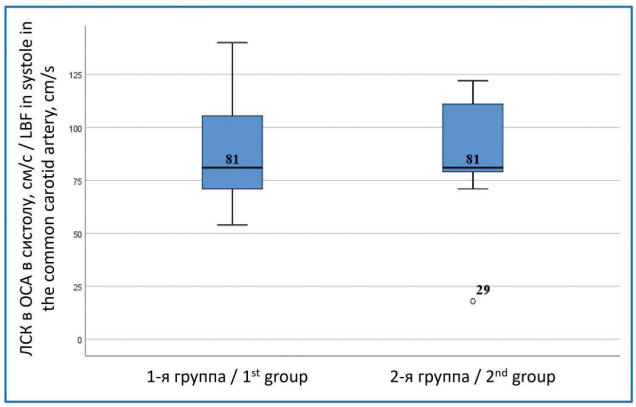

Figure 4. *Linear blood flow velocity in systole in the common carotid artery in patients of the 1st and 2nd groups (p_{1-2} = 0.03)*

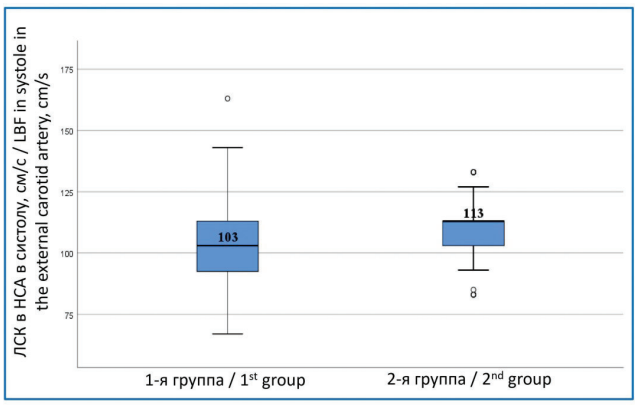

Figure 5. *Linear blood flow velocity into systole in the external carotid artery in patients of the 1st and 2nd groups (p_{1-2} = 0.04)*

When conducting a correlation analysis of factors that had significant differences between groups 1 and 2 using the Spearman test, we discovered synergistic changes in hemodynamic parameters in the vessels of brachial, carotid and renal arteries, myocardial hypertrophy, as well as levels of metabolic and electrolyte imbalance. Correlation analysis of the IS level showed the most significant relationship according to the Chaddock scale with urea (r = 0.6, p < 0.001), phosphorus (r = 0.4, p < 0.001), and the thickness of renal parenchyma (r = 0.66, p = 0.02), and a weak relationship with the diameter of the aorta in the sinotubular region (r = 0.3, p = 0.011) and linear blood flow velocity in the CCA in systole (r = 0.2, p = 0.04), which demonstrates the relationship between the value of the parameter of the indicated uremic molecular marker and the significance of the CVR processes.

We also carried out ROC analysis to get a deeper understanding of the role of IS in the development of CVD and the possibility of using it as a biological marker of the progression of this phenomenon in CKD. The area under the ROC curve, which corresponds to

the relationship between the concentration of IS and the probability of dilation of the brachial artery less than 10 % (as an indirect parameter of the presence of endothelial dysfunction in the patient) after a test with endothelium-dependent vasodilation, was 0.64 ± 0.07 (95% CI = 0.5–0.8). The resulting model was statistically significant (p = 0.04) [17].

The threshold value of the IS level at the cut-off point is 5.76 ng/ml. When equal or higher than this value, the IS level was predicted to have a high risk of CVR. The sensitivity and specificity of the method were 77.3% and 55.2%, respectively (Fig. 6).

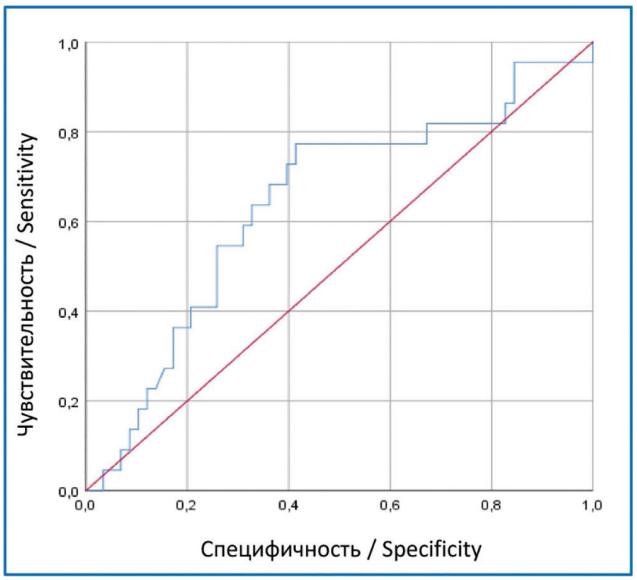

Figure 6. *ROC-curve of the dependence of the narrowing of the brachial artery on the level of Indoxyl sulfate*

Testing with endothelium-dependent vasodilation is an additional method available in practical healthcare for the indirect assessment of endothelial dysfunction in a patient. The determination of IS level and considering this parameter, together with the data obtained on changes in the diameter and LBFV of the brachial artery after the test, improves the prognostic value of this method and represents an effective model for assessing the likelihood of endothelial dysfunction in patients with CKD with underlying uremic intoxication.

The area under the ROC curve of the increasing thickness of intima-media complex (TIMC) of the common carotid artery, as one of the predictors of CVR, on the IS level was 0.680 ± 0.066 (95% CI = 0.6–0.8). The resulting model was statistically significant (p = 0.021). It should be noted that there was no significant difference in TIMC values between CKD stages (p > 0.05).

If the IS threshold point is equal to or greater than 4.8 ng/ml, a high risk of increased TIMC of the common carotid artery is predicted. The sensitivity and specificity of the method are 75.0% and 54.2%, respectively (Fig. 7). An increase in TIMC in patients with CKD with underlying uremic intoxication is a potential unfavorable predictor of not only CVD but also cardiovascular events.

The area under the ROC curve, which corresponds to the relationship between the thickness of renal parenchyma according to ultrasound and IS concentration, was 0.66 ± 0.06 (95% CI = 0.54–0.78). The resulting model was statistically significant (p = 0.03). The cutoff point of the IS level was 5.3 ng/ml with a sensitivity and specificity of 78.8% and 55.3%, respectively (Fig. 8).

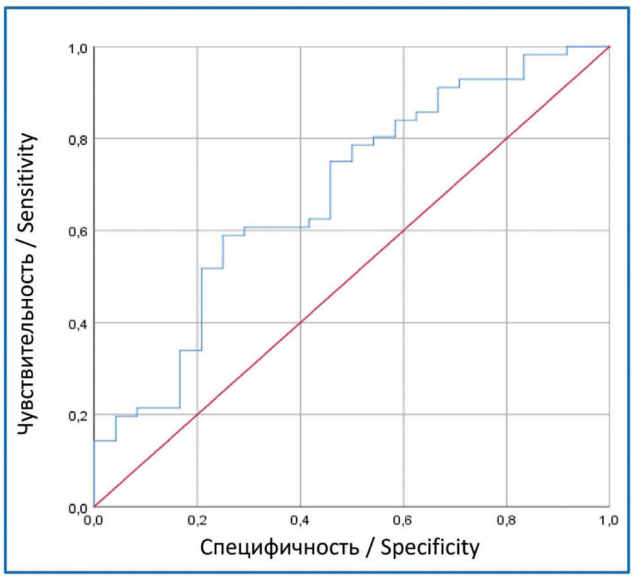

Figure 7. *ROC-curve of the dependence of the increase in ICIM in the common carotid artery on the level of Indoxyl sulfate*

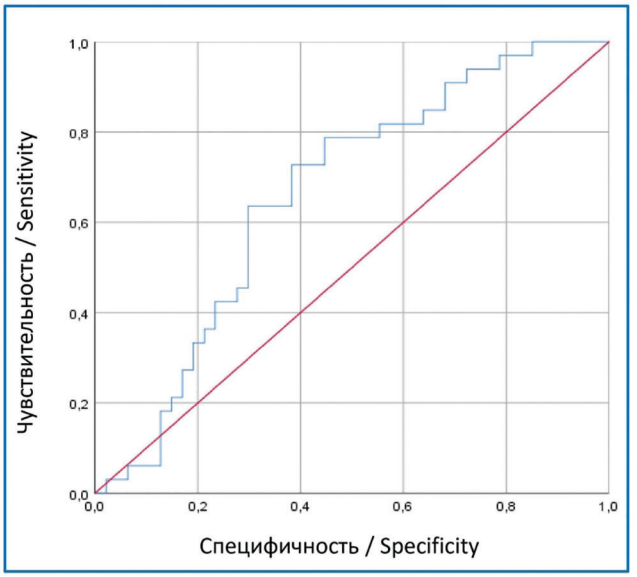

Figure 8. *ROC-curve of the dependence of the thickness of the parenchyma of the right kidney on the level of Indoxyl sulfate*

CKD progression is clearly associated with nephrosclerosis, decreased kidney size, including parenchyma, according to ultrasound data, and impaired kidney function, which is associated with uremic intoxication. The discussed diagnostic model indirectly demonstrates the ability to predict the rate of CKD progression depending on the level of IS.

Conclusion

The analysis of the results obtained made it possible to identify cardiovascular system remodeling features in patients with CKD at different stages of the disease and to assess the contribution of IS as a parameter of uremic intoxication in its development. It was found that in patients receiving treatment with long-term hemodialysis, the indicated changes were observed significantly more often and were accompanied by a high level of IS. This may not only indirectly indicate the role of the latter in this pathological process but also allows using the determination of the IS level as an additional diagnostic marker to determine the severity of the course and prognosis of CKD.

The contribution of other factors to CVR in patients with CKD requires a comprehensive assessment and further study of the pathogenetic mechanisms of their effects. Repeated determination of the IS level, as well as ultrasound examination of the cardiovascular system over time, will allow not only to make a prognostic model for assessing the likelihood of CVR and the rate of its progression in the group of patients under discussion but also to carry out timely pharmacological correction.

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Список литературы/ References:

1. Аринтазина А.М., Нарманова О.Ж., Нускабаева Г.О. и др. Хроническая болезнь почек: распространенность и факторы риска (обзор литературы). Анализ риска здоровью. 2020; 2: 164-174. doi: 10.21668/health.risk/2020.2.18.
   Aringazina A.M., Narmanova O.Zh., Nuskabaeva G.O. et al. Chronic kidney disease: prevalence and risk factors (literature review). Health Risk Analysis. 2020; 2: 164–174. doi: 10.21668/health.risk/2020.2.18. [in Russian].
2. Айдаров З.А., Жамилова Г.К., Юсупов А.Ф. и др. Хроническая почечная недостаточность и сердечно-сосудистые заболевания: проблема междисциплинарная. The Scientific Heritage. 2020; 49-2(49): 10-17.
   Aidarov Z., Zhamilova G., Yusupov A. et al. Chronic renal insufficiency and cardiovascular diseases: an interdisciplinary problem. 1. The Scientific Heritage. 2020; 49-2(49): 10-17. [in Russian].
3. Rakesh Malhotra, Ronit Katz, Vasantha Jotwani et al. Urine markers of kidney tubule cell injury and kidney function decline in SPRINT trial participants with CKD. Clin J Am Soc Nephrol. 2020; 15(3): 349-358. doi: 10.2215/CJN.02780319.
4. Батюшин М.М. Хроническая болезнь почек: современное состояние проблемы Рациональная фармакотерапия в кардиологии. 2020; 16(6): 938-947. doi:10.20996/1819-6446-2020-11-06.
   Batiushin M.M. Chronic Kidney Disease: Current State of the Problem. Rational Pharmacotherapy in Cardiology 2020; 16(6): 938-947. doi:10.20996/1819-6446-2020-11-06. [in Russian].
5. Муркамилов И.Т., Айтбаев К.А., Фомин В.В. и др. Факторы риска развития инсульта у пациентов с терминальной стадией хронической болезни почек: современное состояние проблемы. Казанский медицинский журнал. 2020; 101(6): 825-833.
   Murkamilov I.T., Aitbaev K.A., Fomin V.V. et al. Stroke risk factors in patients with end-stage kidney disease: current status of the problem. Kazan Medical Journal. 2020; 101(6): 825–833. doi: 10.17816/KMJ2020-825. [in Russian].
6. Цыганкова О.В., Худякова А.Д., Латынцева Л.Д. и др. Сердечно-сосудистый континуум: от факторов риска до систолической сердечной недостаточности. Атеросклероз. 2017; 13(4): 42-46.
   Tsygankova O.V., Khudyakova A.D., Latyntseva L.D. et al. Cardiovascular continuum: from risk factors to the systolic heart

failure (the clinical case). Atherosclerosis. 2017; 13(4): 42-46. [in Russian].

7. Faiez Zannad, Patrick Rossignol. Cardiorenal Syndrome Revisited. Circulation. 2018; 138(9): 929-944. doi: 10.1161/circulationaha.117.028814.
8. Левицкая Е.С., Батюшин М.М., Пасечник Д.Г. и др. Ремоделирование почечных артерий — инициатор и мишень кардиоренального континуума. Кардиоваскулярная терапия и профилактика. 2015; 14(1): 90-96. doi: http://dx.doi.org/10.15829/1728-8800-2015-1-90-96.
Levitskaya T.S., Batyushin M.M., Pasechnik D.G. et al. Renal arteries remodelling — the initiator and target of cardiorenal continuum. Cardiovascular Therapy and Prevention. 2015;14(1):90–96. doi: http://dx.doi.org/10.15829/1728-8800-2015-1-90-96. [in Russian].
9. Flore Duranton, Gerald Cohen, Rita De Smet et al. Normal and pathologic concentrations of uremic toxins. J Am Soc Nephrol. 2012;23(7):1258-70. doi: 10.1681/ASN.2011121175.
10. Xiao TAN, Xuesen CAO, Jianzhou ZOU et al. Indoxyl sulfate, a valuable biomarker in chronic kidney disease and dialysis. Hemodialysis International. 2017; 21: 161–167. doi:10.1111/hdi.12483.
11. Гасанов М.З. Саркопения у пациентов с хронической болезнью почек: распространенность, особенности патогенеза и клиническое значение. Нефрология. 2021; 25(1): 47-58. https://doi.org/10.36485/1561-6274-2021-25-1-47-58.
Gasanov M.Z. Sarcopenia in patients with chronic kidney disease: prevalence, pathogenesis and clinical significance. Nephrology (Saint-Petersburg). 2021; 25(1): 47-58. doi: https://doi.org/10.36485/1561-6274-2021-25-1-47-58. [in Russian].
12. Takuya Wakamatsu, Suguru Yamamoto, Toru Ito et al. Indoxyl sulfate promotes macrophage IL-1 production by activating aryl hydrocarbon receptor/NF-/MAPK Cascades, but the NLRP3 inflammasome was not activated. Toxins (Basel). 2018; 10(3): 124. doi: 10.3390/toxins10030124.
13. Emiko Sato, Takefumi Mori, Eikan Mishima et al. Metabolic alterations by indoxyl sulfate in skeletal muscle induce uremic sarcopenia in chronic kidney disease. Sci Rep. 2016; 6: 36618. doi: 10.1038/srep36618.
14. Hideki Fujii, Kentaro Nakai, Masafumi Fukagawa. Role of oxidative stress and indoxyl sulfate in progression of cardiovascular disease in chronic kidney disease. Ther Apher Dial. 2011; 15(2): 125-8. doi: 10.1111/j.1744-9987.2010.00883.x.
15. Yiru Wu, Xue Han, Liyan Wang et al. Indoxyl sulfate promotes vascular smooth muscle cell calcification via the JNK/Pit-1 pathway. Ren Fail. 2016;38(10):1702-1710. doi: 10.3109/0886022X.2016.1155397.
16. Hénaut L, Mary A, Chillon JM et al. The Impact of Uremic Toxins on Vascular Smooth Muscle Cell Function. Toxins (Basel). 2018; 10(6): 218. doi:10.3390/toxins10060218.
17. Самолюк М.О., Григорьева Н.Ю. Оценка эндотелиальной дисфункции и возможности ее коррекции на современном этапе у больных сердечно-сосудистыми заболеваниями. Кардиология. 2019; 59(3S): 4-9. doi: https://doi.org/10.18087/cardio.2524.
Samolyuk M.O., Grigorieva N.Yu. Evaluation of endothelial dysfunction and the possibility of its correction at the present stage in patients with cardiovascular diseases. Cardiology. 2019; 59(3S): 4-9. doi: https://doi.org/10.18087/cardio.2524. [in Russian].

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АССОЦИАЦИИ ПОЛИМОРФИЗМОВ ГЕНОВ И ПРОГНОЗА У ВЫСОКО ПРИВЕРЖЕННЫХ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ ПАЦИЕНТОВ ПОСЛЕ ИНФАРКТА МИОКАРДА

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Associations of Gene Polymorphisms and Prognosis in Highly Adherent to Treatment Patients After Myocardial Infarction

Резюме

Цель. Оценить наличие ассоциаций генетических факторов с риском развития комбинированной конечной точки (ККТ), включающей смертельные исходы, нефатальные инфаркты миокарда (ИМ) и мозговые инсульты в течение однолетнего наблюдения пациентов, перенесших ИМ и высоко приверженных лекарственной терапии. **Материалы и методы.** В исследование включено 250 высоко приверженных медикаментозной терапии пациентов с ИМ (68,8% мужчин, медиана возраста — 62,8 (54,7; 71,4) года), у которых методом полимеразной цепной реакции определяли полиморфизмы Thr174Met и Met235Thr в гене *AGT, Arg389Gly* и Ser49Gly в гене *ADRB1*, Ser447Ter в гене *LPL* и Leu28Pro в гене *APOE*, Trp212Ter и G681A в гене *CYP2C19*, а в дальнейшем оценивали их связь с неблагоприятным исходом. Высоко приверженными медикаментозной терапии считали пациентов, принимавших все назначенные им при выписке лекарственные препараты в течение 12 месяцев наблюдения. **Результаты.** Значимая связь с риском развития ККТ была отмечена для полиморфизма гена *CYP2C19 (G681A)*, участвующего в метаболизме клопидогреля. У лиц с зарегистрированными событиями, объединенными в ККТ, генотип GA гена *CYP2C19 (G681A)* встречался чаще, чем в группе без событий (ОШ 1,97; ДИ 95% 1,05 — 3,69, p=0,03), а генотип GG — реже (ОШ 0,51; ДИ 95%, 0,28 — 0,95, p=0,03). Генотип AA статистической значимой связи с прогнозом не имел ввиду малой численности группы пациентов с данным генотипом (n=3). Для аллеля A гена *CYP2C19 (G681A)* показатель ОШ риска развития ККТ составил 1,96 (ДИ 95%, 1,06 — 3,64, p=0,03). **Заключение.** Полученные результаты свидетельствуют о необходимости индивидуального подхода при выборе препаратов из группы ингибиторов P2Y12-рецепторов для двойной антиагрегантной терапии и, в случае выбора клопидогреля, о необходимости решения вопроса о целесообразности проведения фармакогенетического тестирования по *CYP2C19*.

Ключевые слова: *инфаркт миокарда; неблагоприятный исход; Thr174Met; Met235Thr; Arg389Gly; Ser49Gly; Ser447Ter; Leu28Pro; Trp212Ter; G681A*

Конфликт интересов

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

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Abstract

Aim. To evaluate the influence of genetic factors on the risk of developing a combined endpoint, during a one-year supervision of patients, who had myocardial infarction and highly adherent to drug therapy. **Material and methods.** The research included 250 patients with high adherence to treatment with myocardial infarction, using the method of polymerase chain reaction we determined the polymorphisms Thr174Met and Met235Thr in the *AGT* gene, Arg389Gly and Ser49Gly in the *ADRB1* gene, Ser447Ter in the *LPL* gene and Leu28Pro in the *APOE* gene, Trp212Ter and G681A in the *CYP2C19* gene, and then we evaluated their influence on the prognosis. **Results.** A significant influence on the risk of developing combined endpoint was noticed for the polymorphism of *CYP2C19 (G681A)* gene. For the GA genotype of the *CYP2C19* gene (G6881A), the OR of developing an unsuccessful outcome was 1.97 (95% CI 1.05 — 3.69) (P = 0.03). For carrier-state of A allele the OR was 1.46 (95% CI 1.06 — 3.64) (P = 0.03). **Conclusion.** The results received indicate the need for individual approach for the choice of drugs from the group of inhibitors P2Y12-receptors for dual antiplatelet therapy, and if clopidogrel is chosen it is necessary to resolve the issue of pharmacogenetic testing for *CYP2C19*.

Key words: *myocardial infarction; prognosis; Thr174Met; Met235Thr; Arg389Gly; Ser49Gly; Ser447Ter; Leu28Pro; Trp212Ter; G681A*

Conflict of interests

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ADRB1 — beta-1 adrenergic receptor gene, *AGT* — angiotensinogen gene, *APOE* — apolipoprotein E gene, *CYP2C19* — cytochrome P450 gene of family 2 of subfamily C number 19, *LPL* — lipoprotein lipase gene, BB — beta-blockers, DAPT — double antiplatelet therapy, CI — confidence interval, ACE inhibitors — angiotensin-converting enzyme inhibitors, MI — myocardial infarction, CEP — combined endpoint, QAQ-25 — quantitative adherence questionnaire, CS — cerebral stroke, ACS — acute coronary syndrome, OR — odds ratio

Introduction

Myocardial infarction (MI) is one of the most severe forms of coronary heart disease accompanied by high mortality rates, both in the acute phase and later stages of the disease [1]. While, of late, mortality in the acute period of myocardial infarction has decreased significantly primarily due to the widespread implementation of percutaneous coronary interventions [2–4], mortality rates in the later period of myocardial infarction have been decreasing at a slower rate, although there is also a positive trend [5]. In the LIS-3 study, over an observation period of 14–35 months, 12.5% of patients died [6], and in the later PROFILE-IM register, 10% of patients died over a 1.5-year observation period [5]. Similar data were obtained in the Polish register of acute coronary syndrome (ACS) and acute myocardial infarction in patients with left ventricular ejection fraction ≤ 40% [7]. According to the authors, such an improvement in long-term mortality is exclusively due to the improvement in the quality of secondary prevention [5, 7]. However, the effectiveness of the latter is largely associated not only with the adherence of patients to treatment but also with genetically determined drug resistance [8], which determines both death and adverse cardiovascular events in a particular patient. This fact determines the significant interest in the assessment of possible associations of genetic factors and prognosis.

In accordance with clinical guidelines, if there are no contraindications, all patients with MI should receive drugs that have been proven to improve the prognosis [9] (subject to their use by the patient). In this connection, in our opinion, it is preferable to determine the relationship between polymorphisms of genes that are responsible for the metabolism of these groups of medications and the prognosis in patients who are highly adherent to drug therapy, and when forming a sample of patients for the study, to focus on high potential adherence to treatment, which can be quantified using the QAQ-25 adherence questionnaire [10].

Goal of the study: to investigate associations of polymorphisms of genes involved in the metabolism of drugs

that improve prognosis in MI, with the risk of developing a combined endpoint (CEP) in highly adherent patients after MI.

Material and Methods

From September 1, 2018, to May 1, 2019, 250 patients hospitalized for MI were enrolled in the prospective single-center study.

Inclusion criteria:

- signed informed consent;
- established diagnosis of current MI;
- a high level (more than 75%) of potential adherence to drug therapy, as determined by the QAQ-25 [10].

Patients were enrolled in the study on days 1–3 after their transfer to the general ward from the intensive care unit.

The study had the following exclusion criteria:

- absolute contraindications to angiotensin-converting enzyme inhibitors (ACE inhibitors), beta-blockers (BB), statins, antiplatelet agents;
- mental illnesses;
- alcohol and drug abuse.
- low and medium potential adherence to drug therapy according to the QAQ-25 questionnaire) [10].

The study was approved by the local ethics committee and registered at ClinicalTrials.gov with identification number NCT04424368.

All patients received atorvastatin at a dose of 40 mg per day, ACE inhibitors, BB, clopidogrel as part of dual antiplatelet therapy (DAPT). The patients were given dietary recommendations.

For all patients enrolled in the study, at the time of enrollment, polymorphisms Thr174Met and Met235Thr were determined in the angiotensinogen gene (*AGT*), Arg389Gly and Ser49Gly in the beta-1 adrenergic receptor gene (*ADRB1*), Ser447Ter in the lipoprotein lipase gene (*LPL*) and Leu28Pro in the apolipoprotein E gene (*APOE*), Trp212Ter (*3) and G681A (*2) in the cytochrome P450 gene of family 2 of subfamily C number 19 (*CYP2C19*) via polymerase chain reaction with an electrophoretic scheme for detecting the result "SNP-EXPRESS" (NPF "Litekh", Russia) Subsequently, after 3, 6 and 12 months, the patients were contacted by telephone to assess their level of adherence. After 12 months of follow-up, all of the enrolled patients were adherent to drug therapy. Twelve months after MI, information about the events combined in the CEP was collected for each patient: death, non-fatal MI and cerebral strokes (CS), emergency revascularization of coronary arteries. Then the analysis of the associations of the studied polymorphisms was performed: Thr174Met and Met235Thr in gene *AGT*, Arg389Gly and Ser49Gly in gene *ADRB1*, Ser447Ter in gene *LPL* and Leu28Pro in gene *APOE*, Trp212Ter (*3) and G681A (*2) in gene *CYP2C19* with the risk of developing CEP.

The choice of candidate genes in the study was determined by the known data on the relationship between their polymorphisms and the metabolism of drugs that improve the prognosis, the ambiguity of results of previous studies in groups of patients with MI without considering their adherence to treatment or the absence of such studies according to the literature [11–13]. Clopidogrel was chosen as the second component of DAPT prescribed to patients after MI because of its greater availability for patients and, consequently, the greater frequency of its prescription and use in clinical practice [14–16].

Microsoft Excel 2010 and StatsoftStatistica10.0 were used to analyze the results of the study. Methods of descriptive and nonparametric statistics were fundamental. The results are presented as frequencies (%). The distribution of all quantitative traits differed from normal; the data are presented as the median and interquartile range of Me (Q1; Q3).

The significance of differences in the frequencies of genotypes and alleles of two unrelated groups was determined by the methods of nonparametric statistics depending on the number of observations (chi-square Pearson test, chi-square test with Yates' correction for continuity and Fisher's exact test). Differences were considered significant at $p < 0,05$.

The strength of the identified associations was assessed by the odds ratio (OR) and its 95% confidence interval (95% CI). The CI not including one, i.e. where both values of its limits were above or below one at a significance level of $p < 0.05$, was considered statistically significant.

The determination of the comparability of the distribution of the genotypes of the studied polymorphic genes in the studied sample in relation to the population was carried out by assessing the correspondence to the Hardy — Weinberg equilibrium using software available online http://ihg2.helmholtzmuenchen.de/cgi-bin/hw/hwa1.pl.

Distribution of genetic information in the studied sample corresponded to the Hardy — Weinberg equilibrium for all genes, except for AGT gene (Thr174Met) ($\chi^2 = 4.0$, $p = 0.045$) and ADRB1 (Arg389Gly) ($\chi^2 = 4.4$, $p = 0.037$).

Results

Among the 250 enrolled patients, 68.8% were males (172). 83.6% (209) of patients had a history of hypertension, 30.8% (77) — ischemic heart disease, including 26.4% (66) with a history of MI. In the past, 8.8% (22) of

patients underwent stenting of coronary arteries. Chronic heart failure and atrial fibrillation were observed in 88.8% (222) and 20.8% (52) of patients, respectively. Diagnosis of "diabetes mellitus" or "impaired glucose tolerance" was established in 26.4% (66) of cases. 71.6% (179) of patients had Q-MI at the time of enrollment. Median age was 62.8 (54.7;71.4) years (Table 1).

During one year of follow-up, 11.6% (29) of patients out of 250 died of all causes; 86.2% (25) of them died from cardiovascular causes. One-year survival rate was 88.4%. In one year, 4.8% (12) of patients had MI, which was fatal in three cases, and in 2.4% (6) patients, MI was fatal in one case 10.8% (27) of patients underwent unplanned coronary revascularization. Only 28.0% (70) of patients underwent CEP.

There was a statistically significant difference in the frequency of occurrence of CYP2C19 gene genotypes (G681A) and A allele of the CYP2C19 gene (G681A) between patients with and without registered events.

Data on the distribution of genotypes and the frequency of occurrence of alleles of the analyzed genes among patients with registered events combined in CEP and without such events are presented in Table 2.

Significant associations with the course of the postinfarction period were noted for *CYP2C19 (G681A)* gene polymorphism both at the level of genotypes and at the level of alleles (see Table 3). In individuals with registered events combined in CEP, the GA genotype of*CYP2C19 (G681A)* gene was more common than in the group without events (OR 1.97; CI 95% 1.05–3.69, p = 0.03), and GG genotype was less common (OR 0.51; CI 95%, 0.28–0.95, p = 0.03).

The AA genotype did not have a statistically significant relationship with the prognosis due to the small size of the group of patients with this genotype (n = 3) (OR 1.29; CI 95%, 0.12–14.46, p = 0.63).

For A allele of *CYP2C19 (G681A)* gene, OR of the risk of developing CEP was 1.96 (CI 95%, 1.06–3.64, p = 0.03). For G allele of *CYP2C19 (G681A)* gene, OR of the risk of developing CEP was statistically insignificant and amounted to 0.78 (CI 95%, 0.07–8.70, p = 0.63).

Discussion

The association of minor alleles *2 of the *CYP2C19* gene with an increased risk of developing CEP shown by our study is largely consistent with both the first Russian meta-analysis of the effect of polymorphism of the *CYP2C19* gene on the risk of MI, stent thrombosis, ischemic stroke, transient ischemic attack and cardiovascular death [17], and the latest international studies published in 2018–2019 [18, 19].

Nevertheless, an extensive review published in 2019 on the pharmacogenetics of clopidogrel unequivocally states that the routine clinical genotyping of patients for non-functioning alleles *CYP2C19* is not recommended due to the lack of prospective evidence of the effectiveness of this approach [20]. The large randomized study "Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention" that ended in 2020 revealed no differences in the effect on the primary endpoint between routine antiplatelet therapy and tailored therapy based on genotyping data [21].

Table 1. *Clinical characteristics of patients included in the studies*

Parameter	Patients included in the study (n=250)
Median age, years	62,8 (54,7; 71,4)
Men, % of n	68,8 (172)
Obesity, % of n	30,0 (75)
Diabetes mellitus/impaired glucose tolerance, % of n	22,4 (56)
History of coronary heart disease, % of n	30,8 (77)
Repeated MI, % of n	26,4 (66)
History of PCI, % of n	8,8 (22)
AH, % of n	83,6 (209)
CHF, % of n	88,8 (222)
AF, % of n	20,8 (52)
Q-positive MI, % of n	71,6 (179)
Q-negative MI, % of n	28,4 (72)
Kidney diseases, % of n	26,3 (81)
COPD, % of n	2,4 (6)
Diseases of the gastrointestinal tract, % of n	26,0 (65)
Thyroid diseases, % of n	2,0 (5)

Note: MI — myocardial infarction, PCI — percutaneous coronary intervention, AH — arterial hypertension, CHF — chronic heart failure, AF- atrial fibrillation

Table 2. *Data on the distribution of genotypes, the frequency of occurrence of alleles of the analyzed genes in individuals who have reached and have not reached the combined endpoint*

Genotype/ Allele	Combined endpoint +, % от n=70 (Absolute value)	Combined endpoint –, % от n=180 (Absolute value)	p
ThrThr	65,7 (46)	63,3 (114)	0,72
ThrMet	34,3 (24)	34,4 (62)	0,98
MetMet	0,0 (0)	2,2 (4)	–
Thr	100 (70)	97,8 (176)	–
Met	34,3 (24)	38,9 (70)	0,50
MetMet	25,7 (18)	22,8 (41)	0,83
MetThr	51,4 (36)	57,2 (103)	0,41
ThrThr	22,9 (16)	20,0 (36)	0,37
Met	77,1 (54)	80,0 (144)	0,62
Thr	74,3 (52)	70,2 (139)	0,62
SerSer	69,8 (44)	67,1 (110)	0,81
SerGly	22,2 (14)	29,9 (49)	0,25
GlyGly	7,9 (5)	3,0 (5)	0,11
Ser	82,9 (58)	88,3 (159)	0,25
Gly	27,1 (19)	30,0 (54)	0,66
ADRB1 (Arg389Gly)			
ArgArg	47,1 (33)	57,2 (103)	0,15
ArgGly	47,1 (33)	40,0 (72)	0,30
GlyGly	5,7 (4)	2,8 (5)	0,22
Arg	94,3 (66)	97,2 (175)	0,22
Gly	52,9 (37)	42,8 (77)	0,15
APOE (Leu28Pro)			
LeuLeu	97,1 (68)	96,7 (174)	0,60
LeuPro	2,9 (2)	3,3 (6)	
Leu	100 (70)	100 (180)	–
Pro	2,9 (2)	3,3 (6)	0,60
LPL (Ser447Ter)			
SerSer	92,9 (65)	83,3 (150)	0,04
SerTer	7,1 (5)	16,7 (30)	
Ser	100 (70)	100 (180)	–
Ter	7,1 (5)	16,7 (30)	0,04
CYP2C19 (G681A)			
GG	67,1 (47)	80,0 (144)	**0,03**
GA	31,4 (22)	18,9 (34)	**0,03**
AA	1,4 (1)	1,1 (2)	0,63
G	98,6 (69)	98,9 (178)	0,63
A	32,9 (23)	20,0 (36)	**0,03**
CYP2C19 (Trp212Ter)			
TrpTrp	91,4 (64)	87,2 (157)	0,48
TrpTer	8,6 (6)	12,8 (23)	
Trp	100,0 (70)	100,0(180)	–
Ter	8,6 (6)	12,8 (23)	0,47

Note: for ADRB1 gene (Ser49Gly), n = 227; statistically significant differences are shown in bold

Table 3. *Comparative analysis of the probability of the combined endpoint in patients with MI within 1 year, depending on the genotype/allele*

Genotype/ Allele	Combined endpoint +, % от n=70 (Absolute value)	Combined endpoint -, % от n=180 (Absolute value)	P	OR (95% CI)
		AGT (Thr174Met)		
ThrThr	65,7 (46)	63,3 (114)	0,72	1,11 (0,62–1,98)
ThrMet	34,3 (24)	34,4 (62)	0,98	0,99 (0,56 — 1,77)
MetMet	0,0 (0)	2,2 (4)	–	–
Thr	100 (70)	97,8 (176)	–	–
Met	34,3 (24)	36,7 (66)	0,72	0,91 (0,51 — 1,61)
		AGT (Met235Thr)		
MetMet	25,7 (18)	22,8 (41)	0,83	0,32 (0,62–2,24)
MetThr	51,4 (36)	57,2 (103)	0,41	0,79 (0,46– 1,38)
ThrThr	22,9 (16)	20,0 (36)	0,37	1,19 (0,61 — 2,31)
Met	77,1 (54)	80,0 (144)	0,62	0,84 (0,43 — 1,64)
Thr	74,3 (52)	70,2 (139)	0,62	0,85 (0,45 — 1,62)
		ADRB1 (Ser49Gly)		
SerSer	69,8 (44)	67,1 (110)	0,81	0,32 (0,61 — 2,13)
SerGly	22,2 (14)	29,9 (49)	0,25	0,73 (0,37 — 1,45)
GlyGly	7,9 (5)	3,0 (5)	0,11	2,74 (0,76 — 9,82)
Ser	82,9 (58)	88,3 (159)	0,25	0,64 (0,30 — 1,38)
Gly	27,1 (19)	30,0 (54)	0,66	0,87 (0,47 — 1,61)
		ADRB1 (Arg389Gly)		
ArgArg	47,1 (33)	57,2 (103)	0,15	0,67 (0,38 — 1,16)
ArgGly	47,1 (33)	40,0 (72)	0,30	1,30 (0,75 — 2,27)
GlyGly	5,7 (4)	2,8 (5)	0,22	2,12 (0,55 — 8,14)
Arg	94,3 (66)	97,2 (175)	0,22	0,47 (0,12 — 1,81)
Gly	52,9 (37)	42,8 (77)	0,15	1,50 (0,86 — 2,61)
		APOE (Leu28Pro)		
LeuLeu	97,1 (68)	96,7 (174)	0,60	1,17 (0,23 — 5,95)
LeuPro	2,9 (2)	3,3 (6)		0,85 (0,17 — 4,33)
Leu	100 (70)	100 (180)	–	–
Pro	2,9 (2)	3,3 (6)	0,60	0,85 (0,17 — 4,33)
		LPL (Ser447Ter)		
SerSer	92,9 (65)	83,3 (150)	0,04	2,6 (0,97 — 7,00)
SerTer	7,1 (5)	16,7 (30)		0,39 (0,14 — 1,04)
Ser	100 (70)	100 (180)	–	–
Ter	7,1 (5)	16,7 (30)	0,04	0,39 (0,14 — 1,04)
		CYP2C19 (G681A)		
GG	67,1 (47)	80,0 (144)	**0,03**	**0,51 (0,28 — 0,95)**
GA	31,4 (22)	18,9 (34)	**0,03**	**1,97 (1,05–3,69)**
AA	1,4 (1)	1,1 (2)	0,63	1,29 (0,12 — 14,46)
G	98,6 (69)	98,9 (178)	0,63	0,78 (0,07 — 8,70)
A	32,9 (23)	20,0 (36)	**0,03**	**1,96 (1,06 — 3,64)**
		CYP2C19 (Trp212Ter)		
TrpTrp	91,4 (64)	87,2 (157)	0,48	1,56 (0,61 — 4,02)
TrpTer	8,6 (6)	12,8 (23)		0,64 (0,25 — 1,65)
Trp	100,0 (70)	100,0(180)	–	–
Ter	8,6 (6)	12,8 (23)	0,47	0,64 (0,25 — 1,65)

Note: for *ADRB1* gene (Ser49Gly), n = 227; statistically significant differences are shown in bold

However, despite this, when taking clopidogrel, the Russian clinical guidelines for the management of patients with MI and ACS indicate that "pharmacogenetic testing of *CYP2C19* can be carried out to predict reduced laboratory sensitivity to clopidogrel" [22, 23].

Because a significant percentage of individuals in our study had GA genotype of the *CYP2C19* gene (distribution of genotypes and alleles of the gene *CYP2C19* in our study corresponded to the Hardy Weinberg equilibrium), which was associated with an unfavorable outcome, the recommendation to conduct pharmacogenetic testing can be considered valid and consistent with our results. This genotype (GA of *CYP2C19* gene) determines the need to apply all possible measures to prevent an adverse outcome, including careful selection of DAPT in patients with MI where currently acetylsalicylic acid and a drug from the group of P2Y12 -receptor inhibitors, primarily ticagrelor or prasugrel, should be included [22, 23]. According to clinical guidelines, clopidogrel should be prescribed only when its use is safer for the patient [22, 23]. However, data from actual clinical practice suggest otherwise — clopidogrel is mostly prescribed for patients with MI. In the Russian register "RECORD-3", clopidogrel was prescribed at discharge in 67% of cases, and ticagrelor — in 12% [14]; in one of the registries conducted in the USA, 72.9% of patients received clopidogrel, 17.6% — prasugrel, and 9.5% — ticagrelor [15]; in the analysis of case histories conducted by M. R. Atabegashvili et al (2019), of 854 patients with ACS hospitalized from January to December 2017, clopidogrel was prescribed to 73% of patients, and ticagrelor — to 27% [16].

In such a situation, which implies the prescription of clopidogrel in the absence of contraindications for ticagrelor and prasugrel, the results of genetic testing can be considered an indicator of the safety of its prescription [22, 23]. The cost of the latter (as of May 2021) ranges from 960 to 2,600 rubles depending on the time of analysis, region, laboratory (data from open sources — price lists of laboratories providing the service) and is economically justified [24, 25]. When genotypes associated with the risk of an unfavorable outcome are identified, the results of genotyping will allow the prescription of ticagrelor and prasugrel to such patients, the use of other drug and non-drug methods to improve the prognosis, thereby reducing possible expenses associated with hospitalization, disability, and death of the patient. If a genotype that is not associated with the risk of an unfavorable outcome is identified, genotyping results will allow the prescription of clopidogrel to such patients with a lower risk. The cost of genetic testing will be comparable to the difference in the cost of drugs and will be recovered within the first few months of treatment.

Unlike a number of other authors, we obtained no statistically significant data on the relationship between polymorphisms of other genes that we studied and the prognosis. In the study by M. V. Solodun et al. (2016), the carrier status of allele Ser of polymorphic gene *ADRB1 Ser49Gly* was associated with an increase in the incidence of adverse cardiovascular events within 12 months after STEMI [26]; in another study with hypertrophic cardiomyopathy, genotype ArgGly gene *ADRB1* (polymorphism *Arg389Gly*) was more favorable, since it had a lower chance of being complicated by the development of atrial fibrillation than other genotypes [27].

The distinctive feature of our study, which began in 2018, was the inclusion of patients with only a high level of potential adherence to drug therapy and remote monitoring of adherence to therapy after 3, 6 and 12 months. This study methodology allowed the enrollment of highly adherent patients in the study and the assessment of the associations of gene polymorphisms and prognosis exclusively in patients taking drugs whose metabolism is affected by the studied genes.

Conclusion

The association of a poor prognosis with GA genotype of *CYP2C19* gene, which is involved in the metabolism of clopidogrel, shown by the study among highly adherent patients with MI, suggests the need for a tailored approach to the choice of medication from the group of P2Y12-receptor inhibitors for DAAT and, when clopidogrel is prescribed, consideration of the advisability of pharmacogenetic testing according to CYP2C19.

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Список литературы / References:

1. Марцевич С.Ю., Гинзбург М.Л., Кутишенко Н.П., и др. Люберецкое исследование смертности (исследование ЛИС): факторы, влияющие на отдаленный прогноз жизни после перенесенного инфаркта миокарда. Профилактическая Медицина. 2013; 16(2-1): 32-8
Martsevich S.Yu., Ginzburg M.L., Kutishenko N.P., et al. Lyubertsy mortality study (LMS): factors influencing the long-term survival after myocardial infarction. Preventive Medicine. 2013; 16(2-1): 32- 8 [In Russian]. ISSN: 2305–4948
2. Ibanez B., James S., Agewall S., et al. Acute Myocardial Infarction in Patient Presenting with ST–Segment Elevation (Management of) Guidelines ESC Clinical Practice Guidelines. Eur Heart J. 2018; 39(2): 119–77. doi:10.1093/eurheartj/ehx393
3. Бочаров А.В. Отдаленные результаты аорто–коронарного шунтирования после стентирования клинико–зависимой артерии голометаллическими стентами у больных с острым коронарным синдромом и многососудистым поражением. Российский медико–биологический вестник им. академика И.П. Павлова. 2019; 27(4): 495–502.
Bocharov A.V. Long-term results of coronary artery bypass graft surgery after stenting of obstructed artery with bare metal stent in patients with acute coronary syndrome and multivessel disease I.P. Pavlov Russian Medical Biological Herald. 2019; 27(4): 495–502 [In Russian]. doi:10.23888/PAVLOVJ2019274495-502
4. Якушин С.С., Филиппов Е.В. Анализ смертности от болезней системы кровообращения и сердечно–сосудистой заболеваемости в Рязанской области за период 2012–2016 гг. Наука молодых. (Eruditio Juvenium). 2018; 6(3): 448–461.
Yakushin SS, Filippov EV. Analysis of mortality rate from diseases of circulatory system and cardiovascular diseases in the Ryazan region in the period 2012-2016. Science of the young (Eruditio Juvenium). 2018; 6(3): 448-61. [In Russian]. doi:10.23888/HMJ201863448–461
5. Марцевич С.Ю., Кутишенко Н.П., Сичинава Д.П. и др. Основные сердечно-сосудистые осложнения и показатели смертности в течение первых полутора лет после перенесенного острого инфаркта миокарда: данные проспективного амбулаторного регистра ПРОФИЛЬ-ИМ. Рациональная Фармакотерапия в Кардиологии. 2020; 16(3): 432-43
Martsevich S.Yu., Kutishenko N.P., Sichinava D.P. et al. The Main Cardiovascular Complications and Mortality Rates During the First One and a Half Years after Acute Myocardial Infarction: Data from the Prospective Outpatient Registry PROFILE-IM. Rational Pharmacotherapy in Cardiology. 2020;16(3):432-438. [In Russian]. doi:10.20996/1819–6446–2020–06–11
6. Семенова Ю.В., Кутишенко Н.П., Загребельный А.В. и др. Влияние догоспитальной приверженности пациентов к посещению лечебно-профилактических учреждений на отдаленные исходы острого коронарного синдрома: исследование ЛИС-3. Рациональная Фармакотерапия в Кардиологии. 2017; 13(3): 363-369.
Semenova Yu.V., Kutishenko N.P., Zagrebelnyy A.V. et al. Influence of patients' prehospital attendance at outpatient clinics on long-term outcomes of acute coronary syndrome: LIS-3 study. Rational Pharmacotherapy in Cardiology. 2017;13(3):363-369. [In Russian]. doi:10.20996/1819-6446-2017-13-3-363-369
7. Gasior M., Gierlotka M., Pyka Ł., et al. Temporal trends in secondary prevention in myocardial infarction patients discharged with left ventricular systolic dysfunction in Poland. European Journal of Preventive Cardiology. 2018; 25(9): 960–9. doi:10.1177%2F2047487318770830
8. Practical recommendations for pharmacogenomics based prescription: 2010 ESF–UB Conference on Pharmacogenetics and Pharmacogenomics. 2010; 12(1): 113–24. doi:10.2217/pgs.10.147
9. Федеральный закон от 25.12.2018 г. № 489–ФЗ О внесении изменений в статью 40 Федерального закона «Об обязательном медицинском страховании в Российской Федерации» и Федеральный закон «Об основах охраны здоровья граждан в Российской Федерации» по вопросам клинических рекомендаций. [Электронный ресурс]. URL: http://www.consultant.ru/cons/cgi/online.cgi?base=LAW&n=314269&req=doc#06434705220241377 (дата обращения: 12.03.2021). [In Russian].
Federal Law of December 25, 2018 No. 489-FZ On Amendments to Article 40 of the Federal Law "On Compulsory Health Insurance in the Russian Federation" and the Federal Law "On the Fundamentals of Health Protection of Citizens in the Russian Federation" on clinical guidelines. [Electronic resource]. URL: http://www.consultant.ru/cons/cgi/online.cgi?base=LAW&n=314269&req=doc#06434705220241377 (date accessed 03/12/2021). [In Russian].
10. Николаев Н.А., Скирденко Ю.П. Российский универсальный опросник количественной оценки приверженности к лечению (КОП–25). Клиническая фармакология и терапия. 2018; 27(1): 74–78.
Nikolayev N.A., Skirdenko Yu.P. Russian generic questionnaire for evaluation of compliance to drug therapy. Clinical pharmacology and therapy. 2018; 27(1): 74–78. [In Russian]. ISSN: 0869–5490
11. Хохлов А.Л., Яворский А.Н., Поздняков Н.О. и др. Клинико-генетические аспекты терапии пациентов с атеросклерозом. Архивъ внутренней медицины. 2018; 8(1): 45-52. doi:10.20514/2226–6704–2018–8–1–45–52
Khokhlov A.L., Yavorsky A.N., Pozdnyakov N.O. et al. Pharmacogenetic features of therapy of patients with atherosclerosis. The Russian Archives of Internal Medicine. 2018; 8(1): 45-52. [In Russian]. doi:10.20514/2226–6704–2018–8–1–45–52
12. Замахина О.В., Бунова С.С., Николаева Н.А. и др. Влияние полиморфизмов Arg389Gly и Ser49Gly гена ADRB1 на эффективность лечения бисопрололом у больных стабильной стенокардией, перенесших инфаркт миокарда. РМЖ. Медицинское обозрение. 2018; 11:30–34.
Zamahina O.V., Bunova S.S., Nikolaeva N.A. et al. Effect of the Arg389Gly and Ser49Gly polymorphisms of the ADRB1 gene on the effectiveness of bisoprolol treatment in patients with stable angina who have suffered a myocardial infarction. Russian Medical Journal. Medical examination. [In Russian]. ISSN 2587–6821
13. Казаков Р.Е., Чеча О.А., Муслимова О.В. и др. Фармакогенетические подходы к повышению эффективности и безопасности применения статинов на примере аторвастатина. Безопасность и риск фармакотерапии. 2020; 8(1): 43-51. doi:10.30895/2312-7821-2020-8-1-43-51

Kazakov R.Y., Checha O.A., Mazerkina I.A. et al. Pharmacogenetic Approaches to Enhancing Efficacy and Safety of Statins as Illustrated by the Example of Atorvastatin. Safety and Risk of Pharmacotherapy. 2020;8(1):43-51. [In Russian]. doi:10.30895/2312-7821-2020-8-1-43-51

14. Эрлих А.Д. 12-месячные исходы у пациентов с острым коронарным синдромом, включённых в российский регистр «РЕКОРД-3». Российский кардиологический журнал. 2018; (3): 23-30. doi:10.15829/1560-4071-2018-3-23-30
Erlikh A.D. Twelve months outcomes in patients with acute coronary syndrome, by the national registry RECORD-3. Russian Journal of Cardiology. 2018; (3): 23-30. [In Russian]. doi:10.15829/1560-4071-2018-3-23-30
15. Khayata, M., Gabra, J. N., Nasser, M. F. et al. Comparison of Clopidogrel With Prasugrel and Ticagrelor in Patients With Acute Coronary Syndrome: Clinical Outcomes From the National Cardiovascular Database ACTION Registry. Cardiology Research. 2017; 8(3): 105–110. https://doi.org/10.14740/cr560w
16. Атабегашвили М.Р., Константинова Е.В., Кузнецова В.А. и др. Выбор блокатора P2Y12-рецепторов для лечения пациента с острым коронарным синдромом: опыт городской клинической больницы № 1 им. Н.И. Пирогова. Медицинский Совет. 2019; (5): 74-79. https://doi.org/10.21518/2079-701X-2019-5-74-79
Atabegashvili M.R., Konstantinova E.V., Kuznetsova V.A. et al. The choice of the P2Y12 receptors blocker in the treatment of a patient with acute coronary syndrome: practice of N.I. Pirogov city clinical hospital № 1. Meditsinskiy sovet = Medical Council. 2019; (5): 74-79. [In Russian]. https://doi.org/10.21518/2079-701X-2019-5-74-79
17. Чернов А.А., Мирзаев К.Б., Сычёв Д.А. Первый мета-анализ отечественных фармакогенетических исследований клопидогрела. Фармакогенетика и Фармакогеномика. 2015; (2): 19-23.
Chernov A.A., Mirzaev K.B., Sychev D.A. The first meta-analysis of domestic pharmacogenetic studies of clopidogrel. Pharmacogenetics and Pharmacogenomics. 2015; (2): 19-23. [In Russian]. ISSN: 2588–0527.
18. Zhang Y., Zhou, X., Ji, W. et al. Association between CYP2C19*2/*3 Polymorphisms and Coronary Heart Disease. Current Medical Science. 2019; 39: 44–51. doi:10.1007/s11596–019–1998–2
19. Zhong Z., Hou J., Zhang Q. et al. Effect of cytochrome P450 2C19 polymorphism on adverse cardiovascular events after drug–eluting stent implantation in a large Hakka population with acute coronary syndrome receiving clopidogrel in southern China. Eur J Clin Pharmacol. 2018; 74(4): 423–431. doi:10.1007/s00228–017–2393–1.
20. Pereira, N. L., Rihal, C. S., So et al. (2019). Clopidogrel pharmacogenetics state-of-the-art review and the TAILOR-PCI study. Circulation: Cardiovascular Interventions, 12(4). doi:10.1161/CIRCINTERVENTIONS.119.007811
21. Pereira N.L., Farkouh M.E., So D. et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA. 2020 25;324(8):761-771. doi: 10.1001/jama.2020.12443.
22. Клинические рекомендации. Острый коронарный синдром без подъема сегмента ST электрокардиограммы. Министерство здравоохранения Российской Федерации. 2020; 1–152. [Электронный ресурс]. URL: https://cr.minzdrav.gov.ru/recomend/154_3 (дата обращения: 12.03.2021). [In Russian].
Clinical guidelines. Acute coronary syndrome without ST segment elevation electrocardiogram. Ministry of Health of the Russian Federation. 2020; 1-152. [Electronic resource]. URL: https://cr.minzdrav.gov.ru/recomend/154_3 (date accessed 03/12/2021). [In Russian].
23. Российское кардиологическое общество, Ассоциация сердечно-сосудистых хирургов России. Острый инфаркт миокарда с подъемом сегмента ST электрокардиограммы. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(11):4103. 2020
Clinical practice guidelines for Acute ST-segment elevation myocardial infarction. Russian Journal of Cardiology. 2020; 25(11):4103. [In Russian]. https://doi.org/10.15829/1560-4071-2020-4103
24. Лабораторная служба Хеликс. Цитохром P450 2C19. Генотипирование по маркеру CYP2C19 G681A [Электронный ресурс]. URL: https://helix.ru/Catalog/item/18-084 (дата обращения: 12.03.2021). [In Russian].
Laboratory service Helix. Cytochrome P450 2C19. Genotyping by marker CYP2C19 G681A [Electronic resource]. URL: https://helix.ru/Catalog/item/18-084 (date accessed 03/12/2021). [In Russian].
25. Лаборатория Литех. Анализ определение резистентности к клопидогрелу (плавикс) [Электронный ресурс]. URL: https://analyz24.ru/katalog/opredelenie-rezistentnosti-k-klopidogrelu-plavix-cyp2c19-2-945.html (дата обращения: 12.03.2021). [In Russian].
Litech Laboratory. Analysis determination of resistance to clopidogrel (plavix) [Electronic resource]. URL: https://analyz24.ru/katalog/opredelenie-rezistentnosti-k-klopidogrelu-plavix-cyp2c19-2-945.html (date accessed 03/12/2021). [In Russian].
26. Солодун М.В., Аксентьев С.Б., Никифоров А.А. и др. Оценка влияния генетических факторов на отдаленный прогноз у пациентов, перенесших инфаркт миокарда. Клиническая фармакология и терапия. 2016; 25(3): 31–36.
Solodun M.V., Aksent'ev S.B., Nikiforov A.A. et al. Assessment of the influence of genetic factors on the long-term prognosis in patients who have suffered a myocardial infarction. Clinical pharmacology and therapy 2016; 25(3): 31–36. [In Russian]. ISSN: 0869–5490
27. Комиссарова С.М., Ниязова С.С., Чакова Н.Н. и др. Влияние полиморфных вариантов генов, кодирующих симпатоадреналовую систему, на фенотипические проявления у пациентов с гипертрофической кардиомиопатией. Российский кардиологический журнал. 2015;(6):75-80. doi: 10.15829/1560-4071-2015-6-75-80
Komissarova S.M., Nyazova S.S., Chakova N.N. et al. Polymorphic variants of genes coding sympathoadrenal system influence on phenotype of patients with hypertrophic cardiomyopathy. Russian Journal of Cardiology. 2015;(6):75-80. [In Russian]. doi: 10.15829/1560-4071-2015-6-75-80

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АНАЛИЗ КЛИНИКО-ПАТОГЕНЕТИЧЕСКИХ ВЗАИМООТНОШЕНИЙ ДИНАМИКИ ИЗМЕНЕНИЯ МАССЫ ТЕЛА И ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ У ПАЦИЕНТОВ С ПЕРВИЧНЫМ ОЖИРЕНИЕМ

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Clinical and Pathogenetic Assessment of Relationships Between the Dynamics of Body Weight Changes and Atrial Fibrillation in Patients with Primary Obesity

Резюме

Цель исследования. Оценить влияние динамики массы тела на клиническое течение фибрилляции предсердий у пациентов, страдающих ожирением. **Материал и методы.** В исследование был включен 101 пациент с пароксизмальной либо персистирующей фибрилляцией предсердий, страдающий первичным ожирением. Дизайн исследования: ретроспективное, одноцентровое, сравнительное исследование. Ретроспективно в зависимости от динамики массы тела пациенты были разделены на 3 группы: увеличившие на ≥3% массу тела (группа 1, n=40), сохранившие исходную массу тела ±2,9% (группа 2, n=29), снизившие на ≥3% исходную массу тела (группа 3, n=32). Контрольные осмотры врачом проводились не реже 1 раза в 6 месяцев на протяжении не менее 36 месяцев. Изменение формы фибрилляции предсердий регистрировалось на основании клинической картины заболевания и данных холтеровского мониторирования электрокардиограммы в течение 7 дней. Группы были сопоставимы по полу (p=0,9267), возрасту (p=0,3841), росту (p=0,8900), форме заболевания (пароксизмальная фибрилляция предсердий/ персистирующая фибрилляция предсердий) (p=0,8826), выраженности симптомов фибрилляции предсердий по классификации Европейской ассоциации сердечного ритма (p=0,8687) и цифрам систолического артериального давления на начало исследования (p=0,4500). **Результаты.** При заключительном контрольном осмотре масса тела пациентов 1 группы увеличилась в среднем на 11,4 [9,3; 13,1] кг (p <0,001*), тогда как пациенты 3 группы продемонстрировали снижение массы тела в среднем на -6,2 [-8,4; -5,3] кг (p <0,001*). Снижение массы тела пациентов 2 группы было незначительным (p=0,5377) и составило -0,1 [-2,0; 1,3] кг. Прогрессирование заболевания от пароксизмальной формы к персистирующей наблюдалось у 15 (37%) пациентов 1 группы, у 9 (31%) пациентов 2 группы и у 2 (6%) пациентов 3 группы (p=0,0079*). Регресс аритмии от персистирующей формы к пароксизмальной в 1 группе не зарегистрирован (0%), во 2 группе обратное развитие заболевания отмечено у 1 пациента (3%) и в 3 группе — у 6 пациентов (19%) (p=0,0053*). Самопроизвольного восстановления синусо-

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вого ритма у пациентов 1 группы не наблюдалось, во 2 группе оно было отмечено у двух (7%), а в 3 группе — у 7 (22%) пациентов (p=0,0047*). Клиническая эффективность катетерной абляции оценивалась после окончания 3-месячного слепого периода. Потребность в проведении интервенционных процедур с целью восстановления синусового ритма и их кратность при сравнении групп существенно не отличалась. Однако при попарном сравнении, статистически значимой была разница между 1 и 3 группами участников (p=0,0079* и p=0,0374* соответственно). **Заключение.** Проведенное исследование демонстрирует взаимосвязь между динамикой массы тела и клиническим течением фибрилляции предсердий. Установлено, что прогрессирование ожирения непосредственно ассоциируется с прогрессированием данного типа аритмии. Напротив, снижение массы тела позволяет уменьшить риск усугубления тяжести заболевания, улучшить прогноз и течение фибрилляции предсердий вне зависимости от других значимых факторов риска, повысить эффективность терапии антиаритмическими препаратам и результативность интервенционного лечения.

Ключевые слова: *фибрилляция предсердий, восстановление синусового ритма, ожирение, контроль массы тела, предсердная кардиомиопатия*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Aims. To evaluate the impact of body weight dynamics on the clinical course of atrial fibrillation in obese patients. **Materials and methods.** The study included 101 primary obese patients with paroxysmal or persistent atrial fibrillation. Study design: a retrospective, single-center, comparative study. Retrospectively according to the he body weight dynamics, patients were divided into 3 groups: those who increased their body weight by ≥3% (Group 1, n=40), maintained their initial body weight by ±2.9% (Group 2, n=29), and reduced their initial body weight by ≥3% (Group 3, n=32). Follow-up examinations by a doctor were carried out at least once every 6 months for minimum 36 months. Change in AF type was determined by disease patterns and 7-day Holter monitoring results. The groups were comparable in gender (p=0,9267), age (p=0,3841), height (p=0,8900), and disease form (Paroxysmal atrial fibrillation /Persistent atrial fibrillation) (p=0,8826), the severity of symptoms on the European Heart Rhythm Association score of atrial fibrillations (p=0,8687) and systolic blood pressure at the beginning of the study (p=0,4500). **Results.** At the final control examination, the body weight of patients in Group 1 increased by an average of 11,4 [9,3; 13,1] kg (p <0,001*), while weight loss in Group 3 averaged -6,2 [-8,4; -5,3] kg (p <0,001*). The decrease in body weight of Group 2 patients was insignificant (p=0,5377) and amounted to -0,1 [-2,0; 1,3] kg. The progression of the disease from paroxysmal to persistent form was observed among 15 (37%) patients in Group 1, 9 (31%) patients — in Group 2, 2 (6%) patients — in Group 3 (p=0,0079*). The regression of arrhythmia from persistent to paroxysmal form was not registered in group 1 (0%), in group 2, the reverse development of the disease was noted in 1 patient (3%) and in group 3 — in 6 patients (19%) (p=0,0053*). There were no free from AF patients in Group 1 at the final follow-up, while 2 (7%) patients were free from AF in Group 2 and 7 (22%) — in Group 3 (p=0,0047*). In patients undergoing ablation, procedural success was determined after a 3-month blind period. The need for interventional procedures to restore the sinus rhythm and their multiplicity when comparing the groups did not differ significantly. However, in a pairwise comparison, the difference between groups 1 and 3 of participants was statistically significant (p=0,0079* and p=0,0374*, respectively). **Conclusion.** This study demonstrates the relationships between the dynamics of body weight and the clinical course of atrial fibrillation. The progression of obesity leads to the progression of the disease. Weight-loss management reverses the type and natural progression of AF, improves the prognosis and the course of disease, regardless of other significant risk factors, increases the anti-arrhythmic therapy effect and the effect of interventional treatment.

Key words: *atrial fibrillation, sinus rhythm recovery, obesity, weight control, atrial cardiomyopathy*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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BMI — body mass index, SBP — systolic blood pressure, AF — atrial fibrillation, HR — heart rate, ECG — electrocardiogram, AF — atrial fibrillation, BMI — body mass index, EHRA-score — The European Heart Rhythm Association score of atrial fibrillations

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in modern clinical practice. Despite the consistent improvement of its diagnosis and management methods, AF significantly contributes to a deterioration of the quality of life, higher rates of disability and mortality of the population. AF is a progressive disease. Most patients develop persistent types of arrhythmia over time, and paroxysmal AF persists for a long time only in 2–3% of patients [1]. Several studies show that the clinical type of AF and the likelihood of disease progression are primarily determined by the presence of concomitant risk factors [2, 3].

Most modern studies on AF are aimed at exploring innovative approaches to the management of this disease and its complications. Along with this, a thorough analysis of risk factors contributing to the progression of AF continues.

Overweight and obesity are observed in 25% of patients with AF [2]. There is a direct correlation between the thickness and volume of epicardial adipose tissue and the risk of developing AF [4, 5]. A number of studies have shown that weight loss in the short term reduces the severity of symptoms in patients with AF [6, 7].

This study seeks to examine the long-term effect of body weight changes on the clinical course of AF in obese patients.

Material and Methods

This study randomly included patients with a body mass index > 30 kg/m^2 who were undergoing treatment for symptomatic paroxysmal or persistent AF at the State Budgetary Healthcare Institution "Diagnostic Center No. 5 of the Moscow City Health Department" from October 2016 to November 2019. Study design: retrospective, single-center, comparative study.

The protocol was approved by the local ethics committee. Written informed consent was obtained from all patients prior to enrollment in the study.

All patients were examined by a cardiologist in an outpatient setting at least once every six months for at least three years (36 months). Every six months during the follow-up visit, all patients were assessed for the severity of AF symptoms; electrocardiogram (ECG) in rest was performed, and 24-hour ECG monitoring was performed for seven days. The severity of AF symptoms was assessed according to the EHRA classification (European Heart Rhythm Association) [8]. The treatment strategy (heart rhythm or heart rate control) was determined by the attending cardiologist. Agents used to control the rhythm included class III antiarrhythmic agents according to the Vaughan — Williams classification in D-modification. Harrison: amiodarone and sotalol. The decision to refer for interventional treatment (transcatheter cryoballon ablation or radiofrequency ablation) was made by the attending physician if the symptoms of the disease persisted while taking medications. The "blind" period after ablation was three months. In the case of radiofrequency or cryoballon ablation, 24-hour ECG monitoring was additionally performed three months after the procedure and every six months thereafter.

The exclusion criteria were: persistent AF, a history of acute myocardial infarction or cardiac surgery over the past 12 months, hemodynamically significant congenital and acquired heart valve defects, impaired left ventricular function with a decrease in ejection fraction < 40%, malignant neoplasms in active phase, autoimmune and systemic inflammatory diseases, severe renal or hepatic failure, patients with diabetes mellitus on insulin therapy.

All patients were interviewed on the importance of body weight control; personalized recommendations for healthy eating and instructions on the need for graduated exercise were given. The group of obese patients who lost weight received non-drug therapy, changed lifestyle through dietary adjustments and increased the volume of physical activity. Individual risk factors were also monitored regularly (hypertension, diabetes mellitus, impaired glucose tolerance, obstructive sleep apnea, smoking and alcohol consumption), and, if necessary, treatment adjustment was carried out to modify risk factors. During the study, such indicators as blood pressure, glycemia, and dyslipidemia were corrected for all participants, and target values were achieved. Metformin was used to manage type 2 diabetes mellitus and impaired glucose tolerance, and if necessary, other oral antihyperglycemic agents were prescribed.

During the initial visit, the physician measured anthropometric parameters using medical scales and a stadiometer. Weighing was carried out without shoes and outerwear, then body mass index was calculated. The body weight of patients was subsequently measured at each follow-up appointment and independently at home using household scales.

According to the American Heart Association (AHA) and the American College of Cardiology (ACC) recommendations, a change in body weight of at least 3% from the baseline was considered significant [9]. Patients were retrospectively included in one of three groups depending on the changes in body weight: those who gained ≥ 3% of their baseline body weight (group 1), those who retained their baseline body weight ±2.9% (group 2), those who lost ≥ 3% of their baseline body weight (group 3).

The primary outcome of the study was a change in the type of AF at the time of the final examination (36 months). The type of AF was assessed based on the patient's complaints and 24-hour ECG monitoring data for seven days. Secondary outcomes included the severity of AF symptoms as measured by the EHRA scale and the need for interventional treatment.

Statistical Analysis

Statistical processing of the results was carried out using Python 3.8. Built-in functions from the Scipy module were used for calculations.

Quantitative parameters were assessed for compliance with normal distribution. To this end, the Shapiro — Wilk test was used.

Normal distribution test showed that data in the study were not normally distributed. Therefore, the calculations were subsequently carried out using nonparametric statistical methods.

Summaries of quantitative parameters were described using the median (Me) and lower and upper quartiles (Q1 — Q3): Me [Q1; Q3]. When comparing several samples of quantitative data with a distribution other than normal, the Kruskal-Wallis test was used. When statistically significant differences between the groups were detected, pairwise comparison of the populations was additionally carried out using the Mann — Whitney U-test.

The Wilcoxon W-test was used to test the differences between the two compared paired (linked "before" and "after") samples.

Results of qualitative characteristics are expressed in absolute numbers with the indication of proportions (%). The comparison of nominal data in independent groups was carried out using the Pearson χ^2 test. When the number of expected observations in any of the cells of the four-field table was less than 5, Fisher's exact test was used to assess the level of significance of the differences.

Differences were considered as statistically significant at $p \leq 0.05$.

Sample size was not pre-calculated.

Results

Demographic Parameters and Baseline Characteristics of Patients Included in the Study

Of 246 patients with paroxysmal or persistent AF who were treated at the State Budgetary Healthcare Institution "Diagnostic Center No. 5 of the Moscow Department of Health" from October 2016 to November 2019, 137 patients had a body mass index of more than 30 kg/m^2. After evaluating the exclusion criteria, 101 patients were included in the study.

When determining changes in body weight, all patients were retrospectively divided into three groups: increased body weight by ≥ 3% (group 1, n = 40), retained the baseline body weight ±2.9% (group 2, n = 29), decreased the baseline body weight by ≥ 3% (group 3, n = 32) (Fig. 1).

Groups were similar by gender (p = 0.9267), age (p = 0.3841), height (p = 0.8900), weight (p = 0.7052), BMI (p = 0.3880), type of disease (paroxysmal AF / persistent AF) (p = 0.8826), severity of symptoms on the EHRA scale (p = 0.8687) and the level of systolic blood pressure (SBP) at the beginning of the study (p = 0.4500), as well as the number of smokers (p = 0.6171), the level of alcohol consumption (p = 0.9682), the presence of arterial hypertension (p = 0.7700), diabetes mellitus (p = 0.9289), impaired glucose tolerance (p = 0.8351) and coronary heart disease (p = 0.8833). A statistically significant difference was recorded only in terms of hyperlipidemia (p = 0.0448 *). There were more patients with this risk factor in group 1 — 23 (58%) than in group 3 — 9 (28%) (p = 0.0127 *). The average number of antihypertensive and antiarrhythmic agents used was comparable at the start of the study (p > 0.05).

Clinical characteristics of patients at the time of enrollment in the study are presented in Table 1.

Body Weight Change

At the beginning of the study, the body weight of patients in groups 1, 2 and 3 was comparable (p = 0.7052); at the final examination, it was statistically significantly different (p < 0.001*), including during pairwise comparison of groups (p < 0.05).

The body weight of the patients of group 1 increased during the study from 98.4 [88.6; 106.8] to 110.5 [97.5; 118.2] kg (p < 0.001 *), in group 3, it decreased from 99.3 [89.3; 105.7] to 90.7 [82.4; 98.2] kg (p < 0.001 *), while patients of group 2 showed an insignificant decrease in body weight from 102.2 [88.3; 108.6] to 99.3 [87.9; 109.6] kg (p = 0.5377).

The parameter of change in body weight was different between all groups (group 1 — an increase of 11.4 [9.3; 13.1] kg, group 2 — a decrease of −0.1 [−2.0; 1.3] kg, group 3 — decrease by −6.2 [−8.4; −5.3] kg) (p < 0.001 *).

Effect of Body Weight Changes on the Progression of AF

Table 2 presents the effect of body weight changes on the progression of AF and the frequency of interventional treatment.

At the time of enrollment in the study, groups 1, 2 and 3 were comparable in terms of the disease form (p = 0.8826). Pairwise comparison of groups also revealed no statistical significance of differences between groups (p > 0.05). At baseline, there were 19 (47%) patients with paroxysmal AF and 21 (53%) patients with persistent AF in group 1, in group 2 (n = 29) — 14 (48%) patients with paroxysmal AF and 15 (52%) patients with persistent AF, in group 3 (n = 32) — 17 (53%) patients with paroxysmal AF and 15 (47%) patients with persistent AF (Fig. 1).

According to the results of the final check-up examination, a difference in the form of the disease was revealed between groups 1, 2 and 3 (p < 0.001 *). Pairwise comparison revealed a difference between groups 1 and 3 (p < 0.001 *) and between groups 2 and 3 (p = 0.0132 *). The difference between groups 1 and 2 was not significant (p = 0.2018).

AF progression from the paroxysmal to the persistent form differed between group 1 (15 (37%) patients), group 2 — 9 (31%) and group 3 — 2 (6%) (p = 0.0079 *). There was a significant difference between groups 1 and 3 (p = 0.0019 *) and groups 2 and 3 (p = 0.0119 *); the difference between groups 1 and 2 was insignificant (p = 0.5778) (Fig. 2 and 3).

The regression of arrhythmia from the persistent to the paroxysmal form also showed a difference between the groups (p = 0.0053 *). In group 1, no disease regression was recorded — 0 (0%), in group 2, there was a regression of AF in 1 patient (3%), in group 3 — in 6 patients (19%). However, the pairwise comparison of groups showed a significant difference only when comparing groups 1 and 3 (p = 0.0058 *).

Parameters such as "No changes in AF form" and "Complete recovery from AF" showed no statistically significant differences between the groups (p = 0.1615 and p = 0.7655, respectively). "Spontaneous restoration of sinus rhythm" (without ablation) differed in the groups (p = 0.0047 *): in group 1, no cases of spontaneous restoration of sinus rhythm were recorded — 0 patients (0%), in group 2 there were 2 cases (7%) and in group 3 — 7 (22%). However, a pairwise comparison of the groups showed a difference only between groups 1 and 3 (p = 0.0023 *).

Therefore, the study showed that obese patients whose body weight increased during the follow-up period (group 1 — 37%) and retained their baseline body weight (group 2 — 31%) have a higher rate of disease progression with the transformation of paroxysmal AF into persistent AF, in comparison with patients whose body weight decreased (group 3) — 6%), despite the adjustment of other significant risk factors (Fig. 2 and 3).

Weight loss was a significant mono- and multifactorial predictor of regression of the disease from the persistent to the paroxysmal form (group 3 — 19%, while group 1 — 0%, group 2 — 3%). A comprehensive analysis of obese patients whose body weight decreased (group 3), with concomitant modification of other risk factors showed a high probability of spontaneous restoration of sinus rhythm (group 3 — 22%, group 1 — 0%, group 2 — 7%) (Fig. 2 and 3).

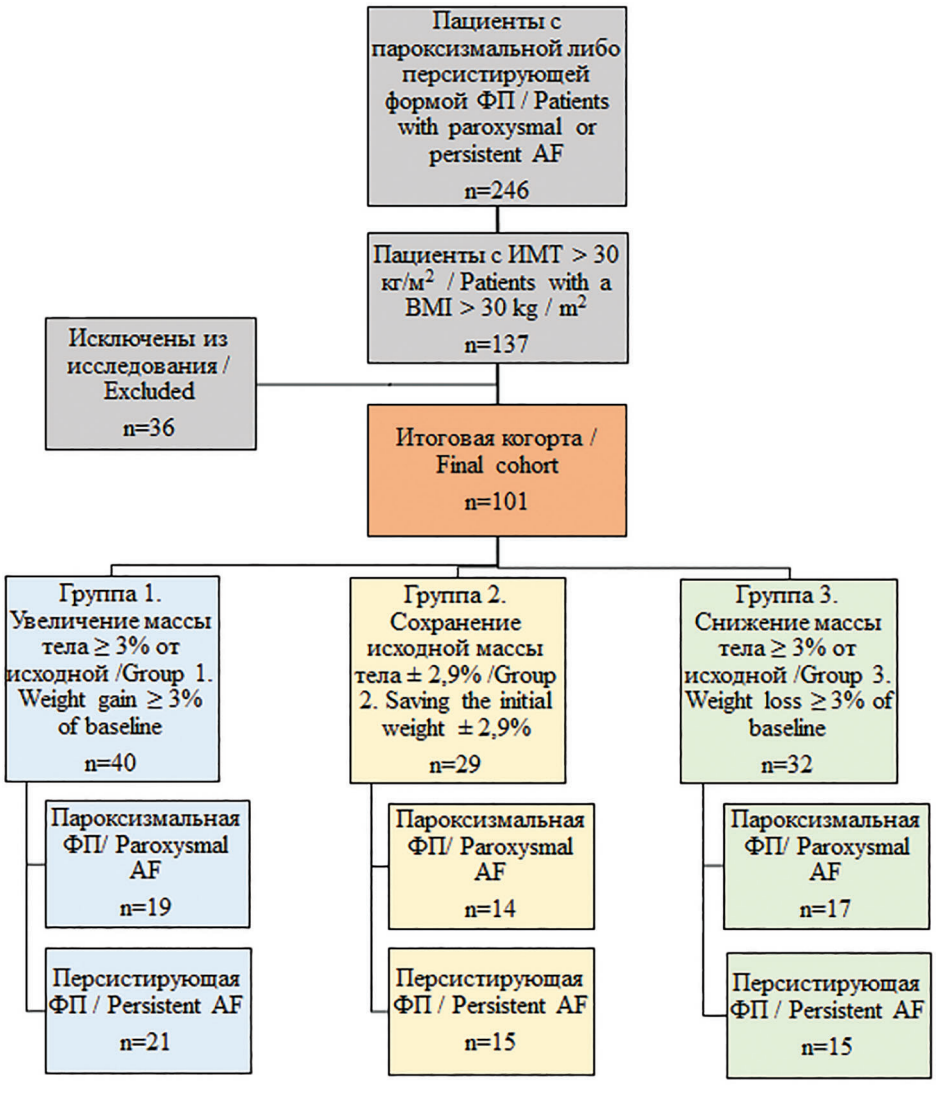

Figure 1. *The process of selecting patients for the study. Groups of patients depending on the dynamics of body weight. BMI — body mass index. AF — atrial fibrillation*

Table 1. Characteristics of patients at the time of inclusion in the study

Options	Group 1 (n=40)	Group 2 (n=29)	Group 3 (n=32)	Multiple comparison, p	Pairwise criterion, p
Age	52,0 [45,0; 65,0]	57,0 [47,0; 66,0]	58,5 [51,0; 70,2]	0,3841	1 2 : p=0,2363 1 3 : p=0,0806 2 3 : p=0,3167
Male, n (%)	31 (78%)	23 (79%)	26 (81%)	0,9267	1 2 : p=0,8572 1 3 : p=0,6970 2 3 : p=0,8491
Height, cm	172,0 [159,8; 177,2]	170,0 [162,0; 178,0]	172,0 [163,0; 178,2]	0,8900	1 2 : p=0,3463 1 3 : p=0,3436 2 3 : p=0,4654
Weight, kg	98,4 [88,6; 106,8]	102,2 [88,3; 108,6]	99,3 [89,3; 105,7]	0,7052	1 2 : p=0,2042 1 3 : p=0,4977 2 3 : p=0,2721
BMI (kg/m^2)	33,8 [32,1; 35,8]	34,4 [31,7; 37,2]	32,7 [31,7; 36,1]	0,3880	1 2 : p=0,1761 1 3 : p=0,2572 2 3 : p=0,1017
SAD (mm Hg st)	142,5 [135,0; 161,2]	139,0 [129,0; 154,0]	144,0 [126,8; 153,0]	0,4500	1 2 : p=0,2075 1 3 : p=0,1082 2 3 : p=0,4086
AF form					
Paroxysmal AF, n (%)	19 (47%)	14 (48%)	17 (53%)	0,8826	1 2 : p=0,9492 1 3 : p=0,6353 2 3 : p=0,7052
Persistent AF, n (%)	21 (53%)	15 (52%)	15 (47%)		
Risk factors					
Arterial hypertension, n (%)	31 (78%)	23 (79%)	23 (72%)	0,7700	1 2 : p=0,8572 1 3 : p=0,5839 2 3 : p=0,5007
Diabetes mellitus, n (%)	11 (28%)	8 (28%)	10 (31%)	0,9289	1 2 : p=0,9937 1 3 : p=0,7279 2 3 : p=0,7540
Impaired glucose tolerance, n (%)	4 (10%)	4 (14%)	3 (9%)	0,8351	1 2 : p=0,7124 1 3 : p=1,0000 2 3 : p=0,6988
Hyperlipidemia, n (%)	23 (58%)	13 (45%)	9 (28%)	0,0448*	1 2 : p=0,2983 1 3 : p=0,0127* 2 3 : p=0,1749
Coronary heart disease, n (%)	4 (10%)	4 (14%)	4 (13%)	0,8833	1 2 : p=0,7124 1 3 : p=1,0000 2 3 : p=1,0000
Excessive alcohol consumption (>140 ml of pure alcohol per week), n (%)	9 (23%)	7 (24%)	8 (25%)	0,9682	1 2 : p=0,8736 1 3 : p=0,8040 2 3 : p=0,9378
Smoking, n (%)	16 (40%)	15 (52%)	15 (47%)	0,6171	1 2 : p=0,3338 1 3 : p=0,5583 2 3 : p=0,7052
Taking medication					
Average number of antihypertensive drugs used	1,0 [1,0; 2,0]	1,0 [0,0; 1,0]	1,0 [0,0; 2,0]	0,7479	1 2 : p=0,2256 1 3 : p=0,3504 2 3 : p=0,3638
Average number of antiarrhythmic drugs used	1,0 [1,0; 1,0]	1,0 [0,0; 2,0]	1,0 [0,0; 1,0]	0,7960	1 2 : p=0,2812 1 3 : p=0,2923 2 3 : p=0,4662
EHRA score	2,5 [2,0; 3,0]	2,5 [2,5; 3,0]	2,5 [2,4; 3,0]	0,8687	1 2 : p=0,4665 1 3 : p=0,3219 2 3 : p=0,3299

Note: The data is presented as: "Me [Q1; Q3]" and "quantity (percentage share)". BMI — body mass index, SAD-systolic blood pressure, AF-atrial fibrillation, EHRA score-severity of AF symptoms according to the classification of the European Heart Rhythm Association [8]

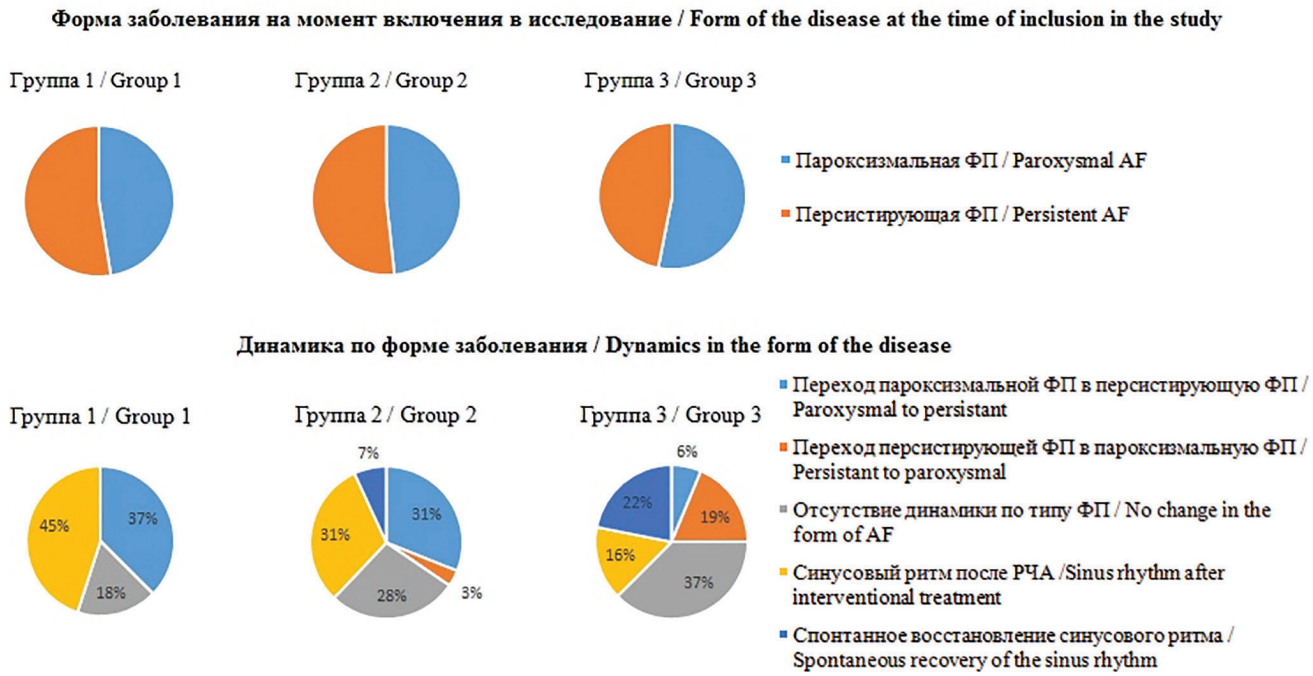

Figure 2. *Changing the form of the disease in dynamics*

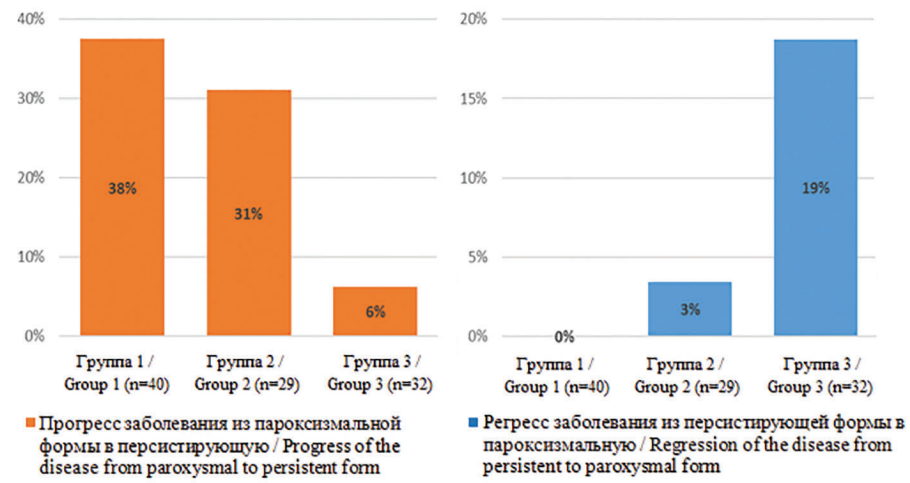

Figure 3. *Dependence of disease progression on changes in body weight*

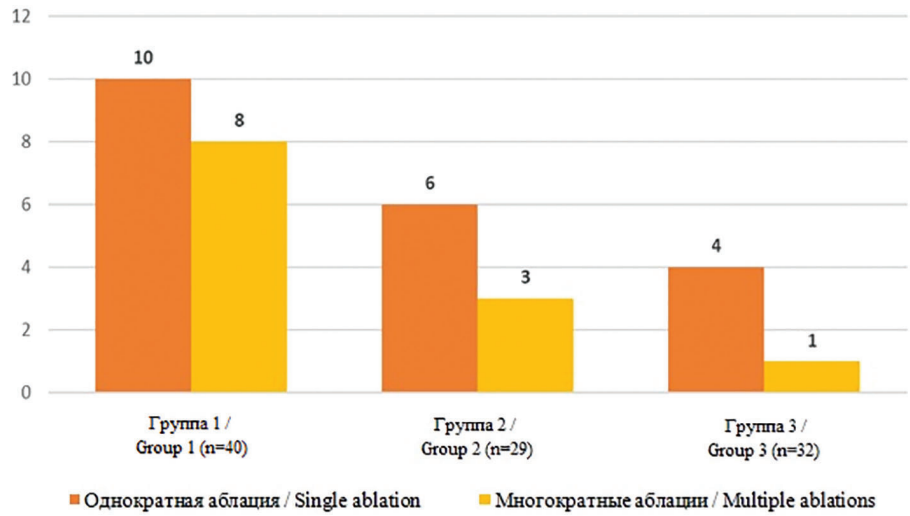

Figure 4. *Interventional treatment with the achievement of sinus rhythm, the need for repeated interventions (single ablation: p=0.4128, multiple ablation: p=0.0851)*

Table 2. *The effect of body weight dynamics on the change in the form of the disease and the frequency of interventional treatment*

Options	Group 1 (n=40)			Group 2 (n=29)			Group 3 (n=32)			value p	
	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value
BMI (kg/m²)	33,8 [32,1; 35,8]	38,1 [35,5; 39,9]	<0,001*	34,4 [31,7; 37,2]	35,1 [32,2; 36,9]	0,4260	32,7 [31,7; 36,1]	30,3 [28,8; 34,2]	0,0011*	1 2 3: p=0,3880 1 2 : p=0,1761 1 3 : p=0,2572 2 3 : p=0,1017	1 2 3:p<0,001* 1 2 : p<0,001* 1 3 : p<0,001* 2 3 : p<0,001*
SAD (mm Hg)	142,5 [135,0; 161,2]	129,0 [120,2; 134,5]	<0,001*	139,0 [129,0; 154,0]	132,0 [120,0; 140,0]	0,0046*	144,0 [126,8; 153,0]	126,0 [115,8; 132,8]	0,0001*	1 2 3: p=0,4500 1 2 : p=0,2075 1 3 : p=0,1082 2 3 : p=0,4086	1 2 3:p=0,2327 1 2 : p=0,1548 1 3 : p=0,1912 2 3 : p=0,0505
Normal pressure (below 140 mm Hg), n (%)	19 (48%)	35 (88%)	0,0001*	15 (52%)	20 (69%)	0,1722	14 (44%)	30 (94%)	<0,001*	1 2 3: p=0,8236 1 2 : p=0,7290 1 3 : p=0,7510 2 3 : p=0,5334	123:p=0,0228* 1 2 : p=0,0588 1 3 : p=0,2215 2 3 :p=0,0119*
Weight, kg	98,4 [88,6; 106,8]	110,5 [97,5; 118,2]	<0,001*	102,2 [88,3; 108,6]	99,3 [87,9; 109,6]	0,5377	99,3 [89,3; 105,7]	90,7 [82,4; 98,2]	<0,001*	1 2 3: p=0,8236 1 2 : p=0,3463 1 3 : p=0,3436 2 3 : p=0,4654	123: p<0.001* 1 2 :p=0,0241* 1 3 : p<0,001* 2 3 :p=0,0106*
Average number of antihypertensive drugs used	1,0 [1,0; 2,0]	2,0 [1,8; 3,0]	0,0002*	1,0 [0,0; 1,0]	2,0 [2,0; 2,0]	0,0010*	1,0 [0,0; 2,0]	0,5 [0,0; 1,0]	0,0035*	1 2 3: p=0,7479 1 2 : p=0,2256 1 3 : p=0,3504 2 3 : p=0,3638	1 2 3:p=0,4500 1 2 :p=0,0060* 1 3 : p<0,001* 2 3 : p<0,001*
Average number of antiarrhythmic drugs used	1,0 [1,0; 1,0]	1,0 [0,0; 1,0]	0,0113*	1,0 [0,0; 2,0]	1,0 [0,0; 1,0]	0,0579	1,0 [0,0; 1,0]	0,0 [0,0; 1,0]	0,0014*	1 2 3: p=0,7960 1 2 : p=0,2812 1 3 : p=0,2923 2 3 : p=0,4662	1 2 3:p=0,0672 1 2 : p=0,2083 1 3 :p=0,0107* 2 3 : p=0,864
EHRA score	2,5 [2,0; 3,0]	2,5 [2,4; 3,0]	0,4917	2,5 [2,5; 3,0]	2,5 [2,0; 3,0]	0,4541	2,5 [2,4; 3,0]	2,0 [1,0; 2,0]	<0,001*	1 2 3: p=0,8687 1 2 : p=0,4665 1 3 : p=0,3219 2 3 : p=0,3299	1 2 3 p<0,001* 1 2:p=0,1680 1 3:p<0,001* 2 3:p<0,001*
AF form											
Paroxysmal AF, n (%)	19 (47%)	-		14 (48%)	-		17 (53%)	-		1 2 3: p=0,8826 1 2 : p=0,9492 1 3 : p=0,6353 2 3 : p=0,7052	
Persistent AF, n (%)	21 (53%)	-		15 (52%)	-		15 (47%)	-			
Transition of paroxysmal AF to persistent AF, n (%)	-	15 (38%)		-	9 (31%)		-	2 (6%)			123:p=0,0079* 1 2 : p=0,5778 1 3 :p=0,0019* 2 3 :p=0,0119*

Options	Group 1 (n=40)			Group 2 (n=29)			Group 3 (n=32)			value p	
	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value
Transition of persistent AF to paroxysmal AF, n (%)	-	0 (0%)		-	1 (3%)		-	6 (19%)			123:p=0,0053* 1 2 : p=0,4203 1 3 :p=0,058* 2 3 : p=0,1064
Lack of dynamics in the form of AF, n (%)	-	7 (18%)		-	8 (28%)		-	12 (37%)			1 2 3:p=0,1615 1 2 : p=0,3160 1 3 : p=0,0557 2 3 : p=0,4101
Restoration of sinus rhythm: spontaneous or as a result of interventional treatment											
Complete freedom from AF, n (%)	-	18 (45%)		-	11 (38%)		-	12 (37%)			1 2 3:p=0,7655 1 2 : p=0,5571 1 3 : p=0,5212 2 3 : p=0,9723
Catheter ablation, n (%)		18 (45%)			9 (31%)			5 (16%)			123:p=0,0287* 1 2 : p=0,2407 1 3 :p=0,0079* 2 3 : p=0,1529
Without ablation, n (%)	-	0 (0%)		-	2 (7%)		-	7 (22%)			123:p=0,0047* 1 2 : p=0,1731 1 3 p=0,0023* 2 3 : p=0,1511
Single ablation, n (%)	-	10 (25%)		-	6 (21%)		-	4 (13%)			1 2 3:p=0,4128 1 2 : p=0,6754 1 3 : p=0,1830 2 3 : p=0,4961
Multiple ablations, n (%)	-	8 (20%)		-	3 (10%)		-	1 (3%)			1 2 3:p=0,0851 1 2 : p=0,3359 1 3 :p=0,0374* 2 3 : p=0,3385

Note: BMI — body mass index, SAD-systolic blood pressure, AF-atrial fibrillation, EHRA score-severity of AF symptoms according to the classification of the European Heart Rhythm Association [8]

Effect of Body Weight Changes on the Need to Take Antiarrhythmic Agents

At the time of enrollment in the study, there were no differences in the number of antiarrhythmic agents taken between the groups (p = 0.7960). To control heart rate (HR), patients of all groups took β-blockers or non-dihydropyridine calcium antagonists, and some patients took class III antiarrhythmic agents according to the Vaughan — Williams classification modified by D. Harrison to control sinus rhythm. In particular, amiodarone and sotalol were taken by 9 (23%) patients in group 1, 6 (21%) — in group 2 and 7 (22%) — in group 3.

During the study period, a decrease in the need for antiarrhythmic agents was revealed in groups 1 (p = 0.0113 *) and 3 (p = 0.0014 *), which was probably associated with a high frequency of restoration of sinus rhythm using interventional procedures in group 1 and spontaneous restoration of sinus rhythm in group 3. In group 2, no significant decrease in the amount of antiarrhythmic agents taken was demonstrated (p = 0.0579).

At the end of the study, there was no significant difference in the use of antiarrhythmic agents by patients (p = 0.0672). However, a pairwise comparison of groups showed a statistically significant difference between groups 1 and 3 (p = 0.0107 *) (Table 2).

Effect of Body Weight Change on Blood Pressure Control

At the end of the study, good blood pressure control was achieved in all groups. The number of patients who achieved the target systolic and diastolic blood pressure levels below 140 and 90 mm Hg was 34 (85%) in group 1, 25 (86.2%) in group 2 and 27 (84.4%) in group 3. However, patients from groups 1 and 2 required an increase in the number of antihypertensive agents to achieve the target blood pressure from 1 to 2 (p = 0.0002 * and p = 0.0010 *, respectively), while in the group of patients whose body weight decreased by more than 3% (group 3), the number of antihypertensive agents was reduced compared to the baseline values (p = 0.0035 *) (Table 2).

Effect of Body Weight Change on the Severity of Disease Symptoms

At the time of enrollment in the study, all participants were assigned a class of AF symptoms according to the modified EHRA scale. The median value of this parameter was comparable in all groups and amounted to 2.5 [2.0; 3.0] in group 1, 2.5 [2.5; 3.0] in group 2, and 2.5 [2.4; 3.0] in group 3 (p = 0.8687). At the final follow-up examination (36 months), the EHRA class was redefined in all patients. A significant decrease in the average severity of the symptoms of the disease was recorded only in group 3 patients whose body weight decreased by ≥ 3% of the baseline (p < 0.001 *) (Table 2).

Effect of Body Weight Change on the Need for Interventional Treatment

The frequency of restoration of sinus rhythm using interventional treatment was different in different groups (p = 0.0287 *). In group 1, sinus rhythm after catheter ablation was recorded in 18 (45%) patients; repeated interventions were performed in 8 (20%) of them. In group 2, sinus rhythm after catheter ablation was achieved in 9 (31%) patients; 3 (10%) of them required repeated interventions. Group 3 patients needed interventional treatment the least: sinus rhythm with catheter ablation was restored in 5 (16%) patients, while the need for multiple ablation was registered in 1 (3%) patient. However, a pairwise comparison of groups showed a significant difference in the use of interventional treatment only between groups 1 and 3 (p = 0.0079 *).

Increased body weight leads to a higher need for interventional treatment. However, no significant differences in the frequency of intervention in the groups were revealed (single ablation: p = 0.4128, multiple ablations: p = 0.0851). The pairwise comparison of groups for the need for multiple ablation revealed statistically significant difference between groups 1 and 3 (p = 0.0374 *) (Fig. 4).

Discussion

This study examines the relationship between body weight change and the progression of AF in obese patients. Results of this study suggest that weight loss not only reduces the severity of AF symptoms but can also lead to the reversal of the disease: transformation of persistent AF into paroxysmal AF, or restoration of sinus rhythm indefinitely.

AF is a disease that tends to progress in most patients. The paroxysmal form becomes persistent and then permanent [10–12]. This is due to the existing dynamic adaptive changes in the atrial myocardium, the so-called structural (electrical) remodeling that not only reduces the likelihood of sinus rhythm restoration and maintains the existing AF but also leads to the emergence of more and more paroxysms, "AF maintains AF" [12, 13]. Structural remodeling causes electrical dissociation (local heterogeneity of conductivity), depression of repolarization processes, and triggers several small foci of excitation circulation (micro re-entry) that stabilize arrhythmia and also ensure the maintenance of long-wavelength loops. The severity of atrial remodeling processes, in turn, determines the resistance of arrhythmia to medication and interventional treatment [14–16]. Even in patients with a single rhythm disturbance, structural and functional changes in the atria were revealed [17].

Successful interventional treatment does not prevent myocardial remodeling in itself [18]. This indicates

the primary role of the arrhythmogenic substrate in the development of AF, which is supported by inadequate treatment and the lack of correction of modifiable risk factors [19]. The most significant risk factors for AF include cardiac factors such as arterial hypertension and heart failure, as well as noncardiac factors, including diabetes mellitus, obesity, obstructive sleep apnea syndrome [20, 21].

Obesity is the main modifiable risk factor for a number of chronic diseases, including type 2 diabetes mellitus and cardiovascular diseases (CVD) [22]. In addition to the effect of obesity on the formation of arrhythmia substrate, associated conditions and, in some cases, pathogenetic diseases caused by obesity (arterial hypertension, obstructive sleep apnea syndrome, type 2 diabetes mellitus, dyslipidemia, and others), the independent role of obesity in arrhythmogenesis was revealed [23, 24]. Unsurprisingly, the exponential increase in AF incidence coincides with the rise in obesity prevalence. The established connection between obesity and AF in the context of a sharp increase in the prevalence of this disease determined the relevance of identifying the underlying pathogenetic mechanisms. Along with increased fatty infiltration of the atria, obesity leads to the diastolic dysfunction of the left ventricle, increased sympathetic activity and higher intensity of inflammation [8]. Today, the role of obesity as an arrhythmogenic substrate remains underestimated.

This study suggests that obesity adversely affects the effectiveness of antiarrhythmic drug therapy and the success of interventional treatment. Significant weight loss (≥ 3% from the baseline), along with the modification of other risk factors, has a beneficial effect on the course of the disease. It can lead to its reversal and restoration of sinus rhythm in some patients indefinitely. In patients taking antiarrhythmic agents, AF is much less likely to progress to more persistent forms in comparison with patients who have chosen a heart rate control strategy [25].

This study demonstrated that a decrease in body weight was associated with a decrease in the need for catheter ablation and its frequency, as well as in the use of antiarrhythmic agents .

Recognition of AF as a progressive disease based on the dynamic remodeling of the myocardium under the influence of risk factors requires early and aggressive intervention in relation to body weight and other modifiable risk factors. Timely correction of risk factors is becoming critical for present-day medicine in the context of the growing epidemic of obesity and AF. Managing risk factors reduces the rate of disease progression and improves long-term prospects for maintaining sinus rhythm.

This study contributes to the evidence base for the need for effective modification of risk factors, which is of strategic importance for both primary and secondary prevention of AF.

The relatively small sample size should be recognized as a limitation of this study.

Conclusion

AF is a progressive disease. Persistent obesity and concomitant weight gain are associated with an accelerated progression of the disease from the paroxysmal to the persistent form. However, this study showed that weight loss plays an inhibitory role on the processes of electrophysiological remodeling of the myocardium and even contributes to the reversal of persistent AF to paroxysmal AF, with the potential for restoration of sinus rhythm indefinitely.

In this regard, weight loss is a promising therapeutic strategy in the comprehensive treatment of patients with AF. Another important aspect is, in our opinion, the need to consider weight loss as a probable predictor of the success of interventional treatment at the planning stage of the latter.

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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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Список литературы/References:

1. Филатов А.Г., Тарашвили Э.Г. Эпидемиология и социальная значимость фибрилляции предсердий. Анналы аритмологии. 2012; 9(2): 5-13.
   Filatov A.G., Tarashvili E.G. Epidemiology and social significance of atrial fibrillation. Annals of Arrhythmology. 2012; 9(2): 5-13 [in Russian].
2. Nabauer M, Gerth A, Limbourg T. et al. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. Europace. 2008; 11(4): 423-434. doi: 10.1093/europace/eun369.

3. Tsang TS, Barnes ME, Miyasaka Y. et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J. 2008; 29(18): 2227-2233. doi: 10.1093/eurheartj/ehn324.
4. Wong CX, Sullivan T, Sun MT et al. Obesity and the Risk of Incident, Post Operative, and Post-Ablation Atrial Fibrillation: A Meta-Analysis of 626 603 Individuals in 51 Studies. JACC Clinical electrophysiology. 2015; 1(3): 139–152. doi: 10.1016/j.jacep.2015.04.004.
5. Голухова Е.З., Громова О.И., Булаева Н.И. и др. Эпикардиальный жир и фибрилляция предсердий: роль профиброгенных медиаторов. Кардиология. 2018; 58(7): 59–65. doi.org/10.18087/cardio.2018.7.10145.
Golukhova E.Z., Gromova O.I., Bulaeva N.I., etc. Epicardial fat and atrial fibrillation: the role of profibrogenic mediators. Cardiology. 2018; 58(7): 59–65. doi.org/10.18087/cardio.2018.7.10145 [in Russian].
6. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013; 310(19): 2050–2060. doi: 10.1001/jama.2013.280521.
7. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014; 64(21): 2222–2231. doi: 10.1016/j.jacc.2014.09.028.
8. Hindricks G, Potpara T, Dagres N. et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021; 42(5): 373-498. doi: 10.1093/eurheartj/ehaa612.
9. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol. 2014; 63(25): 2985–3023. doi: 10.1016/j.jacc.2013.11.004.
10. de Vos CB, Pisters R, Nieuwlaat R. et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol. 2010; 55(8): 725–731. doi: 10.1016/j.jacc.2009.11.040.
11. Schotten U, Verheule S, Kirchhof P. et al. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev. 2011; 91(1): 265–325. doi: 10.1152/physrev.00031.2009.
12. Аракелян М.Г., Бокерия Л.А., Васильева Е.Ю. и др. Фибрилляция и трепетание предсердий. Клинические рекомендации Министерства здравоохранения Российской Федерации. Москва. 2020; 1-185.
Arakelyan M.G., Bokeria L.A., Vasilyeva E.Yu. et al. Atrial fibrillation and flutter. Clinical recommendations of the Ministry of Health of the Russian Federation. Moscow. 2020; 1-185. [in Russian].
13. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol. 2014; 63(22): 2335–2345. doi: 10.1016/j.jacc.2014.02.555.
14. Kannel WB, Abbott RD, Savage DD. et al. Coronary heart disease and atrial fibrillation: The Framingham Study, AM Heart J. 1983; 106(2): 389-396. doi: 10.1016/0002-8703(83)90208-9.
15. Голицын С.П., Панченко Е.П., Кропачева Е.С. и др. Диагностика и лечение фибрилляции предсердий. Евразийский кардиологический журнал. 2019; (4): 4-85.
Golitsyn S.P., Panchenko E.P., Kropacheva E.S., et al. Diagnosis and treatment of atrial fibrillation. Eurasian Journal of Cardiology. 2019; (4):4-85 [in Russian].
16. Camm A.J., Kirchhof P., Lip G.Y. H. et al. Guidelines for the management of atrial fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31(19): 2369-2429. doi: 10.1093/eurheartj/ehq278.
17. Stiles MK, John B, Wong CX. et al. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the "second factor". J Am Coll Cardiol. 2009; 53(14): 1182–91. doi: 10.1016/j.jacc.2008.11.054.
18. Teh AW, Kistler PM, Lee G. et al. Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. Heart Rhythm. 2012;9(4):473–480. doi: 10.1016/j.hrthm.2011.11.013.
19. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999; 100(1): 87–95. doi: 10.1161/01.cir.100.1.87.
20. Ревишвили А.Ш., Рзаев Ф.Г., Горев М.В. и др. Диагностика и лечение фибрилляции предсердий. Клинические рекомендации. Москва. 2017; 201с.
Revishvili A.Sh., Rzaev F.G., Gorev M.V. et al. Diagnosis and treatment of atrial fibrillation. Clinical recommendations. Moscow. 2017; 201p [in Russian].
21. Бокерия Л.А., Бокерия О.Л., Глухова Е.З. и др. Фибрилляция предсердий. Клинические рекомендации. Москва. 2017; 65с.
Bokeria L.A., Bokeria O.L., Glukhova E.Z. et al. Atrial fibrillation. Clinical recommendations. Moscow. 2017; 65p [in Russian].
22. Дедов И.И., Мокрышева Н.Г., Мельниченко Г.А., и др. Ожирение. Клинические рекомендации Министерства здравоохранения Российской Федерации. Москва. 2020; 43с.
Dedov I.I., Mokrysheva N.G., Melnichenko G.A. et al. Obesity. Clinical recommendations. Moscow. 2020; 43p [in Russian].
23. Garvey W.T., Mechanick J.I., Brett E.M. et al. Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocrine Practice. 2016; 22(3): 1-203.
24. Auer J. Fat: an emerging player in the field of atrial fibrillation. European Heart Journal. 2016; 38(1): 62-65. doi: 10.1093/eurheartj/ehw013.
25. De Vos CB, Breithardt G, Camm AJ. et al. Progression of atrial fibrillation in the REgistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation cohort: clinical correlates and the effect of rhythm-control therapy. Am Heart J. 2012; 163(5): 887–893. doi: 10.1016/j.ahj.2012.02.015.