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СОДЕРЖАНИЕ

Лекции

Клинические рекомендации

Обзорные статьи

Оригинальные статьи

С 2016 ГОДА СТАТЬИ В ЖУРНАЛ ПРИНИМАЮТСЯ ЧЕРЕЗ РЕДАКЦИОННУЮ ПЛАТФОРМУ:
http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

НОВЫЕ ПРАВИЛА ПУБЛИКАЦИИ АВТОРСКИХ МАТЕРИАЛОВ (2019):
http://www.medarhive.ru/jour/about/submissions#authorGuidelines

CONTENT

SINCE 2016, ARTICLES IN THE JOURNAL HAVE BEEN ACCEPTED THROUGH THE EDITORIAL PLATFORM:

http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

NEW GUIDELINES OF PUBLICATION FOR AUTHORS OF ARTICLES (2019):

http://www.medarhive.ru/jour/about/submissions#authorGuidelines

ЯКОВ МАКСИМОВИЧ ВАХРУШЕВ

(к 80-летию со дня рождения)

В сентябре 2020 г. исполняется 80 лет заслуженному работнику здравоохранения Удмуртской Республики, заслуженному врачу Российской Федерации, доктору медицинских наук, профессору, заведующему кафедрой пропедевтики внутренних болезней Ижевской государственной медицинской академии Якову Максимовичу Вахрушеву.

Я. М. Вахрушев родился в деревне Верх-Узгино Якшур-Бодьинского района Удмуртской Республики в семье колхозников. В детстве тяжёлые военные и послевоенные годы способствовали формированию трудолюбия, терпения и необыкновенному стремлению к знаниям. С 1960 по 1963 гг. служил в Советской Армии за рубежом. В 1969 году с отличием окончил Ижевский медицинский институт, а затем клиническую ординатуру и аспирантуру на кафедре госпитальной терапии, возглавляемого профессором Л. А. Лещинским. В 1974 г. защитил кандидатскую диссертацию, в 1986 г. — докторскую. С 1986 года заведует кафедрой пропедевтики внутренних болезней ИГМА.

С 1988 по 1995 гг. работал проректором по научной работе Ижевской государственной медицинской академии. За это время им была проведена большая работа по активизации подготовки кадров и внедрению прогрессивной системы планирования научных исследований в академии. В течение ряда лет он в академии возглавляет проблемную комиссию «Пульмонология и фтизиатрия». Перед ним стояла задача активизировать научно-исследовательскую работу и подготовку кадров по данным специальностям. За короткое время были защищены 7 кандидатских и 3 докторских диссертаций.

Я. М. Вахрушев обладает высоким творческим потенциалом и ведёт активную научно-исследовательскую работу, укрепляет и расширяет научную школу. Одним из главных направлений научной деятельности является изучение проблем гастроэнтерологии. Фундаментальные труды по нейроэндокринной регуляции органов пищеварения существенно обогатили теоретическую и клиническую гастроэнтерологию. Впервые им совместно с акад. А. М. Уголевым была выдвинута гормональная теория развития специфического динамического действия пищи. Приоритетными являются его исследования по профилактике и консервативному лечению желчнокаменной болезни, эрозивных поражений желудочно-кишечного тракта и хронического панкреатита. На кафедре в течение ряда лет выполняются научно-исследовательские работы в рамках отраслевой программы по пульмонологии.

Я. М. Вахрушев является автором 1200 научных работ, в том числе 16 монографий, среди которых особой популярностью пользуются «Печень и гормоны» (1992), «Специфическое динамическое действие пищи» (1996), «Полипы желудка» (2005). Яков Максимович является научным руководителем (консультантом) 15 докторских и 50 кандидатских диссертаций. Многие его ученики возглавляют кафедры и являются руководителями лечебно-профи-

лактических учреждений. Он является редактором трудов 19 научно-практических конференций, имеет 4 патента на изобретения.

Педагогическая деятельность Я. М. Вахрушева отличается высоким уровнем и методической направленностью, профессионализмом, требовательностью к себе, преподавателям и обучающимся в клинике студентам, интернам, ординаторам и аспирантам. Он повседневное внимание уделяет совершенствованию учебного процесса, введению новых средств обучения, созданию методических руководств. Написанные им учебники «Непосредственное исследование больного», «Внутренние болезни», «От симптома к диагнозу...» выдержали уже несколько переизданий. Яков Максимович неутомимый труженик, щедро отдаёт свои знания и большой опыт своим ученикам, воспитывая молодые кадры в духе лучших врачебных традиций. Его содержательные лекции проходят при полной аудитории, демонстрации больных сопровождаются описанием патофизиологической сущности симптомов заболевания.

Как врач, Яков Максимович снискал себе репутацию вдумчивого диагноста и специалиста-терапевта. Ведёт большую лечебно-консультационную работу, как на клинической базе кафедры, так и в лечебно-профилактических учреждениях г. Ижевска и Удмуртской Республики. На его регулярных клинических обходах приобретают опыт врачебного мастерства клинические ординаторы, врачи-интерны, аспиранты, преподаватели и практические врачи. Яков Максимович требователен к подчинённым, поэтому к обходу ответственно готовится всё отделение, начиная от докладчика и заканчивая зав. отделением. Внедрение разработанных на кафедре новых методов диагностики, лечения и профилактики позволило улучшить качественные показатели терапевтической помощи больным и получить экономическую эффективность при хронических заболеваниях пищеварительной системы и хронических неспецифических заболеваниях лёгких. При его непосредственном участии впервые в республике организована «Астма-школа», на базе клиники организован центр по лечебному питанию больных с аллергическими заболеваниями. Яков Максимович автор целевой комплексной программы Удмуртской Республики по охране окружающей среды.

Плодотворную научную и педагогическую деятельность Я. М. Вахрушев сочетает с большой общественной работой. При его активном участии происходило становление и развитие в академии факультета высшего сестринского образования. Он с 1985 г. возглавляет научное общество гастроэнтерологов Удмуртии, является членом правления научного общества гастроэнтерологов России. Яков Максимович член редакционного совета журналов «Терапевтический архив», «Экспериментальная и клиническая гастроэнтерология», «Сибирский журнал гастроэнтерологии и гепатологии», «Здоровье, демография, экология финно-угорских народов».

За заслуги в развитии здравоохранения и медицинской науки, подготовку научных и медицинских кадров он награждён Почётной грамотой государственного совета Удмуртской Республики, Почётной грамотой Президента Удмуртской Республики, значком «Отличнику здравоохранения СССР», медалью им. Альфреда Нобеля. Ему присвоено почётное звание «Основатель научной школы». Он почётный академик Ижевской медицинской академии, член ряда зарубежных академий. Его имя занесено на Республиканскую доску почёта.

Редакция журнала «Архивъ внутренней медицины», сотрудники кафедры пропедевтики внутренних болезней и ученики сердечно поздравляют Якова Максимовича с юбилеем и желают ему здоровья, благополучия и творческого долголетия.

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New Coronavirus Infection (Covid-19): Clinical and Epidemiological Aspects

Abstract

Environmental change, climate warming, population density increase, high migration activity of the population and other factors provoke the emergence and spread of new infections around the world.

The emergence in December 2019 of diseases caused by the new coronavirus («coronavirus disease 2019») has already gone down in history as an emergency of international importance. It is known that the most common clinical manifestation of a new infection is pneumonia, and also in a significant part of patients — respiratory distress syndrome. Our article provides a brief analytical review of these temporary guidelines Ministry of Health of the Russian Federation «Prevention, Diagnosis and Treatment of a New Coronavirus Infection (COVID-19)», version 3 (03.03.20) and other published sources. The team of authors expresses the hope that these data will be useful to doctors in providing medical care to patients with a new coronary virus infection, as well as to teachers in preparing students and residents.

Source: Ministry of Health of the Russian Federation. Temporary guidelines «Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)», version 3 (03.03.20). Available on: https://static-0.rosminzdrav.ru/system/attachments/attaches/000/049/629/original/Временные_MP_COVID-19_03.03.2020_%28версия_3%29_6-6.pdf?1583255386.

Key words: *COVID-19, coronavirus, clinic, diagnosis, prevention*

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CT — computed tomography, ARF — acute respiratory failure, ARDS — acute respiratory distress syndrome, SARS — severe acute respiratory syndrome

Introduction

In the new millennium, humanity is faced with unknown infectious diseases. Dangerous viruses have replaced the plague and typhoid. Environmental changes, global warming, population density increase and other factors trigger their emergence, while global migration contributes to their spread around the world. Indeed, infections know no boundaries.

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According to UN forecasts, the world's population will reach 10 billion people by 2050. This means that the processes of migration and urbanization will accelerate [1].

The COVID-19 ("coronavirus disease 2019") epidemic has already gone down in history as an emergency of international concern. To date, the number of infected people in the world has exceeded 470,000 [2]. We have yet to study the features of this epidemic, to draw lessons, to analyze the shortcomings of ensuring the biological safety of the population. One thing is clear: new viruses will appear; it is an integral part of our world. Humanity must learn to counter these threats.

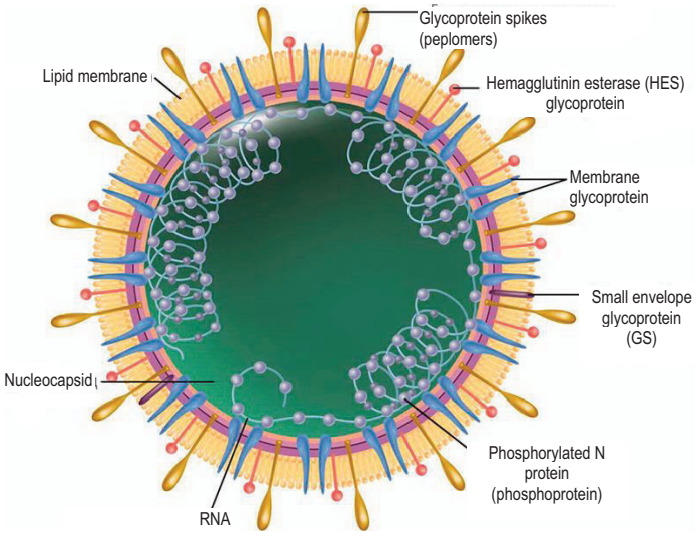

Figure 1. *The structure of coronavirus*

Etiology and Pathogenesis

Coronavirus disease is an acute viral disease with a primary lesion of the upper respiratory tract caused by the RNA virus of the genus Betacoronavirus of the family Coronaviridae.

Coronaviruses (lat. Coronaviridae) are a family of 40 species (as of January 2020) of complex enveloped RNA viruses. They are grouped into two subfamilies that affect humans and animals. The name is associated with the structure of the virus: large spikes protrude from the envelope in the form of a mace, which resemble the crown.

Virions measure 80–220 nm. A nucleocapsid is a flexible helix consisting of a positive RNA strand and a large number of N nucleoprotein molecules. It has the largest genome among RNA viruses. The virus has an envelope, in which glycoprotein trimeric spikes (peplomers), membrane glycoprotein, small envelope glycoprotein, and hemagglutinin esterase are embedded (Fig. 1).

The "crown" of coronaviruses is associated with a specific mechanism of penetrating the cell membrane by simulating the molecules to which transmembrane receptors respond (Fig. 2).

Currently, four coronaviruses (HCoV-229E, -OC43, -NL63, -HKU1) that circulate among the population are known. They are present in the structure of acute respiratory viral infections all year round and normally affect the upper respiratory tract with mild or moderate disease.

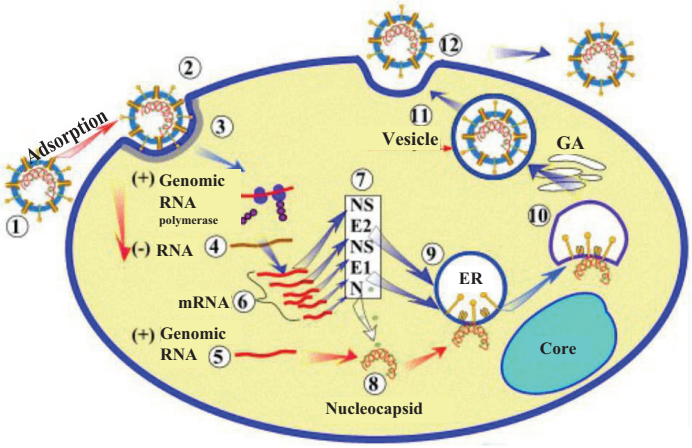

Figure 2. *Coronavirus replication (A.A. Vorobyov. Atlas of Medical Microbiology, Virology and Immunology. 2nd ed., revised. and expanded Medicine. 2003; 236 p. [In Russian].)*

The virus is adsorbed on the target cell (1) via S glycoprotein and penetrates the cell by fusion of the viral and cellular cytoplasmic membrane or receptor-mediated endocytosis (2).

Genomic RNA binds to ribosomes and acts as mRNA in the synthesis of RNA-dependent RNA polymerase (3), which then reads genomic RNA. As a result, a full-length negative strand is synthesized (4). Upon transcription of the negative strand, a new genomic positive-strand RNA (5) and a set of 5–7 subgenomic mRNAs are synthesized (6). Upon translation of each subgenomic mRNA, one protein is synthesized (7). N protein binds to the genomic RNA in the cell cytoplasm, as a result of which a spiral nucleocapsid is synthesized (8). S and M, or E1, E2, glycoproteins are transferred (9, 10) to the endoplasmic reticulum and Golgi apparatus. The nucleocapsid is budded through the membranes into the endoplasmic reticulum, which contains S and M glycoproteins. Virions are transported to the membrane of the host cell (10) and exit the cell via endocytosis (11).

Until 2002, coronaviruses were considered as agents that cause mild diseases of the upper respiratory tract (with extremely rare lethal outcomes). At the end of 2002, coronavirus (SARS-CoV) appeared that became the causative agent of SARS (severe acute respiratory syndrome) in human. This virus belongs to the genus Betacoronavirus. The natural reservoir of SARS-CoV is bats, and camels and masked palm civets are the intermediate hosts. In total, more than 8,000 cases were reported in 37 countries during the epidemic, of which 774 were fatal. Since 2004, no new cases of SARS-CoV-associated disease have been reported.

In 2012, the world faced a new coronavirus (MERS-CoV), a causative agent of the Middle East respiratory syndrome, belonging to the genus Betacoronavirus. The main natural reservoir of MERS-CoV is bats and dromedaries. Since 2012, 2,519 cases of MERS-CoV infection have been reported, of which 866 have been fatal. All cases are geographically associated with the Arabian Peninsula (82% of cases are reported in Saudi Arabia). MERS-CoV continues to circulate and cause new cases of the disease [3].

On February 11, 2020, the World Health Organization assigned the official name to the infection caused by the new coronavirus, COVID-19 ("Coronavirus disease 2019") [1]. The International Committee on Taxonomy of Viruses on February 11, 2020, assigned its own name to the causative agent of COVID-19 — **SARS-CoV-2**.

The new SARS-CoV-2 is a single-stranded RNA virus, and belongs to the Coronaviridae family, to the Beta-CoV of the B lineage.

The virus is assigned to the pathogenicity group II, as well as some other representatives of this family (SARS-CoV virus, MERS-CoV virus).

SARS-CoV-2 is believed to be a recombinant virus between bat coronavirus and coronavirus of unknown origin. The genetic sequence of SARS-CoV-2 is similar to the sequence of SARS-CoV by at least 79% [4].

The main target cells for coronaviruses are cells of the alveolar epithelium, in the cytoplasm of which the virus replicates. After the assembly of virions, they pass into cytoplasmic vacuoles, which migrate to the cell membrane and exit into the extracellular space by exocytosis. Virus antigens are not expressed on the cell surface until virions exit the cell; therefore, antibody formation and interferon synthesis are stimulated relatively late. Virus-driven formation of syncytia facilitates its rapid spread into the tissues. Virus causes an increase in the permeability of cell membranes and enhanced transport of albumin-rich fluid into the interstitium and the lumen of the alveoli. In this case, the surfactant is destroyed, which leads to the collapse of the alveoli. Acute violation of gas exchange causes acute respiratory distress syndrome (ARDS). Immunosuppression contributes to the development of opportunistic bacterial and mycotic infections of the respiratory tract.

The pathogenesis of novel coronavirus disease has not been adequately studied. There are no available data on the duration and intensity of immunity against SARS-CoV-2. Immunity in infections caused by other members of the coronavirus family is not persistent and re-infection is possible.

Epidemiology

The natural reservoir of the SARS-CoV-2 virus is bats. An additional reservoir can be mammals that eat bats, with further spread among humans. Phylogenetic studies of the isolated strains showed that the genomic sequences of viruses found in bats are 99 percent identical to those isolated in patients with COVID-19.

Currently, the main source of infection is an infected person, including those at the end of the incubation period, prodromal period (the beginning of virus isolation from target cells) and during clinical manifestations.

The transmission mechanism is aspiration. Ways of transmission: airborne (release of the virus when coughing, sneezing, talking) during close contact.

The contact way is realized through transmission factors: water, food and objects (door handles, smartphone screens) contaminated with the pathogen. The risk of transmission of the virus from the hands to the mucous membranes of the eyes, nasal and oral cavity and infection is proven. The fecal-oral mechanism is possible (the causative agent was detected in the feces from patients infected with SARS-CoV-2).

The iatrogenic transmission of SARS-CoV-2 has been established. In China, there were more than

1,700 confirmed cases among healthcare providers who worked with COVID-19 patients [4].

Susceptibility to the pathogen is high in all population groups. The groups at risk of severe disease and death include people older than 60 years, patients with chronic diseases (diseases of the respiratory system, cardiovascular system, diabetes mellitus, cancer). Mortality varies from 2 to 4%.

SARS-CoV-2 is characterized by low environmental resistance. It dies under UV radiation, disinfectants, when heated to 40 °C for 1 hour, to 56 °C in 30 minutes. On the surface of objects at 18–25 °C it remains viable for 2 to 48 hours.

Clinical Picture

The incubation period of COVID-19 is 2 to 14 days, 5–7 days on average. In comparison, the incubation period for seasonal flu is about 2 days.

Among the first symptoms of COVID-19, fever (90%), cough — dry or with a small amount of sputum (80%), shortness of breath (55%), myalgia and fatigue (44%), chest tightness (20%), as well as headaches (8%), hemoptysis (5%), diarrhea and nausea (3%) were reported. At the onset, these symptoms can be observed without fever [5].

Clinical patterns and signs of COVID-19:

1. Mild acute respiratory viral infection
2. Pneumonia without signs of respiratory failure
3. Pneumonia with acute respiratory failure (ARF)
4. Acute respiratory distress syndrome
5. Sepsis
6. Septic (toxic) shock

Hypoxemia (SpO_2 decrease below 88%) develops in more than 30% of patients.

There are mild, moderate and severe forms of COVID-19.

Most patients with severe COVID-19 develop pneumonia in the first week of the disease. Dull percussive sound is determined. In the lungs, bilateral crepitant, small-bubbling rales are auscultated. At the maximum of inhalation, the rales become more intense; they do not disappear after coughing, do not change depending on the position of the patient's body (sitting, standing, lying). X-ray shows infiltration in the periphery of the lung fields. As the disease progresses, infiltration increases, the affected areas become larger, and ARDS develops. Sepsis and toxic shock develop.

Diagnosis

The diagnosis is established based on epidemiological history, clinical examination and laboratory test results.

When collecting epidemiological history, it is necessary to take into account the patient's visit to countries and regions affected by COVID-19 during the previous 14 days, the presence of close contacts during this time with people who arrived from endemic areas, as well as contacts with people with diagnosis confirmed by laboratory tests.

Standard laboratory tests:

- Complete blood count with determination of red blood cells, hematocrit, white blood cells, platelets, leukocyte formula;
- Biochemical analysis (urea, creatinine, electrolytes, liver enzymes, bilirubin, albumin, glucose). Biochemical analysis does not provide any specific information, but detected abnormalities can indicate the presence of organ dysfunction, decompensation of concomitant diseases and the development of complications, have a certain prognostic value, and influence the choice of drugs and/or the dosage regimen;
- Serum C-reactive protein (CRP). The level of CRP correlates with the severity of the course, the prevalence of inflammatory infiltration and the prognosis of pneumonia;
- Pulse oximetry with SpO_2 measurement to detect respiratory failure and assess the severity of hypoxemia. Pulse oximetry is a screening method that allows to identify patients with hypoxemia who need respiratory support and to evaluate its effectiveness;
- Arterial-blood gas test with PaO_2, $PaCO_2$, pH, bicarbonates and lactate is indicated to patients with signs of ARF (SpO_2 below 90% according to pulse oximetry);
- Coagulation test with the determination of prothrombin time, international normalized ratio and activated partial thromboplastin time is recommended in patients with signs of ARF.

Investigations:

- Computed tomography (CT) of the chest is recommended for all patients with suspected pneumonia. Chest CT is a more sensitive method for the diagnosis of viral pneumonia. The main

findings in pneumonia are bilateral infiltrates in the form of "ground-glass" or consolidation, which are predominant in the lower and middle areas of the lungs.

- If chest CT is not available, a panoramic chest X-ray is performed in the direct anterior and lateral projections (if the localization of the inflammatory process is unknown, it is advisable to take a picture in the right lateral projection). Chest X-ray shows bilateral confluent infiltrative shadowing. Most often, the most pronounced changes are localized in the basal parts of the lungs. A small pleural effusion may also be present.
- Standard-lead electrocardiography is recommended for all patients. This investigation does not provide any specific information, but viral infection and pneumonia in addition to decompensation of chronic concomitant diseases is currently known to increase the risk of rhythm disturbances and acute coronary syndrome, the timely detection of which significantly affects the prognosis. In addition, certain ECG changes (for example, prolongation of the QT interval) require attention when assessing the cardiotoxicity of a number of antibacterial drugs.

Deciding on the need for hospitalization:

a) with medical history data indicating the likelihood of SARS-CoV-2 infection, regardless of the severity of the patient's condition, hospitalization in an infectious disease hospital/ward in compliance with all anti-epidemic measures is indicated;
b) in the absence of suspicion of SARS-CoV-2 infection, the decision on hospitalization depends on the severity of the condition and another probable diagnosis.

Specific laboratory tests:

- SARS-CoV-2 RNA detection by PCR

The main type of biomaterial for laboratory testing is a nasal, nasopharyngeal and/or oropharyngeal swab, as well as bronchial lavage fluid obtained by fibrobronchoscopy, sputum, lung biopsy or autopsy material, whole blood, serum, and urine.

All samples obtained for laboratory testing are potentially dangerous and the requirements of SP 1.3.3118-13 "Safety of work with microorganisms of I–II pathogenicity groups" should be met. Healthcare workers who collect and/or transport clinical samples to the laboratory should be trained in the safe handling of biomaterial, strictly observe safety precautions and use personal protective equipment.

Samples of biological materials are sent to the research organization of Rospotrebnadzor or the Center for Hygiene and Epidemiology in the constituent entity of the Russian Federation (Appendix 2 of the Temporary Recommendations of Rospotrebnadzor of January 21, 2020, for Laboratory Diagnosis of Novel Coronavirus Infection Caused by SARS-CoV-2) taking into account the convenience of the transport scheme.

For differential diagnosis, PCR studies are carried out for the causative agents of respiratory infections: type A and B influenza viruses, rhinoviruses, respiratory syncytial viruses, parainfluenza viruses, adenoviruses, human metapneumoviruses, and MERS-CoV. Diagnostic microbiology of Haemophilus influenzae type B, Streptococcus pneumoniae, Legionella pneumophila, and Mycoplasma pneumoniae is also mandatory.

Treatment

To date, there is no evidence of the effectiveness of the use of any drugs with COVID-19.

During patient management, for timely treatment, it is necessary to monitor the patient's condition to detect signs of clinical deterioration, such as rapidly progressive ARF and sepsis.

Patients infected with SARS-CoV-2 should receive supportive symptomatic therapy.

Analysis of the literature data on the clinical experience of managing patients with SARS associated with SARS-CoV and MERS-CoV allows us to identify several causative agents that are usually used in combination. These include ribavirin, lopinavir/ritonavir [6] and interferons.

However, the results of the use of these drugs do not allow to make a definitive conclusion about their effectiveness/inefficiency, and therefore their use is permissible by decision of the medical commission in the appropriate manner if the possible benefit to the patient exceeds the risk.

The use of causative agents is justified in the case of moderate and severe infection, when the intended benefit exceeds the potential risk of adverse events.

The list of drugs that can be prescribed for the causal treatment of SARS-CoV-2 infection is indicated in the Interim Guidelines of the Ministry of Health of the Russian Federation (version 4).

According to the WHO recommendations, off-label drugs with the supposed etiotropic efficacy may be prescribed, and their use should comply with ethical standards recommended by WHO and should be carried out on the basis of Federal Law of November 21, 2011, No. 323-FZ "On the Fundamentals of Public Health Protection in the Russian Federation", Federal Law of April 12, 2010, No. 61-FZ "On Circulation of Medicines", National Standard of the Russian Federation GOST R ISO 14155-2014 "Good Clinical Practice", Order of the Ministry of Health of the Russian Federation of April 1, 2016, No. 200n "On the Approval of the Rules of Good Clinical Practice" (registered by the Ministry of Justice of the Russian Federation on August 23, 2016, registration No. 43357), the Helsinki Declaration of the World Medical Association (WMA) on Ethical Principles For Medical Research Involving Human Subjects declared at the 64th General Assembly of the World Medical Academy, Fortaleza, Brazil, 2013.

In February 2020, in a joint project, Chinese and German scientists synthesized a special group of drugs (alpha-ketoamides) that have the ability to inhibit the basic proteases of various viruses, including SARS-CoV-2.

The researchers determined the three-dimensional crystal structure of the main SARS-CoV-2 protease and modified the alpha-ketoamide molecule through the P3-P2 amide bond, which is included in the pyridone ring, which contributed to the specific inhibition of coronaviruses. As a result, the half-life of alpha-ketoamide increased three-fold, and the solubility — 19-fold which, however, led to some decrease in efficiency. In an experimental study in mice, alpha-ketoamide, administered by inhalation, showed pronounced pulmonary tropism and lack of side effects [7].

In addition, umifenovir, remdesivir, and favipiravir are among the studied drugs for COVID-19 treatment.

Pathogenetic therapy involves the intake of a sufficient amount of fluid (up to 3.5 liters per day) in the absence of contraindications, enterosorbents (colloidal silicon dioxide, polymethylsiloxane polyhydrate and others).

In severe patients, infusion therapy is carried out while monitoring blood pressure, chest auscultation pattern, urine output, and other parameters. In order to prevent cerebral and pulmonary edema, it is advisable to carry out infusion therapy combined with forced diuresis. In order to improve sputum discharge during a productive cough, acetylcysteine, ambroxol, carbocysteine and other combined drugs are prescribed.

In the presence of bronchial obstructive syndrome, inhaled bronchodilator therapy (via a nebulizer) with the use of salbutamol, fenoterol and combined agents is actively used.

Symptomatic therapy includes the use of ibuprofen and paracetamol at fever above 38.0 °C. For the treatment of rhinitis, pharyngitis, in case of nasal congestion and/or discharge from the nose, salt preparations for topical administration based on seawater (isotonic, and in case of congestion — hypertonic), various antiseptic solutions are used.

Patients with clinical and laboratory signs of coronavirus pneumonia are prescribed antimicrobial agents (respiratory fluoroquinolones, 3rd and 4th generation cephalosporins, carbapenems, linezolid, etc.) due to the high risk of bacterial superinfection. The choice of antibiotic and method of administration is based on the severity of the patient's condition, the presence of concomitant diseases and the results of diagnostic microbiology.

ARF is one of the most common complications of severe viral pneumonia. ARF management is based on the general principles of respiratory therapy. The optimal level of effectiveness of oxygen therapy is to increase oxygen saturation above 90%, or its steady increase. If primary respiratory therapy (oxygen therapy using a face mask or nasal cannula) is ineffective, mechanical ventilation should be considered.

Prevention

Specific prophylaxis (vaccine) against COVID-19 has not yet been developed.

For drug prevention of COVID-19 in adults, intranasal administration of recombinant interferon alfa is possible.

For drug prevention of COVID-19 in pregnant women, only intranasal administration of recombinant interferon alfa-2b is possible.

Measures to prevent the introduction and spread of COVID-19 in the Russian Federation are regulated by the Decrees of the Government of the Russian Federation of January 30, 2020, No. 140-r, of January 31, 2020, No. 154-r, of February 3, 2020,

No. 194-r, of February 18, 2020, No. 338-r, and Directives of the Chief State Sanitary Doctor of the Russian Federation of January 24, 2020, No. 2, of January 31, 2020, No. 3, etc.

Nonspecific prevention is an activity aimed at preventing the spread of infection and is carried out in relation to the source of infection (sick person), the mechanism of transmission of the causative agent, as well as the potentially susceptible population (protection of persons who are and/or were in contact with a sick person).

Measures regarding the source of infection: isolation of patients in isolation wards / wards in an infectious disease hospital; care and treatment; discharge after a double negative result of laboratory test for SARS-CoV-2.

Measures aimed at the pathogen transmission mechanism [8]:

- observance of personal hygiene (washing hands with soap, using disposable wipes when sneezing and coughing, touching the face only with clean wipes or washed hands);
- use of disposable face masks, which should be replaced every 2 hours;
- use of protective clothing for health workers;
- carrying out disinfection measures;
- disposal of medical waste class B;
- evacuation of patients with special-purpose transport.

Timely visit to healthcare institutions in case of symptoms of acute respiratory viral infection is one of the key factors in the prevention of complications.

Conclusion

Environmental changes, global warming, an increase in population density, the development of biotechnology and other factors trigger the emergence of new infections, and the ever-increasing global migration and economic globalization contribute to their spread.

Biological threats associated with epidemics of infectious diseases are global in nature. The COVID-19 epidemic is not the last threat in the 21st century.

All countries should be prepared for concerted actions to prevent the occurrence and spread of infections, for their timely diagnosis, the development of treatment and prevention methods, and the creation of vaccines.

Author Contribution:

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

T. G. Suranova: collection and analysis of manuscript materials, text editing

T. Ya. Chernobrovkina, Ya. D. Yankovskaya, S. V. Burova: text writing and editing

V. V. Nikiforov: review concept and design, text editing, approval of the final version of the manuscript

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Primary Hyperparathyroidism: Modern Conception and Clinical Observation

Abstract

The article is devoted to one of the current medical and social issues — primary hyperparathyroidism, the late diagnosis of which leads to the development of severe complications and an increased risk of premature death. Unlike developed countries, where mild forms of the disease constitute 80% of cases, in the Russian Federation this figure does not exceed 30%, with overt forms accounting for 70%. For the timely detection of the disease, widespread awareness among doctors of various specialties of the diagnosis of parathyroid adenoma is necessary. The article describes the main stages of studying the disease, examines the pathogenesis of the clinical signs of primary hyperparathyroidism, which classic clinical pattern involves changes in the target organs of the parathyroid hormone: bone tissue, urinary system and gastrointestinal tract. Bone tissue disorders are the most common manifestation of hyperparathyroidism and are characterized by increased bone metabolism with a progressive decrease in mineral density. Typical changes in the kidneys include nephrolithiasis and nephrocalcinosis with renal failure. Gastrointestinal signs of hyperparathyroidism are gastric erosion and ulcers and duodenal ulcer, prone to bleeding, and recurrent pancreatitis. Diagnosis of the disease is based on the results of laboratory tests: elevated blood levels of calcium and parathyroid hormone. Normally, parathyroid adenoma is imaged using ultrasound and scintigraphy. The most effective treatment is the removal of parathyroid adenoma. A clinical case of a severe course of the disease is presented, indicating the urgent need to solve the problem of primary hyperparathyroidism.

Key words: *primary hyperparathyroidism, parathyroid adenoma, hypercalcemia*

Conflict of Interests

The authors declare that this paper, its topic, subject and content do not involve competing interests

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PHPT — primary hyperparathyroidism

In matters of natural science ... cognition of phenomena is what leads us to examining and finding the cause.
Galileo Galilei

Relevance

Primary hyperparathyroidism (PHPT) is an endocrine disease of medical and social significance, which is primarily due to the low level of diagnosis. Its incidence is 1–2 cases per 1,000 people; PHPT is one of the most common endocrine diseases. Untimely detection is the cause of severe disabling complications: osteoporotic fractures, recurrent stone formation in the urinary tract and nephrocalcinosis with renal failure, gastrointestinal bleeding,

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etc., as well as an increased risk of premature death. However, early diagnosis of primary hyperparathyroidism allows to achieve cure [1, 2].

Background

In 1880, the Swedish researcher Ivar Sandström (1852–1889) first described areas of glandular tissue located on the posterior surface of the thyroid gland in humans. He called these structures parathyroid glands (PS), considering them to be underdeveloped thyroid tissue. Ten years later, in 1890, the French physiologist Eugène Gley (1857–1930), while studying the function of the parathyroid glands in dogs, found that the removal of the thyroid gland together with the parathyroid glands causes tetany in experimental animals. By this time, cases of convulsive syndrome in patients undergoing thyroidectomy had been described, and Gley's discovery shed light on the cause of this complication. In 1905, the Canadian-American researcher William George McCollum (1874–1944) found that post-thyroidectomy tetany is associated with the development of hypocalcemia due to parathyroid gland damage and proved that the latter is an independent endocrine organ that affects calcium metabolism.

In 1925, the Canadian biochemist James Bertram Collip (1892–1965) isolated parathyroid hormone (PTH), and almost 40 years later, in 1963, American scientists Solomon Berson (1918–1972) and Rosalyn Yalow (1921–2011) developed the radioimmune method of parathyroid hormone detection. After another 30 years, in 1993, a calcium receptor was discovered on the surface of parathyroid cells. Thanks to the above discoveries, by the end of the 20th century, the issues of parathyroid function regulation and the pathogenesis of various disorders were elucidated.

The history of primary hyperparathyroidism exploration also began in the last decade of the 19th century. In 1891, the German pathologist Friedrich Daniel von Recklinghausen (1833–1910) reported severe damage to the skeletal system, because of which the bones were easily cut with a knife during pathological examination and the skull was easily squeezed like a rubber ball. The disease was named after the researcher — Recklinghausen's disease of bone (osteitis fibrosis cystica), but its cause remained unknown for several decades. Fifteen years later, in 1906, the Austrian pathologist Jakob Erdheim (1874–1937) diagnosed a parathyroid tumor in a patient with Recklinghausen's disease, the development of which was explained by compensatory organ enlargement in response to bone damage. Based on these ideas, over the next twenty years, this disease was treated with a parathyroid gland extract or transplantation of this organ.

In 1915, Erdheim's compatriot, professor Friedrich Schlagenhaufer, first expressed the opposite opinion that the destruction of the skeleton is a consequence of a parathyroid tumor, the removal of which leads to healing. However, he did not find support. In 1924, at the congress of pathologists, the Russian pathologist Arseniy Rusakov (1885–1953) also proposed the extirpation of a parathyroid tumor for the treatment of osteitis fibrosis cystica, which was again rejected. In 1925, the Austrian surgeon Felix Mandl (1892–1957) removed a parathyroid tumor measuring 25×12×15 mm after unsuccessful treatment of severe Recklinghausen's bone disease using parathyroid transplantants. As a result, blood and urine calcium levels returned to the normal values, the patient's condition quickly improved and within a few days he could walk unassisted. From this moment, Recklinghausen's bone disease was given its current name "primary hyperparathyroidism", indicating the primary nature of the parathyroid gland lesion in relation to parathyroid osteodystrophy, and parathyroidectomy became the primary method of treatment.

During the first decades of the study of the disease, osteitis fibrosis cystica was considered the only specific sign of the disease. In 1934, the American endocrinologist Fuller Albright (1900–1969) first reported that 80% of patients have urinary system disorders: urolithiasis or nephrocalcinosis. In 1946, PHPT was associated with the development of peptic ulcers of the stomach and duodenum. In the 1950s, mental disorders in PHPT were reported, and later an increased risk of cardiovascular disorders (hypertension, left ventricular myocardial hypertrophy, left ventricular diastolic dysfunction, cardiac arrhythmias and conduction disorders), type 2 diabetes mellitus, and dyslipidemia was revealed, but their relationship with PHPT requires further study [3].

Until the second half of the 20th century PHPT was considered a rare disease. In the 1970s, in the United States of America and Western Europe, an automated biochemical analyzer allowed to identify the widespread prevalence of hypercalcemia due to PHPT, which is now regarded as one of the most urgent problems in medicine. According to the results of the study, about 80% of PHPT cases

were clinically apparent and approximately 20% were low-symptomatic. In Europe and USA, thanks to the study of PHPT and active early diagnosis of the disease, by 2004 the situation has changed dramatically: 80% of cases involved a mild course of the disease and 20% — overt forms. Over the past decade, the same ratio of overt and mild forms of PHPT has been achieved in China. In India and Latin America, the situation has not changed over the past 50 years: as before, 80% of cases are severe forms of the disease. The situation in Russia remains extremely unsatisfactory: 70% of diagnosed cases are overt forms and only 30% are mild.

As the experience in developed countries shows, the main approach to solving this problem is the detection of hypercalcemia using screening data. In addition, widespread awareness among physicians of various specialties of the basic physiology and pathophysiology of the parathyroid gland is necessary, the knowledge of which is the key to the timely diagnosis of PHPT [3–6].

Regulation of Parathyroid Function and Effects of Parathyroid Hormone

The main regulatory factor of the functional state of the parathyroid gland is the blood calcium level, the decrease of which stimulates specific calcium receptors on the surface of parathyroid cells, which almost immediately leads to the release of PTH. The hormone release is regulated by a negative feedback loop: with the achievement of normocalcemia, the effects of PTH are quickly eliminated, due to its short half-life (about 10 minutes). PTH maintains a concentration gradient of extracellular and intracellular calcium: the level of calcium is 1,000 times higher in the extracellular fluid.

The main target organs for PTH are the bones, which are the main calcium pool, as well as the kidneys that regulate its excretion, and the intestines, which facilitate calcium intake into the body.

In bone tissue, PTH stimulates the functional activity of osteoblasts involved in the formation of bone tissue, which is associated with the activation of osteoclasts, which provide bone lysis and calcium release. In the kidneys, PTH enhances calcium reabsorption and phosphate excretion in the distal tubules, the latter contributing to the development of hypophosphatemia and, as a result, mobilization of calcium from bones.

Enhanced intestinal absorption of calcium has a mediated mechanism: under the influence of PTH in the kidneys, 1α-hydroxylase is activated, which catalyzes the formation of calcitriol — the active form of vitamin D. Calcitriol stimulates the formation of a calcium-binding molecule, with the participation of which calcium is absorbed. In accordance with the negative feedback mechanism, vitamin D deficiency contributes to an increase in PTH synthesis with the development of hyperplasia of one or all parathyroid glands. The effect of PTH on bone demineralization and renal regulation of calcium appears immediately, whereas the intestinal effect appears after a longer period. Under the action of PTH, the level of extracellular calcium rises, which is normally 10,000 times higher than the intracellular calcium content [1, 2].

Causes of Primary Hyperparathyroidism

The majority of cases of PHPT (80–85%) are caused by solitary parathyroid adenoma, 10–15% — by multiple parathyroid hyperplasia, and 1% — by parathyroid cancer. Sporadic PHPT accounts for 90–95% of cases and about 5% is a hereditary variant characterized by multiple parathyroid damage and onset before the age of 40 years.

The cause of the disease is unknown. A triggering factor of parathyroid adenoma is irradiation of the head and neck: at a dose of 1200 rad and higher, the risk increases by more than 50%. It is also assumed that the prevalence of PHPT is associated with vitamin D deficiency.

Pathogenesis and Symptoms

The classic symptoms of PHPT are disorders of the main target organs of PTH — bone tissue, kidneys and gastrointestinal tract. Bone tissue disorders are the most common sign of hyperparathyroidism. Excessive secretion of parathyroid hormone, which enhances bone metabolism, leads to the predominant proliferation of osteoclasts. As a result, endosteal resorption with the expansion of the medullary canal and thinning of the cortical layer develops. Clinical signs of osteoporosis are bone pain and spontaneous fractures. With the progression of the disease, osteitis fibrosis cystica is observed, which includes the formation of cysts and proliferation of connective tissue. The proliferation of cellular

elements of bone tissue causes the formation of a giant-cell tumor of the bone or epulis, which often develop in the bones of the skull and upper extremities and are characterized by a recurrent course in the absence of treatment for hyperparathyroidism. The decrease in bone mineral density (BMD) of the spine is clinically manifested as pain, which is aggravated by physical exertion, prolonged upright position (standing, sitting), as well as reduced growth in the case of compression fractures. Because of demineralization, teeth become loose and fall out, and filling material does not hold well.

With PHPT, damage to the kidneys is observed in more than 60% of cases and can sometimes be the only sign of the disease. PTH activates calcium reabsorption, therefore the calcium content in the urine may be normal. However, with an increase in the severity of hypercalcemia, the level of calciuria also rises. Hypercalciuria causes damage to the epithelium of the renal tubules and the development of nephrolithiasis, the risk of which with PHPT increases up to 40 times, while stone formation is recurrent. As a result of damage to the renal tubules, their sensitivity to the antidiuretic hormone decreases, which leads to impaired water reabsorption with the development of polyuria and polydipsia. Hypercalcemia and hypercalciuria contribute to the deposition of calcium in the renal parenchyma, which causes the formation of nephrocalcinosis and renal failure, the risk of which with PHPT increases to 6.5 times.

Hypersecretion of the parathyroid hormone and hypercalcemia activate the production of hydrochloric acid and digestive enzymes in the gastrointestinal tract, which triggers damage to the mucous membrane of the digestive tract and damage to the pancreas. Gastric ulcer in 15–27% of cases may be the only sign of hyperparathyroidism. Erosions and ulcers of the stomach and duodenum are characterized by frequent exacerbations, severe pain, resistance to treatment, tendency to bleeding and perforation. Pancreatitis is also characterized by a recurrent course; it may be accompanied by the development of pancreatic calcinosis and pancreatolithiasis.

As the disease progresses and parathyroid hormone synthesis increases, the severity of disorders associated with intracellular calcium deficiency increases, which primarily affects muscle tissue. Fatigue and weakness are observed, especially in the proximal muscles, which experience the greatest functional load, which makes it difficult to sit down, get up, climb stairs, and comb hair. Muscle hypotonia and atrophy is the cause of the "waddling gait" and the development of flat feet. In severe cases, patients can be bedridden. A severe decrease in body weight up to cachexia is also characteristic of severe PHPT. PHPT is characterized by a long history with a gradual progression of clinical symptoms. With prolonged duration of the disease, the development of hypercalcemic crisis is possible, which is a result of a significant increase in the calcium level (more than 3.5 mmol/L) and is associated with a high risk of death. It manifests as multiple organ failure, which mainly includes gastrointestinal (anorexia, nausea, vomiting, abdominal pain, acute pancreatitis), renal (dehydration, oliguria, acute kidney injury, renal colic), cardiovascular (rhythm and conduction disturbances, shortening of the QT interval) and neurological (myalgia, severe weakness, confusion, stupor, coma) disorders. Infectious diseases, fractures, prolonged immobilization, pregnancy, and antacids are triggering factors of the crisis [7–10].

Classification

Symptomatic (overt) and asymptomatic PHPT are distinguished, which can be represented by hyper- and normocalcemic variants. Overt PHPT is characterized by the presence of "classical" signs, including bone tissue (osteoporosis, low-traumatic fractures and fibrocystic osteitis) and visceral disorders (nephrolithiasis, nephrocalcinosis, decreased concentration and filtration functions of the kidneys, ulcers of the upper gastrointestinal tract, and pancreatitis). Asymptomatic PHPT is characterized by the absence of typical clinical signs and in most cases has a long-term benign course. However, the question of whether asymptomatic PHPT is an independent form of the disease or its initial stage remains open [4].

The most common is the hypercalcemic variant of the disease. In hypercalcemic PHPT, normocalcemia can be transient or persistent, which is regarded as a normalcalcemic variant of the disease.

Diagnosis

Diagnosis is based on laboratory test results. The main biochemical marker of PHPT is hypercalcemia. The study of blood calcium levels is indicated in the detection of bone system pathology (osteoporosis, low-traumatic fractures, signs of osteitis fibrosa cystica), kidneys (nephrolithiasis, nephrocalcinosis),

gastrointestinal tract (recurrent gastric ulcer or duodenal ulcer, recurrent pancreatitis) as well as in the presence of symptoms of hypercalcemia (polyuria, polydipsia, nausea, vomiting, dehydration).

Blood calcium is presented in two forms: total (or associated with protein), and ionized, accounting for approximately half of total calcium. When the concentration of plasma proteins (blood albumin less than 40 g/L or more than 45 g/L) changes, the measurement of total blood calcium requires adjustment. For this purpose, the formula is used: total plasma calcium (mmol/L) = measured level of total plasma calcium (mmol/L) + 0.02 × (40 — measured plasma albumin level (g/L)) [3].

A combination of hypercalcemia and hypophosphatemia is characteristic of PHPT, which is associated with the multidirectional effect of PTH on these blood components. When hypercalcemia is first detected, retesting is recommended to confirm it. Retesting is also required in cases when the level of calcium is within the reference interval in a patient with clinical signs of PHPT. The second most common cause of hypercalcemia is cancer. However, elevated calcium levels are usually detected at the stage of the disease when the diagnosis of cancer is obvious.

If there is a suspicion of PHPT, blood PTH is studied, the results of which are elevated or high-normal, which reflects the loss of the regulatory role of hypercalcemia on the activity of the parathyroid gland in adenoma. In contrast to PHPT, in paraneoplastic syndromes, hypercalcemia is accompanied by a reduced or low-normal level of PTH.

With the presumptive diagnosis of PHPT, the functional state of the kidneys, one of the main target organs, is assessed. To determine the glomerular filtration rate (GFR) in outpatient practice, the CKD-EPI formula is recommended [4]. With PHPT, the involvement of bone tissue in the pathological process reflects an increased or high-normal level of total alkaline phosphatase, as well as more specific markers of bone metabolism: C-terminal telopeptide of type 1 collagen (resorption) and procollagen type 1 N-terminal propeptide (bone formation). The determination of vitamin D level is recommended for patients with PHPT, the most informative method of assessment of which is a blood test for 25(OH) vitamin D.

With satisfactory renal function (GFR > 60 mL/min/1.73 m^2), to verify the diagnosis of PHPT, it is recommended to determine the content of calcium and creatinine in daily urine, which, with GFR < 60 ml/min/1.73 m^2, is not informative. Calculation of the calcium/creatinine clearance ratio allows to exclude familial benign hypocalciuric hypercalcemia, the only * disease with laboratory changes similar to PHPT (elevated blood calcium level in combination with elevated or highly normal PTH levels). This is a rare genetic pathology with an autosomal dominant type of inheritance caused by a defect in calcium-sensitive receptors in the parathyroid gland and in the kidneys, which perceive the normal level of hypercalcemia as low. As a result, parathyroid cells secrete an excessive amount of PTH, and the kidneys intensely reabsorb calcium, which leads to a pronounced decrease in the calcium/creatinine clearance ratio below 0.01, whereas with PHPT this index ** is usually above 0.02. In addition, in contrast to PHPT, abnormal laboratory test results in familial benign hypocalciuric hypercalcemia are detected in patients from childhood, as well as in their relatives, and are less severe. The disease has a relatively favorable prognosis and does not require treatment [4].

The normocalcemic form of PHPT is diagnosed with a persistent increase in PTH (in at least two studies with an interval of 3–6 months) in combination with normal blood calcium levels, if secondary hyperparathyroidism is excluded and hypercalciuria is absent. The most common causes of secondary hyperparathyroidism include vitamin D deficiency (25-(OH)-D ≤ 30 ng/mL) and chronic kidney disease with GFR ≤ 60 mL/min/1.73 m^2. In addition, secondary hyperparathyroidism can be caused by drugs (bisphosphonates, denosumab, lithium preparations), and diseases of the gastrointestinal tract with malabsorption syndrome and hypercalciuria. For the differential diagnosis of the normocalcemic form of PHPT and secondary hyperparathyroidism, it is recommended to carry out functional tests using vitamin D and a thiazide diuretic.

Vitamin D supplementation in patients with secondary hyperparathyroidism leads to normalization or reduction of PTH at a normal level of blood calcium, while in PHPT hypercalcemia is observed, and the level of PTH remains elevated. Native vitamin D

* Tertiary hyperparathyroidism is also characterized by hypercalcemia and elevated levels of PTH, but it develops in patients with a long-term history of secondary hyperparathyroidism.

** The formula for calculating: Clearance Ca/Cr = Ca_u x Cr_s / Cr_u x Ca_s (Ca_u — urine calcium, Cr_s — serum creatinine, Cr_u – urine creatinine, Ca_s — serum calcium, mmol/L)

supplements (cholecalciferol 50,000 IU per week or 25,000 IU 2 times a week or 7,000 IU daily) are used for 8 weeks until the target level of 25(OH) vitamin D (more than 30 ng/mL) is achieved; or active vitamin D metabolites (calcitriol, alfacalcidol 1 μg per day) are used for 5 days, and with a trend towards a decrease in PTH level and normocalcemia — up to 1 month. Thiazide diuretic increases calcium reabsorption in the kidney, therefore, the use of hydrochlorothiazide (25 mg 2 times a day) for 2 weeks leads to normalization of PTH level in the case of secondary hyperparathyroidism, while in PHPT the level of PTH does not change, and the calcium content in the blood may increase [11].

Topical diagnosis is carried out with the aim of preoperative preparation for selective parathyroidectomy. The first step is ultrasound. According to ultrasound data, parathyroid adenoma can be mistakenly interpreted as a thyroid nodule, which depends on the doctor's experience and knowledge of the disease symptoms. In most cases, functional and topical scintigraphy with 99mTc-methoxyisobutylisonitrile allows to clarify the diagnosis. If this imaging technique is unavailable, computed tomography (CT) of the neck with contrast enhancement, magnetic resonance imaging of the neck and positron emission tomography are recommended, of which multislice CT is preferable [2, 11, 12].

Principles of Treatment

Parathyroidectomy of the affected parathyroid gland is the only radical treatment method with high efficiency. It is indicated for the overt form of PHPT, as well as in the following cases: 1) The patient is aged below 50 years; 2) the level of blood calcium exceeds the upper limit of the reference interval by more than 0.25 mmol/L (regardless of the symptoms); 3) there are signs of osteoporosis (history of low-trauma fracture and/or radiologically verified fractures of the vertebral bodies; BMD of the radial bone, proximal femur or lumbar spine according to X-ray densitometry: T-score is below –2.5 SD in postmenopausal women and men older than 50 years); 4) there are signs of functional and/or structural kidney disease (GFR below 60 mL/min/1.73 m^2, calcium excretion of more than 10 mmol/day, nephrolithiasis/nephrocalcinosis, including asymptomatic forms).

After surgery, most of the clinical symptoms of PHPT regress. In the absence of severe damage to the skeletal system and kidneys, the ability to work is restored.

Conservative treatment is aimed at the correction of hypercalcemia, the prevention of hypercalcemic crises and low-trauma fractures. It can be recommended for patients with asymptomatic PHPT in the absence of indications for surgical treatment, as well as in case of refusal of the patient or contraindications (severe concomitant diseases). The conservative approach involves the dynamic monitoring of the following parameters: calcium levels — 2–4 times a year, creatinine level (with GFR calculation), PTH and daily urinary calcium excretion — once every 6 months, renal ultrasound (CT if necessary) and BMD in three parts of the skeleton — once a year, as well as lateral radiographs of the spine in case of suspected fractures of the vertebral bodies (decreased growth, back pain) and esophagogastroduodenoscopy in the presence of specific complaints [2, 11].

All patients are recommended a diet with moderate amounts of calcium and fluid intake of at least 1.5–2 L per day. Antiresorptive drugs and/or calcimimetic agents are used to correct hypercalcemia and prevent bone loss. The study of the effectiveness of oral bisphosphonates (alendronic acid 10 mg/day for 1–2 years) showed an increase in BMD in the lumbar spine and proximal femur, which is comparable with the results of surgical treatment [11]. Denosumab showed a more pronounced hypocalcemic effect and a greater increase in BMD in the cortical bone compared with bisphosphonates [11]. The use of calcimimetic agents effectively reduces the level of blood calcium to normal values in 80% of cases, but at the same time does not affect the state of bone tissue. The initial dose is 30 mg per day, followed by titration every 2–4 weeks until the level of calcium reaches the upper limit of the normal range. The maximum dose is 90 mg 4 times a day. The results of the study of combination treatment for 1 year (alendronic acid and calcimimetic agent) showed a significant increase in BMD of the lumbar spine and proximal femur, as well as a decrease in blood calcium level [11].

If D-vitamin deficiency is found in patients with PHPT, it is corrected using native vitamin D. If the level of calcium is not higher than 3 mmol/L, replenishment of vitamin D deficiency at the preoperative stage is recommended (no more than 1,000–2,000 IU per day), and if the level of calcium is higher than 3 mmol/L, replenishment is carried out in the early postoperative period [1, 13–17].

Case Report

A female patient, 37 years old, born in 1979, mother of four children. From 2008, after the first birth, teeth began to loosen, and by 2014 they had completely fallen out. In 2014, after suffering psychoemotional stress, she began to lose weight, and by January 2015 she had lost 7 kg. At the same time, weakness and pain in the lumbar spine appeared, and the patient was treated by a physician with a diagnosis of "chronic vertebrogenic low back pain, severe, with frequent exacerbations."

In March 2015, the patient noted a lower jaw tumor, and was operated at the Republican Clinical Oncology Center (Ufa) with a diagnosis of giant-cell tumor of the lower jaw. After 7 months, in November 2015, giant-cell tumor of the upper jaw was diagnosed and a second operation was performed at the Oncology Center, after which the patient was referred for consultation with an endocrinologist. During the examination, the endocrinologist found a node in the lower pole of the left lobe of the thyroid, measuring 27 × 17 × 48 mm, and diagnosed nodular goiter of the II stage, euthyroidism. In February 2016, the formation in the lower jaw reappeared, and the patient was operated on for the third time for a giant-cell tumor at the Oncology Center. One month after the operation, in March 2016, pain appeared in the right forearm, and an ulnar fracture was detected via X-ray. The patient continued to lose weight, weakness increased. She was again referred for consultation to the Oncology Center. The oncologist recommended a blood test for the content of calcium, phosphate and PTH, which revealed hypercalcemia (ionized calcium — 1.8 mmol/L (1.1–1.35) (hereinafter, the reference interval is indicated in parentheses), low-normal phosphate level (0.84 mmol/L (0.81–1.45)) and elevated PTH (1411.6 pg/mL (12–88)). Based on the results, Recklinghausen's bone disease was diagnosed and treatment at the G. G Kuvatov Republican Clinical Hospital (G.G. Kuvatov RCH) (Ufa) was recommended. The patient was examined there only two months after the recommendation: in April 2016 there was pain and swelling of the right foot, X-ray showed fractures of the metatarsal bones, and a fracture of the right ulnar process occurred in early May. At the end of May 2016, the patient visited an endocrinologist at the G.G. Kuvatov RCH accompanied by a relative. The appearance of the emaciated patient caused suspicion of cancer. Laboratory tests revealed a significant increase in blood calcium levels (ionized calcium — 1.94 mmol/L (1.1–1.35), total calcium — 3.71 mmol/L (2.20–2.65)) in combination with a decrease in phosphate concentration (0.77 mmol/L (0.81–1.45)). The level of alkaline phosphatase was 12 times higher than normal (1545.5 U/L (30–120)), and PTH was almost 20 times higher than the upper limit of the reference interval (1420.1 pg/mL (12–88)). Ultrasound of the thyroid confirmed the presence of a node of the left lobe of the previous size (27.5 × 19 × 48 mm) of somewhat reduced echogenicity with a tendency to retrosternal growth. X-ray densitometry detected osteoporosis (BMD L1-L4 was –3 SD).

Based on the results of the examination, primary hyperparathyroidism was established and scintigraphy was planned. When the patient returned home to the district center, she had an injury of her left leg (fracture of the upper third of left thigh). Open reduction and osteosynthesis were performed at the Central Regional Hospital of Belebey. The traumatologist suspected the oncological genesis of the fracture, but the results of the histological examination excluded malignancy. A week after surgery, the patient was transported to the Department of Endocrinology of the G.G. Kuvatov RCH to clarify the diagnosis and determine further management approach.

Upon admission, the patient complained of severe weakness and thirst. At the time of examination, the patient's weight was 37 kg with a height of 165 cm (BMI was 13.6 kg/m^2)). The deformation of the operated leg in a cast was noted, and therefore X-ray examination was performed (a repeated fracture of the left femur was detected, this time in the middle third). In the hospital, scintigraphy was performed, which revealed an extensive area of hyperfixation of the radiopharmaceutical at the level of the middle-lower parts of the left lobe of the thyroid, measuring 35×23 mm, indicating a large parathyroid adenoma. The diagnosis was: primary hyperparathyroidism, parathyroid adenoma. Complications: epulis of the upper and lower jaw (surgery performed in March and November 2015, in February 2016), severe hyperparathyroid osteoporosis (fracture of the right ulnar bone (March 2016), fractures of the metatarsal bones of the right foot (April 2016), fracture of the right ulnar process (May 2016), fracture of the left femur in the upper and middle third (June 2016)), hyperparathyroid myopathy, cachexia.

Initially, the patient was operated on in the Department of Traumatology, and then transferred to the

Department of Vascular Surgery, where, in July 2016, adenoma of the left lower parathyroid gland was removed. Histological examination verified parathyroid adenoma.

Six months after the surgery, the patient noted a significant improvement: no complaints of weakness, 13 kg weight gain (the previous body weight was restored). At the recommendation of the traumatologist, the patient observes low-load movement regimen; for the first six months after the surgery she used a wheelchair, and now uses a cane when walking. The results of the control laboratory test correspond to the normal values (ionized calcium — 1.12 mmol/L (1.1–1.35), total calcium — 2.23 mmol/L (2.2–2.65), PTH — 35.2 pg/mL (12–88), 25-(OH)-D — 35.94 ng/mL (30–100)).

In the described clinical case, the first sign of PHPT in a young woman was tooth problems. In the next 8 years, the progression of the disease caused a predominant lesion of the skeletal system with the development of epulis and severe osteoporosis with multiple fractures, as well as severe myopathy and cachexia. The patient was examined by a number of specialists — general practitioner, dentist, traumatologist, oncologist, and endocrinologist. Nevertheless, the disease was diagnosed at the stage of severe complications. Focal thyroid formation, which was detected in 2015 based on ultrasound results, was interpreted as a thyroid node. This, in particular, was due to the insufficient analysis of the clinical picture. The presented observation indicates the urgent need for attention to PHPT in educational programs, as well as the need to adopt state programs to address the problem of PHPT in Russia. Biochemical screening of the adult population will allow to determine the prevalence of PHPT, to diagnose it at an early stage, to identify the main risk factors for this disease and to develop preventive measures.

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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

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Abstract

Monoclonal gammopathy of renal significance (MGRS) is a new nosology group in modern-day nephrology and oncohematology. MGRS is defined as kidney injury due to nephrotoxic monoclonal immunoglobulin produced by the B cell line clone that does not reach the hematological criteria for initiating cancer treatment according to oncological and hematological indications. The action of the monoclonal protein on kidney parenchyma results in the irreversible decline of kidney function to the point of loss of organ function which, in line with the position of International Consensus of hematologists and nephrologists, determinates the necessity for clone specific treatment in patients with MGRS despite the absence of hematological indications for treatment initiation. The main challenge of MGRS in the Russian Federation is the inaccessibility of timely diagnostic and appropriate treatment for the majority of patients due to the following reasons: 1) limited knowledge about MGRS among hematologists and nephrologists; 2) lack of necessary diagnostic resources in most health-care facilities; 3) lack of approved clinical recommendations and medical economic standards for the treatment of this disease. The consensus document comprises the opinion of Russian experts on nosological classification, diagnosis and approaches to the treatment of MGRS and is based on the results of a joint meeting of leading hematologists and nephrologists of the country. The meeting was held on 15–16 of March 2019 in during the "Plasma cell dyscrasias and lymphoproliferative diseases: modern approaches to therapy" conference at I. P. Pavlov First Saint Petersburg State Medical University. The present Consensus is intended to define the principal practical steps to resolve the problem of MGRS in the Russian Federation that are summarized as final clauses.

Key words: *monoclonal gammopathy of renal significance, monoclonal gammopathy of undetermined significance, onconephrology, kidney injury, clone specific treatment, paraprotein, kidney biopsy, plasma cell dyscrasias, light chains*

Conflict of interests

The authors declare no conflict of interests

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Introduction

The concept of monoclonal gammopathy renal significance (MGRS), proposed by the International Kidney and Monoclonal Gammopathy Research group [1, 2], implies a **pathological condition due to proliferation of a B cell clone or plasma cell that does not reach criteria necessary to start treatment according to oncohematological indications, but produce nephrotoxic monoclonal immunoglobulin (IG), which leads to specific kidney injury with irreversible decline of kidney function and deterioration of the prognosis for the disease.** The progression of renal dysfunction, right up to loss of organ function, according to the opinion adopted by international experts, is **determinative in deciding whether to prescribe treatment targeted at eliminating the pathological clone, despite the absence of criteria for oncohematological indications.** In recent years, a number of publications on MGRS have been released by nephrologists in Russia [3–6]. At the same time, such clinical cases of an obvious connection between an aberrant clone (sometimes minor) and kidney injury remain poorly recognized by both physicians and public health authorities. Due to the lack of knowledge among hematologists and nephrologists of MGRS, the lack of approved recommendations and medical and economic standards of treatment, a number of organizational problems arise, including the lack of an effective, timely diagnosis and treatment for most patients. The use of effective therapy is limited by outdated approaches and standards of care, **based mainly on hematological criteria for**

beginning treatment. Current recommendations on the treatment of lymphatic tumors associated with the secretion of monoclonal paraprotein suggest specific therapy if clinical indications exist. This practice is currently under review, especially in patients with multiple myeloma (MM). Monoclonal lymphocytosis and monoclonal gammopathy of undetermined significance (MGUS) in modern definitions are not regarded as diseases, but as conditions of predisposition to lymphatic tumors with a different risk of transformation and therefore are not subject to therapy. This approach is not true with respect to MGRS, in which a "small" clone is dangerous and life-threatening [7–11], and timely therapy leads to a significant improvement in prognosis [12–15]. This consensus of the country's leading hematologists and nephrologists is intended to outline ways of practically solving the problems of MGRS diagnosis and treatment in the Russian Federation that are critical for this category of patients.

The Concept of Monoclonal Gammopathy of Renal Significance

Monoclonal gammopathy (MG) is the presence of an aberrant clone of the B cell line of differentiation which produces the IG molecule or its fragments. A modern view of the nosologies due to MG, and the role of MGRS in the classification are presented in Fig. 1. A clone is a cell population derived from a single progenitor cell and inherits all its properties, including the ability to produce a monoclonal paraprotein. The produced monoclonal protein, called paraprotein or M-protein, can have pathological properties that are realized in various ways, including deposition in organs and tissues, leading to their damage. Clonal cells can produce a full-sized IG molecule or its fragment (only light chain (LC) or only heavy chain). Cases with the production of two LC isotypes, two or more full-sized immunoglobulins

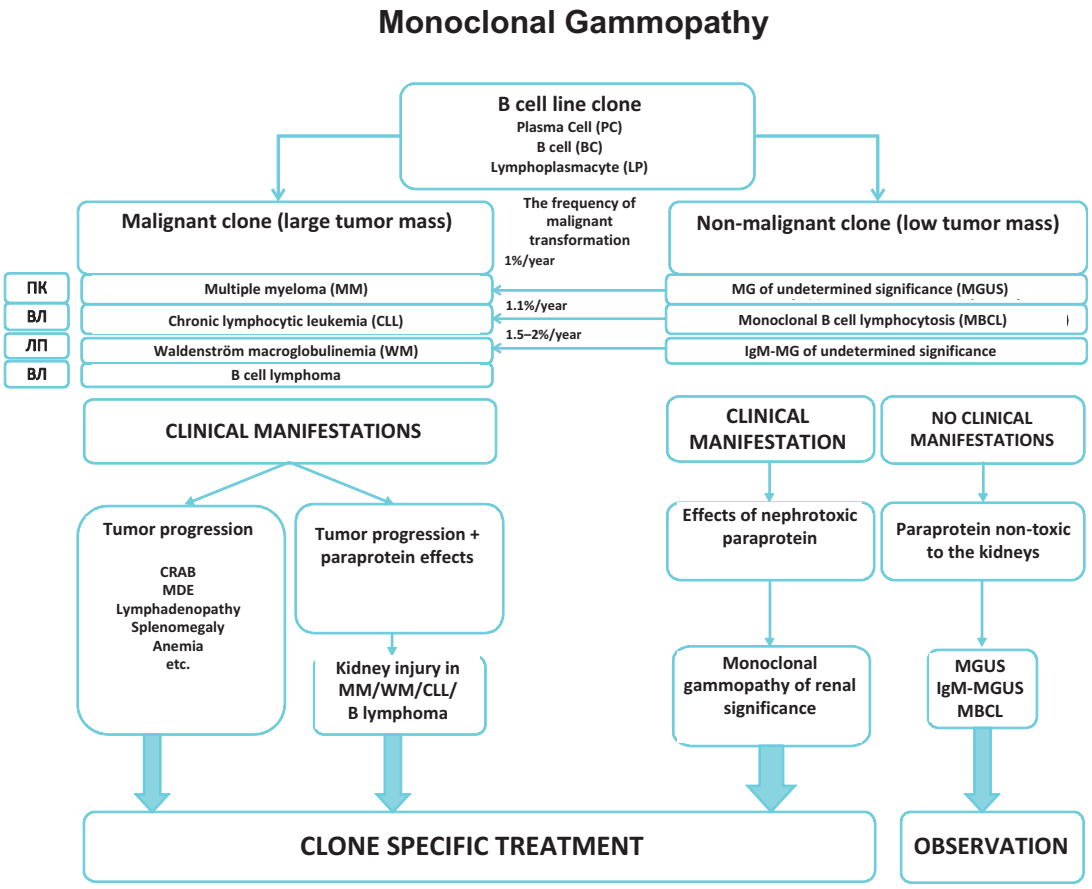

Figure 1. *Clinical variants of monoclonal gammopathies*

CRAB — criteria for organ damage due to plasma cell proliferation in multiple myeloma (hypercalcemia, renal insufficiency, anemia, bone lesions); MDE — myeloma defined events; BC — B cell; LP — lymphoplasmacyte; WM — Waldenström macroglobulinemia; MBCL — monoclonal B cell lymphocytosis; MG — monoclonal gammopathy; MGUS — monoclonal gammopathy of uncertain significance; MM — multiple myeloma, PC — plasma cell, CLL — chronic lymphocytic leukemia

are possible. Depending on the stage of differentiation, B cell clonal proliferation can be divided into: 1) lymphocytic; 2) lymphoplasmacytic; 3) plasma cell. The MG classification based on the type of clonal line, as well as the criteria for each of the states are given in Table 1 [16–20]. Clinical manifestations of MG are associated with: a) an increase in tumor mass; b) the abnormal effects of IG. Most cases of MG occur subclinically, which reflects the early stages of the disease and is included in the concept of MGUS (or monoclonal B cell lymphocytosis in the case of lymphocytic proliferation). In most cases of MGUS, the produced paraprotein does not have nephrotoxicity (i.e., the ability to have any damaging effect on the organ). This condition has a favorable course with a frequency of progression to a malignant form of about 1% per year [21–23]. To assess the low, intermediate, and high risk of MGUS transformation, scales based on an assessment of the ratio of free LCs and the amount of M-protein are used, and treatment is started only when clinical symptoms of the tumor appear (see Table 1).

Table 1. *Classification and Criteria of Monoclonal Gammopathies (According to Leung N. et al. [2] as amended)*

Clone Type	Disease	Clone volume in BM / peripheral blood	M-gradient in peripheral blood	Visceral end organ damage, (criteria for starting treatment)
Plasma cell clone	MGUS	<10 %	<30 g/l	No
	Smoldering (indolent) myeloma	10–60%	≥30 g/l	No
	Multiple myeloma (symptomatic)	≥10% or plasmacytoma	≥30 g/l	Yes *
Clone of lymphoplasmacytic cell line	IgM-MGUS	<10%	<30 g/l	No
	Smoldering Waldenström macroglobulinemia	>10%	≥30 g/l	No
	Waldenström macroglobulinemia (symptomatic)	>10%	≥30 g/l	Yes **
B lymphocyte Clone	Monoclonal B cell lymphocytosis	Monoclonal B cells in peripheral blood $<5 \times 10^9$/l	any	No lymphadenopathy
	Chronic lymphocytic leukemia	Monoclonal B cells in peripheral blood $>5 \times 10^9$ / l	any	Yes ***
	Other forms of B cell LPD	+/–	any	

Note: MGUS — monoclonal gammopathy of uncertain significance; BM — bone marrow; LPD — lymphoproliferative disorder.
* CRAB [15]
C — hypercalcemia R — renal insufficiency; an outdated term in the nephrological literature. In this case, this refers to cylinder nephropathy, which manifests as acute kidney injury (AKI). Previously, the criterion implied serum creatinine >0.177 mmol/l, and creatinine clearance <40 ml/min has now been added [18]. The fact of AKI is not indicated as an essential condition. Before using this criterion as a guide, it is necessary to make sure that the patient does not have kidney injury of any other etiology (diabetic nephropathy, nephroangiosclerosis due to arterial hypertension, etc.). Otherwise, prescribing toxic treatment to such patients may be accompanied by severe adverse reactions.
A — anemia. B — bone lesions
* Myeloma defined events (MDE) [16]
- >60% of plasma cells in the bone marrow
- ratio of involved/uninvolved free LC serum > 100
- >1 focal bone marrow involvement by magnetic resonance imaging with a diameter of more than 5 mm

** Indications for starting treatment of Waldenström macroglobulinemia [17, 27]
- Symptoms associated with tumor growth: lymphadenopathy, splenomegaly, hepatomegaly, organomegaly, anemia, thrombocytopenia, B symptoms
- Symptoms associated with IgM overproduction: cryoglobulinemia, immune hemolytic anemia and/or thrombocytopenia, nephropathy, neuropathy, amyloidosis, hyperviscosity syndrome (increased blood viscosity due to the extremely high plasma protein content due to paraprotein with the development of the following symptoms: mucosal bleeding, neurological deficit, visual impairment), IgM level > 50 g/l

*** Symptomatic lymphadenopathy / cytopenia / splenomegaly / organomegaly / B symptoms

An example is the scale for assessing the risk of progression of MGUS in MM developed at the Mayo Clinic [24]. An increase in tumor mass leads to organ damage in the form of "CRAB" symptoms (C — hypercalcemia; R — renal insufficiency; A — anemia; B — bone lesions) in MM; lymphadenopathy, hepatosplenomegaly, signs of neoplastic suppression of hematogenesis, etc. in chronic lymphocytic leukemia (CLL) and Waldenström macroglobulinemia. The appearance of these symptoms is an indication for treatment. Another part of the clinical spectrum is due to the effects of paraprotein and its damaging effect on tissues and organs, including the kidneys. Symptoms due to paraprotein can occur even with a low tumor mass and a small concentration of paraprotein in circulation. The concept of a "small but dangerous clone" in MG, first proposed by G. Merlini and M.J. Stone in 2006 [25], suggests a clinically dominant organ lesion and poor prognosis due to the pathological effects of paraprotein, but not tumor progression *per se*. To describe such cases, the term MG of clinical significance was recently proposed [26].

MGRS is a term that differentiates the well-known concept of MGUS, removing a number of clinical cases from the confines of "uncertainty". MGRS is also characterized by a clone that is lower than the level corresponding to the criteria for diagnosis of MM or lymphoproliferative disease requiring treatment. According to the Research Institute of Nephrology, the average value of bone marrow plasmatization in case of MGRS was 2.2%, and the level of paraprotein in serum was 1.1 g/l [4]. At the same time, in contrast to cases of MGUS, the produced M-protein in MGRS has nephrotoxicity and leads to clinically significant damage to the kidneys and other organs. Nephrotoxic monoclonal IG can be produced both with low and large tumor mass. If there are grounds for a criteria-based diagnosis of malignant proliferation of a clone of the B cell line of differentiation and kidney injury, this suggests that the produced paraprotein is nephrotoxic. Such cases are not associated with MGRS; a hematological tumor ranks first when articulating the diagnosis, and kidney injury is considered a complication. In the case of nephrotoxicity of monoclonal paraprotein and a "small" clone, the diagnosis should be defined as "MGRS" with a description of the nature of kidney injury, for which the morphological study of renal tissue is crucial. According to the consensus of the International Kidney and Monoclonal Gammopathy Research Group of 2019 [2], the concept of MGRS was expanded compared to the consensus of 2012 [1]. The B cell/plasma cell proliferations, such as "smoldering MM, smoldering Waldenström macroglobulinemia, monoclonal B cell lymphocytosis, as well as CLL and low grade malignant lymphomas (marginal zone lymphoma, mantle cell lymphoma, MALT lymphoma)" were additionally included in the MGRS group as conditions in which the clone produces nephrotoxic IG, but which does not require therapy for hematologic indications.

Epidemiology

Renal damage due to paraprotein is a rare abnormality in the structure of kidney diseases. According to the Research Institute of Nephrology, the prevalence of renal disorders associated with any variant of MG is 7.5% among all patients who underwent diagnostic kidney biopsy. At the same time, MGRS was detected in 4% patients [4]. These figures match the data presented in global literature [11, 28]. According to the Ministry of Health of the Russian Federation, the incidence of "Glomerular, tubulointerstitial kidney diseases, other kidney and ureter diseases" in 2017 amounted to 255 cases per 100,000 adults. Taking into account that a significant part of these cases includes diseases for the diagnosis of which a morphological study of kidney bioptate is not needed (infectious tubulointerstitial nephritis, reflux nephropathy, etc.) and the frequency of MGRS which is 4%, based on morphological verification of the diagnosis, it can be concluded that the incidence of MGRS is generally close to the criteria for orphan disease (10.2 cases per 100,000 adults/year).

Prognosis

MGRS **cannot be considered a benign condition**, because a clone steadily leads to the progression of renal dysfunction due to the effects of paraprotein and, ultimately, to organ death (terminal stage of chronic kidney disease, CKD). The medical and economic importance of CKD is determined by a pronounced increase in the risks of non-fatal and fatal events, disability of patients,

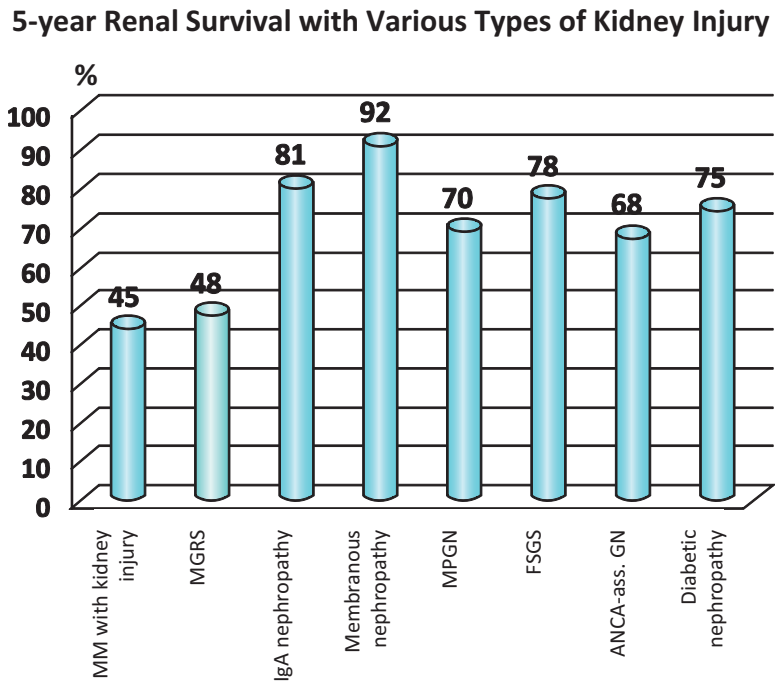

Figure 2. *Renal prognosis for multiple myeloma with kidney injury, monoclonal gammopathy of renal significance, and other nephropathies (according to the Research Institute of Nephrology)*

ANCA-ass. GN – glomerulonephritis associated with anti-neutrophil cytoplasm antibodies; MM – multiple myeloma; MGRS – monoclonal gammopathy of renal significance; MPGN – membrane proliferative glomerulonephritis; FSGS – focal segmental glomerulosclerosis

as well as significant costs of dialysis [29–33]. The renal prognosis for MGRS is comparable to that for MM with kidney injury and significantly worse than for other nephropathies (Fig. 2). In addition, in the presence of MGRS, the risk of malignant clone progression is higher, which means that the prognosis for life expectancy is worse. So, the risk of a clone transforming into a malignant form in MGRS is 3.3 times higher and during the first year is 10% [11], which is comparable with the rate of progression of smoldering MM into symptomatic [34].

The Rationale for Establishment of Nosology of Monoclonal Gammopathy of Renal Significance

The unfavorable prognostic value of MGRS makes obvious the need for treatment of such a "non-life-threatening", from the formal point of view of classical oncohematology, clonal process [2]. A similar "precedent" well known in oncohematology is a systemic AL amyloidosis, a serious disease with a minimal clone of plasmocytes in the bone marrow, which has extremely unfavorable prognosis in the absence of treatment and has long been the subject of irreconcilable differences between hematologists and nephrologists. Effective chemotherapy regimens for AL amyloidosis, designed to eliminate the tumor clone, have been developed and used for a long time, including in Russia [35–38]. The same treatment strategy should be used for non-amyloid forms of kidney injury associated with MG [12, 39–43]. The stereotype of treating only a malignant clone in international practice was overcome in stages with the accumulation of data on the pathophysiology of MG, which is reflected in a number of works in the first decade of the 21st century [7, 25, 44–46]. The most significant milestone was the famous work of N. Leung et al., published in 2012 in the Blood Journal on behalf of the International Kidney and Monoclonal Gammopathy Research Group [1]. The title of this article, "Monoclonal Gammopathy of Renal Significance: When MGUS Is No Longer Undetermined or Insignificant", reveals significant changes in the understanding by the world's leading hematologists and nephrologists of the problem of kidney injury in MG and the awareness of the need for treatment of this condition. Subsequently, numerous articles were published on this subject [47–50], the interest in which, primarily from nephrologists, is due to the possibility of effective etiotropic treatment, minimization/elimination of the effects of nephrotoxic M-protein, and as a result, an improvement in the general and renal prognosis. The recognition by foreign medical communities, including the International Myeloma Working Group [18], of the relationship between clone and kidney injury (monoclonal renal gammopathy) has opened up

the possibility of prescribing highly effective chemotherapy to such patients. The therapeutic effect aimed at suppressing the clone was effective both in terms of renal outcomes and overall survival [7, 9, 12-14].

Mechanisms and Structure of Kidney Injury in MG

The mechanisms of paraprotein action on the renal tissue and body structures are extremely diverse and have not yet been fully elucidated [26, 51]. Due to structural features, physical and chemical properties of the paraprotein molecule itself, as well as the action of local factors, abnormal IG and/or LC can: 1) have a toxic effect on cells; 2) act like antibodies in relation to various molecules; 3) activate the immune system, in particular the complement system; 4) interact with mesangiocytes and other nephron cells and accumulate in the form of deposits of various structures, for example in the form of amyloid fibrils. In MGRS, the pathological effect of monoclonal IG can be realized at the level of any nephron compartment: glomerulus, tubules, interstitium, blood vessels [52]. From here arises the variety of clinical manifestations of MGRS, which may appear as any renal parenchyma lesion syndrome or a combination thereof (Fig. 3). Due to the fact that the PC or B cell clone is "small" and, as a rule, does not cause obvious symptoms associated with the tumor, **patients with MGRS, who have mainly renal manifestations, are primarily nephrologist patients**, complaining of "renal" symptoms (arterial hypertension, edema, hematuria, proteinuria, renal dysfunction, etc.). Fig. 4 shows nephropathy variants associated with MG, according to the Department of Nephrology at the State Budgetary Healthcare Institution "S.P. Botkin City Clinical Hospital" of the Moscow Health Department and the clinic of the Research

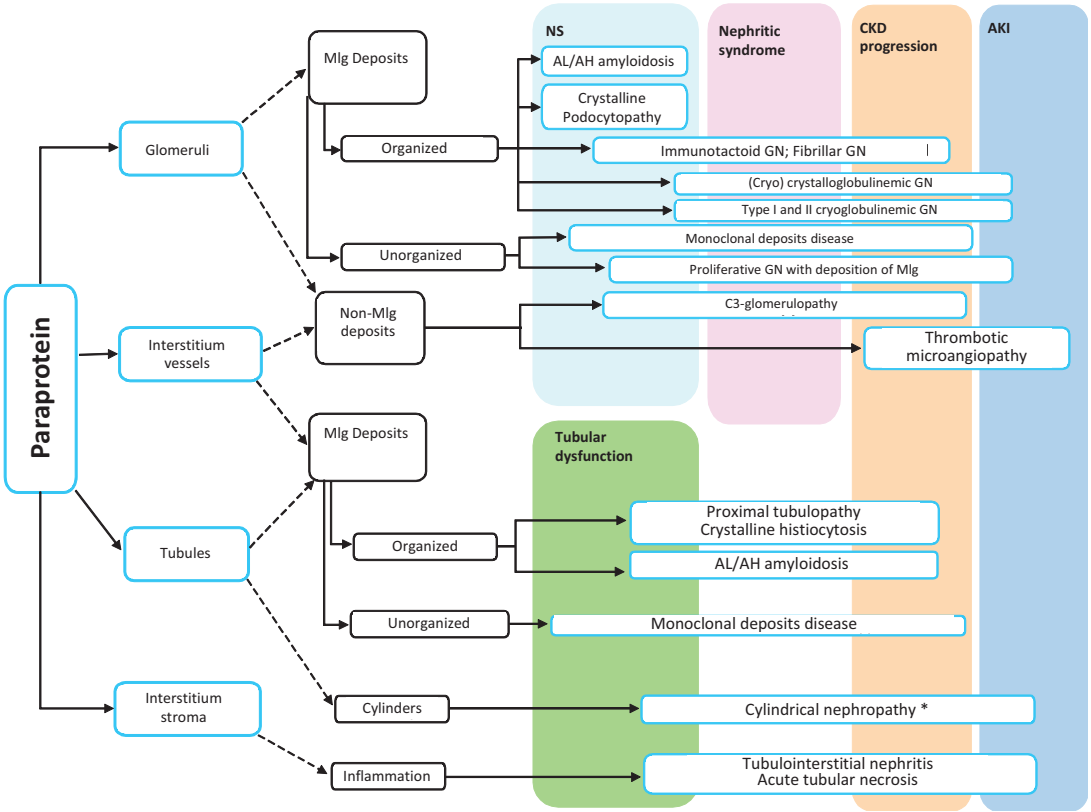

Figure 3. *Pathomorphological variants of kidney injury due to paraprotein and their clinical manifestation*
The variants of kidney injury, the relationship with monoclonal gammopathy of which does not yet have sufficient evidence, include: glomerulonephritis associated with anti-glomerular basement membrane antibodies; membranous nephropathy, including one associated with anti-phospholipase A2 receptor antibodies; IgA nephropathy in Sch nlein—Genoch disease associated with monoclonal IgA [2].
***** Cylindrical nephropathy mainly occurs when there is excessive production of light chains in multiple myeloma and is not associated with MGRS.
MIg — monoclonal immunoglobulin; GN — glomerulonephritis; NS — nephrotic syndrome; AKI — acute kidney injury; CKD — chronic kidney disease.

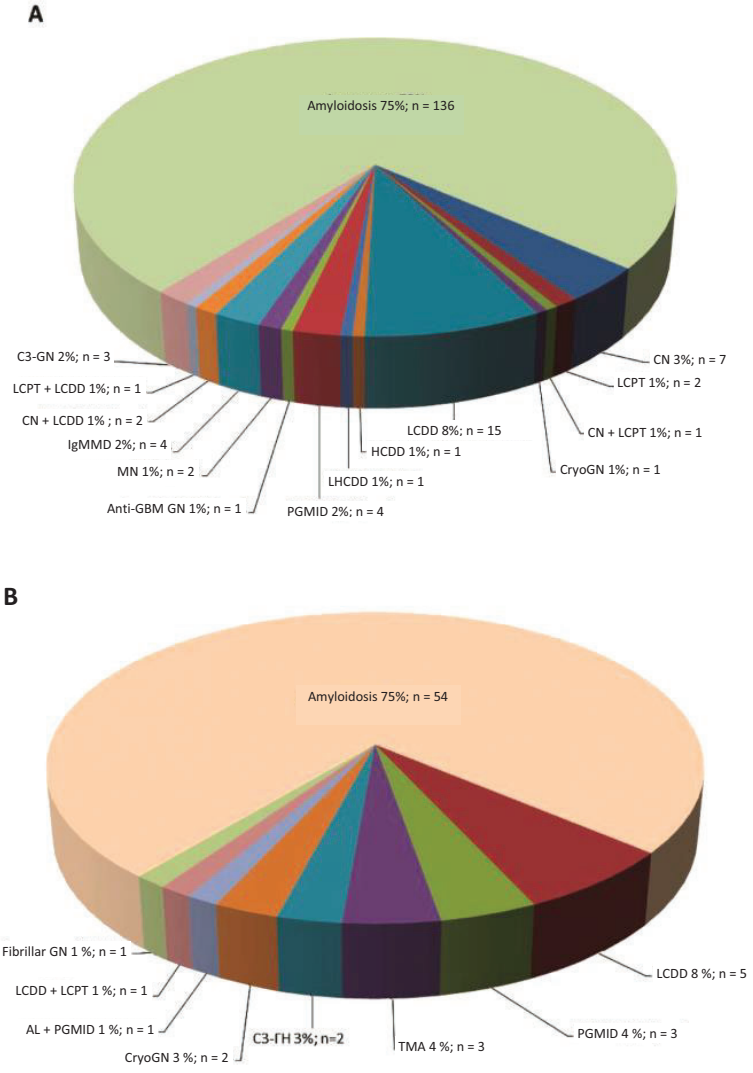

Figure 4. *The spectrum of nephropathies associated with monoclonal immunoglobulins*

A — according to the Department of Nephrology at the State Budgetary Healthcare Institution S. P. Botkin City Clinical Hospital of the Moscow Health Department, 181 patients; B — according to the clinic of the Research Institute of Nephrology at the I. P. Pavlov First Saint Petersburg State Medical University, 72 patients. AL — AL amyloidosis; C3-GN — C3-glomerulonephritis; Anti-GBM GN — glomerulonephritis caused by anti-glomerular basement membrane antibodies; LHCDD — light and heavy chain deposition disease; LCDD — light chain deposition disease; HCDD — heavy chain deposition disease; CryoGN — cryoglobulinemic glomerulonephritis; IgMMD — glomerulonephritis caused by monoclonal IgM deposits; MN — membranous nephropathy; PGMID — proliferative glomerulonephritis with monoclonal immunoglobulins deposition; LCPT — light chain proximal tubulopathy; TMA — thrombotic microangiopathy associated with monoclonal gammopathy; CN — cylinder nephropathy.

Institute of Nephrology at the I. P. Pavlov First Saint Petersburg State Medical University.

Depending on the profile and academic and research orientation of the hospital, the structure of renal lesions associated with monoclonal gammopathy may vary while the tendency towards the dominance of AL amyloidosis remains. According to the multidisciplinary therapeutic hospital at the I. M. Sechenov First Moscow State Medical University, E. M. Tareev Clinic of Nephrology and Internal and Occupational Diseases, 276 patients with monoclonal gammopathy were diagnosed, 51% of whom had AL amyloidosis [3]. Among non-amyloid nephropathies (n = 63, 23%) at an equivalent frequency of morphologically confirmed chronic glomerulonephritis in comparison with a sample from the S. P. Botkin City Clinical Hospital (membrane proliferative — 4%, focal segmental glomerulosclerosis — 1%, membranous — 1%, minimal mesangial changes — 1%), cryglobulinemic glomerulonephritis (6%) is a more significant part, mainly in case of HCV-associated type II cryoglobulinemia, the smaller part is monoclonal immunoglobulin deposition diseases (1%) and cylinder nephropathy (1%).

MGRS and the Structure of the ICD

The recognition by the international community of MGRS as a separate nosology is also reflected in the International Classification of Diseases (ICD). The ICD-11 project, which is available on the official website [53] and scheduled for approval in 2019, includes two of the most common variants for kidney injury in MG: AL amyloidosis and monoclonal immunoglobulin deposition disease (Randall type monoclonal immunoglobulin deposition disease, MIDD). In the new version of the ICD, MIDD is a subsection of the chapter titled "Plasma Cell Neoplastic Diseases" (2A83.0).

Table 2. *The List of Nosologies to Include in the MGRS Group*

AL amyloidosis
AH amyloidosis
Immunoglobulin light chain deposition disease
Immunoglobulin heavy chain deposition disease
Immunoglobulin heavy and light chain deposition disease
Proliferative glomerulonephritis with monoclonal immunoglobulin deposition
Immunotactoid glomerulonephritis
Monoclonal fibrillary glomerulonephritis
Crystalline podocytopathy associated with monoclonal gammopathy
C3-glomerulopathy associated with monoclonal gammopathy
Thrombotic microangiopathy associated with monoclonal gammopathy
Cryoglobulinemic glomerulonephritis as part of type I or II cryoglobulinemia
Light chain proximal tubulopathy
Crystalline histiocytosis
Tubulointerstitial nephritis associated with monoclonal gammopathy
(Cryo)crystal-globulinemic glomerulonephritis
Other forms of glomerulopathy that have been proven to be associated with monoclonal gammopathy, including anti-GBM nephritis associated with monoclonal gammopathy and membranous nephropathy associated with monoclonal gammopathy

Note. MGRS — monoclonal gammopathy of renal significance; anti-GBM nephritis — glomerulonephritis caused by anti-glomerular basement membrane antibodies.

Table 3. *Coding for Kidney Injury Associated with Monoclonal Gammopathy According to ICD-10*

Clone Type	Nomenclature depending on the degree of the clone proliferation and the code of hematological nosology	MGRS type and the code of nephrological nosology
Plasma cell clone	MGUS D47.2 Monoclonal gammopathy of uncertain significance D89.1 Cryoglobulinemia Smoldering (indolent) myeloma C90 Multiple myeloma and plasma cell malignancies AL/AH amyloidosis E85.8 Other forms of amyloidosis	Non-amyloid kidney disease N00-08 Glomerular disorders, including N08.1 Glomerular disorders in neoplastic diseases (MM, WM) N08 * Glomerular disorders in diseases classified elsewhere
Clone of the plasmacyte line	IgM-MGUS D47.2 Monoclonal gammopathy of uncertain significance D89.1 Cryoglobulinemia D89.8 Other specified disorders involving the immune mechanism, not classified elsewhere Smoldering Waldenström macroglobulinemia C88.0 Waldenström macroglobulinemia Monoclonal B cell lymphocytosis D 72.8 Other specified disorders of white blood cells	N10-16 Renal tubulo-interstitial diseases, including N16* Renal tubulo-interstitial disorders in diseases classified elsewhere N16.1 Renal tubulo-interstitial disorders in neoplastic diseases (leukemia, lymphoma, MM) N17-19 Renal failure
B lymphocyte Clone	Chronic lymphocytic leukemia B cell non-Hodgkin lymphoma C91.1 Chronic lymphocytic leukemia C82 Follicular non-Hodgkin lymphoma C83 Diffuse non-Hodgkin lymphoma D89.1 Cryoglobulinemia	Amyloidosis the above codes may apply as well N08.4 Glomerular disorders in amyloidosis

Note: MGUS — monoclonal gammopathy of uncertain significance; MGRS — monoclonal gammopathy of renal significance; WM — Waldenström macroglobulinemia; ICD — International Classification of Diseases; MM — multiple myeloma.

The above is the basis for the recognition of MGRS as a separate group of nosologies in the structure of monoclonal gammopathies, as well as at the level of management by Russian public health authorities. Nosologies that are part of the MGRS group are presented in Table 2.

Hematologists and nephrologists, the authors of this consensus, for the period before the Russian translation of the ICD-11 text in the Russian Federation, came to the conclusion that it was necessary to use the ICD-10 codes to characterize different versions of the MGRS (Table 3). In case of kidney injury associated with MG, the hematological nosology code should be combined with the nephrological nosology code.

A Multidisciplinary Approach to the Diagnosis and Treatment of MGRS

MGRS is a problem at the intersection of two specialties — hematology and nephrology, which **requires a multidisciplinary approach**.

As part of the implementation of the latter, the task of the hematologist is to verify clonality, and at the final stage, decide on the nature of clone specific therapy, i.e., therapy aimed at controlling clone proliferation, including methods of high-dose chemotherapy and hematopoietic stem cell transplantation. The need for the involvement of a nephrologist is due to the fact that in MGRS, a nephrotoxic M-protein is produced, which leads to a wide variety of types of kidney injury and renal dysfunction. The clinical and morphological pattern of MGRS is difficult to differentiate from numerous other abnormalities that are not associated with MG without the use of complex phased research methods and their interpretation.

Diagnosis of MGRS

To establish the diagnosis of MGRS, it is necessary: 1) to determine the presence of a clone of the B cell line of differentiation and 2) establish the specificity of kidney injury due to exposure to a monoclonal protein produced by the clone. In this regard, diagnosis includes hematological and nephrological research methods [2, 52]. Taking into account the significant variety of variants of kidney injury in MGRS, it is obvious that the morphological study of renal tissue is a key step in the diagnosis of this condition [54]. The result of histological examination and clinical and morphological analysis reveal the features of MGRS in each particular case, and also provide information, which is extremely important for the nephrologist with respect to the renal prognosis.

Morphological Diagnosis of MGRS

In order to fully diagnose MGRS, a morphological study of renal tissue should include:

1) **Optical microscopy** with the following staining: hematoxylin/eosin, PAS, Jones staining, Congo red staining, Masson's trichrome stain, stain for elastic fibers;

2) **Immunomorphological examination:** immunofluorescence (IF) or immunohistochemistry (IHC) to detect deposits of monoclonal IG molecules in the renal parenchyma [panel of anti-IgA, IgM, IgG (IgG typing), IgD, kappa, lambda, C3, C1q antibodies]. In some cases, immunomorphological methods should be supplemented with enzymatic demasking of antigen epitopes of monoclonal IG, which allows more efficient diagnosis of MGRS, when routine IHC/IF examinations do not yield results [55–57]. For the differential diagnosis of fibrillary glomerulonephritis, where deposits may be congophilic, an IHC test for DNAJB9, a protein of the chaperone family, is extremely specific for this type of glomerulonephritis [58, 59].

3) **Ultrastructural examination** allows to assess the severity of injury of the kidney structures at the submicroscopic level and the nature of the deposits formed by the monoclonal protein (organized, unorganized). The latter is the key in the differential diagnosis of such forms of MGRS as immunotactoid, fibrillary, cryoglobulinemic glomerulonephritis, etc. Sometimes, in order to detect a monoclonal protein, the examination can be supplemented by ultrastructural IHC with labeled gold nanoparticles [60, 61].

At the final stages of the morphological differential diagnosis of MGRS with the use of omics-technologies and, in particular, proteomics in some centers abroad, laser microdissection is used, followed by separation of the protein components of the renal

tissue by capillary electrophoresis and identification of the molecular composition using MALDI-TOF (matrix-activated laser desorption ionization with time-of-flight analysis and visualizing mass spectrometry) [54, 62, 63].

The above approaches to morphological diagnosis should be carried out exclusively in a highly specialized and well-equipped morphological laboratory, where all the necessary techniques will be applied and evaluated by an experienced nephropathologist.

Hematologic Diagnosis of MGRS

The aim of the hematological examination is to identify paraprotein and a clone of the B cell line of differentiation. The scope of the examination corresponds to that for MM, B lymphoma or Waldenström macroglobulinemia and is described in detail in the relevant recommendations [17–21, 27].

For successful verification of a "small" clone, it is important to use highly sensitive techniques that can detect even a small clone and a small amount of paraprotein: immunophenotyping of bone marrow, genetic studies, immunofixation of blood serum and urine, determination of free LC in serum by the Freelite method or other methods that have been proven to be comparable with Freelite. These methods are the basis not only for primary hematological diagnosis, but also for evaluating the effectiveness of treatment and the progression of the disease.

Treatment of MGRS

The treatment of MGRS should also be based on the **multidisciplinary** approach, it should be clone-specific and include well-known drugs and chemotherapy regimens used for MM, B lymphoma, CLL and Waldenström macroglobulinemia [16–20, 27, 39, 42, 64, 65]. Modern approaches to the etiotropic therapy of MGH are briefly reflected in the Table 4. The aim of treatment is to reduce the production of pathogenic LC/IG, to reduce the deposition of paraprotein in organs and tissues, to prevent further progression of their dysfunction, as well as to prevent the transformation of the clone into a malignant form [11]. In addition to chemotherapy, high-dose polychemotherapy with support for hematopoietic stem cell autotransplantation (autoHSCT) should be considered as an option for the treatment of MGRS.

The tasks of comprehensive nephrological support of therapy include a variety of measures consisting in dose adjustment of drugs taking into account their potential nephrotoxicity, prevention and treatment of AKI, exposure to specific pathogenetic mechanisms of kidney injury (treatment of thrombotic microangiopathy, immunocomplex organ damage, increased clearance of IG deposits), kidney functional evaluation over time and its correction, assessment of the renal response, as well as the use of extracorporeal LC elimination. The latter include renal replacement therapy, such as hemodialysis/hemodiafiltration with high cut-off membranes, as well as SUPRA-HFR (haemodiafiltration with ultrafiltrate regeneration by adsorption on resin). These techniques make it possible to remove free LCs from the body and reduce their toxic effect on tissues and organs, thereby increasing the effectiveness of treatment [66–68]. Also, it is important to prepare potential kidney allograft recipients and include such patients on a waiting list. Given the high frequency of MGRS return to the kidney transplant, the first step is to perform clone specific therapy and consolidate the hematological response using autoHSCT [69].

Consensus is not intended to elucidate MGRS treatment. Issues relating to the treatment of the discussed nosology will be described in detail further in the form of guidelines.

Table 4. *Drugs and Methods Used to Treat Clonal B Cell Line Proliferation [17]*

Cytostatics (cyclophosphamide, bendamustine, chlorambucil, fludarabine, doxorubicin, vincristine, melphalan, etc.)
Corticosteroids (dexamethasone, prednisolone)
Proteasome inhibitors (bortezomib, carfilzomib, etc.)
Monoclonal antibodies (anti-CD20: rituximab, obinutuzumab, ofatumumab; anti-CD 38: daratumumab; etc.)
Bruton tyrosine kinase inhibitors (ibrutinib)
Immunomodulators (lenalidomide, pomalidomide, etc.)
High-dose polychemotherapy followed by autologous transplantation of hematopoietic stem cells

Issues Considering MGRS Treatment in the Russian Federation

At present, in the Russian Federation, MGRS is not considered as a nosology in practical medicine, and such patients are formally assigned to the MGUS group or cases of B cell proliferation without criteria for initiating therapy. As a result of the conventional, but now outdated notions that an exclusively malignant tumor clone should be treated in cases of MG, effective clone specific chemotherapy (bortezomib, lenalidomide, rituximab, etc.) is provided only for patients with malignant forms of MG: MM, lymphomas, CLL. At the same time, MGRS patients, including AL amyloidosis, that do not meet the formal criteria of malignancy, are not included in the programs for providing the necessary medicines (Federal Law No. 299 of August 3, 2018 "On Amending the Federal Law 'On Fundamental Healthcare Principles in the Russian Federation'") and are left without the opportunity to receive therapy that is adequate to the nature and prognosis of the disease. Certainly, this approach to MGRS is unacceptable. The inaccessibility of treatment, primarily due to the fact that the diagnosis "is not listed", as well as due to a lack of understanding of the true nature of the disease and underestimation of its clinical and prognostic value, is detrimental to patients [70]. Patients with this disorder should be provided with the necessary drugs and the possibility of treatment via the high-tech funding channel, including autoHSCT.

Prerequisites for the Establishment of an Onconephrological Center

Renal disorders associated with MG stand at the intersection of two specialties — hematology and nephrology. The understanding of the urgency of this problem in the world has led to the emergence of a new highly specialized field — onconephrology [71, 72]. Obviously, the diagnosis of MGRS, monitoring and treatment of such patients should be conducted in a specialized onconephrological center. The experience of creating and operating such centers was implemented abroad [73]. In the Russian Federation, an onconephrological center can be established at a multidisciplinary hospital, which includes departments of hematology, nephrology, renal replacement therapy, stem cell and kidney transplantation. Another determining factor is the availability of proper diagnostic resources, including an immunomorphological laboratory, which has the necessary techniques for full MGRS diagnosis. It should be noted that the interests of onconephrology are not limited only to renal diseases associated with MG, but include acute kidney injury as a result of treatment of tumor processes, renal lesions associated with solid tumors and hematopoietic stem cell transplantation, secondary tumors in patients with renal allograft, etc. [74].

Conclusion of Consensus of Hematologists and Nephrologists on MGRS

MGRS is not an independent renal disease, a "chronic glomerulonephritis", but a condition in which kidney injury is secondary to clonal B cell proliferation. In other words, MGRS is a precancerous disease in combination with CKD that requires immediate treatment. The latter, however, is not possible for patients in the Russian Federation due to the absence of MGRS diagnosis on the list of nosologies, and therefore, the lack of assistance in case of this disorder.

Within the framework of this consensus, nephrologists and hematologists of national leading clinics came to a collective opinion on MGRS and have submitted a number of proposals for consideration by the professional community and public health authorities of the Russian Federation, the implementation of which will significantly improve the diagnosis and treatment of this category of patients.

The Final Provisions of the Consensus are as Follows:

1. MGRS is a group of diseases in which kidney injury occurs as a result of the pathological action of a monoclonal protein (immunoglobulin or its fragment) produced by a tumor clone of the B cell line of differentiation. At the same time, there are no criteria to start specific therapy for a lymphatic tumor.
2. MGRS is a heterogeneous group of diseases in which the result of the action of a monoclonal

protein on renal tissue can be different, but inevitably leads to progressive renal dysfunction, up to a complete loss of organ function and a decrease in life expectancy.

3. Taking into account the extremely unfavorable prognosis of renal function and life, MGRS should be included in the register of "life-threatening and chronic progressive (orphan) diseases that lead to a reduction in patients' life expectancy or disability", in the form of a generic name that combines a number of separate nosologies, including AL amyloidosis, monoclonal deposit deposition disease, etc. (Table 2).

4. Diagnosis of clonal proliferation in case of MGRS requires immunophenotypic and molecular examination aimed at identifying a "small" clone, including paraprotein in blood and urine using immunofixation and determination of free light chains using Freelite or other methods that have been proven to be comparable with Freelite. These methods should be available, first of all, in specialized oncohematological centers, as well as in other large hospitals in the Russian Federation, as they are the basis not only for primary hematological diagnosis, but also for assessing the effectiveness of treatment and the progression of the disease.

5. Along with the identification of a tumor clone, the diagnosis of MGRS requires a mandatory kidney biopsy with morphological examination to confirm a specific organ lesion. The morphological examination of kidney bioptate should include light-optical, immunomorphological, and ultrastructural methods. The main feature of MGRS is a presence of organized and/or unorganized deposits of monoplastic paraprotein in kidney compartments. The type of monoclonal paraprotein detected in blood serum or in urine should be the same as the type of monoclonal protein, morphologically determined and causing kidney injury.

6. The diagnosis of MGRS should be discussed by a consilium consisting of a hematologist, nephrologist and renal pathologist and should be based on a presence of a pathogenetic relationship between kidney injury and the existing monoclonal proliferation: a clone of a B lymphocyte / plasma cell and/or paraprotein detected in serum/blood.

7. Any variant of MGRS requires the initiation of clone specific treatment, the ultimate goal of which is to preserve renal function and prevent the clone from progressing towards the tumor process. The nature of chemotherapy depends on the type of clonal proliferation. Treatment should be prescribed and performed on a multidisciplinary basis in accordance with the type of clone/paraprotein and the features of kidney injury by a hematologist and nephrologist with similar experience.

8. The group of hematological diseases combined by the term MGRS should be included on the list of disorders which require prescribing expensive chemotherapeutic drugs. Patients should receive treatment via the "high technology" funding channel.

9. Consolidation of the hematological response can be achieved by using high-dose polychemotherapy followed by autoHSCT. Therefore it is advisable to expand the indications for autoHSCT and include other types of MGRS, in addition to AL amyloidosis, in the standards for providing this type of care.

10. For successful diagnosis, timely effective treatment of MGRS and long-term monitoring of patients with this disorder, it is advisable to open specialized departments/centers of oncological nephrology in institutions with proper resources for diagnosis and treatment and qualified medical personnel with relevant experience in oncohematology and nephrology.

11. Based on the consensus provisions, it is advisable to create national guidelines for this clinical issue.

[15] The consensus participants reviewed and expressed solidarity on behalf of the professional communities:

On Behalf of the Association of Nephrologists of Russia and the Scientific Society of Nephrologists of Russia

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Antibiotic Prophylaxis of Infective Endocarditis: from the History of the Concept to Modern Recommendations (Review)

Abstract

This review highlights current ideas about the prevention of infective endocarditis. The history of the concept development, the main approaches and the rationale for changing the principles of antibiotic prophylaxis in recent years are described. Current international and national guidelines, in particular, guidelines of the European Society of Cardiology, the American Heart Association / American College of Cardiology and the Japanese Circulation Society, are covered in detail. A critical assessment of previously approved international guidelines is presented with an analysis of the effect of relative or complete limitation of antibiotic prophylaxis on the incidence of infective endocarditis and the frequency of its complications.

Key words: *infective endocarditis, prophylaxis, antibiotics, antibiotic prophylaxis, international guidelines*

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AB — antibiotic, ABP — antibiotic prophylaxis, ABR — antibiotic resistance, CHD — congenital heart disease, IE — infective endocarditis, ARF — acute rheumatic fever, RCT — randomized clinical trial, AHA — American Heart Association, ACC — American College of Cardiology, ESC — European Society of Cardiology, NICE — National Institute for Health and Clinical Excellence of Great Britain, JCS — Japanese Circulation Society

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Introduction

Despite significant progress in diagnosis, antibiotic therapy, and cardiac surgery procedures for infective endocarditis (IE), the adoption of consensus documents defining optimal patient management approach, this disease today, in the 21st century, is characterized by severe complications and an unfavorable prognosis [1–6]. The in-hospital mortality in IE reaches 20% [7–9], and one-year mortality is 40% [10–13], which exceeds that of some types of cancer. In such conditions, the prevention of IE appears to be one of the most important tasks of scientific and practical medicine. The development and implementation of antibiotic prophylaxis (ABP) of IE has been performed since the middle of the 20th century. ABP affects bacteremia, which is a key factor for the development of valvular infection in patients with an increased risk of IE, and is indicated before invasive procedures [14–16]. Such patients, in particular, include those with congenital heart disease and acquired valvular defects, prosthetic heart valves, and previous IE [15, 17, 18]. ABP is used to prevent the first episode of IE of the native valve and recurrent IE, as well as IE of the prosthetic valve [10, 19]. ABP of IE is among the most complex and debatable issues of all strategic aspects of the IE management, despite the regularly updated international guidelines of authoritative cardiac societies [4, 16]. Largely, this is due to the relative rarity of IE and, consequently, the absence of randomized clinical trials (RCTs) on ABP [6]. Various opinions exist regarding the identification of categories of high-risk patients subject to the prescription of prophylactic antibiotics (AB), types of medical procedures, the regimen of ABP, etc. In addition, approaches to ABP of IE are changed over time as scientific data, mostly obtained from observational studies, accumulate. Decision-making on ABP of IE should consider such aspects as antibiotic resistance (ABR) and side effects of ABs, including the development of anaphylaxis [20, 21].

This review was carried out by a team of authors with experience in managing patients with IE. We attempted to analyze historical and current approaches to IE ABP, including that in different countries; to evaluate the results of the ABP guidelines implementation on the incidence of IE; and to discuss the existing controversial points.

Background

In 1909, Thomas Horder suggested the etiological role of *S. viridans* in the oral cavity in patients with heart disease based on an analysis of 150 cases of IE [22]. In 1923, T. Lewis and R. Grant [23] suggested that bacteria that enter the systemic circulation after dental procedures could cause IE. A little later, C.C. Okell and S.D. Elliot isolated *S. viridans* in blood culture in 84 of 138 (61%) patients with IE [24]. In 1941, C.B. Thomas et al. [25] reported the first results of the prophylaxis of acute rheumatic fever (ARF) with sulfanilamide. Researchers compared the course of ARF and its outcome in groups of patients who received and did not receive sulfanilamide. Although the work is aimed to assess the effect of prophylactic administration of sulfanilamide in patients with ARF, the authors describe two cases of fatal IE in the group of patients without antibiotic therapy. In the same group, two more deaths were reported that were related to ARF and "acute disease of unknown nature". Moreover, there were no fatal outcomes in the group of patients receiving sulfanilamide [25]. At the end of the 1930s, the first guidelines on the use of various sulfanilamides for IE ABP in patients with valvular defects who underwent various dental interventions were published [26].

In 1955, for the first time, the official guidelines of the American Heart Association (AHA) on ABP included recommendations for ABP of IE in patients with predisposing cardiac diseases [14]. The guidelines refer to ABP of IE as a "good medical and dental practice". After this, the recommendations on ABP were updated nine times before 1997, and the changes mainly concerned dental and pulmonary interventions, as well as the choice, route of administration and dosage of AB [27]. Following the American guidelines, recommendations of other scientific societies have begun to appear in different countries [16].

Oral *Streptococci* are commensal bacteria, responsible for 10–30% of cases of IE depending on the geographical location, profile of risk factors, sociodemographic characteristics of the studied population [3, 15, 28].

The approach to ABP of IE, developed on the basis of observational studies and the results obtained in animal models, is aimed at preventing the

attachment of bacteria to the endocardium after transient bacteremia related to invasive procedures [28]. Transient bacteremia is believed to occur in poor oral hygiene, periodontal diseases, after dental procedures or manipulations of teeth and gums in a person's daily activity (e.g., brushing, using of toothpicks, chewing gum, etc.) and, in some cases, precedes the development of IE [28–31]. Of course, bacteremia predisposing to the development of IE can occur not only as a result of odontogenic bloodstream infection, but also after coronary artery bypass grafting, procedures involving skin damage, wound surface interventions, bone marrow biopsy, some types of endoscopy, in particular bronchoscopy, etc. [32, 33].

For more than 50 years, ABP has been administered orally to patients at risk of IE before a variety of dental interventions. Significant changes in ABP of IE occurred over the past 10–12 years, and their main feature was a significant limitation of indications for the use of AB for the prevention of IE [34]. In 2007–2009, a number of associations, including the European Society of Cardiology (ESC), the American College of Cardiology (ACC), AHA, and the UK National Institute for Health and Care Excellence (NICE), issued recommendations that limit the use of ABP to some extent [27, 35, 36].

In Europe and the USA, relative ABP restrictions have been introduced for patients at the highest risk of IE (e.g., previous IE, congenital heart disease (CHD), history of rheumatic endocarditis and selected recipients for heart transplantation) before invasive dental procedures [10, 37]. In the UK, in 2008, the NICE recommendations offered to abandon IE prophylaxis completely (a total restriction of ABP). However, later, in July 2016, NICE experts softened this statement [38].

The idea of a relative or total restriction of ABP was based on three factors. Firstly, the characteristic feature of modern medicine is the increasing commitment to evidence-based practice, which means that the recommendations are based on the results of thoroughly designed RCTs. However, in the near future, RCTs that objectively evaluate the effectiveness of ABP of IE are not expected. Secondly, the relative importance of dental procedures as almost the only source of bacteremia and the immediate cause of IE is questionable, especially in comparison with other "portals of entry" or transient bacteremia that occurs in everyday life [29–31, 39]. Thirdly, in moderate-risk groups (in England, high-risk), the general harm from the use of AB (in particular, anaphylactic reactions and ABR) served as a strong argument against the use of ABP. The NICE Guideline Committee also considered that ABP was not economically viable due to a lack of evidence of its effectiveness and supposed high risks associated with the occurrence and treatment of anaphylaxis [15, 31].

When discussing one of the most important arguments against the widespread use of AB, ABR, it should be noted that the gap between the development of new drugs and the constant variability of bacterial strains has widened recently [40–42]. Under the influence of drugs, a whole range of counteracting microbial mechanisms that can reduce or completely neutralize the effectiveness of AB are activated [40–42]. ABR, which is inherent in many pathogens for almost any AB and complicates the management of patients with infective diseases, including IE [21], is partly due to the unjustified frequent administration of antibacterial agents in clinical practice.

Current National and International Guidelines for the Prevention of Infective Endocarditis

1. Recommendations of the European Society of Cardiology, 2015

The published 2015 ESC recommendations [37, 43] regarding IE ABP were developed taking into account the experience described in the previous guideline [36] and the results of the implementation of strict ABP restrictions in the 2008 NICE guideline [44].

The 2015 ESC recommendations support the principle of prescribing ABP to patients with a high risk of IE for the following reasons:

- uncertainty remains regarding IE risk assessments;
- worse prognosis of IE in high-risk patients, especially in patients with endocarditis, prosthetic heart valve (PHV);
- the number of patients with a high risk of IE is much smaller than patients with an intermediate risk, which generally reduces the potential harm of the adverse effects of ABP.

Table 1. *Recommended regimens of antibiotic prophylaxis in high-risk patients before high-risk dental procedures*

Situation	Antibiotic	Single dose 30–60 minutes before the procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin[a]	2 g per os or IV	50 mg/kg per os or IV
Allergy to penicillin or ampicillin	Clindamycin	600 mg per os or IV	20 mg per os or IV

Notes: [a] — as an alternative, cephalexin 2 g IV in adults or 50 mg/kg IV in children; cefazolin 1 g IV in adults or 50 mg/kg IV in children. Cephalosporins should not be prescribed to patients with anaphylactic reactions, angioedema or urticaria after penicillin or ampicillin use due to their cross-sensitivity. Adapted from G. Habib et al. [37].

According to the ESC 2015 recommendations, patients with the highest risk of IE are represented by three categories:

1. Patients with a prosthetic heart valve or prosthetic material used in cardiac valve repair. This group also includes patients, transcatheter-implanted prostheses and homografts.
2. Patients with previous IE.
3. Patients with untreated cyanotic congenital heart disease (CHD) and those with CHD who have postoperative palliative shunts, conduits or other prostheses

The Task Force recommends prophylaxis for the first 6 months after the procedure without residual defects until complete endothelialization of the prosthetic material.

Patients with an intermediate or high risk of IE should be advised to follow dental and skin hygiene measures. These general hygiene measures are applicable to patients and healthcare workers and are ideal for the general population, given the fact that IE may develop without cardiac risk factors [37].

ABP is recommended for all patients undergoing "risk procedures", which includes manipulations the gingival or periapical region of the teeth (including plaque removal and procedures in the root canal), or perforation of the oral mucosa.

The Task Force believes that due to lack of data, there are no contraindications to installing implants for all persons at risk of IE. There is also no convincing evidence that bacteremia that occurs after procedures on the respiratory, gastrointestinal and genitourinary tracts, including vaginal delivery or cesarean section, after dermatological or musculoskeletal manipulations, can lead to IE. Therefore, in these cases, ABP is not required.

Thus, ABP is indicated only for patients with the highest risk of IE who are subject to high-risk dental procedures [37]. Table 1 presents the main regimens of ABP recommended before dental procedures. It is not recommended to use fluoroquinolones and glycopeptide AB due to their unproven effectiveness and the possible development of ABR [37].

Systematic ABP is not recommended when performing non-dental interventions. ABP of IE is necessary if invasive procedures are performed during the treatment of infections. For example, patients who are at high risk of IE due to existing cardiac disease and need an invasive respiratory tract procedure (in particular, drainage of an abscess) should receive antibacterial drugs. The recommendations indicate, as examples, systemic or local infections of the gastrointestinal tract, genitourinary system, dermatological and musculoskeletal infections for the selection of adequate AB in high-risk patients to prevent IE [37].

2. The Russian Society of Cardiology endorses the 2015 ESC recommendations [45], which were translated and published in a timely manner [43].

3. NICE Recommendations, 2008 (updated in 2015–2016)

UK Guidelines for IE prevention dated 2008 were slightly updated in 2015–2016 [44]. In particular, the following phrase was added: "Antibiotic prophylaxis against infective endocarditis is not routinely recommended". The addition of "routinely" emphasizes the standard advice from the NICE committee to healthcare providers: "Doctors and dentists should offer the most appropriate treatment options, in consultation with the patient and/or their carer or guardian. In doing so, they should take account the recommendations in this guideline, and the values and preferences of patients, and apply their clinical judgment" [44].

4. American Heart Association / American College of Cardiology Guidelines, 2014

AHA/ACC recommendations for the prevention of IE were published in the Guidelines for the Management of Patients with Valvular Heart Disease in 2014 [10], a year before the publication of the "IE in Adults: Diagnosis, Antimicrobial Therapy and Treatment of Complications" guideline [19]. They emphasize that at present, ABP is indicated only for patients with the highest risk of an adverse outcome in the event of IE (Table. 2, [6, 10, 37, 46, 47]). We would like to emphasize the exact wording for the characteristics of patients with indications for ABP: "for patients with the highest risk of IE adverse outcome before dental procedures" [10], since in the literature they are often limited to the term "high risk". This wording is also available in the 2015 ESC recommendations [37] on the list of cardiac conditions associated with the "highest risk of IE".

It was noted that when using artificial material to repair a valve defect (with the exception of surgically created palliative systemic pulmonary shunts or conduits), such as annuloplasty, implantation of neochords, Amplatzer devices, clips (MitraClips), only a few cases of infection of such materials were observed [10]. Given the low level of frequency and lack of information, there is no convincing evidence that there is a need for IE ABP in such patients, if there is no other high risk of intracardiac infection.

The American guideline notes that the incidence rate of IE is significantly higher in patients who underwent heart transplantation than in the

Table 2. *Comparison of the main statements of the guidelines of the American Heart Association / American College of Cardiology 2014 and the European Society of Cardiology 2015 on the use of antibiotic prophylaxis of infective endocarditis.*

Procedures	AHA/ACC, 2014 †	Class, LE	ESC, 2015 §	Class, LE
Dental procedures that involve manipulating gum tissue, the periapical region of the teeth or perforation of the oral mucosa	1. Patients with PHV 2. Patients with history of IE. 3. Recipients of a donor heart due to structural changes in the valvular apparatus 3. Patients with CHD, including: a. Non-operated cyanotic CHD, including those with palliative shunts and conduits; b. Fully restored CHD using artificial materials or devices installed by cardiac surgery or catheter method for 6 months after the procedure; or c. Reconstructed CHD with residual defects in place or adjacent to the site of an artificial flap or device	IIa, B	1. Patients with any PHV, including those placed using transcatheter procedure, or persons who have used any artificial material for the heart valve repair 2. Patients with history of IE. 3. Patients with CHD, including: a. Any type of cyanotic CHD; b. Any type of CHD reconstructed using artificial material placed using cardiac surgery procedure or percutaneous techniques up to 6 months after the procedure or during lifetime if residual shunts or valve regurgitation persist.	IIa, C
Vaginal Delivery*	1. Patients with PHV or artificial material used to repair a heart valve ‡ 2. Patients with unoperated or palliatively corrected cyanotic CHD, including surgically performed palliative shunts and conduits ‡	IIa, C	Not recommended: "During childbirth, the indications for ABP are contradictory and, given the lack of convincing evidence that IE is associated with childbirth via the vaginal delivery or cesarean section, prophylaxis is not recommended. It is important that non-specific hygiene and aseptic measures be taken to prevent IE	III, C

Notes: † — Recommendations of the American College of Cardiology / American Heart Association (ACC/AHA) 2014 on the management of patients with valvular heart disease; § — Recommendations for the management of patients with infective endocarditis (IE) of the European Society of Cardiology (ESC) 2015.* — ACC/AHA 2008 Guidelines for the management of adult patients with CHD;** — 2018 ESC Guidelines for the treatment of cardiovascular diseases during pregnancy; ‡ — Prevention of IE during vaginal delivery is controversial and is not included as evidence in the 2014 ACC/AHA Valvular Heart Disease Guidelines and the main recommendations of the ESC 2015; LE — level of evidence; PHV — prosthetic heart valve; CHD — a congenital heart disease. Modified from T. J. Cahill et al. (2017) [6].

general population. The highest risk of IE exists during the first 6 months after surgery due to the endothelium injury, intensive immunosuppressive therapy, endomyocardial biopsy, and frequent central venous catheter placement. The importance of oral hygiene to reduce the sources of bacterial dissemination is also emphasized. In this regard, a follow-up by a professional dentist and the use of appropriate facilities (manual, electric, ultrasonic; dental floss and other dental plaque devices) are recommended. There is no evidence of the usefulness of IE ABP when performing procedures on the gastrointestinal or genitourinary tract in the absence of established enterococcal infection [10].

5. Japanese Circulation Society Recommendations, 2019

When developing the Japanese Circulation Society (JCS) guidelines for the prevention and treatment of IE, the experts also relied on the experience of implementing the guidelines of other scientific societies [48], which is reflected in the recommendations, rationale and references. The presented statements (the latest available guidelines) recommend the ABP use for patients with high-risk of IE, including those at highest and moderate risk (Table. 3, [48]).

In addition, there was a graduation in the need for AB for the prevention of IE, depending on the type and place of the invasive treatment and diagnostic procedures from "highly recommended" to "not recommended". In our opinion, the 2019 JCS guidelines deserve close attention and the study of the possibility of their application in individual clinical situations. In real practice, IE develops not only in patients with previous cardiac disorder of the highest risk and only after dental procedures, but also in patients undergoing other invasive procedures (tonsillectomy, adenoidectomy, transurethral resection of the prostate, etc.) [48]. Therefore, it is reasonable to discuss the prescription of AB to patients who, for example, have a moderate risk of IE and have undergone invasive diagnostic and treatment interventions on an infected organ or tissue.

Assessment of the Effectiveness of the 2007–2009 Recommendations

Today, only data that evaluate the effectiveness of recommendations published in 2007–2009 have been obtained. It should be noted that the interpretation of data on changes in the incidence of IE under conditions of relative or absolute limitations of ABP is quite difficult [49]. The obtained contradictory results can be due to not only and not so much by the policy of limiting the ABP of IE, as by heterogeneous methodological approaches when conducting research.

Table 3. *The risk of infective endocarditis in adults according to underlying heart disease, recommendations of antibiotic prophylaxis during dental and oral surgical procedures.*

Risk of IE	Class of recommend.	LE
1. Highest risk: high incidence rate, complications and mortality in IE		
• Patients after implantation of PHV (bioprosthesis / mechanical valve) • Patients with history of IE • Patients with complex, "cyanotic" CHD (one ventricle, complete transposition of large arteries, Fallot's tetrad) • Patients undergoing shunting between systemic and pulmonary circulation	**I**	**B**
2. Moderate risk: lower levels of complications and mortality, despite the high incidence of IE		
• Most CHD * • Acquired heart valve diseases § • Hypertrophic cardiomyopathy with obstruction • Mitral valve prolapse with regurgitation	**IIa**	**C**
• Patients with intracardiac devices (CP, ICD) • Patients with a long-term central venous catheter	**IIb**	**C**

Notes: * — except a simple atrial septal defect (such as *ostium secundum*); § — in mitral valve stenosis without regurgitation, the risk of infective endocarditis (IE) is low. LE — level of evidence; CHD — congenital heart disease; CP — cardiac pacemaker; ICD — implanted cardioverter defibrillator. Adapted from S. Nakatani et al. (2019) [48].

Some surveys have studied the effect of limiting oral ABP on the incidence rate of IE. In France, where ABP was limited to high-risk patients, the incidence rate of IE over three years of study (in 1991, 1999, and 2008) remained steady, amounting to 35, 33, and 32 cases per 1 million people, respectively. This suggested that there was no significant change in the incidence of IE after the implementation of limited oral ABP [50, 51].

Analysis of the incidence rate of streptococcal IE (*Viridans* group), conducted before and after changes to the 2007 ACC/AHA guidelines based on data of the Rochester Epidemiology Project (Rochester, USA), D.C. DeSimone et al. [52, 53], did not reveal increase in IE incidence. On the contrary, there was a decrease in the incidence of IE from the level of 3.6 cases per 100 thousand people in the period 1999–2002 to 1.5 cases per 100 thousand in the period 2011–2013.

In turn, the results of three national epidemiological studies in the United States, United Kingdom and Canada provided a matter for reasonable concern. S. Pant et al. [54] found a significant increase in the incidence rate of streptococcal IE, although there was no significant increase in overall hospital admission rate or cases of staphylococcal IE. In calculating the incidence rate of IE, this study included cases caused by streptococci of all groups, without defining of the *Viridans* group spp. In addition, no information was provided on changes in the number of AB prescribed by doctors, which would make it possible to assess the effect of the recommended limitations of ABP on the incidence rate of IE more accurately. The authors themselves are not sure what a reason of the rise in the IE cases: improving the coding of the disease in accordance with the International Classification of Diseases or a real increase in the incidence rate [54].

In the UK, where national guidelines recommended to avoid the use of any type of AB for the prevention of IE in 2008 [35, 44], there was no increase in IE incidence rate in early studies [55]. However, in 2015, M.J. Dayer et al. [56] published an extended analysis of the diagnoses established upon discharge from the Hospital of the National Health Service before April 2013. After the introduction of NICE guidelines, the number of ABP prescriptions dropped sharply, from 10.9 thousand/month to 2,236 thousand/month. Along with this, there was a significant increase (above the predicted trend) in the number of IE cases — by 0.11 cases per 1 million people/month (or by an additional 35 cases in England), which coincided with the implementation of new recommendations [56].

The systematic review and meta-analysis of research results performed by T. Cahill et al. are of undeniable interest [15]. They directly or indirectly studied the clinical experience of the use of ABP in patients at risk of IE development and undergoing dental procedures. In all countries where ABP is recommended to the categories of patients with the highest risk of IE, there was no significant increase in the incidence rate of IE, although some studies showed an increase in streptococcal endocarditis [15].

In 2019, another study was published, which assessed the impact of the 2007 AHA revised guidelines on prescribing ABP among groups of patients with moderate/high risk of IE and determined significant changes in its incidence rate after the implementation of these recommendations [57]. The study included data from adults of moderate/high risk of IE, divided into two age groups: 18–64 years old and ≥65 years old. Among people aged over 65 in the groups of high and moderate risk, there was an increase in the quarterly level of the number of new cases of IE: from 336 to 1,915 new cases per 1 million people at the highest risk of IE and from 180 to 440 per 1 million in patients with moderate risk. The most significant increase in new cases of IE was noted in the second half of 2010, that is, more than 3 years after the publication of recommendations for the prevention of IE.

A similar rise in new cases of IE was also observed among patients aged 18–64: the most significant change was recorded in the second quarter of 2010 in both groups (of moderate and high risk): from 1,061 to 1,754 in the high-risk group and from 308 to 423 cases per 1 million in the moderate-risk group [57]. The authors suggest that such a time difference (about 3 years), along with an increase in the incidence rate of IE in both risk groups, is not associated with a change in the principles of ABP described in the 2007 AHA guidelines.

All these data are obtained during observational studies and cannot be used to establish a relationship

between the limitation of ABP and the incidence rate of IE reliably. Many studies contain methodological inaccuracies, for example, the inclusion of implantable cardiac devices and related complications in recent years, although this factor has been corrected in some works. Despite the long-term controversy and problems with the data obtained from observational studies, it is rather difficult to conduct RCTs due to the high costs, the complexity of the logistics and ethical debate whether there is a real balance to perform a placebo-controlled study. Nevertheless, a more extensive evidence base is required with respect to the justification of the implementation of national and international recommendations on ABP of IE.

It is worth discussing a parameter that determines the attitude to the prescription of ABP: an assessment of the risk group of IE. There are two groups of patients in the 2015 ESC Guidelines with the highest and intermediate risk of IE [37], who are advised to comply with dental and skin hygiene measures. In the highest-risk patients, ABP should be considered during high-risk procedures. On the other hand, there are certain groups of patients in whom IE develops much more often than in the general population. For example, among patients undergoing dialysis, the incidence rate of IE is 17 times higher than in the general population [58], and in intravenous drug addicts it is approximately 100 times higher [59]. IE often develops in older people [60], people suffering from diabetes mellitus [61], cancer [62] and other disorders. Is it possible to ignore patients without cardiac diseases of the highest risk and undergoing various diagnostic and treatment procedures, while the incidence rate of IE in this group is tens to hundreds of times higher than that in the general population?

In conclusion, we would like to cite the very reasonable argument made by F. van den Brink et al., published in November 2019 in the Annals of Cardiothoracic Surgery [63]. "And so, we have arrived at 2019. Guidelines on chemoprophylaxis for IE are just as strict as they were when we designed them between 2007–2009. In the meantime, we have seen a rise in IE in almost all studies. What we have not seen an improvement in survival of patients suffering from the devastating disease. Still, despite an increasing number of studies that show not only an increase in IE incidence, but also a relationship between stricter IE chemoprophylaxis and an increase in preventable IE, we still consider the evidence not to be enough to change the guidelines back to what they were. Another thing that we have also not witnessed is patients suffering from chemoprophylaxis with lethal consequence [64]. In short, we do very little harm in giving patients chemoprophylaxis and we probably do a lot of good in giving patients chemoprophylaxis to prevent IE from rearing its ugly head" [63].

F. van den Brink et al. [63] believe that physicians now have "a rare opportunity to conduct an almost worldwide study in restoring the principles of ABP, as it was before 2007, and then analyze what happens with the incidence of IE".

Conclusions

1. Considering the severity and unfavorable prognosis of IE, it is advisable to conduct ABP before invasive procedures in order to prevent endocarditis and its relapses.
2. Based on the accumulated evidence, ABP of IE should be used in patients at the highest risk of IE, who are undergoing high-risk dental procedures. The decision on its use in other patients and for non-dental interventions is taken by a specialist depending on the individual clinical situation and taking into account the degree of risk, the individual characteristics of the patient and other circumstances.
3. In patients with intermediate and high risk of IE, the compliance with dental and skin hygiene measures detailed in national and international recommendations is of great importance.
4. When assessing the risk of IE or selecting the scheme/regimen of ABP, a physician should rely on the recommendations of the relevant sections of international/national consensus documents.
5. In IE prevention, interdisciplinary interaction of specialists (cardiologists, cardiac surgeons, dentists, etc.) is important, as well as informing high-risk patients about the need for ABP during invasive procedures.
6. Further studies are needed to evaluate the impact of the ABP of IE implementation on the incidence rate of new cases or recurrent IE, as well as possible changes in the microbiological spectrum of the main causative agents of the disease.

Contribution of Authors

All authors made a significant contribution to the preparation of the article, read and approved the final version before publication.

G. G. Taradin (ORCID ID: https://orcid.org/0000-0003-3984-8482): principal creation of review idea, literature search, collection and an analysis of data, writing of separate sections, final text editing.

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Clinical Course of Coronary Heart Disease Concomitant with Asthma

Abstract

The objective: to study features of the clinical course of coronary heart disease (CHD) concomitant with asthma (BA). **The materials and methods:** 180 patients were enrolled, 90 of them suffered from both CHD and BA (the first group), and 90 had CHD only (the second group). The examination included complaint collection, studying medical history, medical examination, percussion, auscultation, blood pressure (BP) measurement using Korotkoff method twice a day (in the morning and in the evening), heart rate (HR) measurement, 24-hour ECG monitoring, and echocardiography. Besides, standard biochemical analysis, including total cholesterol and low-density lipoprotein cholesterol, was performed. **The results.** The shortness of breath was the main complaint among 86 (95.5%) patients with both CHD and asthma; moreover, shortness of breath combined with palpitations in 73.8% of cases, and with angina pectoris only in 20% of cases. There was a significant difference between systolic and diastolic blood pressure; BP values were higher in CHD concomitant with asthma. The signs of left ventricular hypertrophy were revealed in the first group, these signs significantly differed from the ones in the second group. 24-hour ECG monitoring showed that myocardial ischemia was more frequent in the group, which consisted of patients with CHD. Besides, duration of ischemic depression per day was longer in this group. **The conclusion.** According to our findings, bronchial asthma occurs among patients with coronary heart disease in 16.6% of cases. A distinctive feature of bronchial asthma concomitant with coronary heart disease is that a patient often complaints to shortness of breath and palpitations, increase in blood pressure and heart rate, which indirectly indicates the activation of rennin-angiotensin-aldosterone and sympathoadrenal systems. It requires the inclusion of appropriate drug groups in the treatment of patients.

Key words: *coronary heart disease, bronchial asthma, comorbidity, 24-hour ECG monitoring*

Conflict of interests

The authors declare no conflict of interests.

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24ECG — 24-hour ECG monitoring, AH — arterial hypertension, BA — bronchial asthma, BP — blood pressure, CHD — coronary heart disease, DBP — diastolic blood pressure, EchoCG — echocardiography, FC — functional class, HR — heart rate, PICS — post-infarction cardiosclerosis, RV — right ventricle, SBP — systolic blood pressure, SCHD — stable coronary heart disease.

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The study of various diseases in their combined course has been very relevant in the clinical treatment of internal diseases in recent years [1].

It is quite obvious that for the successful treatment of a comorbid patient, physicians should have an idea of the main reasons for the development of combined pathologies, which, according to some authors, can be divided into internal and external ones. Internal causes include similar etiopathogenesis of a number of diseases, one disease being a risk factor for another one, as well as widely discussed genetic disposition. Similar lifestyle and behavioral characteristics, the environment, the patient's microbiome, which is being actively investigated, and drug interactions should be classified as external causes.

Based World Health Organization (WHO) data on noncommunicable diseases of the 21st century, most deaths in economically developed countries will be associated primarily with cardiovascular diseases. However, it is also noted that the leading and competing reasons will include oncological diseases, pathologies associated with disorders of carbohydrate metabolism, and, of course, bronchopulmonary diseases [2, 3].

At present, the course of coronary heart disease (CHD) in patients with chronic obstructive pulmonary disease has been studied quite well [4, 5].

At the same time, there is evidence that the prevalence of CHD in patients with bronchial asthma (BA) is higher than in the general population. Therefore, it is of interest to study the characteristics of the course of coronary heart disease in patients with BA, as well as to find any common pathogenic mechanisms. Currently, patients with BA mainly use inhaled glucocorticoids, which excludes a distinct probability of atherosclerosis developing in the setting of BA, which can be associated with side effects of drugs [5]. Mechanisms of coronary heart disease developing in connection with BA are not well understood. CHD and BA that are developing in the same patient are likely to have pathogenic relations at a certain stage, although the relationship of these diseases at the level of risk factors is hardly in evidence. However, there is some evidence that BA and CHD have common development factors, as well as overlapping pathogenesis pathways [6-9].

Among the features of the clinical course of coronary heart disease in patients with BA, a significant number of atypical forms of myocardial infarction development [7, 10, 11], as well as of low-symptom and painless forms of chronic CHD (40.7-66.7% of cases) can be distinguished [11]. It is critically important that in up to 75% of cases, patients with BA die from CHD and not from complications of pulmonary disease [6-9]. Moreover, patients with BA may have no history of cardiovascular diseases, but an asymptomatic or atypical CHD is a common cause of sudden death [10, 11]. The definition of the following separate phenotype is justified: when bronchial asthma and cardiovascular diseases in one patient have characteristic features that have an effect on the development, prognosis and outcome of both diseases [5].

As early as the 1970s, scientists have proved the development of heart rhythm disorders in patients with chronic bronchopulmonary pathology. The most important factors that can cause arrhythmias related with BA include hypoxemia and related acid-alkaline and electrolyte imbalance, pulmonary hypertension and chronic cor pulmonale, as well as concomitant CHD [1, 10, 12].

Thus, the study of the course of coronary heart disease in patients with BA is important today.

In this regard, the **aim** of this research was to study the features of the clinical course of CHD concomitant with BA.

Materials and Methods

The study included the analysis of the outpatient medical records of patients who received treatment at local clinic No. 3 of the city of Arzamas in the Nizhny Novgorod Region and were diagnosed with CHD, namely stable coronary heart disease (SCHD) of functional class (FC) II and III. Out of 2,150 people who met the criteria for enrollment, 358 subjects, i. e. 16.6%, had bronchial asthma as a concomitant disease.

One hundred and eighty subjects underwent further analysis; 90 of them had a combination of CHD and BA (group 1), and the other 90 had CHD without BA (group 2). A retrospective study was conducted; patients were selected by free conversion

Table 1. *The distribution of patients by gender and age*

	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	P
Male, n (%)	33 (36)	38 (43)	0.8
Female, n (%)	57 (64)	52 (57)	0.6
Age, M±SD, y.o.	62.5±7.2	59.7±8.2	0.07

Note: CHD — coronary heart disease, BA — bronchial asthma

Table 2. *The characteristics of the studied groups*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)
CHD duration, years	7.2 [6.9; 8.1]	8.2 [8.0; 8.5]
BA duration, years	11.7 [9.2; 13.1]	-
History of smoking, n (%)	26 (28.8)	24 (26.6)
Functional class of CHD II FC, n (%)	25 (28.8)	29 (32.2)
III FC, n (%)	65 (72.2)	61 (68.8)
History of MI, n (%)	11 (12.2)	14 (15.5)
AH, st. I or II, n (%)	82 (91.1)	72 (80)
Functional class of CHF, n (%)		
I	22 (24.4)	18 (20)
II	68 (75.5)	72 (80)
DM, n (%)	18 (20)	16 (17.7)
Mild BA n (%)	24 (26.6)	-
Moderate BA, n (%)	66 (73.4)	-
BA combined, n (%)	90 (100)	-
RF, n (%)		
1st Degree	28 (31.1)	-
2nd Degree	62 (68.8)	-

Note: CHD — coronary heart disease, BA — bronchial asthma, SCHD — stable coronary heart disease, FC — functional class, MI — myocardial infarction, CHF — chronical heart failure, DM — diabetes mellitus, RF — respiratory failure

method, outpatient records of the patients of local clinic No. 3 were analyzed.

Table 1 shows the distribution of patients in groups by gender and age.-

Table 2 presents the characteristics of the patients.-

Concomitant pathology in the group of patients with CHD and BA was represented by arterial hypertension of stage 1-2 (82; 90%) and type II diabetes mellitus (18; 20%). In group 2, arterial hypertension of stage 1-2 (72; 80%) and type II diabetes mellitus (16; 17.7%) were also found.

There were no significant differences in the duration of CHD course in patients with BA. In the studied patients, CHD developed alongside existing BA.

All patients underwent general clinical examination that included data acquisition (complaints), studying case history, examination, percussion and auscultation, blood pressure (BP) measurement according to Korotkoff method twice a day in the morning and evening for one month, which was recorded by patients in an observation diary, heart rate (HR) measurement, 24-hour ECG monitoring (24ECG), transthoracic echocardiography (EchoCG). Standard blood biochemistry was also performed, with determination of total cholesterol and low-density lipoprotein cholesterol.

Patients were diagnosed with coronary heart disease based on anamnesis, clinical data, functional

diagnostic methods according to the Federal Clinical Recommendations (2016); diagnosis was confirmed with selective coronary angiography in 68% of patients. Patients were diagnosed with BA based on anamnesis, clinical data, and functional diagnostic methods in accordance with the Federal Clinical Recommendations for the Diagnosis and Treatment of Bronchial Asthma 2016; Clinical Recommendations 2019 were taken into account when analyzing the data [12]. To assess the severity of BA, the recommendations described in "Global Initiative for Asthma" International Program (GINA, 2018) [5] were used. In accordance with the recommendations for mild persistent BA, all patients received inhaled glucocorticoids, for moderate BA — combined therapy with beta2-agonist and inhaled glucocorticoid. All patients with CHD received antiplatelet agents and statins. As antianginal treatment, patients with CHD and BA received calcium antagonist verapamil. The average daily dose was 193.3 ± 10.2 mg per day. Verapamil was prescribed earlier as patients were prone to tachycardia. The drug does not cause bronchial obstructive syndrome, and CHF signs in patients with SCHD did not exceed stage I-IIA. Patients with no BA received a beta-blocker (bisoprolol). Patients with arterial hypertension also received thiazide diuretics and renin-angiotensin-aldosterone system blockers (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker).-

Statistical data processing was carried out using the following software packages: IBM SPSS Statistics 24 (IBM), STATISTICA 10.0 for Windows (StatSoft), and Microsoft Office Excel 2016 (Microsoft). Difference was considered statistically reliable at significance level $p<0.05$. The normality of the distribution of the analyzed characteristics was evaluated with the help of Scheffe's test, as well as on the basis of descriptive statistics analysis: coefficient of variation, average value and median, skewness and kurtosis normality test. Characteristics close to normal distribution were described by mean values, standard deviations (M±sd, where M is mean value, sd is standard deviation). Distributions of quantitative data, different from normal distribution, were described using median and interquartile range as 25% and 75% percentiles, i. e. the upper boundary of the 1st and lower boundary of the 4th quartile (Me [25p; 75p]). Qualitative data were summarized by calculating the proportion of observations (as percent) of a particular category in the study sample. The comparison of two samples in the analysis of variables measured using interval scales and having a normal distribution was carried out using parametric Student t-test for independent groups and non-parametric Mann-Whitney U test. To study the relationships between random variables, correlation analysis was used with the calculation of nonparametric Spearman correlation coefficient with obligatory visual control of scatterplots and removal of outliers. Difference was considered statistically reliable at significance level $p\leq0.05$. Values of p less than 0.001 were indicated as $p<0.001$. The study was carried out in accordance with Good Clinical Practice standards and principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee. Prior to enrollment, all participants gave their written informed consent.

Results and Discussion

It was found that the main complaint in the group of CHD with BA was shortness of breath — 86 (95.5%) patients; in 73.8% of cases shortness of breath was combined with palpitations, and only in 20% of cases — with chest pains. All patients complained of coughing. In the group of CHD without BA, patients most often complained of chest pains — 56 (50.4%), shortness of breath occurred in 51 (45.9%) patients.

Blood pressure in all patients included in the study was measured in the morning and in the evening, at the same time, for one month, on both hands, according to Korotkoff method. According to the analysis results in the group with CHD and BA, systolic blood pressure (SBP) in the daytime was 165.34 [112.4; 176.3] mm Hg ($p = 0.004$), diastolic blood pressure (DBP) was 95.21 [86.3; 102.1] mm Hg ($p = 0.001$). In the group with CHD and with no BA, SBP in the daytime was 155.3 [132.4; 173.6] mm Hg ($p = 0.003$), and DBP was 82.7 [74.3; 93.21] mm Hg ($p = 0.002$). In the evening, SBP in the group with CHD and BA was 160.7 [109.2; 169.1] mm Hg ($p = 0.002$), and DBP was 90.9 [82.7; 103.5] mm Hg ($p = 0.001$). In the

group with CHD and with no BA, SBP in the evening was on average 152.8 [129.9; 171.2] mm Hg (p = 0.012), and DBP was 78.4 [69.8; 91.31] mm Hg (p = 0.014). There was a significant difference in SBP and DBP between the groups in both morning and evening time (p<0.05).

Thus, despite the fact that there were no significant differences in the number of patients with AH between the groups, significantly higher blood pressure was observed in patients with BA and CHD. According to the literature, patients with BA and AH are characterized by poor adherence to treatment with antihypertensive drugs, as they focus on pulmonary disease [3]. In addition, the achievement of the target BP level in cases of BA is more difficult, since BA itself, especially its exacerbation, as well as drugs used for treatment, can contribute to arterial hypertension [3]. Steady rise in systemic blood pressure related to BA leads to postcapillary pulmonary hypertension, interstitial edema and pneumosclerosis with the formation of irreversible components of bronchial obstruction [6, 11]. There is evidence that BA can accelerate the rate of AH development, as well as the degree of left ventricular hypertrophy [6].

A comparative analysis of echocardiographic findings is shown in Table 3.

In the group with CHD and BA, signs of LV hypertrophy were found. Left ventricular myocardial mass index (LVMI) in women of the CHD+BA group was 142.7 ± 12.6 g/m2, of the CHD group — 118.3 ± 9.2 g/m2 (p = 0.024); in men of the CHD+BA group — 162.6 ± 7.4 g/m2, of the CHD group — 148.34 ± 11.1 g/m2 (p = 0.046). It can be assumed that not only cardiac, but also pulmonary pathology has an effect on the development of myocardial hypertrophy in patients with CHD combined with BA [11].

Table 3. *The EchoCG parameters in groups of patients*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	P
LV ESD, cm	4.1 [3.2; 4.1]	3.6 [2.9; 5.3]	p = 0.008
LV EDD, cm	5.6 [4.3; 6.8]	4.2 [2.7; 6.4]	p = 0.012
LV ESV, ml	63 [58.21; 67.3]	60 [53.31; 64.2]	p = 0.017
LV EDV, ml	121 [112; 139]	111 [103; 131]	p = 0.022
SV, ml	57 [54; 65]	52 [49; 59]	p = 0.023
EF, %	58 [53; 64]	61 [56; 70]	p = 0.008
LVPWd, cm	1.3 [1.1; 1.6]	1.0 [0.8; 1.3]	p = 0.003
IVSTd, cm	1.3 [1.1; 1.6]	1.1 [0.9; 1.4]	p = 0.004
LVM, g	251 [220; 312]	245 [220; 260]	p = 0.003
WMSI	1.2 [1.1; 1.3]	1.0 [1.0; 1.3]	p = 0.03
LA, cm	3.85 [3.7; 4.2]	3.67 [3.5; 4.3]	p = 0.006
E/A LV	0.62 [0.4; 0.8]	0.84 [0.4; 0.9]	p = 0.09
LVDF, ms	218 [120; 224]	215 [208; 225]	p = 0.02
RA, cm	3.7 [3.5; 4.2]	3.3 [3.0; 3.7]	p = 0.003
L RV, cm	6.68 [4.8; 8.0]	5.8 [3.7; 7.8]	p = 0.009
S RV, cm	4.6 [2.9; 6.8]	4.1 [3.3; 6.2]	p = 0.084
RVWT, cm	0.5 [0.5; 0.7]	0.4 [0.3; 0.5]	p = 0.003
mPAP, mm Hg	24.1 [19.4; 30.0]	20.3 [17.3; 27.6]	p = 0.001
E/A RV	0.47 [0.28; 0.74]	0.51 [0.42; 0.83]	p = 0.029

Note: CHD — coronary heart disease, BA — bronchial asthma, LV ESD — left ventricular end systolic dimension, LV EDD — left ventricular end diastolic dimension, LV ESV — left ventricular end systolic volume, LV EDV — left ventricular end diastolic volume, SV — stroke volume, EF — ejection fraction, LVPWd — left ventricular posterior wall thickness, IVSTd — interventricular septum thickness, LVM — left ventricular mass, WMSI — wall motion score index, LA — left atrium, E/A LV — peak early diastolic LV filling velocity / peak atrial filling velocity ratio, LVDF — left ventricular diastolic filling, RA — right atrium, L RV — right ventricle mid-diameter, S RV — right ventricle basal diameter, RV T — right ventricular wall thickness, mPAP — mean pulmonary arterial pressure, E/A RV — peak early diastolic RV filling velocity / peak atrial filling velocity ratio

The evaluation of right heart parameters is of great importance for patients with CHD and BA. A statistically significant difference in the size of right atrium (RA) was revealed in patients of the CHD+BA group compared with the group with CHD but without BA (p = 0.003). Dimensions of RA and right ventricle (RV) in both groups were within the normal range. This suggests that patients still have no dilatation and no right heart hypertrophy. This is probably because the study included patients with non-severe bronchial asthma, and there were no patients with fixed bronchial obstruction, which could lead to the development of chronic cor pulmonale.

According to 24ECG results, it was found that the number of myocardial ischemia episodes in the group with CHD but without BA was greater than in the CHD+BA group (p = 0.003) (Table 4).

The duration of ischemic depression per 24 hours in the group with CHD but without BA was also longer than in the CHD+BA group (p = 0.03).

According to A.L. Vertkin et al. (2015), episodes of myocardial ischemia are revealed in 0.5-1.9% of apparently healthy individuals. The interpretation of ischemia in patients with BA is complicated because degenerative myocardial changes related to pulmonary hypertension and hypoxemia can be found not only in the right but also in the left ventricle [1].

In the CHD+BA group, in comparison with the CHD group without BA, average daily HR was significantly higher (p = 0.008), as well as average HR during daytime (p = 0.004) and during nighttime (p = 0.007) (Table 5).

Increased heart rate in patients with BA is probably not associated with beta2-agonists, since most patients with BA (92%) received a combination drug with a selective beta2-agonist vilanterol, which has no adverse effect on cardiovascular system [13].

According to 24ECG results in the CHD+BA group, a greater number of extrasystoles of different types were recorded in comparison with the patients with CHD but without BA. However, there was no significant difference in the number of supraventricular extrasystoles (217.12 [212; 223] extrasystoles in the CHD+BA group; 205.08 [202; 208] extrasystoles in the CHD group, p = 0.07). Ventricular extrasystoles associated with CHD and BA were recorded statistically more frequently — 78.6 [68.9; 80.2] than related to CHD without BA — 58.4 [56.2; 62.2], p = 0.007. Results of 24ECG are comparable with patients' complaints of palpitations, which were more common in CHD with BA. One of the triggers of arrhythmias in patients with

Table 4. *The 24ECG parameters in groups of patients*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	p
The number of episodes of ischemic ST-segment depression/24 hours	5 [4.4; 5.2]	8 [4.9; 9.4]	0.003
The mean duration of ischemic ST-segment depression/24 hours, min	2.02 [1.02; 3.18]	5.06 [0.9; 7.0]	0.03
Maximal ST-segment depression, mm	1.59 [1.03; 1.9]	1.8 [1.04; 2.02]	0.03

Note: 24ECG — 24-hour ECG monitoring, CHD — coronary heart disease, BA — bronchial asthma

Table 5. *Heart rate values in groups of patients*

Parameter	Group 1 (CHD and BA) (n = 90)	Group 2 (CHD without BA) (n = 90)	p
Average daily HR, bpm	82.2 [80.5; 84.2]	73.6 [70; 78]	0.008
Average HR during daytime, bpm	78.4 [76.8; 80]	65.4 [62.4; 74.7]	0.004
Average HR during nighttime, bpm	74.6 [74.0; 78]	67.4 [64.2; 72.8]	0.007

Note: HR — heart rate, CHD — coronary heart disease, BA — bronchial asthma

CHD and BA is hypoxia and the intake of several bronchodilators, namely beta2-agonists, especially short-acting ones [11]. In addition, during this study, patients with CHD but without BA took beta-blockers that reduce ectopic myocardial activity [14].

The study of lipid metabolism revealed that in patients with CHD combined with BA, higher total cholesterol (TC) was observed in comparison with the CHD group without BA (5.8 ± 0.13 mmol/L and 5.2 ± 0.24 mmol/L, p = 0.013). The level of triglycerides (TG) in the CHD+BA group was 1.4 ± 0.04 mmol/L, and in the CHD group without BA — 1.4 ± 0.06 (p = 0.022). Low-density lipoprotein cholesterol (LDL-C) in group 1 was 1.4 ± 0.01 mmol/L, and in group 2 — 0.99 ± 0.03 mmol/L (p = 0.014); high-density lipoprotein cholesterol (HDL-C) in the CHD+BA group was 0.7 ± 0.04 mmol/L, and in the CHD group without BA — 0.9 ± 0.06 (p = 0.034). Patients with BA were characterized by poor adherence to lipid-lowering treatment, as they focus on pulmonary disease. According to the literature, a more aggressive course of atherosclerosis is discussed in presence of BA due to the prolonged circulation of pro-inflammatory cytokines in the blood which induce inflammatory process in plaques, their growth and damage [3].

Conclusion

According to this study, BA occurs in patients with CHD in 16.6% of cases. According to the literature, the incidence of CHD combined with BA is 6.8-34.3% [1].

Our study allowed finding a number of characteristic features of the course of CHD in patients with BA. First, patients quite often complain of shortness of breath and palpitations and rarely of typical angina pain. This is because shortness of breath related to CHD and BA will prevail in the clinical evidence and will be of mixed nature. A physician should figure out the leading cause of dyspnea — whether it is cardiac or pulmonary. This is necessary for the choice of drug therapy. It is impossible to answer this question during routine examination. A number of diagnostic tests are required, in particular a cardiopulmonary stress test, which is very informative and safe for this category of patients.

Secondly, patients with CHD and BA have increased BP and HR, which indirectly indicates the activation of renin-angiotensin-aldosterone and sympathoadrenal systems and requires appropriate groups of drugs in the treatment of such patients. Objective hypersympathicotonia related to BA is also confirmed by the results of 24ECG, which reveal different types of arrhythmias in patients; they may be caused by the state of chronic hypoxia, or by certain medications for the treatment of BA itself. In our opinion, studying the possibility of using highly selective beta blockers for concomitant BA is very promising.

Thus, the issues of pathogenic mechanisms, clinical and functional features of the course of CHD concomitant with BA, and the choice of optimal treatment for this category of patients require further study, and we will continue this study in future.

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Assessment of Risk Factors of Cardiovascular Diseases and Arterial Stiffness in Women of Different Ages

Abstract

Objective: a comprehensive study of the prevalence and structure of risk factors (RF) for cardiovascular diseases (CVD), daily changes in central aortic pressure and arterial stiffness in healthy women of different age groups. **Materials and methods:** the study involved 161 women aged 18 to 65 years with one or more CVD RFs. All volunteers filled in a questionnaire and underwent daily monitoring of blood pressure with determination of arterial stiffness and daily changes in central aortic pressure, determination of carotid-femoral pulse wave velocity and vascular stiffness using volume sphygmography. **Results:** the patients were divided into 3 groups: group 1: 52 women of young age from 18 to 30 years (23.8 ± 5.3 years); group 2: 54 women from 31 years to menopause (41 ± 5.9 years); group 3: 55 women in the postmenopausal period (55.4 ± 5.8 years). High prevalence of modifiable CVD RFs was revealed among women of different ages: smoking, non-compliance with dietary recommendations, lack of physical activity. Obstetric and gynecological disorders prevailed in younger age groups. In group 1, the studied indicators corresponded to normal across most parameters. Significant differences in central and peripheral pressure, arterial stiffness parameters, with the exception of carotid-femoral pulse wave velocity (cfPRV), were revealed in group 2 in comparison with young women. A comparative analysis of groups 2 and 3 showed a significant deterioration in the parameters characterizing the degree of arterial stiffness, the contribution of the reflected wave and the associated dysfunction of the left ventricle. **Conclusion:** a comprehensive examination of arterial stiffness allows to identify subclinical changes in the vascular wall and evaluate their progression in women of different age groups.

Key words: *arterial stiffness, women, risk factors*

Conflict of Interests

The authors state that this work, its theme, subject and content do not affect competing interests

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BP — blood pressure, HDP — hypertensive disorders during pregnancy, DPI — double product index, BMI — body mass index, cfPRV — carotid-femoral pulse wave velocity, LV — left ventricle, MS — metabolic syndrome, DM — diabetes mellitus, BPDM — blood pressure daily monitoring, CVD — cardiovascular diseases, CVS — cardiovascular system, RF — risk factor, AI — augmentation index, Aix75 — augmentation index, reduced to heart rate = 75 bpm, ASI — arterial stiffness index, CAVI — cardio-ankle vascular index, dp/dt max ao — the maximum rate of increase in blood pressure in the aorta, ED — ejection duration, PPA — pulse pressure amplification, PEP — preejection period, PWVao — the velocity of the pulse wave in the aorta, RWTT — reflected wave transit time, SEVR — subendocardial viability ratio

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Introduction

Despite the improvement of diagnostic and treatment methods, CVDs still lead in the structure of morbidity and mortality. In recent years, CV mortality among women from has increased in European countries, and has become 9% higher than that among men. In this regard, the interest of researchers in the problem of women's health is growing, and multicenter studies are being conducted, research centers are being set up, and the list of special female CVD RFs is being studied and expanded. In various countries, recommendations are being developed on the prognosis and prevention of CVD in women with a history of obstetric and gynecological abnormalities [1, 2].

In our country, smoking among women is on the rise. The development of endothelial dysfunction in women smokers leads to an increase in arterial stiffness, and with the onset of menopause, this process is only gaining momentum [3]. The SAPALDIA study [4] and The Anglo-Cardiff Collaborative Trial [5] identify smoking as a predictor of increased arterial stiffness. According to the Rotterdam study, the consumption of fruits and vegetables, adequate physical activity and the avoiding of smoking contribute to the improvement of vascular stiffness [6]. Similarly, moderate alcohol consumption among women leads to a decrease in pulse wave velocity (PWV) [7]. The presence of occupational hazards, including night shift work, has a much greater detrimental effect on women than on men. The results of a large prospective study conducted among nurses (Gu F. et al., 2015) indicate that night shift work for 5 years or more contributed to a significant increase in the risk of death for cardiac reasons [8]. Obstetric and gynecological abnormalities are of great importance as CVD RFs. Hypertensive disorders during pregnancy (HDP) contribute to the development of vascular and metabolic disorders [2], increase the stiffness of the vascular wall, namely the augmentation index (AI) [9], predisposing women to the development of CVD. The negative detrimental effect of estrogen deficiency during menopause on vascular function, which is associated with a risk of CVD, has been proven. Arterial stiffness is significantly higher in women with early, including surgical, menopause [10]. For young women, metabolic syndrome (MS) poses a greater threat to reproductive health, and when menopause occurs, it causes CVD. The development of MS and diabetes mellitus (DM) leads to a progressive deterioration in vascular function. Postpartum and menopausal MS are of particular importance. Many studies show a direct correlation of gestational diabetes with the development of CVD and their fatal complications, which is partially mediated by an increased risk of type 2 diabetes in future [11].

The aim of this study is a comprehensive study of the prevalence and structure of CVD RFs, the daily changes in central aortic pressure and arterial stiffness in healthy women of different age groups.

Materials and Methods

The study protocol was approved by the Ethics Committee of the A.I. Yevdokimov Moscow State University of Medicine and Dentistry (A.I. Yevdokimov MSMDU). Prior to enrollment in the study, all participants gave written informed consent.

A cross-sectional comparative study was conducted in which 161 women aged 18 to 65 years with one or more CVD RFs with various medical specialties took part. All the patients were divided into 3 groups: group 1: 52 women of young age from 18 to 30 years (23.8 ± 5.3 years); group 2: 54 women from 31 years to menopause (41 ± 5.9 years); group 3: 54 women in natural or surgical menopause (55.4 ± 5.8 years). The women did not receive treatment during the examination period. All volunteers underwent clinical examination, measurement of anthropometric indices, survey, blood pressure daily monitoring (BPDM) with determination of arterial stiffness and daily changes in central aortic pressure, determination of carotid-femoral PWV (cfPWV) and vascular stiffness by volume sphygmography.

The survey was performed using a questionnaire specially developed for the purpose of scientific research and improving the quality of the collection of anamnesis history taking into account literature data ("National Recommendations for Cardiovascular Prevention" Russian Society of Cardiology, 2011; European Guidelines for the Prevention of Cardiovascular Diseases in Clinical Practice, European Society of Cardiology, 2016).

This questionnaire was used in the project "Three ages of women" [12]. The questions on the questionnaire are aimed at identifying complaints, CVD RFs, the presence of chronic diseases and the features of obstetric and gynecological history.

During anthropometry, height, weight, waist circumference (WC) and hip circumference (HC) were measured, body mass index (BMI) was calculated using the Ketle formula (BMI = body weight (kg) / height $(m)^2$).

The cfPWV was determined non-invasively by the Doppler method from the carotid to the femoral artery using the Pulse Trace PWV ultrasound Doppler device (Micro Medical, UK). The distance traveled by the pulse wave was determined between the points of application of the sensors above the carotid and femoral arteries and multiplied by a factor of 0.8.

Volumetric sphygmography was used to study arterial stiffness using a sphygmomanometer and a VaSera VS-1500N sphygmograph (Fukuda Denshi, Japan).

BPDM was performed using the blood pressure (BP) daily monitoring system with the BPLab ® oscillometric method using the Vasotens technology (Petr Telegin Ltd., Nizhny Novgorod).

Statistical Methods

For statistical processing, the statistical package Statistica for Windows 10.0 was used. To check for the normality of distributions, the Shapiro—Wilk test was used (to assess the possibility of using parametric or nonparametric criteria for comparing the groups under consideration; this criterion was chosen for checking for normality because it has the greatest power). A comparative analysis of quantitative variables was carried out using the Student's parametric T-test for dependent populations (according to the results of the previous test for normality, the distribution of parameters in the groups did not differ from the normal one; the choice of this criterion was determined by its greatest power for the groups under consideration). A comparative analysis of qualitative categorical variables was carried out using contingency tables with the chi-square (χ^2) test. The differences were considered significant at $p < 0.05$. The data are presented as M ± SD, where M is the mean value, and SD is the standard deviation.

Results

A comparative analysis revealed a significant difference in the social status, level of employment and education of the women in group 1 compared to the other two groups ($p < 0.01$), while no differences were seen between groups 2 and 3. Group 1 was mainly composed of full-time and evening students at the A.I. Yevdokimov MSMDU. Women with secondary vocational education were predominant in groups 2 (74%) and 3 (56.4%), most of them worked as nurses. The analysis of social status revealed a significant predominance of 40 women (76.9%) who were never married in group 1, while there were predominantly married women in groups 2 and 3.

Most of the patients assessed their health as satisfactory or good, with a significant predominance of positive characteristics in group 1 ($p < 0.01$).

The general characteristics of the groups according to the presence of CVD RF, the characteristics of obstetric and gynecological history and the results of the comparative analysis are presented in Table 1.

More than half of the patients had various complaints with significance predominance of members of group 3 (postmenopausal women). A high percentage of occupational hazards in groups is noteworthy, namely night shift work, which undoubtedly increases the risk of CVD in women. Among the patients, a large number of women smokers were identified and most of all (50%) in group 1, which was mainly composed of students. However, women of groups 2 and 3 showed a great commitment to smoking. Most of the patients do not follow a diet and do not consume the recommended 400 grams of fruits and vegetables per day. Only a few recognize themselves as physically inactive. Most women claim regular exercise and walking. Despite this, more than a quarter of women lead a predominantly sedentary lifestyle, and half of them have complaints during exercise. Women with moderate exercise at least for 150 min/week or with intense exercise at least for 75 min/week, or with a combination thereof with equivalent load were considered physically active. A sedentary lifestyle is a variant of a lifestyle with lack of physical activity: work in a sitting position combined with inactive leisure

time. There are complaints of shortness of breath and palpitations during physical exertion, including among women in group 1 (50%). It should be noted that there was no significant difference in the frequency of complaints during exercise in groups 2 and 3.

Analysis of the obstetric and gynecological history showed a high frequency of pregnancy pathologies. HDP, edema and proteinuria of pregnant women occupy leading positions. A significantly greater number of pregnancy pathologies were detected in groups 1 and 2. In group 1, 100% of women giving birth had pregnancy pathologies, of which 2/3 noted an increase in blood pressure during pregnancy. More than half of women who had a pregnancy had an abortion. About half of the women of group 2 underwent gynecological operations. Surgical menopause was noted in 12 (21.8%) women of group 3.

Table 1. *General characteristics of groups according to CVD RFs and obstetric and gynecological history*

Groups	Group 1	Group 2	Group 3
n	52	54	55
Mean age (M ± SD)	23.8 ± 5.3	41 ± 5.9	55.4 ± 5.8
Complaints, abs (%)	29 (55.8) #	37 (69.5) #	49 (89)
Family history of CVD, abs (%)	37 (71.1)	35 (64.8)	38 (69)
Occupational hazards, abs (%)	14 (26.9) *	31 (57.4)	22 (40)
Smoking, abs (%)	26 (50)	23 (42.6)	21 (38.2)
Daily smoking, abs (% of smokers)	18 (69.2)	20 (86.9)	19 (90.5)
Secondhand smoke, abs (% of smokers)	10 (19.2)	2 (3.7)	1 (1.8)
Duration of smoking more than 10 years, abs (% of smokers)	6 (23) *#	20 (87)	19 (90.5)
Desire to quit smoking, abs (% smokers)	17 (65.3)	15 (65.2)	15 (71.4)
Alcohol consumption, abs (%)	38 (23.6)	47 (87)	44 (80)
Dieting, abs (%)	14 (26.9)	14 (25.9)	18 (32.7)
Eating less than 400g of fruits and vegetables per day, abs (%)	41 (78.8)	44 (81.5)	39 (70.9)
Salt consumption over 5 g/day, abs (%)	7 (13.5)	12 (22.2)	10 (18.2)
Physically inactive, abs (%)	2 (3.8) *	8 (14.8)	7 (12.7)
Sedentary lifestyle	17 (32.7) *	14 (25.9)	20 (36.4)
Exercise Complaints, abs (%)	26 (50) **	37 (68.5)	35 (63.6)
Mean age of menarche (M ± SD)	12.56 ± 0.96	12.78 ± 1.87	12.78 ± 1.42
Menstrual irregularities, abs (%)	20 (38.5)	21 (38.9)	15 (27.3)
History of pregnancy, abs (%)	9 (17.3) *#	48 (88.8) ##	52 (94.5)
Number of women giving birth, abs (%)	7 (13.5)	43 (89.6)	51 (98)
Pregnancy pathologies, abs (% giving birth)	7 (100) #	37 (86) #	32 (62.7)
HDP abs (% giving birth)	5 (71.4)	17 (45.9)	12 (37.5)
Edema during pregnancy, abs (% giving birth)	3 (42.8)	26 (70.3)	16 (50)
Proteinuria during pregnancy, abs (% giving birth)	3 (42.8)	9 (24.3)	7 (21.9)
Anemia during pregnancy, abs (% giving birth)	3 (42.8)	16 (43.2)	4 (12.5)
Caesarean section, abs (% giving birth)	4 (57.1)	9 (20.9)	7 (13.7)
Abortion, abs (% of pregnancies)	5 (55.6) *#	26 (54.2)	36 (69.2)
Miscarriages, abs (% of pregnancies)	1 (11.1) *#	10 (20.8)	13 (25)
Fetal macrosomia, abs (% of pregnancies)	0 (0) *#	7 (16.3)	9 (17.6)
Gynecological surgery, abs (%)	10 (19.2) *#	24 (44.4)	33 (60)

Note: * — Significant difference (p < 0,01) with the parameters in group 2
** — Significant difference (p < 0.05) with the parameters in group 2
# — Significant difference (p < 0,01) with the parameters in group 3
— Significant difference (p < 0.05) with the parameters in group 3

Table 2. *Anthropometric data*

	All examined	Group 1	Group 2	Group 3
n	**161**	**52**	**54**	**55**
Height (M ± SD), cm	164.9 ± 5.9	166.3 ± 6.2 **	163.9 ± 5.5	164.6 ± 6
Body weight (M ± SD), kg	71.3 ± 14.7	60.5 ± 8.5 *#	75.6 ± 15.5	77.3 ± 12.9
BMI (M ± SD), kg/m²	26.3 ± 5.68	21.7 ± 3.3 *#	28.2 ± 6.3	28.6 ± 4.4
WC (M ± SD), cm	84.3 ± 15.7	71 ± 8.2 *#	88.4 ± 15.9	92.8 ± 12.6
HC (M ± SD), cm	103.8 ± 9.2	97.3 ± 6.6	106.5 ± 9.4	106.7 ± 8.5
WC/HC (M ± SD)	0.8 ± 0.12	0.73 ± 0.06	0.83 ± 0.1	0.86 ± 0.13

Note: * — Significant difference (p < 0,01) with the parameters of group 2
** — Significant difference (p < 0.05) with the parameters of group 2
# — Significant difference (p < 0,01) with the parameters of group 3

Table 3. *Parameters of daily monitoring of central aortic pressure and peripheral blood pressure in groups*

Groups: / (M ± SD)	Group 1	Group 2	Group 3
Mean SBP (mm Hg)	110.3 ± 8 *#	120.4 ± 11.9	122.8 ± 13.1
Mean DBP (mm Hg)	69.2 ± 5.5 *#	76.5 ± 7.9	78.2 ± 8.3
Mean BP (mm Hg)	83.7 ± 6.2*#	93 ± 8.9	96.3 ± 10.1
Mean PBP (mm Hg)	41.2 ± 5.4 ##	44 ± 8.7	44.6 ± 8.5
SBP variability (mm Hg)	12.5 ± 2.7 *#	15.5 ± 5	15.5 ± 3.9
DBP variability (mm Hg)	10.4 ± 2.3 *##	12.5 ± 3.6	11.7 ± 3
MBP variability (mmHg)	10.9 ± 2.3 *#	13.4 ± 3.8	12.9 ± 3.3
PBP variability (mm Hg)	9.2 ± 2.1 *#	11.3 ± 3.5	11.8 ± 3.8
Mean SBPao (mmHg)	100.4 ± 7.2 #	111.8 ± 10.7	115.1 ± 12.3
Mean DBPao (mmHg)	71.1 ± 6.3 #	79.1 ± 8.1	80.5 ± 8.7
SBPao variability (mmHg)	11 ± 2.5 *#	13.8 ± 4.3	13.7 ± 3.4
DBPao variability (mmHg)	10.7 ± 2.3 *##	12.8 ± 3.6	11.8 ± 3
PBPao variability (mmHg)	6.7 ± 1.5 *#	8.4 ± 2.5	9 ± 2.7
SBPao DND (%)	11.2 ± 5.1 *	13.2 ± 6.6	10.5 ± 8.5
DBPao DND (%)	16.9 ± 7.4 *	18.6 ± 7.4	15.8 ± 7.8
DPI day (mmHg/min)	88.9 ± 17.2 *	102.2 ± 16.6	93.5 ± 19.2
DPI night (mmHg/min)	62 ± 10.9 *##	71.4 ± 13	70.1 ± 13.4
DPI variability	22.6 ± 4.8 ##	23.7 ± 6.6 #	20.6 ± 5
AIao (%)	0.7 ± 7.4 *#	12.4 ± 7.5	13.6 ± 9.1
AIao to heart rate 75 (%)	1.9 ± 6.8 *#	15.1 ± 8.8	17.7 ± 7.3
PPA (%)	139.5 ± 6.2 *#	133.6 ± 6.6 #	128.3 ± 5.8
PPA to heart rate 75 (%)	140 ± 5.1 *#	132.1 ± 3.5	129.1 ± 15.7
ED (ms)	319.2 ± 22.2 *#	333.9 ± 27.1 #	356.2 ± 28.7
ED to heart rate 75 (ms)	316.7 ± 13.4 *#	336.9 ± 12.5	339.8 ± 17.4
SEVR (%)	123.5 ± 11.9 #	121.4 ± 9.7 ##	114.6 ± 17
SEVR to heart rate 75 (%)	122.2 ± 11.8	123.6 ± 11.7	120.7 ± 10
AIao variability (%)	11 ± 2.4 *#	13.8 ± 3.7	14.9 ± 4
PPA variability (%)	11.9 ± 2.2	11.2 ± 2.7 ##	10 ± 2.8

Note: * — Significant difference (p < 0,01) with the parameters of group 2
** — Significant difference (p < 0.05) with the parameters of group 2
# — Significant difference (p < 0,01) with the parameters of group 3
— Significant difference (p < 0.05) with the parameters of group 3
SBP — systolic blood pressure, DBP — diastolic blood pressure, MBP — mean hemodynamic blood pressure, PBP — pulse blood pressure, SBPao — central (aortic) systolic pressure, DBPao — central (aortic) diastolic pressure, DND — degree of nighttime decrease

Table 4. *Arterial stiffness parameters by groups*

Groups: (M± SD)	Group 1	Group 2	Group 3
	Doppler ultrasound		
cfPWV	7.77 ± 2.5	10.8 ± 4	11.9 ± 4.4
	Volumetric sphygmography		
R_CAVI	5.75 ± 0.5 **	6.57 ± 0.8 #	7.65 ± 0.9
L_CAVI	5.81 ± 0.6 **	6.65 ± 0.8 #	7.64 ± 1
R_AI	0.79 ± 0.1 **	1.01 ± 0.2 ##	1.09 ± 0.2
PEP	96.9 ± 21	95.6 ± 15.9 #	103.4 ± 13.5
ET	307.7 ± 16.2 #	308.3 ± 18.6 #	320.4 ± 21.2
	BPDM with an oscillometric method and using Vasotens Technology		
PWVao (m/s)	5.7 ± 0.7 **	8.05 ± 1.3 #	9.75 ± 1.1
PWVao (m/s) MBP100 HR 60	8.1 ± 1 *	9.9 ± 1.5 ##	10.5 ± 1.3
AIx (%)	–51.1 ± 10.6 *	–23.2 ± 10.7 #	–11.8 ± 8.4
AIx75 (%)	–49.7 ± 12.5 **	–25.2 ± 8.3 #	–15.8 ± 9.9
ASI (mm Hg)	126.7 ± 12.2 **	134 ± 15.5 ##	143 ± 20.4
RWTT (ms)	153 ± 12.7 **	129.6 ± 11.9 ##	124.9 ± 10.5
RWTT (ms) MBP 100 HR 60	170.2 ± 14.4 **	144.1 ± 16.2 ##	137.4 ± 12
dp/dt max ao (mm Hg)	556.1 ± 125.7 #	543.5 ± 121.6 #	480.4 ± 96.2
dPdt variability	163.6 ± 37.8 **	185.3 ± 68.6 ##	157.5 ± 55.4
RWTT variability	22.3 ± 4.9 **	18.8 ± 4.6	18.3 ± 4.6
PWVao variability	0.9 ± 0.2 **	1.1 ± 0.3	1.1 ± 0.2
CAVIao variability	1.4 ± 0.4 **	1.8±0.5 #	2.15 ± 0.5
IE variability	0.1 ± 0.03 **	0.1 ± 0.03	0.1 ± 0.03

Note: * — Significant difference (p < 0,01) with the parameters of group 2
** — Significant difference (p < 0.05) with the parameters of group 2
# — Significant difference (p < 0,01) with the parameters of group 3
–Significant difference (p < 0.05) with the parameters of group 3

The data obtained indicate a high prevalence of various CVD RFs among women who are medical workers. In a comparative analysis, the frequency of such RFs as smoking, alcohol consumption, non-compliance with dietary recommendations is comparable in all groups, regardless of age and reproductive status. The frequency of obstetric and gynecological pathologies was significantly higher in younger age groups.

A comparative analysis of anthropometric data showed the presence of significant differences between group 1 and the older groups in the presence of general and abdominal obesity, while there were no significant differences between the groups. More than half of women of groups 2 and 3 are obese or overweight. Half of women of group 3 and more than a third of women of group 2 have an abdominal type of obesity (Table 2).

During analysis of the results of the study of daily monitoring of central aortic pressure and peripheral blood pressure, significant differences were revealed when comparing the parameters of women of group 1 with older groups without a significant difference between the latter. Based on the results presented in Table 3, parameters of vascular stiffness in young women of group 1 are normal, despite the presence of a significant number of CVD RFs. However, an insufficient degree of nighttime decrease in blood pressure was found in a quarter of the patients of group 1, and the rate of morning BP rise was exceeded in 60%. An analysis of the morning changes and daily profile of BP showed the absence of significant differences between group 1 and groups 2 and 3, with the exception of parameters of the degree of nighttime decrease in aortic pressure. Most of the studied parameters

of daily monitoring of central aortic pressure and peripheral BP in women of groups 2 and 3 did not differ significantly, despite the development of menopause in group 3.

At the same time, it seems important to analyze parameters that have a significant difference in groups 2 and 3, as potentially significant initial markers of the development of arterial stiffness. A significant difference was seen between the variability of the double product index (DPI), the pulse pressure amplification index (PPA) and its variability, the subendocardial viability ratio (SEVR), and the length of the left ventricular (LV) ejection duration (ED). An increase in arterial stiffness in group 3 is evidenced by a decrease in SEVR, PPA and PPA variability, as well as an increase in ED, which leads to a decrease in LV systolic function due to a decrease in coronary blood flow and an increase in afterload (Table 3).

When analyzing arterial stiffness in groups 1 and 2, significant differences were revealed for all the studied parameters except for cfPWV and the preejection period (PEP). In groups 2 and 3, significant differences were seen between the cardio-ankle vascular index (CAVI) and the augmentation index (AI), determined by the volume sphygmography method, as well as the average daily rate of the pulse wave velocity in the aorta (PWVao), variability of PWVao, AI, and AI reduced to heart rate = 75 bpm (Aix75). At the same time cfPWV did not show a significant difference in the groups. It is necessary to pay attention to such parameters as the preejection period (PEP), ejection time (ET), the arterial stiffness index (ASI), the reflected wave transit time (RWTT), the maximum rate of increase in blood pressure in the aorta (dp/dt max ao), the variability of these parameters and the variability of CAVI in the aorta (CAVIao), which also showed a significant difference in groups 2 and 3. These indicators reflect the dynamic load on the walls of the great vessels during the passage of the pulse wave, the degree of arterial stiffness and the associated impaired LV function (Table 4).

Discussion

The large number of smoking female medical workers revealed is consistent with the data of various studies, despite the special role of doctors in promoting a healthy lifestyle. According to the extensive Champlain Nurses' Study, smoking is particularly prevalent among nurses [13]. As the age increases, the prevalence of smoking among women decreases, and BMI increases [14]. According to the results of our study, there is no significant difference in BMI between middle-aged and older women, regardless of the reproductive function.

The prevalence of traditional CVD RFs among women and men was estimated in a national multicenter population ESSE-RF study [15]. Compared with the results of that study, we found a higher level of physical activity among the women surveyed, lower consumption of salt, but insufficient consumption of fruits and vegetables.

According to the results of the analysis of the health status of pregnant women in the Russian Federation over 16 years of follow-up, anemia leads among pregnancy pathologies (32.6%), and the frequency of edema, proteinuria, and HDP progressively decreases to 10% [16]. On the contrary, our study revealed the highest frequency of HDP, proteinuria, and edema during pregnancy. The frequency of anemia during pregnancy among the examined women of a younger age was 43%.

The revealed significant differences between postmenopausal women and women with preserved reproductive function in CAVI, aortic pulse wave velocity (PWVao), augmentation index obtained by volume sphygmography and in the analysis of the central pulse wave are consistent with the results of many studies [17–20]. At the same time, cfPWV, the comprehensively studied parameter with the proven predictive ability in our study, was not significant, which may be due to its dependence on BP and heart rate during the study, which corresponded to normal values in our work.

Less studied parameters, which demonstrated significant differences between women with preserved reproductive function and postmenopausal women, are of greater interest. The preejection period and ejection time of the left ventricle, determined by two methods, reflect the systolic function of the left ventricle [21]. An increase in arterial stiffness index (ASI) in the postmenopausal group is associated with a risk of developing subclinical coronary atherosclerosis and has proven prognostic value in the development of coronary heart disease [22]. The reflected wave transit time RWTT

determines the contribution of the reflected wave to the formation of pulse pressure and the creation of LV afterload, decreases with age concurrently with the rise of PWVao, which corresponds to the results of the study [22]. The rate of increase in blood pressure in the aorta (dp/dt max ao) is a complex parameter that depends on the totality of the functions of the main and peripheral arteries, which makes it possible to track changes in LV contractility under inotropic effects [23]. The subendocardial viability ratio (SEVR) reflects the balance between coronary perfusion and LV afterload [24]. A decrease in SEVR in menopausal women indicates an imbalance and the likely development of systolic dysfunction.

In general, the above parameters are of great applied significance for determining the state of the cardiovascular system (CVS) in practically healthy women in relation to CVD identified in said women. These parameters reflect the development of early, preclinical changes and their progression with age, and also determine the beginning of primary and secondary CVD prevention. The objective need to expand these studies primarily in young and middle-aged groups should be noted.

Conclusions

1. High prevalence of CVD RFs among women of various age was revealed. The most common RFs are modifiable: smoking, non-compliance with dietary recommendations and lack of physical activity. Attention should be paid to the high frequency of obstetric and gynecological pathologies, as CVD RFs that are specific to women in younger age groups.

2. In women below the age of 30 with CVD RFs, arterial stiffness, central and peripheral blood pressure correspond to normal values across most parameters.

3. Significant changes in the studied parameters (with the exception of cfPWV and PEP) in the analysis of arterial stiffness, in comparison with women aged under 30, are already observed in group 2, despite their age and preservation of reproductive function, which indicates the need to start implementing preventive measures at this stage.

4. In the group of postmenopausal women, changes in arterial stiffness were detected, which mark the end of the reproductive period and the development of menopausal changes in CVS.

Comprehensive examination, including BPDM with determination of arterial stiffness and daily changes in central aortic pressure, determination of vascular stiffness by volume sphygmography, allows to detect subclinical changes in the vascular wall and evaluate their progression in women of different age groups.

Further studies are needed to determine the relationships between individual CVD RFs and their most frequent combinations with arterial stiffness in women.

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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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Liver Cirrhosis as the Outcome of Non-Alcoholic Fatty Liver Disease Associated with *PNPLA3* Gene *RS738409* Polymorphism

Abstract

Relevance. Non-alcoholic fatty liver disease is the most common hepatic disorder in the world. Despite the fact that, in general, this disease has a favorable prognosis and asymptomatic course, in some cases, it can develop as non-alcoholic steatohepatitis, and in some patients the development of liver cirrhosis and hepatocellular carcinoma is possible. Growing number of foreign studies demonstrate the association of genetic factors and the progression of non-alcoholic fatty liver disease. However, there is scarce information about this association in the Russian Federation. **Objective:** To assess the prevalence of the variants of patatin-like phospholipase domain-containing 3 gene in patients with liver cirrhosis as the outcome of non-alcoholic fatty liver disease in the population of RF as well as the effect of mutation on the disease course. **Materials and methods.** Patients were divided into three groups. Group I included 30 patients with liver cirrhosis as the outcome of non-alcoholic fatty liver disease. Group II included 46 patients with non-alcoholic fatty liver disease at non-cirrhotic stage. Group III included 25 healthy volunteers. A retrospective analysis of these patients' medical records was performed. For patients of groups I and II, the results of blood biochemistry, coagulogram, and abdominal ultrasound were obtained from medical records. Shear wave liver elastography was additionally performed using Aixplorer MultiWave ultrasound system (SuperSonic Imagine, USA). Alleles of patatin-like phospholipase domain-containing 3 gene were determined using polymerase chain reaction via terminal restriction fragment length polymorphism. **Results.** In this study we obtained significant associations between non-alcoholic fatty liver disease and mutations in patatin-like phospholipase domain-containing 3 gene (HR-2.171; 95% CI: 1.131-4.170; χ^2= 6.730769; p = 0.00948); between cirrhosis and the mutations in the *PNPLA3* gene (HR-4.011; 95% CI: 1.558-10.324; p = 0.0003). The relationship between the frequency of GG genotype of the *PNPLA3* gene with an increase in the liver fibrosis stage was shown for the population of the RF. **Conclusion.** rs738409 polymorphism of patatin-like phospholipase domain-containing 3 gene is a factor of the progression of non-alcoholic fatty liver disease to advanced stages of fibrosis and the development of liver cirrhosis. Determination of the polymorphism in patients with NAFLD in the population of the RF may be useful for defining groups at high risk of disease progression.

Keywords: *non-alcoholic fatty liver disease, liver cirrhosis, PNPLA3, non-alcoholic steatohepatitis*

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BMI — body mass index, DM — diabetes mellitus, HCC — hepatocellular carcinoma, NAFLD — non-alcoholic fatty liver disease, NASH — non-alcoholic steatohepatitis, PCR — polymerase chain reaction, *PNPLA3* — patatin-like phospholipase domain-containing protein 3, TRFLP — terminal restriction fragment length polymorphism, US — ultrasound

Introduction

Non-alcoholic fatty liver disease (NAFLD) is an urgent problem facing present-day gastroenterology, since despite the fact that this disease, in general, has a favorable course without complications, some patients may develop non-alcoholic steatohepatitis (NASH), and subsequently, liver cirrhosis. In addition, there are reports that NAFLD can lead to the development of hepatocellular carcinoma (HCC) [4].

Prevalence of NAFLD is reported to be 20–30% in Western countries and 5–18% in Asia [5]. In 2015, a study conducted by V.T. Ivashkin in the Russian Federation demonstrated that the incidence of this disease among outpatients in 16 regions of the country was 37.3% [2]. It should be noted that in 2007 this figure was lower and stood at 27% [1].

The most aggressive course has been reported in patients with type 2 diabetes mellitus (DM), high body mass index (BMI), obesity of abdominal type and signs of liver inflammation according to histological tests [6-8]. In addition, genetic factors also play a role [9]. In particular, several foreign studies revealed that polymorphism of patatin-like phospholipase domain-containing 3 gene (*PNPLA3*) *rs738409* makes a significant contribution to the development and progression of NAFLD [10-14]. *PNPLA3* gene is located on chromosome 22 and encodes adiponutrin. This protein consists of 481 amino acids, is expressed most in hepatic stellate cells, hepatocytes and retinal cells, and belongs to the family of patatin-like phospholipases. Adiponutrin exhibits triglyceride hydrolase activity, lysophosphatidic acid acyltransferase activity, and retinol palmitate esterase activity. Replacing isoleucine with methionine in the 148th position of the amino acid sequence leads to the loss of these functions and the accumulation of triglycerides and retinol-palmitate in the liver [15, 16].

Romeo S. et al. was the first to notice the *PNPLA3 I148M* polymorphism in 2008. Using the method of genome-wide association study, the authors revealed a higher susceptibility to NAFLD and a higher level of alanine aminotransferase (ALT) in carriers of mutations (G allele) [10]. These results were repeatedly confirmed in other studies [11-13]. Moreover, a number of studies showed that homozygous carriers of G allele demonstrated more significant histopathological changes in the liver tissue [11, 13]. Moreover, in 2010, Valenti et al. analyzed the results of polymerase chain reaction (PCR) in 591 patients with NAFLD confirmed by histological tests and revealed that NASH and advanced liver fibrosis are more often observed in homozygous carriers of G allele in comparison with heterozygous ones and with homozygous carriers of C allele. This association was observed irrespective of metabolic syndrome [11]. In addition, an association was found between the mutation and increased risk of HCC. In 2014, results of a meta-analysis of 24 studies were published. This analysis was conducted in order to assess the relationship between polymorphism of *PNPLA3* I148M and severity of liver fibrosis, risk of HCC and prognosis in patients with HCC with underlying liver diseases of various etiologies. The authors found a statistically significant relationship between *PNPLA3 I148M* polymorphism and advanced liver fibrosis with underlying NAFLD (OR 1.23, 95% CI

1.10–1.37), as well as in the course of analysis of the association of this polymorphism and increased risk of HCC with underlying NAFLD (OR 1.67, 95% CI 1.27–2.21) [17].

Despite the fact that researchers around the world proved the relationship between the development and progression of NAFLD and PNPLA3 I148M polymorphism, this association is understudied in the Russian Federation. Only in 2018, results of the first study was published. The study included 35 patients and its goal was to study the effect of *PNPLA3* I148M polymorphism on the progression of NAFLD [3]. According to the author of this study, only G-allele carriers had a high stage of fibrosis, i.e. stage 3 according to liver elastography, and patients with stage 2 were heterozygous in 70%. However, patients with cirrhosis were not enrolled in this study. Moreover, the results of genetic testing showed only *CC* (no mutation) and *CG* genotypes in study participants.

The objective of this research was to assess the prevalence of *PNPLA3* gene variants in patients with liver cirrhosis as the outcome of NAFLD and the effect of mutations on the course of this disease as illustrated by the population of the RF.

Materials and Methods

To achieve this goal, a retrospective analysis of case histories was performed for the patients of the State Budgetary Institution of Healthcare "Buyanov City Clinical Hospital of the Moscow Healthcare Department" (Buyanov State Clinical Hospital), Federal State Budgetary Healthcare Institution "Central Clinical Hospital of the Russian Academy of Sciences" (Central Clinical Hospital of the Russian Academy of Sciences), Federal State Autonomous Educational Institution of Higher Education "Pirogov Russian National Research Medical University" of the Ministry of Health of the Russian Federation (Pirogov Research Medical University), Loginov Moscow Clinical Research Center of the Moscow Healthcare Department (Loginov Clinical Research Center) treated in these institutions in 2007-2019 in order to select participants. Inclusion criteria were: age over 18 years; no mental disorders; signed informed consent; for group III, BMI less than 25 kg/m^2; for groups I and II, BMI more than 25 kg/m^2; liver damage (signs of cirrhosis and signs of chronic liver disease at non-cirrhotic stage, respectively). Exclusion criteria were: type 1 diabetes, viral hepatitis, storage diseases, alcohol abuse, autoimmune liver diseases, contact with other hepatotoxic substances; additional exclusion criteria for group III were NAFLD, type 2 diabetes, metabolic syndrome. 101 patients were included and divided into 3 groups: group I — patients with liver cirrhosis (n = 30), group II — patients with NAFLD at non-cirrhotic stage (n = 46), group III — healthy volunteers (n = 25). All study participants gave written informed consent. The study was approved by the Ethics Committee of the Pirogov Research Medical University of the Ministry of Health of Russia.

Initial diagnoses of NAFLD and cirrhosis were made based on the results of abdominal ultrasound (US) and laboratory tests. Subsequently, in order to confirm liver cirrhosis for group I and to exclude it for group II, shear-wave liver elastography was performed using Aixplorer MultiWave ultrasound system (SuperSonic Imagine, USA).

In order to determine variants of *PNPLA3* gene, DNA was extracted from peripheral blood WBC using AmpliPrime DNA-sorb-B commercial kit (InterLabService, Russia, No. K-1-2-100). Analysis of p.I148M mutation in the *PNPLA3* gene (rs738409) was performed using polymerase chain reaction (PCR) by terminal restriction fragment length polymorphism (TRFLP) analysis of PCR products. The fragment of *PNPLA3* gene, 333 bps in length, was amplified using a pair of primers (forward primer: 5'-TGGGCCTGAAGTCCGAGGGT-3'; reverse primer: 5'- CCGACACCAGTGCCCTGCAG-3') on a Tertsik PCR thermocycler (DNA-Technology, Russia). PCR mixture: 9μL ddH2O, 5μL 5x PCR buffer, 2.5 μL 25 mM MgCl2, 2.5 μL 25mM dNTP Mix, 1.5 μL (10pkmol/μL) of each primer, 0.3 μL (5 e.a.) Taq polymerase, and 3 μL DNA. PCR conditions: 95°C — 5 min, 94°C — 30 s, 66°C — 30 s, 72°C — 40 s, 37 cycles, 72°C — 5 min.

Obtained PCR products were subjected to enzymatic treatment with BstF5 I restrictase (SibEnzyme, Russia) at a temperature of 65°C for 10-12 hours. The products were subjected to electrophoretic separation in 40% polyacrylamide gel. Genotype test for patients was carried out in

accordance with the following principle: *CC* genotype — 300, 133 bps, *CG* genotype — 333, 200, 133 bps, *GG* genotype — 333 bps. The results of TRFLP analysis are shown in Figure 1.

Statistical analysis was performed using STATISTICA 10 software (StatSoft.Inc., 2010). Since the distribution of the results differed from normal distribution, nonparametric statistics methods were used. Median (Me) and interquartile range (IQR) (Q1-Q3) were used to describe the data. When comparing nominal values, contingency tables were used followed by calculation of Fisher, χ^2 Pearson, Yates's correction for χ^2 Pearson correlation criteria. Relative risk (RR) and its boundaries in the form of a 95% confidence interval (95% CI) were additionally calculated. Results were considered statistically significant with $p<0.05$.

Results and Discussion

Among the participants with NAFLD at non-cirrhotic stage and liver cirrhosis, the same percentage of men and women was observed, 27% and 73%, respectively. In the group of healthy volunteers, there were 12 women and 13 men. Median age of group I was 64.0 years (IQR 55; 68), of group II — 58.5 years (IQR 51; 65), of group III — 21 year (IQR 20; 24). Liver elastography was performed for 26 patients in group I. This study was not conducted for 2 patients in this group due to severe ascites, and for 2 patients due to a high degree of obesity. Median liver elasticity was 18.95 (IQR 15.1; 25.1) kPa. According to the results of liver elastography, 10 participants in group II had no liver fibrosis, and 8 participants had liver fibrosis of F1 stage, 17 participants — of F2, 11 participants — of F3. Median liver elasticity was 7.8 kPa (IQR 5.8; 9.1). Figure 1 shows the distribution of PNPLA3 gene variants in patients enrolled in the study.

As shown in Figure 2, *CG* genotype was most often observed in patients with liver cirrhosis, *CC* genotype was found in patients with NAFLD at non-cirrhotic stage and healthy volunteers. These results are consistent with published data [12].

Subsequently, the relationship between NAFLD and mutation (G allele) was analyzed. For this purpose, patients of groups I and II were nominally combined and compared with the group of healthy volunteers. This analysis revealed a statistically significant relationship between NAFLD and the mutation (OR-2.171; 95% CI: 1.131-4.170; χ^2=6.730769; p=0.00948).

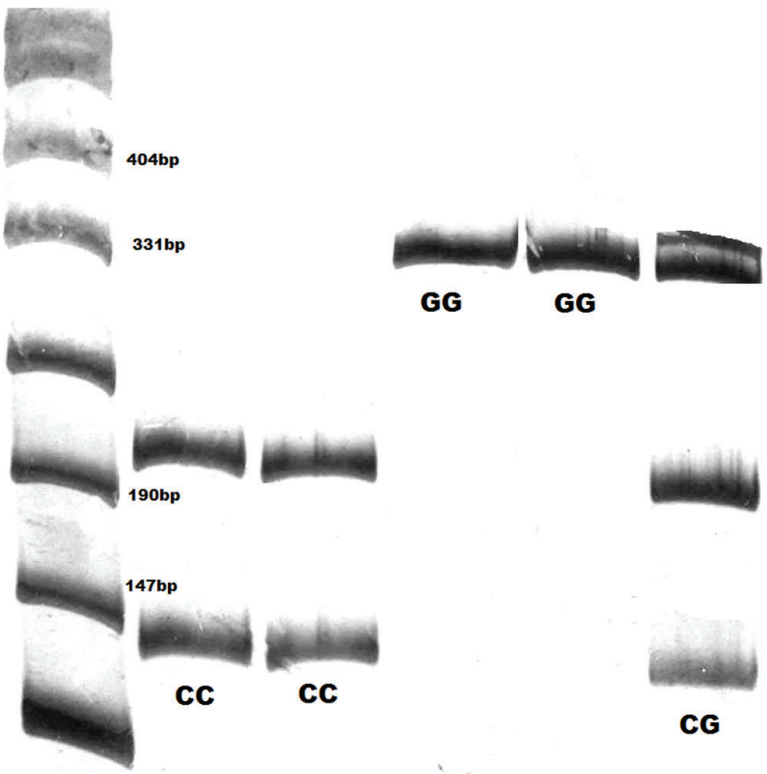

Figure 1. *TRFLP analysis results. PNPLA3 gene*

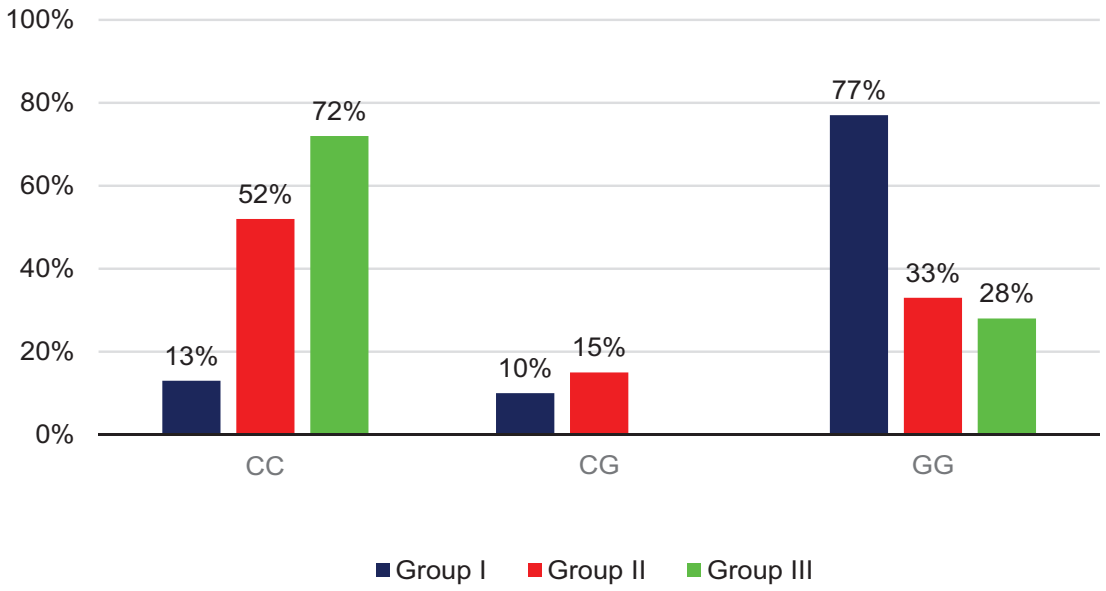

Figure 2. *Distribution of PNPLA3 gene variants among study participants*

Table 1. *Prevalence of PNPLA3 genotypes in patients with NAFLD at various stages of fibrosis*

Stage of fibrosis / Genotype	F0 (n=10)	F1 (n=8)	F2 (n=17)	F3 (n=11)	F4 (n=26)	χ^2	ρ (for the trend)
CC	8	5	8	3	3		
GG	1	2	6	6	21	22.623	<0.01
CG	1	1	3	2	2		

In addition, results of further analysis showed a statistically significant relationship between liver cirrhosis and mutations in *PNPLA3* gene in patients with NAFLD (OR-4.011; 95% CI: 1.558-10.324; p= 0.0003).

The next step was to analyze the prevalence of genotypes of *PNPLA3* gene in patients with different stages of fibrosis with underlying NAFLD. The results are shown in Table 1.

As shown in Table 1, patients with NAFLD demonstrated increasing incidence of *GG* genotype with increasing liver fibrosis stage, and, on the contrary, decreasing incidence of *CC* genotype. These results were statistically significant.

To illustrate the results obtained, here is the clinical case of a patient with liver cirrhosis as the outcome of NAFLD and a positive result for *PNPLA3* rs738409 gene polymorphism (*GG* genotype).

Clinical Case

Patient R., 61 years, was treated in the Gastroenterology Department of Buyanov City Clinical Hospital of the Moscow Healthcare Department from November 20 to November 30, 2018. He complained of pain in the upper abdomen, discomfort in the right hypochondrium, weakness. According to the data provided by medical records, the patient was diagnosed with liver cirrhosis for the first time in 2011. Subsequently, every year he underwent routine inpatient treatment for this disease. The patient had the abovementioned complaints for a month and it was the reason for hospitalization. According to the examination, laboratory tests and instrumental examination, the diagnosis was: Liver cirrhosis as the outcome of NAFLD, Child-Pugh class B (7 points). MELD score =10. Portal hypertension: esophageal varices grade 1 according to N. Soehendra, K. Binmoeller; splenomegaly; ascites. Liver cell failure: coagulopathy; persistent hepatic encephalopathy, stage I; hypoalbuminemia. Axial hiatal hernia. Erosive esophagitis. Impaired glucose tolerance. Benign prostatic hyperplasia." Drug treatment during hospitalization: omeprazole 20 mg 2 times a day; lactulose 10 mL 3 times a day; anaprilin 5 mg 3 times a day; verospiron 25 mg in the morning; L-ornithine-L-aspartate 3 g 3 times a day. On November 30, 2018 the patient

was discharged with improvement; it was recommended to continue taking the following drugs: omeprazole 20 mg 2 times a day; lactulose 10 mL 3 times a day, anaprilin 5 mg 3 times a day, verospiron 25 mg in the morning.

At the time of inclusion visit, the patient complained of general weakness and periodic insomnia. Results of physical examination showed a slightly enlarged abdomen due to excessive subcutaneous fat. Liver does not protrude below the costal margin; the margin is dense on palpation, rounded, smooth, spleen is not palpable. Height 172 cm, weight 86 kg, BMI 29 kg/m^2. Signs of hepatic encephalopathy, stage I. The Connect-the-Numbers Test was completed in 68 seconds. The patient denied alcohol abuse. Results of AUDIT (Alcohol Use Disorders Identification Test) questionnaire — 2 points, CAGE (Cut down, Annoyed, Guilty, Eye-opener) — 0 points, alcohol/non-alcohol index — 4.24.

Results of laboratory tests and instrumental examination (extract from Buyanov City Clinical Hospital from 11/30/2018):

1) blood biochemistry: AST — 34 IU/L, ALT — 37 IU/L, γ-GT — 38 IU/L, ALP — 170 IU/L, total cholesterol — 5.04 mmol/L, albumin — 33 g/L, total bilirubin — 26.5 μmol/L, glucose — 5.7 mmol/L, creatinine — 83 μmol/L, GFR according to CKD-EPI — 92 mL/min/1.73 m^2, sodium — 142 mmol/L, iron — 13 μmol/L;

2) serological test: HBsAg — negative, anti-HCV — negative; 3) complete blood count: platelets — 212×103/μL, WBC — 4.2×109/L, RBC — 4.44×106/μL, mean cell volume — 92 fL, hemoglobin — 153 g/L;

4) coagulogram: Quick's value — 98%, INR — 1.21;

5) Abdominal ultrasound: Diffuse changes in liver and pancreas. Signs of portal hypertension: mild splenomegaly (spleen dimensions 124 × 58 mm), portal vein dilated to 16 mm

6) Esophagogastroduodenoscopy: Conclusion: Hiatus hernia. Erosive esophagitis. Esophageal varices grade I (convoluted venous trunks with varicose nodes up to 5 mm in size in the middle and lower third of esophagus).

Moreover, we performed additional tests: 1) results of laboratory blood tests: AMA — <1:40, ANA — <1:40, ANCA — <1:40, SMA — <1:40, ceruloplasmin — 42 mg/dL, ferritin — 40 μg/L, iron — 18 μmol/L; 2) liver elastography — 22.5 kPa (F4 METAVIR); 3) PCR diagnostics: PNPLA3, GG genotype.

This clinical case includes the results of examination of a patient with a comprehensive clinical picture of liver cirrhosis. We excluded alcoholic, viral, autoimmune etiology of liver damage, as well as storage diseases (hemochromatosis, Wilson's disease), so, we suggested that NAFLD caused liver cirrhosis in this patient. Analysis of the clinical and laboratory picture revealed mild signs of MS: the patient has impaired glucose tolerance, BMI corresponds to overweight stage. At the same time, according to the results of PCR diagnostics, the patient is homozygous for G allele of *PNPLA3* gene. In our opinion, this clinical case demonstrates the cirrhogenic potential of *PNPLA3* gene polymorphism and emphasizes the importance of its detection in patients with NAFLD in order to predict the risk of an aggressive course of this disease.

Conclusion

There are many foreign studies proving the relationship of *PNPLA3* I148M gene polymorphism with the development and progression of NAFLD [11-15, 18]. However, information on this association is limited in the Russian Federation [19]. This paper is the first study of the prevalence of various *PNPLA3* gene genotypes in patients with liver cirrhosis as the outcome of NAFLD; more frequent disease progression in homozygous carriers of G allele was demonstrated in the case of the population of the RF. In general, the results of our work confirm the results obtained by foreign researchers. Detection of *PNPLA3* I148M gene polymorphism in patients with NAFLD in the population of the RF may be useful for defining high-risk groups for disease progression.

Author contribution:

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

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Role of Gene Polymorphisms of Matrix Metalloproteinases-2, -3 and -13 in the Development of Coronary Artery Atherosclerosis in Patients with Primary Polyosteoarthrosis

Abstract

Rationale. Osteoarthrosis is a chronic non-communicable disease that is observed in more than 10-20% of the world population, and has a leading position in the frequency of patients' disability. In recent years, the development of hypertension, atherosclerosis, as well as cardiovascular complications, has often been reported with underlying progressive osteoarthrosis. The role of matrix metalloproteinases in the course of atherosclerosis in patients with osteoarthrosis is not well understood. **Objective.** To determine the effect of genetic polymorphism of the genes of matrix metalloproteinases (MMPs) -2 (*rs2285053*), -3 (*rs3025058*) and -13 (*rs2252070*) on the development of coronary artery atherosclerosis in patients with primary polyosteoarthrosis. **Methods.** Gene polymorphisms of matrix metalloproteinase-2 (*rs2285053*), -3 (*rs3025058*) and -13 (*rs2252070*) and their relationship with the development of atherosclerosis in patients with osteoarthrosis were defined. **Results.** The study of the polymorphism (*rs2252070 T/C*) of the *MMP-13* gene revealed that the carriage of the homozygous T allele of MMP-13 gene polymorphism was 1.76-fold higher in the group of patients without verified coronary artery atherosclerosis when compared with the group of patients with verified coronary artery atherosclerosis. Therefore, this genotype variant can be positioned as a protective one in relation to the development of atherosclerosis of coronary arteries. The heterozygous variant of *T/C* genotype was more common in the group of patients with verified coronary artery atherosclerosis — 59.1%. Calculation of odds ratio shows that the possibility of coronary artery atherosclerosis in patients with this genotype is 2.7-fold higher than in patients with a homozygous variant. **Conclusion.** Taking into account the results obtained, the heterozygous variant of rs2252070 T/C of matrix metalloproteinase-13 increases the odds of developing coronary artery atherosclerosis in patients with osteoarthrosis.

Keywords: *matrix metalloproteinase-2, matrix metalloproteinase-3, matrix metalloproteinase-13, osteoarthrosis, coronary artery atherosclerosis*

Conflict of interests

The authors declare that this paper, its topic, subject and content do not involve competing interests.

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Introduction

Knee and/or hip osteoarthrosis was ranked first in the nosological structure of rheumatic diseases in 2018; its prevalence among all residents of Russia that are 18 years and older was 13% [1]. OA occupies a leading position among diseases that most often lead to the disability of patients. Currently, hypertension [2], atherosclerotic lesions, as well as cardiovascular complications frequently develop in the setting of progressive osteoarthrosis. Genetic predisposition and epigenetic variants with their mutual influence can provoke the development of OA [3] and cardiovascular diseases [4] that often interfere and can be considered as comorbid pathology. This fact is defining for a more severe course of pathological processes [5]. Family history of OA can be the result of the pathological cartilage structure due to a mutation of type II collagen gene CLOL2A1 (localized on chromosome 12); this mutation can lead to the development of cartilage dysplasia and more severe variants of OA [6]. In present-day literature, there are not enough studies of the role of gene polymorphisms of matrix metalloproteinases in the development of OA. In the case of *MMP-31171 5A / 6A* polymorphism, allele *6A*, according to published data, can provoke reduced enzyme synthesis. Therefore, in the presence of variant *5A,* a larger amount of *MMP-3* is formed, which can trigger the rupture of an atherosclerotic plaque [7, 8]. The role of matrix metalloproteinases in the development and progression of atherosclerosis in patients with osteoarthrosis is an urgent problem, but it has not been studied enough.

Objective: to determine the effect of genetic polymorphism of matrix metalloproteinase-2 (*rs2285053*), -3 (*rs3025058*), and -13 (*rs2252070*) genes on the development of coronary artery atherosclerosis in patients with primary polyosteoarthrosis.

Materials and Methods

Study design:

This study enrolled 90 patients diagnosed with primary polyosteoarthrosis (OA). Patients were treated at the Regional Clinical Hospital and at the Clinical Medical Center, Chita, from November 2017 to October 2019. Laboratory tests were conducted at the Laboratory of Experimental and Clinical Biochemistry and Immunology, Research Institute of Molecular Medicine, Chita State Medical Academy.

Inclusion criteria

1. Primary polyosteoarthrosis with damage to three or more groups of joints. Diagnosis was verified based on the clinical classification criteria of the American College of Rheumatology (ACR) taking into account X-ray criteria of Kellgren and Lawrence system [9].
2. The age of subjects ranges from 35 to 55 years.
3. Body mass index (BMI) was under 30 kg/m^2.
4. History of blood pressure (BP) not higher than 179/109 mm Hg with achieved target BP level controlled with antihypertensive drugs (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, diuretics, beta-blockers).

The study had the following exclusion criteria:

1. Refusal of the patient to participate in this study
2. Secondary osteoarthrosis
3. Systemic connective tissue diseases
4. Oncological diseases
5. Chronic and acute blood diseases
6. Endocrine diseases
7. Pregnancy and lactation
8. Women in menopause (including surgical)

Description of healthcare intervention:

Molecular genetic analysis was performed using DNA samples extracted from whole blood WBC. Extraction was carried out using a set of reagents for genotyping of polymorphic markers by Real-Time

Table 1. *Polymorphic genetic variants analyzed in the studied patients*

Gene	Chromosomal localization	Single-nucleotide polymorphism
MMP-2	Chr16:55478465 GRCh38 38.1/141	*rs2285053*
MMP-3	Chr11: 1022845217 GRCh38 38.1/141	*rs3025058*
MMP-13	Chr11:10295580 GRCh38 38.1/142	*rs2252070*

PCR (OOO Test-Gene, Russia) according to the manufacturer's recommendations. Expected and observed studies of genotype frequencies were calculated in order to determine compliance with the Hardy-Weinberg equilibrium.

Further analysis included studying association of risk factors, medical history, echocardiography (ECHO-CG), coronary anatomy (according to the results of coronary angiography), lipid profile, and OA characteristics with individual gene polymorphisms. Then, intergenic interactions were analyzed.

Analysis by subgroups:

The patients were divided into 2 groups. Group 1 included 44 patients (mean age 48.79 ± 5.01 years) with primary OA and verified coronary artery atherosclerosis (CA) confirmed by coronary angiography. Group 2 included 46 patients (mean age 44.32 ± 5.4 years) with primary OA and no atherosclerotic changes in vessels according to Doppler ultrasound of brachiocephalic arteries, vessels of lower extremities, no clinical or medical history of coronary heart disease (CHD).

For all study participants, genotypes of *MMP-2, MMP-3, MMP-13* were defined (Table 1).

Ethical review:

All patients signed an informed consent to participate in this study.

This study was approved by the Local Ethics Committee of Chita State Medical Academy of the Ministry of Health of the Russian Federation (No. 86 dated November 1, 2017).

Statistical data analysis:

Microsoft Excel 2016 and Statistica, version 10.0 (StatSoft) were used for statistical data processing. Yates's correction for continuity of Pearson's csquare (c^2) was used to compare discrete values, as well as to calculate the correspondence of the observed frequency distributions of genotypes theoretically expected according to the Hardy Weinberg law. Since the distribution of signs differed from normal distribution, nonparametric statistics methods were used. To compare the two groups, Mann-Whitney U test with Bonferroni correction was used. Differences were considered as statistically significant at $p < 0.05$.

Association assessment was calculated in terms of OR (odds ratio) and RR (relative risk) values indicating 95% confidence interval (CI).

Results

Distribution of genotype frequency in the groups of patients was found to correspond to the Hardy Weinberg continuum.

Genetic test revealed that carriage of a homozygous C allele of polymorphism (*rs2285053 C/T*) of *MMP-2* gene in groups of patients with verified coronary artery atherosclerosis was observed in 77.27% (Table 2).

Analysis of baseline data in study groups showed no difference between the genotypes. Homozygous *T/T* variant of *MMP-2* gene was not found.

A comparative study of the frequencies of genotypes of *MMP-3* polymorphic loci demonstrated that the carriage of homozygous T allele of (*rs3025058 T/C*) of *MMP-3* gene polymorphism and of heterozygous variant of *T/C* genotype was almost equally distributed in the groups of patients with and without verified coronary artery atherosclerosis (Table 3). Homozygous *C/C* variant of *MMP-3* gene was not found in any of the studied groups. Analysis of baseline data in study groups showed no difference between the genotypes. There were no statistically significant differences in the prevalence of alleles and genotypes in the studied groups.

Table 2. *Distribution of allele frequency and genotypes of MMP 2 rs2285053 C/T gene polymorphism in patients with OA*

Groups of patients	Genotypes, n (%): RR (95% CI)			χ²/p	Alleles		χ²/p
	CC	CT	TT		C	T	
Group I (n=44)	34 (77.27) RR =1.23 (0.58-3.82) OR =1.49	10 (22.72)	0	p_{I-II} 0.56	78 (88.6)	10 (11.4)	p_{I-II} 0.58
Group II (n=46)	32 (69.56)	14 (30.43)	0		78 (84.8)	14 (15.2)	

RR — risk of coronary artery atherosclerosis in the presence of the studied genetic marker in comparison with the group without coronary artery atherosclerosis; 95% CI — confidence interval; OR — odds ratio whether coronary artery atherosclerosis will develop upon detection of this genetic marker or no coronary artery damage will develop

Note: P-value for the difference is < 0.05, OR — odds ratio, RR — relative risk, CI — confident interval

Table 3. *Distribution of allele frequency and genotypes of MMP-3 rs2285053 C/T gene polymorphism in patients with OA*

Groups of patients	Genotypes, n (%), RR (95% CI)			χ² / p	Alleles		χ² / p
	TT	TC	CC		T	C	
Group I (n=44)	26 (59) RR =1 (0.44-2.36) OR =1.02	18 (41)	0	pI-II 0.87	70 (79.54)	18 (20.46)	pI-II 0.87
Group II (n=46)	27 (58.69) RR=0.99 OR=0.98	19 (41.31)	0		73 (79.34)	19 (20.66)	

RR — risk of coronary artery atherosclerosis in the presence of the studied genetic marker in comparison with the group without coronary artery atherosclerosis; 95% CI — confidence interval; OR — odds ratio whether coronary artery atherosclerosis will develop upon detection of this genetic marker or no coronary artery damage will develop

Note: P-value for the difference is < 0.05, OR — odds ratio, RR — relative risk, CI — confident interval

Studying the polymorphism (*rs2252070 T/C*) of *MMP-13* gene revealed that the carriage of homozygous *T* variant of *MMP-13* gene polymorphism was 1.9 times higher in patients without verified coronary artery atherosclerosis compared with the group of patients with severe CA where the prevalence of this genotype amounted to only 31.8% (p = 0.031) (Table 4). Heterozygous variant of *T/C* genotype was more common in patients with verified coronary artery atherosclerosis — 59.1%, which is 1.7 times more often than in the group without coronary artery atherosclerosis (p = 0.036). Calculation of the odds ratio for *MMP-13* genotype showed that carriage of *MMP-13 TC* genotype (CI 95% 1.15-6.36) increases the risk of CA development by 2.7 times.

Discussion

The studies proved the great role of the metalloproteinase component in the degradation of extracellular matrix and, as a result, in the pathogenesis of various CVDs (atherosclerosis, restenosis, cardiomyopathy, myocardial infarction, chronic heart failure, aortic aneurysm) [4, 7]. It was found that the intensity of immune reactivity is a genetic component, and single nucleotide polymorphisms (SNPs) in the sense parts of genes that are responsible for the synthesis of the interleukin component of inflammation and MMP often have an effect on the following: stability of tertiary protein structures, variants of binding of protein components to the substrate. In accordance with the changes occurred,

Table 4. *Distribution of allele frequency and genotypes of MMP-13 rs2285053 C/T gene polymorphism in patients with OA*

Groups of patients Genotypes and alleles, n (%), RR (95% CI)	Group I (n=44)	Group II (n=46)	χ^2/ p_{I-II}
TT	14 (31.81) RR =0.58 (0,15-0.85) OR =0.36	26 (56.52)	**0.031**
TC	26 (59.1) RR =1.65 (1.29-7.42) OR =2.7	16 (34.78)	**0.036**
CC	4 (9.09) RR =1.02 (0.26-4.48) OR =1.05	4 (8.7)	0.76
T	54 (61.36)	68 (73.9)	0.1
C	34 (38.64)	24 (26.1)	

Note: RR — risk of coronary artery atherosclerosis in the presence of the studied genetic marker in comparison with the group without coronary artery atherosclerosis; 95% CI — confidence interval; OR — odds ratio whether coronary artery atherosclerosis will develop upon detection of this genetic marker or no coronary artery damage will develop. P-value for the difference is <0.05, OR — odds ratio, RR — relative risk, CI — confident interval

functional activity of synthesized proteins becomes unstable. Genetic polymorphism can have a neutral effect, and can also severely disrupt the functional characteristics of the synthesized protein product. This fact means that genetic polymorphisms under certain conditions predispose or prevent a number of pathologies [7]. At present, the study of genetic polymorphisms predisposing to the occurrence of various diseases is ongoing. Researchers proved that MMPs expressed in myocardium could participate in the degradation of cardiac extracellular matrix that becomes an important factor in the processes of myocardial remodeling [7]. It was found that MMPs in heart tissues are synthesized by fibroblast-like cells and cardiomyocytes mainly in an inactive state; their expression and degree of activity increase during the course of pathological processes in myocardium [10].

If there are no pathological processes, a large number of MMPs (including -2, -3, -13) are synthesized in the joint tissue in small quantities; at the same time the level of MMP component increases rapidly during the course of inflammatory processes. During OA pathogenesis, proinflammatory cytokines (TNF-α and IL-1β) can bind to complementary chondrocyte receptors and cause activation of signaling pathways followed by hyperactivation of the expression of matrix metalloproteinases [3]. The most intense synthesis of MMP-13 takes place in chondrocytes.

MMP-13 plays a major role in the degradation of cartilage tissue, since a large number of catabolic reactions increases its activity. In addition, the study of atherosclerotic plaques allowed the detailed study of two polymorphic variants in the promoter of the gene that encodes this substrate. These polymorphisms include the insertion of additional adenine residue -291 (11A/12A), as well as the transition of -77G/A in the regulatory element of the promoter (*rs17860523*). According to the data [3], the presence of estrogen receptors of a certain type increased the expression of all of the listed polymorphic variants of *MMP-13*, which may be related to joint dysfunction leading to the development of OA in menopausal women.

In our study, analysis of baseline data in the study groups revealed no statistically significant differences in the prevalence of alleles and genotypes of *MMP-2 (rs2285053 C/T) and MMP-3 (rs3025058 T/C*). At the same time, a significant increase in the carriage of the homozygous T allele variant of MMP-13 polymorphism (*rs2252070 T/C*) was found in the group of patients with primary OA without verified atherosclerotic lesions, while there were significantly more carriers of the heterozygous variant of the studied *MMP-13* polymorphism in the group of patients with primary OA with hemodynamically significant coronary artery atherosclerosis.

Conclusions

Thus, in patients with primary osteoarthrosis in combination with hemodynamically significant coronary artery atherosclerosis, the carriage of homozygous T polymorphism of *MMP-13* gene (*rs2252070*) is most likely protective, while the heterozygous variant of *MMP-13* polymorphism (*rs2252070 T/C*) increases the risk of developing hemodynamically significant atherosclerotic lesions of coronary arteries in patients with osteoarthritis by 2.7 times. These data can be used to reach a firmer consensus in terms of additional testing of patients with primary polyosteoarthrosis for the presence of hemodynamically significant coronary artery atherosclerosis, which is very important for successful treatment of this category of patients.

Author Contribution:

Portyannikova, O.O. (ORCID ID: https://orcid.org/0000-0002-2565-3839): The author selected patients for the study taking into account special aspects of clinical and medical histories

Romanova, E.N.: The author developed the study design: ideas, goals and objectives, analyzed local and foreign literature

Govorin, A.V.: The author performed detailed statistical analysis of information

Zwinger S.M. (ORCID ID: https://orcid.org/0000-0001-8030-7659): The author independently carried out blood sampling and a number of laboratory research methods

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