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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

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ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

Keywords: Percutaneous coronary intervention (PCI), Coronary artery disease (CAD), Kazakhstan, outcomes, incidence, mortality.

РЕЗЮМЕ

РЕЗУЛЬТАТЫ И НЕБЛАГОПРИЯТНЫЕ ИСХОДЫ ПОСЛЕ ЧРЕСКОЖНОГО КОРОНАРНОГО ВМЕШАТЕЛЬСТВА: РЕТРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Целью исследования явился анализ исходов после чрескожного коронарного вмешательства на примере двух регионов Казахстана (Восточно-Казахстанская и Павлодарская области) за период 2012-2018 гг.

В ретроспективное когортное исследование включены данные о пациентах, перенесших чрескожное коронарное вмешательство (ЧКВ). Данные представлены в виде среднего±стандартного отклонения или частот и процентов. Показатели заболеваемости рассчитывались как количество случаев на 100000 населения с 95%ДИ. Для выявления независимых предикторов внутрибольничной смертности использован многомерный логистический регрессионный анализ. В исследование включен 11931 пациент, перенесший ЧКВ, из них 8349 (70,0%) - мужчин, 3582 (30,0%) - женщины. Внутригоспитальная смертность после ЧКВ составила 320 (2,7%) случаев, в основном, мужчины (55,9%), средний возраст 67,8±9,71 лет. В результате проведенного анализа выявлены высокие показатели смертности у женщин и пациентов в возрасте 70 лет и старше, а также у больных с диагностированным инфарктом головного мозга. Показатели внутрибольничной смертности были выше у женщин, чем у мужчин, а ее независимыми предикторами были возраст и пол.

რეზიუმე

კანგავლითი კორონარული ჩარევის შედეგები და არაკეთილსაიმედო გამოსავალი: რეტროსპექტული კოჰორტული კვლევა

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კვლევის მიზანს წარმოადგენდა კანგავლითი კორონარული ჩარევის გამოსავლის ანალიზი ყაზახეთის ორი რეგიონის მაგალითზე (აღმოსავლეთ ყაზახეთის და პავლოდარის ოლქები) 2012-2018 წწ.

რეტროსპექტულ კოჰორტულ კვლევაში ჩართული იყო მონაცემები პაციენტების შესახებ, რომელთაც ჩაუტარდა კანგავლითი კორონარული ჩარევა. მონაცემები მოტანილია საშუალო სტატისტიკური გადახრის, ან სიხშირისა და პროცენტების სახით. ავადობის მაჩვენებლები გამოითვლილია, როგორც შემთხვევათა რაოდენობა 100000 მოსახლეზე 95%-იანი დაშვების ინდექსით. შიდაჰოსპიტალური სიკვდილობის დამოუკიდებელი პრედიქტორების გამოსავლენად გამოყენებული იყო მრავალფაქტორული ლოგისტიკური რეგრესიული ანალიზი. კვლევაში ჩართული იყო 11931 პაციენტი, რომელთაც ჩაუტარდა კანგავლითი კორონარული ჩარევა, მათგან 8349 (70,0%) – მამაკაცი, 3582 (30,0%) – ქალი. შიდაჰოსპიტალურმა სიკვდილობამ კანგავლიტი კორონარული ჩარევის შემდეგ შეადგინა 320 (2,7%) შემთხვევა, მათგან უმეტესობა - მამაკაცები (55,9%), საშუალო ასაკი – 67,8±9,71 წელი. ჩატარებული ანალიზის შედეგად გამოვლინდა სიკვდილობის მაღალი მაჩვენებელი ქალებში და 70 წლის და მეტი ასაკის პაციენტებში, ასევე, პაციენტებში დიაგნოსტირებული ტვინის ინფარქტით. შიდაჰოსპიტალური სიკვდილობის მაჩვენებლები, ასევე, უფრო მაღალი იყო ქალებში, ვიდრე მამაკაცებში, მის დამოუკიდებელ პრედიქტორებს კი წარმოადგენდა ასაკი და სქესი.

THE MAIN CAUSES OF THE COMPLICATED COURSE OF COVID-19 IN PATIENTS WITH DIABETES MELLITUS AND TREATMENT (REVIEW)

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Coronavirus disease 2019 (COVID-19) has confidently and aggressively marched across the planet since December 2019. Among the main risk factors for the development of a severe course of COVID-19 are old age, arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases [1]. Recently, based on the epidemiological data DM is not considered as a risk factor for SARS-CoV-2 infection, but diabetes is associated with a more severe course of COVID-19 [2]. What is the reason for the severe course of COVID-19 in diabetic patients? The need to provide an answer to this question led to this study.

The aim of this study was to determine the main causes of complicated COVID-19 course in diabetic patients.

Material and methods. Literature search was conducted through PubMed and Google Scholar using keywords: COVID-19, diabetes, hyperglycemia, carbohydrate metabolism disorders, complications. 946 publications were initially identified. Articles were published between December 2019 and July 15, 2020.

Results and discussion. In our opinion, there are three groups of factors that can worsen the course of infectious disease in patients with diabetes:

1. Features of DM and the mutual influence of the DM and COVID-19.
2. Influence of separate groups of drugs used in the treatment of both diseases.
3. Shortcomings in the organization of patients treatment and care.

Let's consider all the reasons in sequence.

Features of diabetes mellitus and the mutual influence of diabetes and COVID-19

Currently, there are only a limited number of experimental studies that directly concern the role of hyperglycemia and DM in the pathogenesis and prognosis of viral respiratory diseases [3]. Thus, Morra ME, et al. [4] discovered that elevated blood glucose levels can directly increase the concentration of glucose in respiratory mucosal secretions. Due to the influence of elevated glucose concentrations on lung epithelial cells, virus penetration and replication significantly increase in vitro, which let us suggest that hyperglycemia may increase virus replication in vivo. Elevated glucose levels can also lead to inhibition of the antiviral immune response. These results are similar to those in studies of patients infected with highly pathogenic avian influenza, where hyperglycemia was associated with a fatal outcome. Hyperglycemia can also affect lung function, that is why the respiratory dysfunction induced by the influenza virus is amplified in patients with DM. Diabetes is associated with numerous structural changes in the lungs, in particular with increased vascular permeability and collapse of the alveolar epithelium in animal models [5].

Another reason that complicates the course of coronavirus disease is the features of the autonomic nervous system in patients with DM. The severity of COVID-19 in diabetic patients may be hidden by a milder presentation of viral infection, with fewer patients experiencing fever, chill, chest tightness, and shortness of breath [6]. This phenomenon resembles the "silent" symptoms that are observed in DM. Thus, a disorder of the autonomic innervation of the heart which is described as "cardiac autonomic neuropathy" leads to damage to afferent autonomic fibers which determine the perception of pain during myocardial injury. As a result, diabetic patients often have painless "silent" myocardial infarction [7]. The same situation can be observed in patients with diabetes and COVID-19 who underestimate their symptoms. Thus, adequate treatment is not prescribed in time. As a result, medical help is delayed, complications develop, and treatment results worsen.

The next mechanism that influences the course of coronavirus disease is a pancreatic dysfunction in the background of infection. It is considered that SARS-CoV-2 leads to temporary disorders of the function of pancreatic islet cells [8]. It was found that coronaviruses attach to host cells using dipeptidyl peptidase-4 (DPP-4), which is physiologically involved in modulating the action of insulin, and as an enzyme plays a major role in glucose metabolism, and is responsible for the degradation of incretins such as glucagon-like peptide-1 (GLP-1) [9,10]. Hyperglycemia observed in patients with COVID-19 can be caused by these (or similar) mechanisms [11]. The problem of the need to prescribe DPP-4 inhibitors during the COVID-19 pandemic has been actively discussed in the scientific literature and there is currently no data on the need to cancel treatment with these drugs.

Another phenomenon that is observed in the case of the development of viral infection in patients with DM is the mutual influence of these two diseases. Thus, hyperglycemia itself can negatively affect lungs function and immune response [12], and diabetes is a risk factor influencing on the progression and prognosis of COVID-19. Guo W, et al. (2020) in their study founded that COVID-19 patients who had no other comorbidities except diabetes had a high risk of severe pneumonia, the release of tissue-related enzymes, excessive uncontrolled reactions to inflammation, and hypercoagulation associated with impaired glucose metabolism [13]. In addition, the serum level of inflammation biomarkers, such as interleukin-6 (IL-6), C-reactive protein, serum ferritin, prothrombin index, and D-dimer, were significantly higher ($p<0.01$) in diabetic patients compared to patients without DM, which indicates the development of a broader complex of inflammatory reactions in patients with diabetes, and this, in turn, leads to a rapid worsening of COVID-19 course [13].

In turn, COVID-19 can worsen the course of DM in patients. As Maddaloni E. and Buzzetti R. (2020) emphasize, the interaction between COVID-19 and diabetes can be bi-directional since SARS-CoV-2 can potentially worsen the course of co-existing diabetes or even predisposition to diabetes in individuals who do not suffer from DM [6].

Thus, hyperglycemia and insulin resistance are often registered in seriously ill patients, including COVID-19 patients. This happens due to the release of contrinsular hormones such as glucagon, cortisol, and epinephrine, as well as increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α, which leads to a "cytokine storm" [14]. Their effect on insulin-sensitive tissues leads to a decrease in glucose uptake in muscles, increased lipolysis, and increased glucose synthesis in the liver [15].

COVID-19 can also manifest by dyspeptic symptoms, such as vomiting and diarrhea, leading to dehydration [16]. Research by Li J, et al. (2020) showed that SARS-CoV-2 infection was associated with ketoacidosis in 12% of diabetic patients [17].

It is generally recognized that some viral diseases can cause autoimmune type 1 diabetes in genetically predisposed patients, or even cause rapid development of diabetes from the mass collapse of β-cells [16]. COVID-19 uses the angiotensin-converting enzyme type 2 receptor (ACE-2) as a "gateway" to invade human target cells [18]. This enzyme is expressed by various tissues and cell types, including the lungs, as well as the endocrine part of the pancreas [18]. In a study by Yang JK, et al. (2010) it has been suggested that SARS-CoV-2, which also uses the ACE-2 receptor as an entry receptor, may damage the islets of Langerhans, causing hyperglycemia during the infection course [8]. Drucker DJ. (2020) reported a pancreatic injury characterized by elevated plasma amylase and lipase levels in 17% of patients with COVID-19, among whom 67% had moderately elevated plasma glucose levels [19].

The influence of certain groups of drugs used in the treatment of diabetes mellitus and COVID-19. ACE inhibitors

ACE inhibitors are currently the most controversial group of drugs often used in patients with hypertension and diabetes, including the cases of coronavirus disease. Although well-known angiotensin-converting enzyme 1 (ACE-1) promotes the conversion of angiotensin I to angiotensin II, its homologous analogue, ACE-2, is a membrane-bound enzyme (carboxypeptidase) that usually contributes to the inactivation of angiotensin II, and therefore physiologically contracts the activation of the renin-angiotensin-aldosterone system (RAAS) [18-20].

ACE-2 has many physiological roles, in particular: negative regulation of RAAS and facilitation of amino acid transport. Recently, ACE-2 was identified as a SARS-CoV-2 receptor that provides a critical link between immunity, inflammation, and cardiovascular diseases [21]. ACE-2 also acts as a receptor that

allows coronaviruses (SARS-CoV-2 and SARS-CoV) to enter human cells [22]. SARS-CoV-2, associated with ACE-2, is activated by type II transmembrane protease, serine 2 (TMPRSS2) to promote virus invasion and replication within human target cells, including type II pneumocytes [22]. On the other hand, ACE-2 plays a crucial role in maintaining glucose homeostasis and B-cell functions [19,23].

ACE inhibitors usually suppress ACE-1 but not ACE-2 [24]. However, studies have shown that these drugs enhance the regulation of the ACE-2 receptor, which the SARS-CoV-2 uses to enter host cells [25]. In turn, SARS-CoV-2 entering into human alveolar epithelial cells often leads to acute respiratory distress syndrome (ARDS), a clinical condition with high mortality associated with poor prognosis in patients with COVID–19 [26]. In addition, DM increases the expression of ACE-2, as shown in several experimental models [27,28], and the resulting increase in viral load may also explain the more severe course of COVID-19 in diabetic patients [29]. All this can complicate the course of COVID-19 and worsen the condition of patients taking ACE inhibitors. Some publications suggest replacing ACE inhibitors and angiotensin II receptor blockers in patients with hypertension and diabetes with other groups of drugs, such as calcium channel blockers [30].

However, there are other thoughts. In particular, a group of American and Dutch researchers led by Danser AHJ, et al. (2020) argue that ACE inhibitors do not inhibit ACE-2, since ACE-1 and ACE-2 are different enzymes, and therefore ACE inhibitors cannot contribute to the entry of the virus into the cell [22]. Also, there is no precise evidence to support the statement that ACE inhibitors or angiotensin II type 1 receptor blockers facilitate the entry of SARS-CoV-2 coronavirus by increasing the expression of ACE-2 [22]. Some other researchers agree with this position. Moreover, it is not known whether alternative antihypertensive agents do not have the same risk. Because of the lack of evidence, the European Medical Association (EMA) advises not to stop taking ACE inhibitors during the COVID-19 pandemic [31].

Ibuprofen and other non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used to treat hyperthermia in the case of viral infections. However, Day M. (2020) demonstrates four cases in which young patients with COVID-19 who did not have any underlying health problems developed serious symptoms after using NSAIDs at an early stage of the disease [32]. Somewhat earlier Voiriot G, et al. (2019) described cases of severe disease course with increased frequency of empyema, lung cavitation, and prolonged stay in the ICU of patients had used NSAIDs to treat pneumonia [33]. However, today WHO notes the current lack of evidence of severe adverse events and the need for additional medical care (hospitalization, intensive care, oxygen support) in patients with COVID-19 due to the use of NSAIDs [34].

NSAIDs, including ibuprofen, must be used with caution in patients with concomitant diseases of the gastrointestinal tract and cardiovascular system. It is contraindicated to use NSAIDs in the case of renal failure [35]. The NICE review (the UK, 2020) indicates that available evidence suggests that although the anti-inflammatory effect of NSAIDs reduces acute symptoms (e.g. fever), these drugs may either not affect or worsen long-term treatment outcomes, possibly due to masking symptoms of progression of acute respiratory infection. Additional evidence from randomized clinical trials is needed to confirm the effect of NSAIDs on the course of COVID-19 [36].

The use of NSAIDs to treat fever in patients with COVID-19 is still discussed. Until more evidence is found, Surviving Sepsis Campaign (2020) suggests that severely ill adults with COVID-19 should use acetaminophen (paracetamol) to treat fever [37]. It should be noted that the use of NSAIDs in patients with diabetic nephropathy is contraindicated due to the possibility of developing an acute renal injury. Therefore, we recommend to avoid using ibuprofen and other NSAIDs for the treatment of pain or hyperthermia and use paracetamol in patients with DM and COVID-19.

Glucocorticosteroids

Treatment protocols of critically ill patients often include extensive use of glucocorticosteroids (GCS), which significantly worsens infection-related hyperglycemia. A report from the Italian National Institute of Health (ISS, Istituto Superiore di Sanità) indicates that GCS was used in 34% of ICU patients [38]. At the same time, GCS therapy increases glucose levels in 80% of diabetic patients and in many non-diabetic patients, which may increase the risk of mortality in the case of coronavirus infection [39]. It should be remembered that GCS are not recommended to all patients with severe COVID-19. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19 recommends using GCS only for patients who have mechanical ventilation due to severe ARDS, as well as for patients with refractory shock [37]. Using of GCS for patients without ARDS and in other routine cases is not recommended [37]. In the case of GCS prescription blood sugar level should be carefully monitored to maintain euglycemia, which contributes to optimal respiratory and immunological functions [37].

Hydroxychloroquine

Hydroxychloroquine and chloroquine are used to prevent and treat malaria and certain autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus. These medications are considered by researchers as one of the potential agents in the fight against COVID-19 [35]. However, hydroxychloroquine and chloroquine can have serious side effects. Thus, cases of cardiomyopathy, which led to the development of heart failure, have been reported, in some cases with a fatal outcome [40]. It is also noted that due to hydroxychloroquine using, QT interval is often prolonged, which can lead to dangerous arrhythmias [41]. It is interesting that in the mentioned study the administration of hydroxychloroquine was stopped prematurely in ten patients due to side effects: overwhelming nausea, hypoglycemia, and one case of ventricular arrhythmia torsades de pointes [41]. Besides, patients with DM may have severe hypoglycemia during treatment with hydroxychloroquine [42].

It is worth remembering that the molecule of hydroxychloroquine has a hypoglycemic effect and is used in India as an alternative means to reduce blood sugar level [43]. The mechanisms underlying this hypoglycemic effect are not well understood; a series of complex molecular effects can improve both insulin sensitivity and insulin secretion [16]. The dosage of hypoglycemic drugs should be adjusted.

However, there are some positive reviews. In particular, Singh AK, et al. (2020) believe that given the minimal risk of use, long-term experience in other diseases, cost-effectiveness and availability, hydroxychloroquine and chloroquine can be considered for clinical use as experimental drugs, even in patients with concomitant DM [43]. Taking into account the literature data, we consider that hydroxychloroquine can be used in patients with DM and COVID-19 only in exceptional cases within the clinical studies, and, of course, only in a hospital, under strict monitoring, and cannot be used by patients themselves.

Azithromycin

Azithromycin is a broad-spectrum macrolide antibiotic that has activity against bacteria and other microorganisms. There

are only insufficient evidence or contradictory evidence about the use of azithromycin together with hydroxychloroquine in COVID-19 patients [35]. In a study by Gautret P, et al. (2020) a positive result was obtained in 6 patients with lower respiratory tract infection due to COVID-19 treated with hydroxychloroquine together with azithromycin [44]. In a study by Rosenberg ES, et al. (2020) azithromycin treatment was performed in 211 patients, including 58 (27.5%) patients with DM, among 1,438 hospitalized patients diagnosed with COVID-19 in New York. However, this treatment did not lead to changes in the mortality rate [45]. If azithromycin is intended to be used for the treatment of COVID-19, it is necessary to check prescriptions and cancel unnecessary medications that may prolong the QT interval. While treating patients with a known hereditary long QT syndrome or a history of drug-induced polymorphic ventricular tachycardia (torsades de pointes) a decision about using these drugs must be made only after consulting a cardiologist [35].

Metformin and other oral hypoglycemic agents

Metformin was approved by the FDA in 1995 as an oral hypoglycemic agent, which has become one of the most commonly prescribed drugs to treat DM worldwide [46]. In recent years, it has been suggested that metformin may inhibit the activity of viruses by increasing insulin sensitivity [47]. In the United States, a retrospective cohort study was conducted from 2002 to 2012 for elderly patients over the age of 65 and with a history of diabetes who were hospitalized with pneumonia. It is interesting that pre-administration of metformin to these patients was associated with significantly lower mortality [48]. According to some authors, it is advisable to add to the indications for metformin using in the official instructions an option "as adjunctive therapy to reduce the risk of mortality from COVID-19 in elderly, obese and diabetic patients due to weight loss and reduced risk of pneumonia" [49]. Also, there are reports of the effectiveness of metformin in concomitant liver diseases and liver functional changes due to SARS-Cov-2 infection [50]. However, most researchers are not sure about the possibility of using metformin in coronavirus disease. Thus, Orioli L, et al. (2020) believe that patients with severe forms of COVID-19 should cancel metformin due to the risk of lactic acidosis [16]. In addition, metformin is contraindicated to patients with acidosis or risk of acidosis, including patients who have hemodynamic instability, hypoxia, and/or severe renal injury [51].

Thus, in severe forms of COVID-19, metformin and SGLT-2 inhibitors should be discontinued, taking into account their own risk of lactic acidosis and ketoacidosis.

There are several important issues to consider when using DPP-4 inhibitors in a hospital. The DPP-4 enzyme has been identified as a co-receptor for Middle East respiratory syndrome coronavirus (MERS-CoV), but not for SARS-CoV or SARS-CoV-2. At present, no data would demonstrate the harmful or beneficial effect of these drugs in patients with COVID-19 [19]. The use of saxagliptin and alogliptin is not recommended due to concerns about increasing the frequency of heart failure. It is important to note that all published trials of DPP-4 inhibitors usage in inpatient settings were conducted in combination with insulin for correction, and several were in combination with basic insulin therapy. Due to the unstable nature of acutely ill patients hospitalized with COVID-19, DPP-4 inhibitors are not generally recommended [52].

Thus, insulin therapy remains the standard of care for hyperglycemia in patients hospitalized with COVID-19. Selective use of DPP-4 inhibitors, sitagliptin and linagliptin may be considered for patients with type 2 diabetes or mild hyperglycemia when they have regular meals and are expected to be discharged home [52]. In the case of severe decompensation of DM and with disorders of consciousness, the transition to insulin as the optimal way to correct disorders of carbohydrate metabolism is mandatory.

Shortcomings in the organization of patients treatment and care

The first shortcomings in the treatment of patients with COVID-19 with concomitant DM have appeared since outpatient stage. It is known that most patients with diabetes cancel regular appointments to the endocrinologist. Many patients develop excessive stress associated with social isolation and lack of exercise, which contributes to the deterioration of glycemic control and further increases the risk of developing COVID-19 in this vulnerable category of patients [3]. Improper organization of outpatient appointments, insufficient and unbalanced nutrition, lack of medicines and diagnostic devices, insufficient communication with an endocrinologist and family doctor, disregard for personal hygiene and social distance – these are not all problems in the organization of treatment and care of patients during COVID-19 pandemic.

There are no fewer problems in the management of patients with DM and COVID-19 at the inpatient stage of treatment too. Thus, experimental data support the important thesis that glycemic control may favourably influence on clinical outcomes in patients with concomitant diabetes and viral respiratory diseases such as COVID-19 [3]. At the same time, most emergency medicine practitioners are not professional endocrinologists and they may not be concerned about the patient's blood glucose level and may have lack of clinical experience in diabetes therapy, which can lead to sharp fluctuations in glycemia and the development of acute disorders of carbohydrate metabolism in diabetic patients as shown by experience in outbreak centers [53]. Therefore, it is very important to raise awareness among doctors who are directly involved in the treatment of COVID-19 patients about the importance of controlling glycemia in these patients and to establish standardized management of glycemia in diabetic patients with COVID-19.

Zhou J. and Tan J. (2020) draw attention to the fact that during a stay in a quarantined hospital, it is impossible to exercise through limited indoor space and reduced respiratory function of the patient. In addition, a diet for COVID-19 patients or a personalized diet is often not available [54], while in a study by Li X, et al. (2020) it is shown that insufficient and improper nutrition is often observed in patients with severe disease [55].

Due to these factors, the optimal treatment of COVID-19 patients with concomitant DM should include a multi-disciplinary team approach involving specialists in emergency medicine, endocrinology, infectious diseases, respiratory support, nutrition and rehabilitation.

Performed analyses suggest that the main factor that is crucial in the management of COVID-19 patients with co-existing DM is the normalization of blood sugar level and carbohydrates metabolism by all possible means.

Conclusions:

1. Existing DM can complicate the course of COVID-19, worsen patients' condition and increase mortality.
2. According to the data analysis, in our opinion, there are three groups of factors that can worsen the course of infectious disease in patients with diabetes:

1) Features of the DM and the mutual influence of diabetes and COVID-19.

2) Influence of separate groups of drugs used in the treatment of both diseases.

3) Shortcomings in the organization of patients' treatment and care.
3. The main factor that is crucial in the management of COVID-19 patients with co-existing DM is the normalization of blood sugar level and carbohydrates metabolism achieved by all possible means.

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SUMMARY

THE MAIN CAUSES OF THE COMPLICATED COURSE OF COVID-19 IN PATIENTS WITH DIABETES MELLITUS AND TREATMENT (REVIEW)

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Among the main risk factors for the development of a severe course of Coronavirus disease 2019 (COVID-19) are old age, arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases.

The aim of this study was determinating the main causes of complicated COVID-19 course in diabetic patients.

Publications were searched using PubMed and Google Scholar for keywords: COVID-19, diabetes, hyperglycemia, carbohydrate metabolism disorders, and complications.

The review of scientific literature considers the main causes and pathogenetic mechanisms of COVID-19 complications development in patients with DM. Groups of factors that worsen the disease course were identified. We also proved that modern treatment of COVID-19 in diabetic patients should consider all risk factors and include a multidisciplinary team approach with specialists in emergency medicine, endocrinology, infectious diseases, respiratory support, nutrition and rehabilitation.

The main reasons that worsen the course of COVID-19 in patients with DM are features of DM and mutual influence of DM and COVID-19; the influence of separate medicines groups used in the treatment of both diseases; shortcomings in the organization of patients' treatment and care. The main factor that is crucial in the management of these patients is the normalization of blood sugar level and carbohydrates metabolism achieved by all possible means.

Keywords: COVID-19, diabetes mellitus, hyperglycemia, complications.

РЕЗЮМЕ

ОСНОВНЫЕ ПРИЧИНЫ ОСЛОЖНЕННОГО ТЕЧЕНИЯ COVID-19 У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ (ОБЗОР)

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Факторами риска тяжелого течения новой коронавирусной болезни (COVID-19) являются преклонный возраст, артериальная гипертензия, сахарный диабет (СД), хронические обструктивные заболевания легких, сердечно-сосудистые и цереброваскулярные заболевания.

Целью исследования явилось определение основных причин осложненного течения COVID-19 у больных сахарным диабетом.

Проведен поиск и анализ публикаций в системах PubMed и Google Scholar по ключевым словам: COVID-19, сахарный диабет, гипергликемия, нарушение углеводного обмена и осложнения. В обзоре рассматриваются основные причины и патогенетические механизмы развития осложнений COVID-19 у пациентов с СД. Выявлены группы факторов, ухудшающие течение заболевания.

Продемонстрировано, что при лечении пациентов с COVID-19 и сопутствующим СД основным фактором является нормализация уровня сахара в крови и углеводного обмена, достигаемая всеми возможными способами.

Основными причинами, ухудшающими течение COVID-19 у больных СД, являются: особенности СД и взаимное влияние СД и COVID-19; взаимодействие отдельных групп лекарственных средств, применяемых при лечении обоих заболеваний.

რეზიუმე

COVID-19-ის გართულებული მიმდინარეობის ძირითადი მიზეზები შაქრიანი დიაბეტით ავადმყოფებში (მიმოხილვა)

ა.გალუშკო, ო.ლოსკუტოვი, ი.კუჩინსკაია, მ.სინიცინი, მ.ბოლიუკი

პ.შუპიკის სახ. დიპლომისშემდგომი განათლების ეროვნული სამედიცინო აკადემია, კიევი, უკრაინა

ახალი კორონავირუსული დაავადების (COVID-19) მძიმე მიმდინარეობის რისკის ფაქტორებს მიეკუთვნება ხანდაზმული ასაკი, არტერიული ჰიპერტენზია, შაქრიანი დიაბეტი, ფილტვების ქრონიკული ობსტრუქციული დაავადება, გულ-სისხლძარღვთა და ცერებროვასკულური დაავადებები.

კვლევის მიზანს წარმოადგენდა COVID-19-ის გართულებული მიმდინარეობის მიზეზების განსაზღვრა შაქრიანი დიაბეტით ავადმყოფებში.

ნატარებულია პუბლიკაციების ძიება და ანალიზი სისტემებში PubMed და Google Scholar შემდეგი საკვანძო სიტყვებით: COVID-19, შაქრიანი დიაბეტი, ჰიპერგლიკემია, ნახშირწყლოვანი ცვლის დარღვევა და გართულებები.

სტატიაში განხილულია COVID-19-ის გართულებების განვითარების ძირითადი მიზეზები და პათოგენეზური მექანიზმები შაქრიანი დიაბეტით პაციენტებში. გამოვლენილია დაავადების მიმდინარეობის გაუარესების განმაპირობებელი ფაქტორების ჯგუფი.

ნაჩვენებია, რომ COVID-19-ის და თანმხლები შაქრიანი დიაბეტით პაციენტების მკურნალობის დროს ძირითად ფაქტორს წარმოადგენს შაქრის დონის და ნახშირწყლოვანი ცვლის ნორმალიზების მიღწევა ყველა შესაძლო საშუალებით.

შაქრიანი დიაბეტით ავადმყოფებში COVID-19-ის მიმდინარეობის გაუარესების განმაპირობებელი ძირითადი მიზეზებია: შაქრიანი დიაბეტის თავისებურებანი და შაქრიანი დიაბეტის და COVID-19-ის ურთიერთგავლენა; ორივე დაავადების მკურნალობისათვის გამოყენებული სამკურნალწამლო საშუალებების ცალკეული ჯგუფების ურთიერთქმედება.