GEORGIAN MEDICAL NEWS

ISSN 1512-0112

No 10 (307) Октябрь 2020

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

No 10 (307) 2020

Published in cooperation with and under the patronage
of the Tbilisi State Medical University

Издается в сотрудничестве и под патронажем
Тбилисского государственного медицинского университета

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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Ежемесячный совместный грузино-американский научный электронно-печатный журнал
Агентства медицинской информации Ассоциации деловой прессы Грузии,
Академии медицинских наук Грузии, Международной академии наук, индустрии,
образования и искусств США.
Издается с 1994 г., распространяется в СНГ, ЕС и США

Website:
www.geomednews.org

The International Academy of Sciences, Education, Industry & Arts. P.O.Box 390177,
Mountain View, CA, 94039-0177, USA. Tel/Fax: (650) 967-4733

Версия: печатная. **Цена:** свободная.
Условия подписки: подписка принимается на 6 и 12 месяцев.
По вопросам подписки обращаться по тел.: 293 66 78.
Контактный адрес: Грузия, 0177, Тбилиси, ул. Асатиани 7, IV этаж, комната 408
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По вопросам размещения рекламы обращаться по тел.: 5(99) 97 95 93

GEORGIAN MEDICAL NEWS
Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press; Georgian Academy of Medical Sciences; International Academy of Sciences, Education, Industry and Arts (USA).
Published since 1994. Distributed in NIS, EU and USA.

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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:

классификации видов спорта А.Г. Дембо, разделены на две группы: группа А – скоростно-силовые виды спорта, группа Б – виды спорта на выносливость. Контрольную группу составили ученики: девушки (n=117), юноши (n=106) 13-15 лет и студенты: девушки (n=115), юноши (n=150) 17-20 лет, которые не занимались спортом. Исследование функции восприятия времени проводилось по методике В.Л. Маришука и соавт. Установлен факт возможного использования групп крови в генетическом прогнозировании развития восприятия времени. Выявлено, что лица мужского и женского пола с В(III) группой крови имеют лучшие ассоциативные связи со свойствами данной функции, тогда как худшая связь продолжает оставаться невыясненной. Свойства восприятия времени более выраженно проявляются у студенток юношеского возраста, чем у учениц-подростков. Установлено, что половой диморфизм не вносит существенных изменений в специфику показателей функции восприятия времени, однако генетические маркеры групп крови более информативны в прогнозировании развития данного психического качества у юношей с В(III) группой крови, чем у девушек с такой же группой крови.

რეზიუმე

დროის შეგრძნების ფუნქციის განვითარების თავისებურება
13-15 წლის სპორტსმენებში სისხლის სხვადასხვა ჯგუფით

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კ.უშინსკის სახ. სამხრეთუკრაინის ეროვნული პედაგოგიური უნივერსიტეტი, ოდესა, უკრაინა

კვლევის მიზანს წარმოადგენდა სისხლის ჯგუფის სეროლოგიური მარკერების გავლენის შესწავლა დროის შეგრძნების ფუნქციის განვითარებაზე მოზარდ სპორტსმენებში სასქესო დიმორფიზმის გათვალისწინებით.

კვლევაში მონაწილეობდა სპეციალიზებული სპორტული დაწესებულების 178 ქალიშვილი და 139 ვაჟი, რომლებიც დ.დემბოს სპორტის სახეობების კლასიფიკაციის თანახმად გაყოფილი იყო 2 ჯგუფად: ჯგუფი A - ჩქაროსნულ-ძალოსნური და ჯგუფი B - გამძლეობითი. საკონტროლო ჯგუფი შეადგინა 13-15 წლის მოსწავლეებმა (117 ქალიშვილი და 106 ვაჟი) და 17-20 წლის სტუდენტებმა (115 ქალიშვილი და 150 ვაჟი), რომლებიც არ იყვნენ დაკავებული სპორტით. დროის შეგრძნების ფუნქციის გამოკვლევა ჩატარდა ვ.მარიშუკის და თანაავტ. მეთოდით. დადგენილია დროის შეგრძნების განვითარების გენეტიკურ პროგნოზირებაში სისხლის ჯგუფის შესაძლებელი გამოყენების ფაქტი. გამოვლინდა, რომ B(III) სისხლის ჯგუფის მქონე მამრობითი და დედრობითი სქესის პირები ამჟღავნებენ საუკეთესო ასოციაციურ კავშირს აღნიშნულ ფუნქციასთან. დროის შეგრძნების თვისება უფრო გამოხატული აღმოჩნდა სტუდენტებში, ვიდრე მოზარდ-მოსწავლეებში. დადგენილია, რომ სასქესო დიმორფიზმს მნიშვნელოვანი კორექტივები არ შეაქვს დროის შეგრძნების ფუნქციის მაჩვენებლების ცვლილებებში, ხოლო სისხლის ჯგუფის გენეტიკური მარკერები უფრო ინფორმატიულია აღნიშნული ფსიქიკური თვისების განვითარების პროგნოზირებაში B(III) სისხლის ჯგუფის მქონე ვაჟებში, ვიდრე ამავე სისხლის ჯგუფის ქალიშვილებში.

BIOCHEMICAL ASPECTS OF SYMPTOMATIC TREATMENT IN PATIENTS WITH COVID-19 (REVIEW)

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The most urgent problem of the 21st century, which put in crisis not only the health of the population, also the social and economic situation of all countries, is the SARS-CoV-2 virus. SARS-CoV-2 became the newly discovered virus. The first outbreak was identified in China, in Wuhan and it already spread to almost all countries of the world and the number of infected reached nearly several million.

It should be noted, that the transmission of the virus is very quick through airborne droplets. There are data of a long-time vital capacity of the virus on different surfaces, however cultivation time from the same surfaces should be much less, otherwise the outspread of the virus would be wider.

SARS-CoV-2 fastens to the angiotensin-converting enzyme 2 (ACE2) receptor, located on the host cell membrane by S protein, which has a receptor-binding domain (RBD). As a result, the virus crosses the cell membrane and enters the cytosol, where the favorable conditions are created for its multiplication and prevalence of the infection. SARS-CoV-2 has a high ACE2 receptor-binding affinity. ACE2 is synthesized in the kidneys, intestinal and vascular epithelial cells, as well as in heart and brain. It is noteworthy that, ACE2 is abundantly synthesized in the type II alveoli. Consequently, if the virus enters the respiratory tract, a person can be easily infected. Such distribution of ACE2 in the body is the cause of various clinical manifestations

in patients with COVID-19, including acute respiratory distress syndrome, diarrhea, dysgeusia, anosmia, etc. Transmembrane serine protease 2 (TMPRSS2) participates in the entry into the cells along with SARS-CoV-2 which is followed by the breakdown of ACE2 and reduction of its amount. ACE2 protects lung from injury, while angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and angiotensin receptor (AT1R) contribute to lung tissue damage [1, 11].

Recent studies have shown, that ACE2 reduction in mice also worsened the cardiac contractile function. Thus, a large amount of ACE2 improves the result, however, it increases the scale of the infection [16]. Angiotensin 1,7 produced by this membrane enzyme ACE2, has antioxidant, anti-inflammatory, cardioprotective properties, increases endothelial and neuronal NO-synthase activity, generates NO, has an antiarrhythmic effect, and promotes the production of prostacyclin. The fact, that the mortality rate in children and women is low, while high in men and the elderly should be related to the amount of ACE2. The amount of this enzyme is high in children and young people and decreases with age. In young women, ACE2 levels are high because estrogens increase its expression. We suppose, that the severity of the disease is determined not by the number of ACE2 before infection, but by its critical decrease due to the entry of the virus into the cell.

As for Transmembrane serine protease 2 (TMPRSS2), which helps SARS-CoV-2 to enter the cell, an increase in the expression of a gene encoding this protein occurs by androgen hormones, in case of prostate cancer, the exact function of the protein is unknown. This may explain the fact, that cancer patients are at high risk [26].

As the amount of TMPRSS2 is increased under the influence of androgens, supposedly its expression will be low in women because a reduction of ACE2 is related to the bad outcome, TMPRSS2 supports the connection of virus with ACE2 and its reduction. Increasing the expression of TMPRSS2 should lead to a severe form of the disease. The reason for the high mortality rate in men can be caused by the growth of this protein by androgen hormones.

Thus, Camostatmesylate, an inhibitor of serine protease 2 (TMPRSS2) can block entry of the virus in a cell and maintain the amount of ACE2, the research is ongoing in this regard [25]. This medicine is used in Japan to treat pancreatitis. It is also interesting, that heparin inhibits serine proteases, it is not known whether it has a specific effect on TMPRSS2, but the use of heparin, when the risk of thrombosis is increased during COVID-19, may have a double benefit.

According to the recently published study, in patients with failure, a relatively high number of ACE2 were detected in men (the average age of 69) compared with women (the average age of 75). The authors of the study explain the high mortality rate during SARS-CoV-2 infection by this fact. However, the study was not performed in patients infected with SARS-CoV-2, so the increased mortality rate associated with the increased number of ACE2 is incorrect [2, 20]. A decrease in the number of ACE2 in COVID-19 patients will also lead to a decrease in produced angiotensin 1,7, which increases the permeability of the alveolar-capillaries and worsens gas exchange. Due to a decrease in angiotensin 1,7 vasoconstriction will be increased, caused by the action of Ang II on AT1-receptor, vascular permeability, and pulmonary edema. Vasoconstriction in turn will disrupt gas exchange, which will lead to decrease PH of blood. All these worsen the condition, facilitates the release of iron from the transferrin and develop bacterial infections [12].

Angiotensin 1,7 stimulates prostaglandin synthesis, has an antioxidant and anti-inflammatory effect, stimulates endothelial eNO and neuronal nNO synthesis, which eventually produces NO, has an antiarrhythmic effect and promotes the synthesis of prostacyclin. The latter should be the cause of the microvascular thrombosis.

ACE2 produces angiotensin 1,7 from both angiotensin II and angiotensin I. Neprilysin and TOP (Thimet oligopeptidase) both are involved in the synthesis of angiotensin I from angiotensin 1,7. Because angiotensin 1,7 deficiency is one of the causes of the severity of the disease, it should be discontinued from the treatment regimen (Fig.).

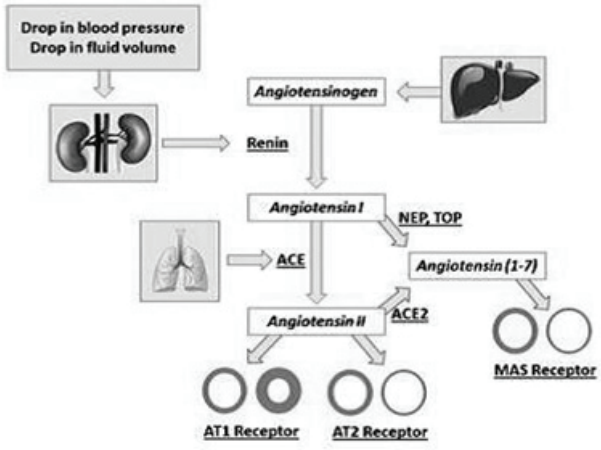

Fig. Renin-Angiotensin System

Angiotensin 1,7 produced by ACE 2, activates NO-synthase and stimulates NO secretion. Consequently, it is like that, NO will no longer be released during ACE2 deficiency caused by the virus. We suppose that decrease of NO should play an important role in the pathogenesis of COVID-19. Decreased NO levels lead to the development of endothelial dysfunction [5]. Hypercholesterolemia, hyperhomocysteinemia, hyperglycemia, hypertension, smoking, and age, characterized by endothelial dysfunction, worsen the COVID-19 infection.

There are 3 forms of NO-synthase: neuronal, endothelial, and inducible. Angiotensin 1,7 activates only endothelial and neuronal forms. Factors causing endothelial dysfunction are diverse and include a reduction of vasodilators, an increase of vasoconstrictors, excessive production of oxygen reactive species, activation of an inflammatory immune response, imbalance between coagulation and fibrinolysis [9].

Endothelin 1 (ET 1) is a peptide with strong vasoconstrictive properties derived from endothelium consisting of 21 amino acids. 0.05 fmol/ml is considered normal. Determination of ET1 would be important to confirm an endothelial dysfunction and its association with severity of disease in patients with SARS-CoV-2 [29].

NO has a diverse role in physiological and pathological processes, in the development of inflammatory reactions and immune response. NO reduces the activity of nuclear

factor-kappa B (Nf-kB), has antithrombotic and antioxidant effects. It enhances the expression of superoxide dismutase, which converts superoxide to hydrogen peroxide and protects tissues from damaging effects of superoxide.

Substances that enhance eNOs signaling pathway and improve endothelial dysfunction can also affect the course and outcome of COVID-19, especially when pathogenetic treatment is not yet known.

These substances are:
1. Estrogen - that's why the disease in women is less lethal. Genistein is a phytoestrogen derived from soybeans, which has an antioxidant effect. Genistein reduces endothelial dysfunction in patients with hypertension and hyperhomocysteinemia. The protective effect is caused by an increase of eNO activity, it's expression and decrease of production of cytokines and ROS. Genistein also increases the number of endothelial-dependent vasodilators in the postmenopausal period in women and reduces the number of ET1. We can assume that other phytoestrogens will also have a positive effect on the course of the disease. Soybean, which is rich with L-arginine, not only enhances eNOs expression but also inhibits NF-kB activity and prevents cytokine storms, thus phytoestrogens should have a positive effect on the course and outcome of the disease [7,20].
2. ACE-inhibitors - these medications are widely used to treat high blood pressure. It is established, that ACE inhibitors can improve endothelial function in patients with heart failure and coronary diseases. This effect is associated with a decrease of angiotensin 2, as well as an increase in the amount of bradykinin. Also, ACE inhibitors increase expression of eNO, which is caused by the effect of bradykinin on B2 receptors. It should be noted, that quinapril can act directly on the eNOs signaling pathway [22,23,28].
3. Bradykinin - is synthesized by the vascular wall, which acts on type B1 and B2 receptors. Activation of B2 by bradykinin enhances eNOs and prostacyclin, protects endothelial cells from the harmful impact of ROS (Reactive Oxygen Species). ACE inhibitors increase the amount of bradykinin that improves endothelial dysfunction [3,17,27].
4. Beta blockers - especially cardioselective beta blockers have a protective effect on the endothelium. For example, nebivolol improves the effect of endothelium-dependent vasodilators in patients with arterial hypertension and in smokers. Non-selective beta blockers, such as carvedilol also improve the endothelium-dependent response in patients with hypertension, as it seems this is associated with their antioxidant properties. A combination of carvedilol with ACE inhibitors shows better effect in patients with arterial hypertension and obese patients [15].
5. Statins - are used to treat hypercholesterolemia, especially to reduce LDL. They improve the endothelial function because LDL and OxLDL reduce the amount of eNOs and increase the level of caveolin-1. Statins also increase the bioavailability of NO. Statins have anti-inflammatory effects, for example, treatment with atorvastatin reduces the amount of cytokines, TNF alpha, IL-1, and IL-6. Therefore, it would be advisable to identify the lipid spectrum in patients with COVID-19 and treat with statins in case of dyslipidemia [6,10,14,19].
6. Calcium channel blockers - some dihydropyridine calcium channel blockers, such as Azelnidipine, Nifedipine, and Amlodipine, have been shown to have anti-inflammatory effects by reducing CRP and IL-6. Nicardipine and Nifedipine protect endothelial cells from damage caused by ROS and reduce glutathione. The combination of amlodipine with renin inhibitors has improved endothelial dysfunction in patients with hypertension associated with NO release and anti-inflammatory effects. Combination therapy of Amlodipine and Statins, compared to their monotherapy causes positive effects on endothelium in patients with diabetes and hypertension [30].
7. PDE-5 inhibitors - PDE-5 is an enzyme that is localized in heart, vascular smooth muscle, placenta, platelets, skeletal muscle, liver, pancreas, and lungs. PDE-5 inhibitors increase eNOs expression and therefore increases NO release, followed by prolonged vasodilator effect. PDE-5 inhibitors improve the function of the endothelium of coronary and peripheral blood vessels and inhibit platelet activation. They also improve endothelium-dependent vasorelaxation in diabetic patients, reduce the concentration of ET1, and improve Raynaud syndrome [4, 24].
8. Metformin - because of AMP-dependent protein kinase causes phosphorylation of serine 1177 and activation of eNOs in the NOs signaling pathway, metformin helps to enhance NO synthesis.
9. Vitamin D - it also enhances cellular immunity, in part by reducing the cytokine storm induced by the innate immune system. The innate immune system generates pro-inflammatory and anti-inflammatory cytokines in response to viral infections, as observed in COVID-19 patients 1,25(OH)2D3 promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes. Serum 25(OH)D concentrations tend to decrease with age, which can explain case-fatality rates increase with age in COVID-19 patients. Reasons include less time spent in the sun and reduced production of vitamin D as a result of lower levels of 7-dehydrocholesterol in the skin. Besides, some pharmaceutical substances reduce serum 25(OH)D concentration by activating the pregnane-X receptor. Such drugs include antibiotics, antiepileptics, antineoplastics, anti-inflammatory agents, antihypertensives, antiretrovirals, and endocrine drugs. Pharmaceutical drug use typically increases with age. Vitamin D supplementation also enhances the expression of genes related to antioxidation. The increased glutathione production spares the use of ascorbic acid (vitamin C), which has antimicrobial activities and has been proposed to prevent and treat COVID-19 [8].
10. Antioxidant agents - especially vitamin C, E, and N-Acetylcysteine have an antioxidant effect. Vitamin C protects the endothelium from the superoxide, platelet and neutrophil activation, as well as inhibits the types of reactive nitrogen produced by peroxidase. Vitamin C can improve endothelial function in smokers, in patients with hypercholesterolemia and diabetes. Vitamin C is notable for helping NO synthesis to maintain the coenzyme tetrahydrobiopterin in the BH4 state, while folic acid provides a strong link between BH4 and NO synthesis, which is a necessary prerequisite for NO synthesis [13]. Vitamin E has a protective effect on the endothelium in smokers and during hypercholesterolemia, although its effects on diabetic patients are arguable. N-acetycysteine is the first-line drug for acute coughs, However, experimental studies have shown that it is a powerful antioxidant, acting on glutathione products that protect the cardiovascular system from the damaging effects of TNF-alpha, that on one's part led to a reduction of the amount of glutathione and an increase of ROS production. N-acetylcysteine also inhibits the aggregation of platelet-dependent Willebrand factor and binding of collagen to glycoprotein receptors. Also important is prostacyclin (PGI2), which is generated by arachidonic acid from COX in endothelial cells, Activation of IP receptors by prostacyclin causes vascular relaxation. However, the synthesis of PGI2 may be inactivated by an increase of cytokines, which once again indicates a decrease in the severity of prostacyclin in patients with COVID-19 and inadequacy of nonsteroidal anti-inflammatory drugs.

As mentioned above, Angiotensin 1,7, produced by ACE 2 stimulates NO production. In addition to its antiarrhythmic and antioxidant effects, NO blocks NF-kB, which determines the main immune response during infections. Its improper regulation is associated with the development of tumors, inflammation and autoimmune diseases, septic shock, viral infections, and excessive immune responses [18]. SARS-CoV-2 reduces

the amount of ACE 2, accordingly decreases the synthesis of angiotensin 1,7 and NO production. In the absence of NO, not only worsens oxygenation-ventilation and endothelial dysfunction but also NF-kB is activated and cytokine storm begins. In such a case it is not allowed to use drugs, that also promote the development of cytokine storms.

Activation of NF-kB leads to an increase in osteoprotegerin, which is associated with an increase in cardiovascular mortality. Its activation may also be related to the development of schizophrenia.

It is known, that ROS-reactive oxygen spices activate NF-kB (therefore, the positive effect of ozone on the course of the disease is doubtful), also TNF, IL-1, Cocaine, and isoproterenol (the use of albuterol inhalers will also help with cytokine storm). The structural analog of isoproterenol is adrenaline, so it would be best to use other medications to stabilize hemodynamic status if there is an alternative. Some substances interfere with the activation of NF-kB, such as the protein SIRTUIN 1, which inhibits the NF-kB factor because of its deacetylation, however, it should be noted that SIRTUIN 1 is inhibited under conditions of hyperglycemia. A high mortality rate could be explained by this fact also. It should be noted that the substance resveratrol (one of the components of red wine) causes an increase in the amount of SIRTUIN 1 protein, which leads to inhibition of NF-kB.

Activation of NF-kB is also caused by hydroxychloroquine (Plaquenil), that is why the positive effect on the course of the disease is doubtful [21]. Methylene blue inhibits NF-kB and also the synthesis of NO, which helps to enhance endothelial dysfunction. As for metformin, it inhibits NF-kB and stimulates NO synthesis, which is why it should have a doubly positive effect in patients with COVID-19, because hydroxychloroquine predominates in the treatment protocols of COVID-19 in many countries, patients treated with metformin before being infected were more likely to be discontinued, because the combination of metformin and hydroxychloroquine is contraindicated. Accordingly, the positive effect of metformin was out of focus.

The medications listed here can theoretically have a positive or negative effect on the course of the disease. Therefore, if there is an alternative, it would be better to use medications that compensate for the changes caused by the decrease in ACE2, the reduction of NO synthesis and the activation of NF-kB.

REFERENCES

1. Bastolla U. The differential expression of the ACE2 receptor across ages and gender explains the differential lethality of SARS-Cov-2 and suggests possible therapy. arXiv preprint arXiv:2004.07224. 2020 Apr 15.
2. Bukowska A, Spiller L, Wolke C, Lendeckel U, Weinert S, Hoffmann J, Bornfleth P, Kutschka I, Gardemann A, Isermann B, Goette A. Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. // Experimental Biology and Medicine. 2017 Aug;242(14):1412-23.
3. Dabiré H, Barthélémy I, Blanchard-Gutton N, Sambin L, Sampedrano CC, Gouni V, Unterfinger Y, Aguilar P, Thibaud JL, Ghaleh B, Bizé A. Vascular endothelial dysfunction in Duchenne muscular dystrophy is restored by bradykinin through up-regulation of eNOS and nNOS. // Basic Research in Cardiology. 2012 Jan 1;107(1):240.
4. De Young LX, Domes T, Lim K, Carson J, Brock GB. Endothelial rehabilitation: the impact of chronic PDE5 inhibitors on erectile function and protein alterations in cavernous tissue of diabetic rats. //European Urology. 2008 Jul 1;54(1):213-20.
5. Ferrario CM. ACE 2: More of Ang 1-7 or less Ang II?. // Current opinion in nephrology and hypertension. 2011 Jan;20(1):1.
6. Fleming I, Mohamed A, Galle J, Turchanowa L, Brandes RP, Fisslthaler B, Busse R. Oxidized low-density lipoprotein increases superoxide production by endothelial nitric oxide synthase by inhibiting PKCα. // Cardiovascular Research. 2005 Mar 1;65(4):897-906.
7. Gagliardi MC, Tieri P, Ortona E, Ruggieri A. ACE2 expression and sex disparity in COVID-19. Cell Death Discovery. 2020 May 26;6(1):1-2.
8. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. // Nutrients. 2020 Apr;12(4):988.
9. Hadi HA, Carr CS, Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. // Vascular Health and Risk Management. 2005 Sep;1(3):183.
10. Heeba G, Hassan MK, Khalifa M, Malinski T. Adverse balance of nitric oxide/peroxynitrite in the dysfunctional endothelium can be reversed by statins. //Journal of Cardiovascular Pharmacology. 2007 Oct 1;50(4):391-8.
11. Iwai M, Horiuchi M. Devil and angel in the renin–angiotensin system: ACE–angiotensin II–AT 1 receptor axis vs. ACE2–angiotensin-(1–7)–Mas receptor axis. //Hypertension Research. 2009 Jul;32(7):533-6.
12. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. // Nature Medicine. 2005 Aug;11(8):875-9.
13. Landmesser U, Dikalov S, Price SR, McCann L, Fukai T, Holland SM, Mitch WE, Harrison DG. Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. // The Journal of Clinical Investigation. 2003 Apr 15;111(8):1201-9.
14. Li DY, Zhang YC, Philips MI, Sawamura T, Mehta JL. Upregulation of endothelial receptor for oxidized low-density lipoprotein (LOX-1) in cultured human coronary artery endothelial cells by angiotensin II type 1 receptor activation.// Circulation Research. 1999 May 14;84(9):1043-9.
15. Li Z, Liu B, Zhao D, Wang B, Liu Y, Zhang Y, Tian F, Li B. Protective effects of Nebivolol against interleukin-1β (IL-1β)-induced type II collagen destruction mediated by matrix metalloproteinase-13 (MMP-13). // Cell Stress and Chaperones. 2017 Nov 1;22(6):767-74.
16. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective.// European Respiratory Journal. 2020 Apr 1;55(4).
17. Mombouli JV. Kinins and vascular endothelium. // Curr Sci Nephrol Hypertens. 1994;3:481-4.
18. Morigi M. Angioletti S, Imberti B, Donadelli R, Micheletti G, Figliuzzi M, Remuzzi A, Zoja C, Remuzzi G. Leukocyte-endothelial interaction is augmented by high glucose concentrations and hyperglycemia in a NF-kB-dependent fashion. // J Clin Invest. 1998;101:1905-15.
19. Nakata S, Tsutsui M, Shimokawa H, Yamashita T, Tanimoto A, Tasaki H, Ozumi K, Sabanai K, Morishita T, Suda O, Hirano H. Statin treatment upregulates vascular neuronal nitric oxide synthase through Akt/NF-κB pathway. Arteriosclerosis, Thrombosis, and Vascular Biology. 2007 Jan 1;27(1):92-8.
20. Novella S, Pérez-Cremades D, Mompeón A, Hermenegildo C. Mechanisms underlying the influence of oestrogen on cardiovascular physiology in women. // The Journal of Physiology. 2019 Oct;597(19):4873-86.

21. Park J, Kwon D, Choi C, Oh JW, Benveniste EN. Chloroquine induces activation of nuclear factor-κB and subsequent expression of pro-inflammatory cytokines by human astroglial cells. // Journal of Neurochemistry. 2003 Mar;84(6):1266-74.
22. Rabelo LA, Nunes-Souza V, Bader M. Animal models with a genetic alteration of the ACE2/Ang-(1-7)/Mas axis. // The Protective Arm of the Renin Angiotensin System (RAS). 2015:161.
23. Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JG, Rienstra M, Friedrich AW, Samani NJ, Ng LL, Dickstein K. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors. // European Heart Journal. 2020 May 14;41(19):1810-7.
24. Schäfer A, Fraccarollo D, Pförtsch S, Flierl U, Vogt C, Pfrang J, Kobsar A, Renné T, Eigenthaler M, Ertl G, Bauersachs J. Improvement of vascular function by acute and chronic treatment with the PDE-5 inhibitor sildenafil in experimental diabetes mellitus.// British Journal of Pharmacology. 2008 Mar;153(5):886-93.
25. Sessa WC. eNOS at a glance. //Journal of Cell Science. 2004 May 15;117(12):2427-9.
26. Song H, Seddighzadeh B, Cooperberg MR, Huang FW. Expression of ACE2, the SARS-CoV-2 receptor, and TMPRSS2 in prostate epithelial cells. // Eur Urol. 2020 Aug; 78(2):296-298.
27. Su JB, Hoüel R, Héloire F, Barbe F, Beverelli F, Sambin L, Castaigne A, Berdeaux A, Crozatier B, Hittinger L. Stimulation of bradykinin B1 receptors induces vasodilation in conductance and resistance coronary vessels in conscious dogs: comparison with B2 receptor stimulation. // Circulation. 2000 Apr 18;101(15):1848-53.
28. Vicenzi M, Corsini A, Ruscica M. Angiotensin-converting enzyme-2 (ACE2) : New opportunity or red herring? // PHARMADVANCES. - 2:1(2020 Apr), pp. 11-13.
29. Vizza CD, Letizia C, Badagliacca R, Poscia R, Pezzuto B, Gambardella C, Nona A, Papa S, Marcon S, Mancone M, Iacoboni C. Relationship between baseline ET-1 plasma levels and outcome in patients with idiopathic pulmonary hypertension treated with bosentan. // International Journal of Cardiology. 2013 Jul 15;167(1):220-4.
30. Yasu T, Kobayashi M, Mutoh A, Yamakawa K, Momomura SI, Ueda S. Dihydropyridine calcium channel blockers inhibit non-esterified-fatty-acid-induced endothelial and rheological dysfunction. // Clinical Science. 2013 Sep 1;125(5):247-55.

SUMMARY

BIOCHEMICAL ASPECTS OF SYMPTOMATIC TREATMENT IN PATIENTS WITH COVID-19 (REVIEW)

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The new Coronavirus has challenged modern medicine. The disease caused by this virus, COVID-19, is characterized by a high rate of lethality, especially in the older age group. There is still no vaccine and no specific treatment, therefore prevention remains the main way to fight the virus. SARS-COV-2 is characterized by high virulence and contagiousness, that's why the main preventive recommendation is social distance.

The article reviews the features of this virus, ways of invading the virus in the body, the possible pathogenesis of the disease and the biochemical and pharmacological aspects of symptomatic treatment. The article also discusses the views of various authors, the results of previous studies and sets new perspectives on fighting the virus. The article discusses the mechanism of action of all drugs and the possible impact on the course and outcome of the disease, which has led to differences of opinion among various groups of scientists since the spread of the virus.

Keywords: SARS-CoV-2 virus, COVID-19, cytokine storm.

РЕЗЮМЕ

БИОХИМИЧЕСКИЕ АСПЕКТЫ СИМПТОМАТИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С COVID-19 (ОБЗОР)

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Новый коронавирус бросил вызов современной медицине. Заболевание, вызываемое этим вирусом, COVID-19, характеризуется высокой летальностью, особенно в старшей возрастной группе. По сей день вакцины и специального лечения не существует, поэтому профилактические меры остаются одним из основных средств борьбы. Вирус SARS-COV-2 характеризуется высокой вирулентностью и контагиозностью, поэтому основной профилактической рекомендацией является социальная дистанция.

В статье рассматриваются особенности вируса SARS-COV-2, пути проникновения в организм, возможный патогенез заболевания, а также биохимические и фармакологические аспекты симптоматического лечения. В статье обсуждаются взгляды различных авторов, результаты предыдущих исследований и отражаются новые пути борьбы с вирусом, обсуждаются механизмы действия всех лекарств и возможное влияние на течение и исход заболевания, которые привели к разногласиям среди различных групп ученых с момента распространения вируса.

რეზიუმე

COVID-19-ით დაავადებული პაციენტების სიმპტომური მკურნალობის ბიოქიმიური ასპექტები (მიმოხილვა)

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COVID-19 ხასიათდება ლეტალობის მაღალი მაჩვენებლით, განსაკუთრებით ხანდაზმულ ასაკობრივ კატეგორიაში. ბრძოლის ერთ-ერთ მთავარ საშუალებას წარმოადგენს პრევენციული ღონისძიებები. Sars-Cov-2 ვირუსი ხასიათდება მაღალი ვირულენტობით და კონტაგიოზურობით, რის გამოც მთავარი საპრევენციო რეკომენდაციას სოციალური დისტანცირება წარმოადგენს.

სტატიაში აღწერილია აღნიშნული ვირუსის გავრცელების თავისებურებები, ორგანიზმში შეჭრის გზები, დაავადების შესაძლო პათოგენეზი და სიმპტომური მკურნალობის ბიოქიმიური ასპექტები. განხილულია სხვადასხვა ავტორთა შეხედულებები, აქამდე არსებული კვლევების შედეგები, დასახულია ვირუსთან ბრძოლის გზები და პარსპექტივები, ასევე, მედიკამენტის მოქმედების მექანიზმი და შესაძლო გავლენა დაავადების მიმდინარეობასა და გამოსავალზე.

ANDROGEN INSENSITIVITY SYNDROME, REVIEW OF LITERATURE BASED ON CASE REPORTS

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Congenital conditions with diverse pathophysiology are described as Disorders of sex development (DSD). These disorders can be determined at different development stages of the life-cycle in fetuses or newborns with atypical external genitalia, dysgenetic gonads and internal genitalia. In older children and adolescents it manifests with delayed puberty, unexpected virilization or gynaecomastia, infertility, or gonadal tumors and primary amenorrhea [1]. Based on etiology DSD is divided into five subclasses differentiated by numerical or structural variations in sex chromosomes, disorders in gonadal and/or adrenal steroidogenesis and hormone functions, variations in genes involved in gonadal and/or genital development (bringing to inactivation or activation), endogenous or exogenous maternal factors or endocrine disruptors that possibly can affect genital development [2-5].

The purpose of this article is to describe one of the forms of 46 XY DSD which is related to androgen peripheral actions. There are two disorders related to DSD with preserved testosterone production by the testes, which are Androgen insensitivity syndrome (AIS) and type 5α-reductase deficiency. Although the above-mentioned conditions have similar clinical manifestations, they are initiated by different pathogenetic mechanisms. AIS has X-linked recessive inheritance pattern and is presented by total or partial insensitivity of androgen receptors to male sex hormones.

The androgen receptor (AR) is one of the nuclear receptor superfamily which is responsible for mediating the physiological effects of androgens. Proper functioning of the AR is required for normal male foetal sex development and mutations in the gene encoding the AR may result in a variable degree of resistance to androgens, leading to AIS. The type of AR mutation determines failure of sexual differentiation: either complete (CAIS) or partial (PAIS).

Individuals with CAIS have normal female external genitalia with absence of female internal genitalia. Before puberty masses in the inguinal canal subsequently identified as testes or primary amenorrhea and sparse to absent pubic or axillary hair at puberty may be detected. Breasts and female adiposity develop normally. They typically have female sexual identity and heterosexual orientation [6,7].

PAIS with predominantly female external genitalia manifests similarly to CAIS. However, these individuals have expressions of external genital masculinization which includes posterior labial fusion or clitoromegaly.

Sex of rearing. Determining the sex of rearing may be challenging for children with frank genital ambiguity. The management is defined only for individuals without genital ambiguity for which no management disagreements exist: female with CAIS [8]. Usually these infants are brought up as girls because of female appearance which masks the CAIS. These individuals usually have no expressions of gender dysphoria showing typical female gender development and behavior.

Nonetheless, individuals with CAIS may be unhappy with their primary sex organs, even without apparent signs of gender atypism [9]. Their insecurity may be caused by their body perception due to inconsistency between phenotypic gender and karyotype. In families with PAIS, phenotypic disparity may warrant male sex of rearing in one affected sib and female sex of rearing in another affected sib [10]. Children with PAIS who have predominantly male genitalia are brought up as males. At adolescence all individuals with PAIS develop gynecomastia and impaired spermatogenesis. Typically, they have moderate pubic hair; facial, body, and axillary hair are often scarce [11]. Individuals with PAIS may develop gender dysphoria [12]. Nearly 25% of them develop gender dysphoria regardless of the sex they are brought up [13]. Research of outcomes of gonadectomy and vaginoplasty in females affected by CAIS range from satisfaction with surgery [14,15] to preference for early surgery, to a lack of sexual desire and dyspareunia attributed to these procedures [16,17]. Among the factors contributing to the high dissatisfaction with treatment in this subgroup are the lacks of information provided to the patient about their condition and its management; therefore they hardly can make an informed decision for themselves. It is unclear if improved surgical techniques have resulted in higher patient satisfaction, since age did not influence the satisfaction rates with surgery [18-20].

Material and methods. Four patients with Androgen insensitivity syndrome were selected from the initial cohort of 32 DSD patients with karyotype 46XY. Selection criteria were absence of Mullerian ducts derivatives, as well as preserved testosterone biosynthesis evaluated by basal profile of steroids and/or after stimulation of hCG.

Patients were assessed by experienced paediatric endocrinologists. This study was approved by the Local Ethics Committee.