

GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (376-377) Июль-Август 2026

ТБИЛИСИ - NEW YORK



ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

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.
Published since 1994. Distributed in NIS, EU and USA.

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 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.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией 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 ВИНТИ 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.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

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.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

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).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

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.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

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.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

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.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

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

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების 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 ფხიხლებში 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.

Nana Shavlakadze, Irine Phkhakadze, Ana Silagadze, Dali Kobuladze, Alina Pakhuridze. CHRONIC URTICARIA AND LEAD EXPOSURE: EVALUATION OF IMMUNOLOGICAL MARKERS.....	6-16
Jangirashvili T, Kikoria G, Tevdorashvili N, Kapanadze L, Odikadze N. PSYCHOLOGICAL WELL-BEING AMONG MEDICAL STUDENTS AT FIVE UNIVERSITIES IN TBILISI, GEORGIA: A CROSS-SECTIONAL STUDY OF PERCEIVED STRESS, ANXIETY, AND SLEEP QUALITY.....	17-23
Yueyue Lu, Yigao Wu. ADVANCES IN RESEARCH OF PSYCHOTHERAPY FOR SOCIAL ANXIETY DISORDER.....	24-31
Saburov Alisher, Kemelbekov Kanatzhan, Arybzhanov Dauranbek, Abdurakhmanov Babur, Huseinov Zafar, Saburova Saidakhon, Tuktibayeva Saule, Yernazarov Adlet, Alipbekova Sandugash. ROLE OF NEOADJUVANT THERAPY FOR PATIENTS WITH GASTRIC CANCER: MULTIDISCIPLINARY HOSPITAL WITH ONCOLOGY CENTER.....	32-37
David Tchkonია, Nino Gabashvili, Teona Mskhaladze, Tamari Kevlishvili, Mikolay Chkonia. EFFICACY OF ENDOBRONCHIAL VALVE PLACEMENT IN THE MANAGEMENT OF PULMONARY HEMORRHAGE: A COMPARATIVE STUDY.....	38-42
Baglan Kemelbekov, Ainur Amanzholykyz, Samat Saparbayev, Manarbek Askarov, Edgaras Stankevicius. IMPACT OF STEM CELL THERAPY ADDED TO GUIDELINE-DIRECTED MEDICAL THERAPY ON QUALITY OF LIFE IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY.....	43-50
Abramishvili T, Papava K, Mamisashvili M, Tkeshelashvili M, Tsinamdzgvrishvili B. CARDIAC STRAIN IN WOMEN WITH A DOCUMENTED HISTORY OF OVERT OR SUBCLINICAL HYPOTHYROIDISM: AN EXPLORATORY SPECKLE-TRACKING ECHOCARDIOGRAPHY STUDY.....	51-56
TEREZA Y. AZATYAN. FORMATION AND DISTRIBUTION PATTERNS OF FUNCTIONAL INTERHEMISPHERIC BRAIN ASYMMETRY IN CHILDREN WITH INTELLECTUAL DISABILITIES.....	57-63
Fai Twrki Althoini, Ebtehal Solaiman Almogbel. CARDIOMETABOLIC RISK PROFILES IN ADULTS WITH DIABETES: ASSOCIATIONS WITH GLYCEMIC CONTROL, DIABETES TYPE, AND DEMOGRAPHIC CHARACTERISTICS.....	64-77
Datumyan G.S, Shaboyan K.R, Muradyan A.A, Shaboyan E.K, Galstyan A.S, Badalyan A, Sargsyan M.V. IMPACT OF THE COVID-19 PANDEMIC ON THE SEVERITY AND OUTCOMES OF GUNSHOT INJURIES.....	78-84
Zhanar Kozhakhmetova, Nazym Yelemessova, Syzdykova Dinara, Abdullina Sayagul, Nagima Issatayeva, Assiya Turgambayeva, Gulnara Kamalbekova, Diana Zhumagaleyeva, Akmaral Mussakhanova. CRITICAL VALUES OF HEMOSTASIS PARAMETERS IN AN ONCOLOGY CENTER: A RETROSPECTIVE REGISTRY-BASED STUDY.....	85-92
Gradil G.I, Torianyk I.I, Yurko K.V, Shiyan D.M, Merkulova N.F, Mohylenets O.I, Tkachenko V.G, Karmazina I.S, Lantukh A.P, Hryhorov Y.B, Gargin V.V. ASSOCIATION OF PULMONARY AND CUTANEOUS CHANGES IN COVID-19-RELATED CONDITIONS.....	93-98
Alaa MA. Albayaty, Alaa M. Sadiq, Ali SJ. Al Qaissi. ASSOCIATION BETWEEN INFLAMMATORY MARKERS, LIVER ENZYMES, LIPID PROFILE, AND VITAMIN D STATUS IN ADULTS WITH OBESITY: A CROSS-SECTIONAL STUDY.....	99-104
Kenzhebaeva B, Baimuratova M, Kalmakhanov S, Budakoğlu I.I, Laktionova M, Abdukalikova D. IMPACT OF CLINICAL, ORGANIZATIONAL, AND PSYCHOSOCIAL FACTORS ON THE QUALITY OF LIFE OF PATIENTS WITH DERMATOVENEREOLGICAL DISEASES.....	105-114
Obidov F. Kh, Shamsiev E. A, Samatov F. F, Naimov Dilshod Kayim ugli, Khalimova F. T, Marwan Ismail. BIOMARKER-ORIENTED REHABILITATION IN CHRONIC CEREBRAL ISCHEMIA.....	115-122
Raghad Alkhalify, Lina Almutairi, Fatimah Alghofaili, Wasan Alhawaish, Thekra Alhumidi. COMPARATIVE IN-VITRO QUALITY EVALUATION OF COMMERCIALY AVAILABLE DICLOFENAC SODIUM TABLETS.....	123-131
Ali S. Jumaah, Ali A. Younis, Shamil H. Othman. EFFECTS OF CURCUMIN ON CLINICAL OUTCOMES AND INFLAMMATORY BIOMARKERS IN KNEE OSTEOARTHRITIS: A RANDOMIZED TRIAL.....	132-138
Ashot Markosyan, Diana Alaverdieva, Mark Danghyan, Ani Mkrtchyan, Lusine Balayan, Khachik Hakobyan, Arpine Geolchanyan, Tigran Soghomonyan, Volodya Mirzoyan. SYNTHESIS AND SOME BIOLOGICAL PROPERTIES OF DERIVATIVES OF 2,3-DISUBSTITUTED 5,5-DIMETHYL-BENZO[h]QUINAZOLIN-4(1H)-ONES.....	139-143

J. Gobadze, M. Nagervadze, T. Gogitidze, N. Bejanidze, N. Zarnadze, K. Dolidze. IMPACT OF GESTATIONAL DIABETES MELLITUS ON NEONATAL BIRTH WEIGHT, LENGTH, AND GESTATIONAL AGE: A RETROSPECTIVE CASE-CONTROL STUDY	144-151
Liudmyla Bashkistrova, Iryna Romanova, Vitalii Yatsynovych, Oleksandr Zlobin, Artem Lanskoi. EVIDENCE-BASED PHARMACOTHERAPY FOR ANXIETY DISORDERS COMORBID WITH PTSD: A SYSTEMATIC REVIEW	152-163
Madina Makhmudova, Tolegen Kerimbekov, Zhaina Berikbayeva, Dinara Turebekova, Lyudmila Akhmaltdinova, Yefim Alisseiko, Olga Avdienko, Madina Rashova. IN VITRO INVESTIGATION OF THE POTENTIAL OF C60 FULLERENES AS ADJUVANTS OF NONSPECIFIC IMMUNITY	164-168
Tchernev G, Tchernev KG Jr, Kordeva S. DERMATOLOGIC SURGERY ROUNDS: THE LIMBERG FLAP AND V-TO-T CLOSURE FOR CUTANEOUS/ MUCOCUTANEOUS DEFECTS FOLLOWING SKIN CANCER EXCISION IN HIGH-RISK FACIAL REGIONS	169-174
Nino Nadiradze, Zurab Ckhaidze. SELF-RATED HEALTH IN THE POPULATION OF MEDICAL WORKERS IN GEORGIA	175-180
Argjend Shala, Nexhmedin Shala, Fisnik Jashari, Blert Jashari, Rushit Jashari. SPORADIC CREUTZFELDT-JAKOB DISEASE: CLINICAL FEATURES, DIAGNOSIS AND THERAPEUTIC HORIZONS	181-189
Omar S. Salman, Adeeb A. Al-Zubaidy. ACEBROPHYLLINE REPROGRAMS INFLAMMATORY AND REDOX SIGNALLING IN EXPERIMENTAL ULCERATIVE COLITIS: A DOSE-DEPENDENT STUDY	190-199
Eib K. Eibov, Solikhabonu Khavaskhonova, Kamshat S. Taubay, Karlygash Zh. Sadykova. CALCULATED WHOLE BLOOD VISCOSITY IS SPECIFICALLY ASSOCIATED WITH ABDOMINAL OBESITY, BUT NOT WITH OTHER COMPONENTS OF METABOLIC SYNDROME: A CROSS-SECTIONAL STUDY IN A CENTRAL ASIAN ADULT COHORT	200-208
Shqiponje Gashi, Erza Voca Mulaj, Naser Rugova, Suzana Dvojakovska, Filip Koneski. MANAGEMENT OF PERIOPERATIVE BLEEDING IN PATIENTS WITH PLATELET HYPOAGGREGABILITY DURING DENTOALVEOLAR SURGERY: CLINICAL OUTCOMES AND THERAPEUTIC APPROACHES	209-214
Alina Articulo, Rigor Rey Cuevas, Hani Al-Najjar, Rahaf Alkhuraif, Rasha Aburmeishan, Abdulaziz Almatrody. EXPLORING THE SATISFACTION OF NEWLY HIRED NURSES USING AN EVIDENCE-BASED, PERSONALIZED ONBOARDING PROGRAM: A CROSS-SECTIONAL ANALYSIS	215-222
Nagima Issatayeva, Samal Duisekova, Meruert Saberbekova, Roza Tumanova, Larisa Guruleva, Sholpan Mukanova. APPLICATION OF THE FAILURE MODE AND EFFECTS ANALYSIS METHOD IN HEALTHCARE: A CASE STUDY OF A UNIVERSITY MEDICAL CENTER IN KAZAKHSTAN	223-237
Hisham R. Ezzat, Ibrahim M. Faisal. CARDIOPROTECTIVE EFFECTS OF SILYMARIN AND VITAMIN E AGAINST DOXORUBICIN-INDUCED CARDIOTOXICITY IN RATS: EVIDENCE FROM OXIDATIVE STRESS MARKERS AND HISTOPATHOLOGICAL ANALYSIS	238-245
Shishniashvili D.S, Bedinashvili Z.J, Tsomaia K.B, Svanadze L.M, Chkhikvishvili N.M, Durglishvili G.A. FIRST-VOID URINE VERSUS URETHRAL SWAB FOR MOLECULAR DETECTION OF SEXUALLY TRANSMITTED INFECTIONS IN MEN WITH MULTIPLE SEXUAL PARTNERS	246-252
Chekhovska G.S, Pustova N.O, Syzon O.O, Chaplyk-Chyzho I.O, Dashko M.O, Vozniak I.Ya, Volbyn S.V, Ivaniushko-Nazarko N.V, Zhemela O.D, Gargin V.V. NAIL PLATE DAMAGE INDEX IN DERMATOSCOPIC EXAMINATION OF PATIENTS WITH ONYCHOMYCOSIS	253-258
Meng-Yun Zhou, Shi-qi Yu, Shao-jie Zhu, Xiang Kong, Xin-Ming Yao. A NOVEL KCNJ5 GENE MUTATION ASSOCIATED WITH FAMILIAL ALDOSTERONISM TYPE III WITHOUT HYPERTENSION	259-265
Koba Kamashidze, Tina Beruchashvili, Irina Nakashidze, Sarfraz Ahmad, Tamar Peshkova. BRIDGING THE COVERAGE-PARTICIPATION GAP: BEHAVIORAL DETERMINANTS OF CERVICAL CANCER SCREENING AMONG WOMEN IN ADJARA, GEORGIA	266-273
T.N. Kosayeva, A.T. Amiraslanov, H.K. Muradov, A.Y. Gaziyeu, B.E. Abbasov. PD-L1 EXPRESSION AND SERUM CA125: CLINICOPATHOLOGICAL CORRELATIONS IN HIGH-GRADE SEROUS OVARIAN CARCINOMA	274-280
Ruziyeva Amira Asrorovna, Khamidov Obid Abdurakhmanovich, Murodqosimov Saidolim, Doniyorov Bakhridin Baxrom ugli, Khalimova F.T, Marwan Ismail. ACE I/D AND NOS3 G894T POLYMORPHISMS AND CARDIOVASCULAR ADAPTATION PROFILES IN ADOLESCENT FOOTBALL PLAYERS	281-288

Mukhriddin Umbarov Ochilovich, Shamsutdinova Maksuda Ilyasovna, Abdullayev Ravshanbek Babajonovich, Rokhila Bakhridinovna Mengliyeva. ASSOCIATIONS OF CYTOKINE PROFILE AND EXOCRINE PANCREATIC FUNCTION WITH A SYMPTOM-BASED DEHYDRATION CATEGORY AND SEASON OF PRESENTATION IN CHRONIC PANCREATITIS: A RETROSPECTIVE STUDY.....	289-297
Saeed H. Hussein, Hiba M. Ahmed, Ahmed A. Ahmed. DETECTION OF HEPATITIS B AND C VIRAL INFECTION AMONG CHILDREN WITH ACUTE LEUKAEMIA.....	298-302
Davit Kobuladze, Ahishtan Febrian Nishanthan, Nino Kedelidze, Rusudan Vadatchkoria, Magda Davitashvili, Lamara Zuroshvili, Darejan Margalitashvili, Nani Gvarishvili, Nazi Turmanidze, Tamar Peshkova, Naman Chauhan, Teona Gogitidze, Nameera Parveen Shaikh, Aleena Parveen Shaikh, Abeshana Febrian Nishanthan, Irina Nakashidze. SELECTED LABORATORY PARAMETERS IN PEDIATRIC PATIENTS WITH COVID-19 STRATIFIED BY WHITE BLOOD CELL AND PLATELET PROFILES.....	303-309
Rawan Waleed, Abrar Fadlalla, Jana Abdullah, Marwan Ismail, Mohammed Ibrahim Saeed, Ahmad Luay Osman Hashim, Abdelgadir Elamin Eltom. IMPACT OF HELICOBACTER PYLORI INFECTION ON VITAMIN B12 DEFICIENCY LEVELS: A RETROSPECTIVE STUDY.....	310-315
T.A. Asgarova, K.M. Rahimli, G.A. Valiyeva, Sh.I. Hasanova, F.E. Guliyeva, Kh.R. Mammadova. SOME HEREDITARY DISEASES PREVALENT IN THE REPUBLIC OF AZERBAIJAN.....	316-319
Sahadete Shala, Ferdita Haxhiu Derguti. PSOAS MUSCLE ABSCESS FOLLOWING CESAREAN SECTION: A CASE REPORT.....	320-322
N. Kajaia, L. Gabunia, M. Mantskava, S. Kalmakhelidze, G. Ormotsadze, S. Turabelidze-Robaqidze, T. Sanikidze. PRO-INFLAMMATORY INTERLEUKINS AND OXIDATIVE IMBALANCE IN L-NAME-INDUCED HYPERTENSION: COMPARATIVE EFFECTS OF β -BLOCKERS.....	323-330
Hussein Fadhil Abdulameer, Raed Aziz Badeia. COMPARATIVE EVALUATION OF TWO HERBAL MOUTHWASHES AND CHLORHEXIDINE ON CALPROTECTIN IN GINGIVITIS PATIENTS: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL.....	331-340
J. Gobadze, M. Nagervadze, T. Gogitidze, N. Bejanidze, T. Koiava. SOME BIOLOGICAL CHARACTERISTICS ASSOCIATED WITH GESTATIONAL DIABETES.....	341-348
Yurevych N. O, Sazonova O. N, Kachailo I.A, Hnidyk Yu. V, Pokotylo P. B, Podolyuk M.V, Blyschak N. B, Mykhalevych M. M, Zherebkin V. V, Kosynskyi O. V, Aliksieieva V. V. THREE-DIMENSIONAL CT-BASED MORPHOMETRIC ASSESSMENT OF THE MAXILLARY SINUS.....	349-355
Simbarashe Magaisa. PERCEPTIONS AND PRACTICES OF HEALTHCARE PROVIDERS IN MATERNAL MORTALITY AND STILLBIRTH PREVENTION AND MANAGEMENT: INSIGHTS FROM LEJWELEPUTSWA DISTRICT.....	356-363
Akezhan Rustemuly Astrakhanov, Ainur Amanzholkyzy, Samat Sagatovich Saparbayev, Meirambek Sagnaevich Kurmangazin, Aigerim Iskakova, Gulzhanat Nurlanova. THE ROLE OF CELL THERAPY IN THE COMPREHENSIVE TREATMENT OF CHRONIC HEPATITIS C-RELATED LIVER CIRRHOSIS.....	364-370
Miranda Shervashidze, Khatia Dolidze, Tamar Bakhtadze, Tamar Shervashidze. PREVENTING EXERCISE-RELATED SUDDEN CARDIAC DEATH THROUGH SYSTEMATIC PREPARTICIPATION CARDIOVASCULAR SCREENING: A TWO-YEAR REGIONAL COHORT STUDY OF PEDIATRIC ATHLETES IN ADJARA, GEORGIA.....	371-380
Waseem Hashim Alkhaffaf, Muhammad A. Alkataan. COMPARATIVE EFFICACY OF 200 UNITS VERSUS 155 UNITS OF ONABOTULINUMTOXIN A FOR CHRONIC MIGRAINE.....	381-388
K. Tovar Calderón, J. Orozco Pilco, C. Calderón Cabezas, K. Caiza Cuello. ETHNIC DISPARITIES IN BIRTH WEIGHT AND PRENATAL CARE UTILIZATION IN ECUADOR, 2024.....	389-394
Gaukhar Issakova, Suriya Yessentayeva, Daniyar Amangaliyev, Askhat Bralov, Assiya M. Issayeva, Yestay Abzalbek, Marat Akhetov. INDICATIONS FOR REMOVAL OF A PORT SYSTEM IN A PATIENT WITH SUSPECTED SEPTICEMIA IN THE ABSENCE OF OTHER LOCAL SOURCES OF INFECTION.....	395-398
Mohammed A. Hayawi, Duaa M. Al-Nafoly. PREDOMINANCE OF FOLLICULAR ADENOMA AND PAPILLARY CARCINOMA IN THYROID NEOPLASMS.....	399-403
Nino Buadze, Nata Kazakhashvili. POPULATION KNOWLEDGE, RISK PERCEPTION, GOVERNANCE AND PUBLIC HEALTH DETERMINANTS OF COVID-19 IN GEORGIA: A NATIONAL CROSS-SECTIONAL STUDY.....	404-422

Alaa H. Alfarhan, Bahir S. Allawi, Mohammed A. Aljodah, Ahmed Jawad. MINIMALLY INVASIVE FAT TRANSPOSITION IN LOWER BLEPHAROPLASTY	423-427
Ospanova Meruyert, Ospanova Saniya, Yernazarov Adilet, Amanbaev Rauan, Rakhmankulov Umarali. LOW-FREQUENCY ULTRASOUND AND OZONE/NO TECHNOLOGIES IN THE COMBINED TREATMENT OF EXUDATIVE HEMISINUSITIS USING THE YAMIK-3 SINUS CATHETER.....	428-432
Sodikjon Mashraf Ugli Makhmatkulov, Ibragimova Malika Shavkatovna, Khasanov Alisher Yurevich, Mavlyanova Zilola Farkhadovna, Khalimova F.T, Marwan Ismail. COMBINED BOTULINUM TOXIN THERAPY AND PERCUTANEOUS TIBIAL NERVE STIMULATION IN THE REHABILITATION OF WOMEN WITH URGENCY URINARY INCONTINENCE ASSOCIATED WITH DIABETES MELLITUS.....	433-444
Nellia Veretova, Alfiya Samigullina, Aigul Baialieva, Ruslan Abdyldaev, Begimai Muratbekova. PSYCHONEUROLOGICAL THERAPY FOR POST-COVID SYNDROME: A COMPREHENSIVE REVIEW OF METHODS AND CLINICAL EFFECTIVENESS.....	445-451
Azhar Giniyat, Natalya Slivkina, Viktor Tkachev, Gulbana Khussainova, Ayan Baigaliyev, Sara Kubekova, Aizat Seidakhmetova, Zilola Mavlyanova, Mirbanu Aikhozhayeva, Raikhan Burumbaeva, Larissa Pavlovets, Raikhan Tleulinova, Raushan Baigenzheyeva, Mereke Alaidarova, Joseph Almazan, Aizhan Altynbekova, Bakyt Zhangabulova, Zinugul Baissova, Manzura Kankina, Parida Pirmanova, Magira Shaizadinova, Aliya Utenova, Zhansaya Raiymkul. DEVELOPMENT AND EVALUATION OF A NURSE-LED SELF-DIRECTED PEDIATRIC REHABILITATION MODEL: COMPARATIVE ANALYSIS OF INTERNATIONAL PRACTICES.....	452-465
Florina Sahiti, Argjira Veseli, Marija Peeva Petreska, Shera Kosumi, Nora Berisha, Enis Veseli, Kaltrina Veseli. BIOMARKERS OF BONE REMODELING AND INFLAMMATION IN CHRONIC PERIAPICAL LESIONS: A NARRATIVE REVIEW	466-473

ACE I/D AND NOS3 G894T POLYMORPHISMS AND CARDIOVASCULAR ADAPTATION PROFILES IN ADOLESCENT FOOTBALL PLAYERS

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Abstract.

Aim: To assess the associations of ACE I/D (rs4646994) and NOS3 G894T (rs1799983) polymorphisms with cardiovascular adaptation profiles, autonomic regulation, exercise tolerance and responsiveness to individualized training-load correction in adolescent football players.

Materials and methods: This controlled comparative study with an observational pre-post follow-up component included 228 male adolescents aged 13-17 years: 168 football players with at least two years of regular training and 60 non-athlete peers. The examination included anthropometry, body composition assessment, resting and exercise electrocardiography, echocardiography, short-term heart rate variability (HRV) analysis, submaximal bicycle ergometry with PWC170 and estimated VO₂max, heart-rate recovery (HRR), and genotyping of ACE I/D and NOS3 G894T polymorphisms. The 3-month individualized training-load correction was analyzed as a non-randomized observational component; therefore, its results were interpreted as post-correction dynamics rather than as definitive evidence of causal efficacy.

Results: Football players had a lower resting heart rate than controls (58.6±6.8 vs 72.4±7.5 beats/min; p<0.001), higher PWC170 (196±32.6 vs 142±28.4 W; p<0.001), higher relative PWC170 (3.42±0.52 vs 2.40±0.46 W/kg; p<0.001), higher estimated VO₂max (54.0±4.8 vs 42.5±5.2 ml/kg/min; p<0.001) and faster HRR1 (43.6±11.3 vs 25.3±10.4 beats/min; p<0.001). ACE and NOS3 genotype distributions were comparable between football players and controls. Within the athletic cohort, ACE DD and, to a lesser extent, NOS3 T-allele carriage were associated with lower SDNN, RMSSD and pNN50, higher LF/HF and less favorable diastolic indices. After three months of individualized training-load correction, positive HRV and diastolic dynamics were observed mainly in favorable and intermediate genetic profiles, whereas the unfavorable profile showed limited changes.

Conclusion: ACE I/D and NOS3 G894T polymorphisms should not be interpreted as markers of football participation or selection. They may be considered exploratory modifiers of autonomic reserve, diastolic adaptation and response to individualized training-load monitoring. Integration of genotyping with ECG, echocardiography, HRV, HRR and PWC170 appears promising for personalized monitoring in adolescent football players but requires further external validation. The results of the dynamic stage should be interpreted as observational, since the training-load correction was not randomized.

Key words. Adolescent athletes, football, cardiovascular adaptation, heart rate variability, ACE I/D, NOS3 G894T, personalized sports medicine.

Introduction.

Cardiovascular adaptation in adolescent athletes is a key issue in contemporary sports medicine, because at this age the training stimulus is superimposed on intensive somatic growth, hormonal reorganization and maturation of autonomic regulation. Football is characterized by combined aerobic-anaerobic and intermittent loads; therefore, it induces not only signs of physiological cardiac remodeling but also pronounced interindividual variability in chronotropic, hemodynamic and recovery responses [1-4].

In practical sports cardiology, increasing importance is attached to multilevel monitoring models that combine electrocardiography, echocardiography, heart rate variability, response to graded exercise and the rate of post-exercise heart-rate recovery. This approach helps distinguish the physiological "athlete's heart" from functional strain and early signs of maladaptation [5-8].

Genetic factors are of particular interest. The ACE gene is involved in regulation of the renin-angiotensin system and vascular tone, whereas NOS3 encodes endothelial nitric oxide synthase, which determines NO-dependent vasodilation. Data from sports genomics indicate that these polymorphisms should not be regarded as isolated "sports genes"; nevertheless, they may influence individual exercise tolerance, autonomic reserve, hemodynamic response and the effectiveness of training adaptation [9-15].

In the present study, ACE/NOS3 genetic variants were considered not as markers of sports selection, but as possible modifiers of the functional adaptation profile in adolescents who were already engaged in regular training. This approach avoids overinterpretation of genotype and is consistent with the modern concept of personalized but non-discriminatory medical supervision of young athletes.

The aim of the study was to assess the associations of ACE I/D and NOS3 G894T polymorphisms with the cardiovascular adaptation profile in adolescent football players and to determine whether an integrated genetic-functional profile can be used for personalized monitoring and training-load correction. The main research question was whether ACE I/D and NOS3 G894T variants are associated not with football participation itself, but with differences in autonomic regulation, diastolic adaptation, recovery responses, and post-monitoring dynamics after

individualized training-load management in adolescents who are already engaged in regular training.

Materials and Methods.

The study was designed as a controlled comparative clinical-functional and molecular-genetic investigation with elements of prospective observation. The main block included a single-time assessment of cardiovascular functional status and genotyping, whereas the final block consisted of a 3-month individualized correction of training load followed by repeated assessment of HRV, ECG and echocardiography. Since this stage was not randomized and did not include a separate standard-care comparison group, the results were interpreted only as observed post-correction dynamics, rather than as evidence of its causal efficacy.

A total of 228 male adolescents aged 13-17 years were examined in 2021-2025. The main group consisted of 168 adolescent football players who had trained regularly at the Samarkand Regional Football Academy for at least two years. The control group included 60 practically healthy peers who did not participate in regular sports training.

Inclusion criteria for football players were male sex, age 13-17 years, organized training at least 3-4 times per week, sports experience of at least two years, absence of acute illness at examination, medical clearance for sports participation after routine medical screening, and ability to perform a standardized exercise test. The control group included adolescents of the same age and sex without systematic sports training and without clinically significant cardiovascular disease.

Training load was recorded from the sports history and team documentation: sports experience, number of training sessions per week, average session duration, playing position, participation in the competitive period and presence of high-intensity microcycles. Adherence to individualized recommendations was monitored jointly by the sports physician and coach. Genetic data were not used for sports selection, restriction of participation, or allocation of adolescents to playing positions.

Exclusion criteria for both groups were congenital or acquired heart disease, cardiomyopathies, clinically significant rhythm or conduction disorders, arterial hypertension, chronic diseases in exacerbation, endocrine disorders, acute infectious disease within two weeks before examination, use of drugs affecting heart rate, vascular tone or HRV, and incomplete functional or genetic data.

All examinations were performed in the morning after nocturnal sleep, under standardized conditions and not earlier than 12 hours after the last intensive training session. Anthropometric assessment included height, body weight, body mass index and bioimpedance analysis of body composition. ECG was recorded in 12 standard leads at rest and during functional assessment.

Echocardiography was performed at rest in the left lateral decubitus position using an expert-class ultrasound device with a phased-array transducer. Left ventricular end-diastolic and end-systolic diameters, interventricular septal thickness, posterior wall thickness, left ventricular mass index, left ventricular ejection fraction, transmitral E/A ratio and tissue Doppler indices with calculation of E/e' were assessed.

HRV was evaluated using a short-term resting ECG recording of at least 5 minutes during quiet wakefulness and stable

breathing. The analysis included time-domain indices (SDNN, RMSSD, pNN50), spectral indices (LF, HF) and the LF/HF ratio. Artifact segments and extrasystoles were excluded; recordings were obtained in the absence of acute infection, marked fatigue and intensive exercise on the previous day.

Physical performance was assessed by a submaximal bicycle ergometry test with calculation of PWC170, relative PWC170 (W/kg), estimated VO₂max and heart-rate recovery at 1, 3 and 5 minutes after exercise cessation. PWC170 was calculated using the standard interpolation formula: $PWC170 = W1 + (W2 - W1) \times (170 - HR1) / (HR2 - HR1)$, where W1 and W2 are the powers of two consecutive stages and HR1 and HR2 are the corresponding heart rates. Estimated VO₂max was calculated using the formula: $VO2max = (1.7 \times PWC170 + 1240) / \text{body weight}$; therefore, this indicator is interpreted throughout the article as estimated rather than as a direct gas-analysis measurement.

The molecular-genetic study included collection of 3-5 ml of venous blood into EDTA tubes, extraction of genomic DNA from peripheral blood leukocytes and genotyping of ACE I/D (rs4646994) by PCR with electrophoretic detection of amplification products. The NOS3 G894T polymorphism (rs1799983, Glu298Asp) was analyzed by PCR-RFLP using BanII restriction enzyme. Quality control included negative controls in each PCR run and repeat genotyping of 10% of samples.

An integrated genetic profile was formed on the basis of the combined ACE I/D (II=0, ID=1, DD=2) and NOS3 G894T (GG=0, GT=1, TT=2) variants: favorable (0-1 point; GP-1), intermediate (2 points; GP-2) and unfavorable (3-4 points; GP-3). This score was used as an exploratory stratification model with equal weighting of ACE and NOS3, not as a validated clinical scale. Its purpose was to organize dynamic monitoring and select monitoring frequency, not to restrict an adolescent's access to sports participation.

The type of adaptation was determined using a set of functional criteria. The economical type was defined by low resting heart rate, high HRR1, high SDNN/RMSSD, low LF/HF and favorable diastolic indices. The compensated type included moderate HRV reduction or moderate LF/HF elevation without marked reduction in performance. The strained type was characterized by low HRV, high LF/HF, delayed HRR and less favorable diastolic indices with preserved systolic function.

Individualized load correction was performed by the sports physician together with the coach. For GP-1, planned load progression was maintained with recovery monitoring; for GP-2, the frequency of high-intensity microcycles was limited and recovery days were strengthened; for GP-3, the proportion of high-intensity loads was reduced, recovery intervals were increased and more frequent monitoring of HRV, resting heart rate, HRR and echocardiography was prescribed. Genetic data were not used for sports selection, restriction of participation, or allocation of adolescents to playing positions.

Statistical analysis included testing quantitative variables for normality using the Shapiro-Wilk test, presentation of normally distributed data as $M \pm SD$, between-group comparisons using Student's t-test or the Mann-Whitney test, comparison of three or more groups using ANOVA or the Kruskal-Wallis test, Pearson chi-square test or Fisher's exact test for categorical variables, Hardy-Weinberg equilibrium testing, and calculation of odds ratios and 95% confidence intervals. Pre-post dynamics were

assessed using the paired t-test or Wilcoxon test. Multivariable regression and correction for multiple comparisons were not performed in the present version; therefore, findings for secondary parameters are interpreted as exploratory associations requiring further verification. To clarify the independent contribution of genotypes, future studies should include a multivariable model incorporating age, BMI, training experience, body composition, and training-load volume.

Ethical aspects: the study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal representatives of the adolescents, and age-appropriate assent was obtained from the adolescents themselves. The study protocol was approved by the Ethics Committee of Samarkand State Medical University (Protocol No. 11, January 20, 2021).

Results.

Baseline characteristics showed that football players and controls were comparable in age, height, body weight and body mass index, which reduces the probability of systematic bias when interpreting functional parameters. At the same time, football players had a more favorable body composition: lower fat mass and higher muscle mass and total body water, reflecting training-related adaptation.

As shown in Table 1, training status was not associated with significant differences in the main anthropometric parameters, but it was associated with lower fat mass and higher muscle mass, supporting the validity of the subsequent analysis of functional differences.

Football players showed marked economization of the chronotropic response: resting heart rate was 13.8 beats/min lower than in controls ($p < 0.001$). At the first and second exercise stages, heart rate remained significantly lower in football players, whereas differences at peak exercise were attenuated. At the same time, HRR and physical performance indices were substantially higher in football players.

The data in Table 2 demonstrate that adaptation in football players was manifested not by a higher peak heart rate, but by lower resting heart rate, a more economical response during the early stages of exercise, faster recovery and substantially greater physical performance.

Figure 1 shows that heart rate decreased faster in football players than in controls at all recovery time points. The first minute of recovery was the most clinically informative: high HRR1 (≥ 40 beats/min) was recorded in 70.2% of football players versus 20.0% of controls, whereas reduced HRR1 (< 25 beats/min) occurred in only 3.6% of athletes versus 33.3% of controls.

Molecular-genetic analysis showed that the distribution of ACE I/D and NOS3 G894T genotypes was consistent with Hardy-Weinberg equilibrium and did not differ significantly between football players and controls. Thus, the studied polymorphisms did not determine membership in the football-player group, but they could influence the individual adaptation phenotype within the athletic cohort.

Within the football-player group, ACE I/D genotype was significantly associated with autonomic regulation. The most favorable profile was recorded in ACE II carriers: as genotype shifted from II to DD, SDNN, RMSSD, pNN50 and HF

decreased, whereas LF and LF/HF increased. This indicates a shift toward sympathetic predominance in DD carriers.

Table 4 shows a pronounced genotype-dependent gradient: in the DD genotype, SDNN values were 17.9% lower than in II carriers, RMSSD was 27.1% lower and LF/HF was 38.0% higher. This profile corresponds to lower autonomic reserve and a potentially higher risk of regulatory strain during intensive training loads.

A similar pattern was observed for the NOS3 G894T polymorphism. GG carriers had higher time-domain HRV indices and a lower LF/HF ratio, whereas the TT genotype was associated with the least favorable autonomic profile. Because the TT subgroup was small ($n = 13$), these data should be interpreted cautiously as an associative signal requiring verification in a larger sample. They should not be used as an independent basis for individual clinical decision-making or for restricting sports participation.

As shown in Table 5, NOS3 T-allele carriage was accompanied by gradual decreases in parasympathetic markers and an increase in the sympathovagal index. The most pronounced differences were observed between GG and TT carriers: SDNN decreased by 18.8%, RMSSD by 31.4%, whereas LF/HF increased by 32.9%.

Echocardiographic data are presented separately because interpretation of diastolic function and physiological remodeling should rely on numerical indicators. ACE II and NOS3 GG carriers showed more pronounced features of physiological remodeling and more favorable diastolic indices with preserved systolic function.

Table 6 demonstrates that, in the transition from ACE II to ACE DD, LV end-diastolic diameter, LV mass, LV mass index and E/A decreased, whereas E/e' increased. LVEF remained comparable, confirming the predominantly functional-adaptive rather than pathological nature of the observed differences.

Table 7 confirms the same directionality for NOS3: TT carriers had lower LVEDD, LVMI and E/A, and higher E/e' than GG carriers. However, owing to the small size of the TT subgroup, these results should be considered a basis for closer monitoring rather than an independent criterion for restricting sports activity.

At the next stage, genetic data were integrated into a personalized algorithm. According to the total ACE/NOS3 score, 60 football players had a favorable genetic profile (GP-1), 72 had an intermediate profile (GP-2) and 36 had an unfavorable profile (GP-3). After three months of load correction, the most pronounced positive dynamics were observed in GP-1 and GP-2, whereas the effect in GP-3 was limited.

Given the non-randomized nature of this stage, the data reflect post-correction dynamics but do not allow definitive causal conclusions regarding its effectiveness.

Figure 2 shows that the increase in SDNN was maximal in athletes with a favorable profile and moderate in athletes with an intermediate profile. In carriers of an unfavorable profile, the increase in SDNN was small, supporting the need for more cautious and prolonged monitoring in this group. These differences should be regarded as a basis for more cautious and prolonged monitoring, rather than as evidence of differential effectiveness of training-load correction across genetic profiles.

Figure 3 shows a decrease in LF/HF in GP-1 and GP-2, reflecting improved sympathovagal balance after load

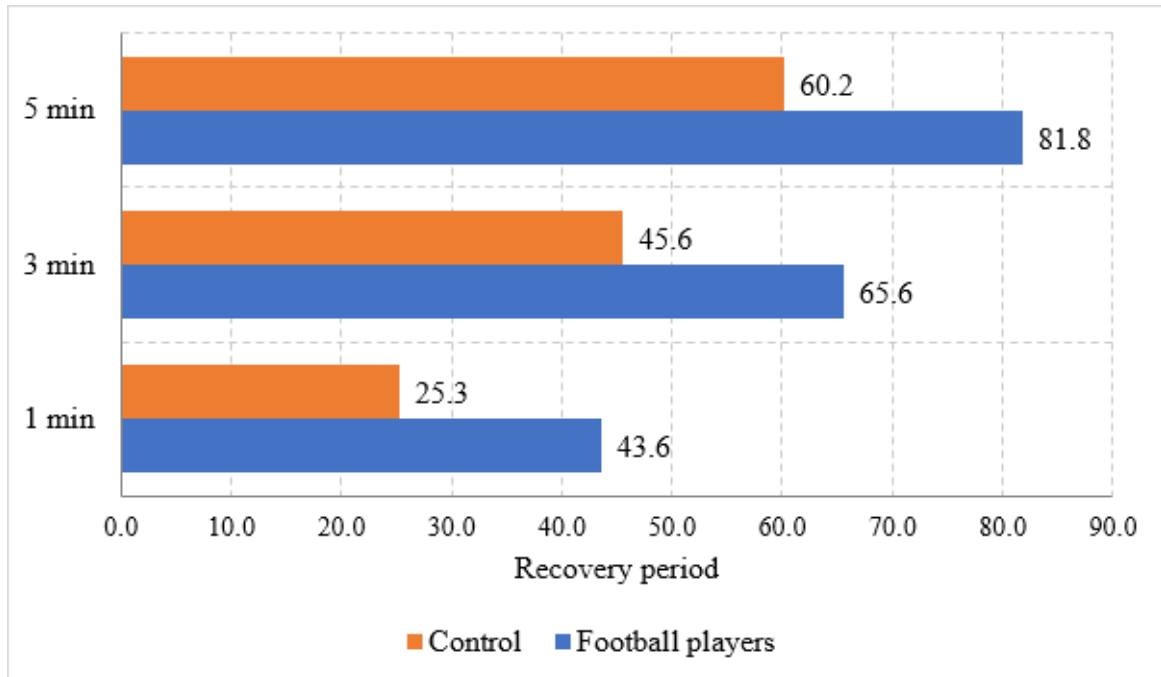


Figure 1. Heart-rate recovery after standardized exercise testing in football players and controls.

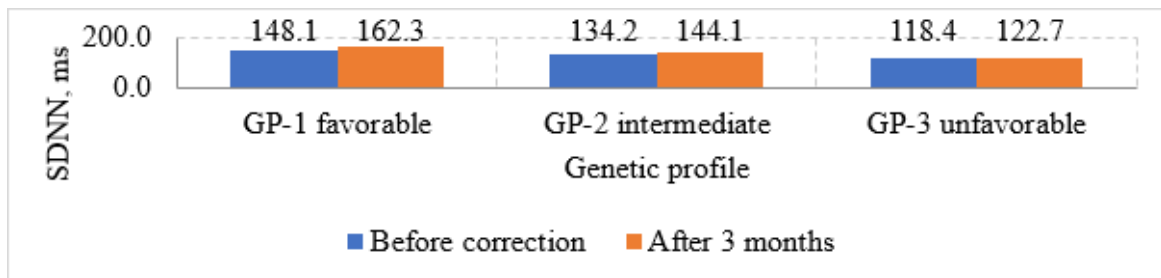


Figure 2. SDNN dynamics after 3-month personalized training-load correction.

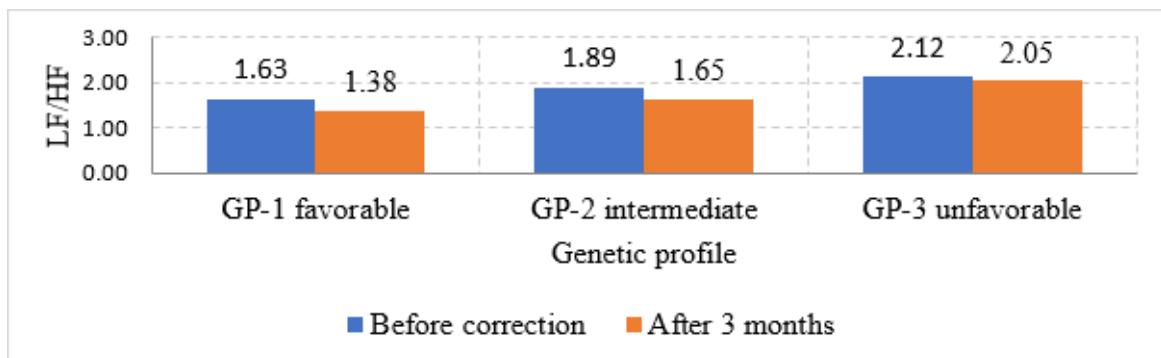


Figure 3. Dynamics of sympathovagal balance after 3-month personalized training-load correction.

Table 1. Baseline characteristics of the examined adolescents.

Parameter	Football players (n=168)	Controls (n=60)	p
Age, years	15.2 ± 1.1	15.1 ± 1.0	0.58
Height, cm	170.4 ± 7.6	168.9 ± 7.2	0.21
Body weight, kg	62.8 ± 8.4	64.1 ± 9.1	0.34
BMI, kg/m ²	21.6 ± 2.1	22.4 ± 2.3	0.07
Fat mass, %	14.8 ± 3.6	19.2 ± 4.1	<0.001
Muscle mass, %	53.9 ± 4.2	49.8 ± 4.5	<0.001
Total body water, %	56.1 ± 3.9	52.4 ± 4.2	<0.001

Table 2. Cardiovascular response to standardized exercise testing.

Parameter	Football players (n=168)	Controls (n=60)	p
Resting heart rate, beats/min	58.6 ± 6.8	72.4 ± 7.5	<0.001
Heart rate at stage 1, beats/min	124 ± 10.1	135 ± 11.1	<0.001
Heart rate at stage 2, beats/min	149 ± 11.2	158 ± 12.2	<0.001
Peak heart rate, beats/min	189 ± 7.6	187 ± 8.4	0.09
Peak SBP, mmHg	172 ± 15.5	178 ± 16.2	0.03
Peak DBP, mmHg	70 ± 7.3	73 ± 8.4	0.04
HRR1, beats/min	43.6 ± 11.3	25.3 ± 10.4	<0.001
HRR3, beats/min	65.6 ± 12.2	45.6 ± 11.6	<0.001
HRR5, beats/min	81.8 ± 12.5	60.2 ± 12.2	<0.001
PWC170, W	196 ± 32.6	142 ± 28.4	<0.001
PWC170, W/kg	3.42 ± 0.52	2.40 ± 0.46	<0.001
VO2max, ml/kg/min	54.0 ± 4.8	42.5 ± 5.2	<0.001

Table 3. Distribution of ACE I/D and NOS3 G894T genotypes and alleles.

Gene / parameter	Football players (n=168)	Controls (n=60)	p
ACE II / ID / DD	46 / 82 / 40	14 / 29 / 17	0.34
ACE I, n (%)	174 (51.8%)	57 (47.5%)	0.34
ACE D, n (%)	162 (48.2%)	63 (52.5%)	0.34
ACE HWE, χ^2 ; p	0.12; 0.94	0.04; 0.98	-
NOS3 GG / GT / TT	87 / 68 / 13	28 / 26 / 6	0.61
NOS3 G, n (%)	242 (72.0%)	82 (68.3%)	0.52
NOS3 T, n (%)	94 (28.0%)	38 (31.7%)	0.52
NOS3 HWE, χ^2 ; p	0.003; 0.95	0.0001; 0.99	-

Table 4. HRV parameters in football players according to ACE I/D genotype.

Parameter	II (n=46)	ID (n=82)	DD (n=40)	p
SDNN, ms	156 ± 22	142 ± 20	128 ± 18	<0.001
RMSSD, ms	64.2 ± 12.1	55.6 ± 11.4	46.8 ± 10.2	<0.001
pNN50, %	28.6 ± 6.2	22.9 ± 5.8	18.4 ± 5.1	<0.001
LF, ms ²	710 ± 140	820 ± 150	940 ± 160	0.002
HF, ms ²	520 ± 110	430 ± 100	350 ± 90	<0.001
LF/HF	1.42 ± 0.31	1.68 ± 0.35	1.96 ± 0.38	<0.001

Table 5. HRV parameters in football players according to NOS3 G894T genotype.

Parameter	GG (n=87)	GT (n=68)	TT (n=13)	p
SDNN, ms	150.4 ± 21	138.3 ± 20	122.1 ± 18	<0.001
RMSSD, ms	60.1 ± 11.7	52.4 ± 11.0	41.2 ± 9.8	<0.001
pNN50, %	26.4 ± 6.0	21.0 ± 5.6	15.9 ± 5.0	<0.001
LF, ms ²	760 ± 150	860 ± 160	980 ± 170	0.004
HF, ms ²	470 ± 105	390 ± 95	320 ± 85	<0.001
LF/HF	1.55 ± 0.33	1.80 ± 0.36	2.06 ± 0.40	<0.001

Table 6. Echocardiographic parameters in football players according to ACE I/D genotype.

Parameter	II (n=46)	ID (n=82)	DD (n=40)	p
LVEDD, mm	51.8 ± 3.2	50.6 ± 3.1	49.4 ± 3.0	0.01
LVESD, mm	32.1 ± 2.8	31.6 ± 2.7	31.2 ± 2.6	0.19
IVS, mm	9.8 ± 0.8	9.6 ± 0.8	9.4 ± 0.7	0.14
LVPW, mm	9.7 ± 0.7	9.6 ± 0.7	9.5 ± 0.7	0.32
LVM, g	156 ± 18	150 ± 17	144 ± 16	0.02
LVMI, g/m ²	86.2 ± 8.1	82.4 ± 7.9	78.9 ± 7.6	0.01
LVEF, %	62.8 ± 3.6	63.2 ± 3.7	63.6 ± 3.9	0.42
E/A	1.86 ± 0.24	1.78 ± 0.22	1.69 ± 0.21	0.03
E/e'	6.1 ± 0.9	6.5 ± 1.0	6.9 ± 1.1	0.04

Table 7. Echocardiographic parameters in football players according to NOS3 G894T genotype.

Parameter	GG (n=87)	GT (n=68)	TT (n=13)	p
LVEDD, mm	51.2 ± 3.1	50.2 ± 3.0	49.1 ± 2.9	0.02
LVESD, mm	31.8 ± 2.7	31.5 ± 2.6	31.3 ± 2.6	0.62
IVS, mm	9.7 ± 0.8	9.6 ± 0.8	9.4 ± 0.7	0.46
LVPW, mm	9.6 ± 0.7	9.6 ± 0.7	9.5 ± 0.7	0.88
LVMI, g/m ²	84.9 ± 8.0	82.0 ± 7.8	79.1 ± 7.5	0.03
LVEF, %	63.0 ± 3.7	63.3 ± 3.8	63.7 ± 3.9	0.71
E/A	1.83 ± 0.23	1.74 ± 0.22	1.63 ± 0.21	0.02
E/e'	6.2 ± 0.9	6.6 ± 1.0	7.1 ± 1.1	0.02

Table 8. HRV dynamics after personalized training-load correction.

Profile	SDNN baseline	SDNN after	RMSSD baseline	RMSSD after	LF/HF baseline	LF/HF after
GP-1, n=60	148.1±23.2	162.3±25.1*	58.6±11.8	68.2±12.4*	1.63±0.35	1.38±0.31*
GP-2, n=72	134.2±21.4	144.1±22.4*	50.9±11.1	56.3±11.7*	1.89±0.38	1.65±0.36*
GP-3, n=36	118.4±19.3	122.7±20.1	42.1±9.6	44.0±9.8	2.12±0.41	2.05±0.39

Note: * statistically significant within-group change compared with baseline ($p < 0.05$). Between-profile differences and the profile $\times$ time interaction are presented as exploratory and require additional verification using a repeated-measures model based on individual-level data.

Table 9. Echocardiographic dynamics after personalized correction.

Parameter	GP-1 baseline	GP-1 after	GP-2 baseline	GP-2 after	GP-3 baseline	GP-3 after
LVEDD, mm	51.3±3.1	51.8±3.2	50.2±3.0	50.6±3.1	49.0±2.9	49.2±3.0
LVMI, g/m ²	84.6±8.1	86.9±8.3*	81.9±7.8	83.2±8.0*	78.8±7.4	79.4±7.5
LVEF, %	63.1±3.7	63.4±3.8	63.3±3.8	63.6±3.9	63.6±3.9	63.7±4.0
E/A	1.78±0.22	1.88±0.23*	1.69±0.21	1.77±0.22*	1.58±0.20	1.61±0.21
E/e'	6.3±1.0	5.8±0.9*	6.8±1.1	6.3±1.0*	7.4±1.2	7.2±1.1

Table 10. Practical scheme for personalized training-load correction.

Adaptation type	Functional profile	Recommended loads	Restrictions	Medical monitoring
Economical	High adaptive reserves, low resting heart rate, high HRV, diastolic function	Full aerobic and mixed loads; planned increase in volume and intensity	Avoid abrupt increases in training volume	Monitoring every 3-4 months: HRV and resting heart rate
Compensated	Moderate reserves; signs of regulatory strain with preserved performance	Stepwise load progression; mandatory recovery microcycle	the frequency of high-intensity loads	Monitoring every 2-3 months: HRV, ECG and diastolic function
Strained	Reduced reserves, increased resting heart rate, low HRV, sympatheticotonia	Predominantly moderate-intensity aerobic loads; prolonged recovery	Avoid high-intensity overload during signs of fatigue	Monitoring every 1-2 months: HRV, ECG and echocardiography

correction. In GP-3, the index remained high, indicating relative persistence of sympathetic predominance and lower plasticity of the adaptation response. However, this observation requires confirmation in a randomized or externally validated study.

Table 9 shows that after load correction, diastolic parameters improved in GP-1 and GP-2: E/A increased and E/e' decreased. Changes in GP-3 were minimal, confirming lower adaptive plasticity of the unfavorable genetic-functional profile.

The practical scheme demonstrates that the correction algorithm was based on the combination of functional status, HRV, recovery indices and genetic profile. The genetic profile was not used to exclude adolescents from sport; it served only as an additional instrument for selecting monitoring frequency, recovery duration and caution when increasing high-intensity loads.

Discussion.

The obtained results confirm that adolescent football players have a more economical cardiovascular functional profile

than non-athletes: lower resting heart rate, higher physical performance, better estimated aerobic capacity and faster post-exercise recovery. These data are consistent with the contemporary concept of training-induced adaptation in young athletes, in which not only peak response but also recovery kinetics and autonomic regulation are of key importance [3,4,16-18].

An important finding is the absence of significant differences in ACE I/D and NOS3 G894T frequencies between football players and controls. This means that these polymorphisms should not be interpreted as criteria for sports selection or as a "genetic passport" of a football player. Their relevance appears at another level, namely as modifiers of the individual adaptation profile in adolescents who are already engaged in training.

ACE DD and, to a lesser extent, NOS3 T-allele carriage were associated with a less favorable autonomic profile: decreased SDNN, RMSSD, pNN50 and HF, and increased LF/HF. From a physiological perspective, this may reflect lower parasympathetic reserve and greater dependence of heart rhythm on sympathetic

activation. For sports medicine this is particularly important because reduced HRV and delayed recovery are considered sensitive markers of functional overstrain, especially in team sports [4,16,18].

Echocardiographic differences mainly concerned diastolic parameters and left ventricular mass index with preserved ejection fraction. It is important to emphasize that these shifts did not correspond to pathological diastolic dysfunction but rather reflected a less favorable adaptation profile within preserved systolic function. The combination of an unfavorable genetic-functional profile with low HRV, high LF/HF and less favorable diastolic indices is a basis for more frequent dynamic control.

The practical value of the study lies in the transition from simple description of genetic associations to a monitoring algorithm: stratification of the adaptation profile, individualized load correction and repeated assessment of dynamics. After correction, the most pronounced positive changes were observed in GP-1 and GP-2, whereas GP-3 required a more cautious approach: gradual load progression, mandatory recovery, and monitoring of HRV, resting heart rate, HRR and diastolic parameters every 6-8 weeks. At the same time, the interventional stage was observational in nature; therefore, the reported changes should not be interpreted as direct evidence of the algorithm's effectiveness.

Special attention should be paid to the small number of NOS3 TT carriers. Despite the consistency of the direction of changes in HRV and echocardiography, results for this subgroup should not be interpreted as definitive evidence of an unfavorable effect of the TT genotype. It is more appropriate to consider them a clinically meaningful signal for further testing in a multicenter sample with prespecified statistical power.

Multivariable regression analysis at the individual-data level was not performed in this journal version; therefore, the results are not presented as an independent predictive model. The obtained data should be interpreted as genotype-dependent associations that require further confirmation with adjustment for age, BMI, training experience, training volume and body composition. This is particularly important because these factors may simultaneously influence HRV, physical performance indices, and echocardiographic parameters.

Limitations of the study.

The limitations of the study include the inclusion of only male adolescents, the regional nature of the sample, absence of independent external validation of the algorithm, the small number of NOS3 TT carriers, estimated rather than directly gas-analytically measured VO₂max, absence of a randomized control group for the interventional stage, absence of multivariable regression and correction for multiple comparisons, and the possible influence of sleep, nutrition, psychoemotional stress and training-season phase. These limitations do not reduce the practical relevance of the study, but they require cautious interpretation and further confirmation in multicenter investigations. Therefore, conclusions regarding post-correction training-load dynamics are hypothesis-generating and should be verified in studies with randomization, external validation, and a prespecified multivariable statistical model.

Conclusion.

Compared with non-athletes, adolescent football players demonstrate a more economical profile of cardiovascular adaptation: lower resting heart rate, higher PWC170 and estimated VO₂max, and faster heart-rate recovery after standardized exercise testing.

2. The distribution of ACE I/D and NOS3 G894T genotypes does not differ between football players and controls, excluding their direct role as markers of sports specialization or sports selection.

3. Within the football-player group, ACE DD and, to a lesser extent, NOS3 T-allele carriage were associated with a less favorable autonomic and diastolic profile: decreased SDNN, RMSSD, pNN50 and HF, increased LF/HF, decreased E/A and increased E/e'. The results for NOS3 TT require confirmation in a larger sample.

4. After individualized training-load correction based on the genetic and functional profile, positive dynamics of HRV and diastolic function were observed mainly in athletes with favorable and intermediate genetic profiles. Given the observational design, these data do not prove the causal effectiveness of training-load correction. Integration of ACE/NOS3 genotyping with ECG, echocardiography, HRV, HRR and PWC170 may be considered a promising direction for personalized monitoring, but it requires further external validation.

Practical recommendations.

1. Medical monitoring of adolescent football players should include regular assessment of HRV, HRR1, PWC170 and echocardiographic diastolic parameters together with ECG and standard clinical control.

2. Carriers of ACE DD and/or the NOS3 T allele should undergo more frequent monitoring of resting heart rate, SDNN, RMSSD, LF/HF and diastolic parameters, especially in the pre-competitive and competitive periods. At the same time, genetic testing should be used only as an additional monitoring tool and should not be applied to exclude an adolescent from sports participation.

3. In the economical adaptation type, planned intensity progression is acceptable while maintaining recovery days. In compensated and strained types, more gradual load progression, limitation of high-intensity training frequency, longer recovery and repeated monitoring after 6-8 weeks are recommended.

Ethical considerations.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Samarkand State Medical University (Protocol No. 11, January 20, 2021). Written informed consent was obtained from the parents or legal representatives of the adolescents; the adolescents themselves provided age-appropriate assent to participate in the study.

Conflict of interest.

The authors declare no conflict of interest.

Funding.

The study received no external funding.

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