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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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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 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.

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

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. Корректура авторам не высылается, 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 compu-ter-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 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.

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, 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.

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Содержание:

Dariy V, Sikorska M, Vizir I, Khramtsov D, Serikov K.
DIFFERENTIATED THERAPY OF PATIENTS WITH INTRACEREBRAL COMPLICATED HEMISPHERIC ISCHEMIC CEREBRAL STROKE WITH SECONDARY BRAINSTEM HEMORRHAGES AGAINST THE BACKGROUND OF HYPERTENSIVE ENCEPHALOPATHY……6-10

Turayev T.M, Velilyaeva A.S, Aziza Djurabekova, Umarova Marjona, Fariza Khalimova, Marwan Ismail.
UNRAVELING THE LINK BETWEEN EPILEPTIC FOCUS LATERALIZATION AND DEPRESSION IN FOCAL EPILEPSY…..……11-18

T. Nikolaishvili, Cicino Farulava, Sh. Kepuladze, G. Burkadze.
IMMUNE DYSREGULATION AND EPITHELIAL STRESS IN CELIAC DISEASE PROGRESSION: A FOCUS ON REFRACTORY CELIAC DISEASE SUBTYPES…….19-26

Z.S. Khabadze, A.V Vasilyev, Yu.A. Generalova, O.G. Avraamova, A.A. Kulikova, A.A. Generalova, L.A. Vashurina, V.M. Slonova, N.A. Dolzhikov, A.U. Umarov, A. Wehbe, E.A. Klochkovich.
DETERMINATION OF ROOT CANAL MICROBIOTA IN CHRONIC APICAL PERIODONTITIS AND EVALUATION OF THE MICROBIOLOGICAL ACTIVITY SPECTRUM OF POLYHEXANIDE AGAINST THE IDENTIFIED MICROBIAL FLORA…..……27-36

Machitidze Manana, Grdzelidze Irma, Kordzaia Dimitri.
ASSESSING GEORGIAN NURSES' KNOWLEDGE AND ATTITUDES ON SAFE MEDICATION ADMINISTRATION: GAPS AND COMPLIANCECHALLENGES…….37-42

Aissulu Kapassova, Gulmira Derbissalina, Baurzhan Iskakov.
EPIDEMIOLOGY, CLINICAL FEATURES AND DIAGNOSIS OF CELIAC DISEASE AMONG PEDIATRIC POPULATION IN KAZAKHSTAN…….43-48

Abdulrahman Z. Al-Najjar, Tabark A. Rasool, Basma K. Ahmed, Faehaa A.Al-Mashhadane.
MECHANICAL PROPERTY CHANGES IN ORTHODONTIC WIRES AFTER EXPOSURE TO CHLORHEXIDINE MOUTHWASH: A REVIEWSTUDY…….49-53

Chigareva Irina S, Karelova Alina D, Zeinalova Narmin E, Abdulkhadzhiev Akhmed A, Isaev Akhmed Kh, Kurbanov Gadzhi K, Israpilov Ibragim R, Dagaeva Imani I, Dashaeva Maryam I, Petchina Anastasia I, Delimkhanov Rustam S.-Kh, Musaev Emin R, Pandyashkina Karina G.
PHENOTYPIC SWITCHING OF VASCULAR SMOOTH MUSCLE CELLS: KEY MECHANISM IN ATHEROSCLEROSIS PROGRESSION…….54-58

D. Saussanova, M. Baymuratova, A. Amirzhanova, K. Uspanova, T. Slyambayev, Z. Tobylbayeva, A. Izbassarova.
ASSESSMENT OF PEDIATRIC INTERNS' COMMITMENT TO PNEUMOCOCCAL VACCINATION: A CROSS-SECTIONAL STUDY IN MEDICAL UNIVERSITIES OF ALMATY, KAZAKHSTAN…….59-66

Velilyaeva A.S, Turayev T.M, Aziza Djurabekova, Umarova Marjona, Fariza Khalimova.
THE IMPACT OF EPILEPTIC FOCUS LATERALIZATION ON THE STRUCTURE OF DEPRESSIVE SYMPTOMATOLOGY IN FOCAL EPILEPSY…….67-72

Ruaa N. AL-Saraj, Safa M. AL-Ashou.
ABO BLOOD GROUPS IN RELATION TO ANXIETY, STRESS AND DEPRESSION…….73-79

Tchernev G, Broshtilova V, Lozev I, Kordeva S, Pidakev I, Ivanova V, Tchernev KG Jr.
NITROSAMINES IN METFORMIN AND HYDROCHLOROTHIAZIDE: ″HUMAN SAFE PHOTOCARCINOGENS″ WITHIN THE POLYPHARMACY AS GENERATOR FOR PHOTOTOXICITY/ PHOTOCARCINOGENICITY AND THE SUBSEQUENT DEVELOPMENT OF MULTIPLE KERATINOCYTE CARCINOMAS. DOUBLE HATCHET FLAP AS OPTIMAL AND NECESSARY DERMATOSURGICAL DECISION IN TWO NEW PATIENTS…….80-89

Tigran G. Makichyan, Elena V. Gusakova, Zurab S. Khabadze, Alexey V. Rylsky.
SOMATIC DYSFUNCTIONS IN THE MODELING OF OCCLUSAL AND EXTRAOCCLUSAL DISORDERS……..90-93

Teremetskyi VI, Astafiev DS, Mosondz SO, Pakhnin ML, Bodnar-Petrovska OB, Igonin RV, Lifyrenko SM.
MEDICAL TOURISM AS A DRIVER OF UKRAINE'S ECONOMIC RECOVERY: PRE-WAR EXPERIENCE AND STRATEGIC GUIDELINES FOR THE POST-WAR PERIOD…….94-103

Tameem T. Mayouf, Mohammed B. Al-Jubouri.
THE EFFECT OF SOFT ROBOTIC GLOVE ON THE FLEXION AND EXTENSION OF HAND FOR STROKE PATIENTS: A CLINICAL TRIAL……..104-108

Lesia Serediuk, Yurii Dekhtiar, Olena Barabanchyk, Oleksandr Hruzevskyi, Mykhailo Sosnov.
INNOVATIVE APPROACHES TO THE DIAGNOSIS AND TREATMENT OF HYPERTENSION: USE OF TECHNOLOGY AND PROSPECTS…….109-120

Yerkibayeva Zh.U, Yermukhanova G.T, Saduakassova K.Z, Rakhimov K.D, Abu Zh, Menchisheva Yu. A.
NON-INVASIVE ESTHETIC TREATMENT OF INITIAL CARIES WITH RESIN INFILTRATION IN A PATIENT WITH AUTISM SPECTRUMDISORDER…….121-126

Niharika Bhuyyar, Bhushan Khombare, Abhirami Panicker, Shubham Teli, Mallappa Shalavadi, Kiran Choudhari.
NICOLAU SYNDROME: CUTANEOUS NECROSIS FOLLOWING DICLOFENAC INTRAMUSCULAR INJECTION……127-128

Dramaretska S.I, Udod O.A, Roman O.B.
RESULTS OF COMPREHENSIVE TREATMENT OF PATIENTS WITH ORTHODONTIC PATHOLOGY AND PATHOLOGICAL TOOTH WEAR……129-134

Tigran G. Makichyan, Elena V. Gusakova, Zurab S. Khabadze, Albert R. Sarkisian.
THE EFFECTIVENESS OF OSTEOPATHIC CORRECTION IN THE COMPLEX REHABILITATION OF PATIENTS WITH TEMPOROMANDIBULAR JOINT DYSFUNCTION……135-141

Diyan Gospodinov, Stamen Pishev, Boryana Parashkevova, Nikolay Gerasimov, Guenka Petrova.
PILOT STUDY ON THE CARDIOVASCULAR MORBIDITY IN OLDER PEOPLE IN THE REGION OF BURGAS IN BULGARIA……142-147

Zainab N. Al-Abady, Nawal K. Jabbar, Sundus K. Hamzah, Mohammed N. Al-Delfi.
EFFECTS OF HYPERBARIC, HYPEROXIA, PRESSURE AND HYPOXIA ON CD38 AND CD157 EXPRESSION IN ISOLATED PERIPHERAL BLOOD MONOCYTES: IN VITRO STUDY……148-154

Serhii Lobanov.
THE PHENOMENOLOGY OF EARLY DEVELOPMENTAL DISORDERS AS A FORMATIVE FACTOR IN THE DEVELOPMENT OF ADDICTIVE BEHAVIOUR IN THE MODERN CONDITIONS OF UKRAINIAN SOCIETY……155-163

Jing Liu.
QUALITY CONTROL CIRCLES (QCCS) PLAY A TRANSFORMATIVE ROLE IN INDWELLING NEEDLE NURSING MANAGEMENT……164-167

Evloev Kharon Kh, Snitsa Daniil V, Pankov Danil S, Gasparyan Mariya A, Zaycev Matvey V, Koifman Natalya A, Buglo Elena A, Zefirova Margarita S, Rachkova Tamara A, Gurtiev Dmitrii A, Zaseeva Victoria V, Tolmasov Jaloliddin M.
SGLT2 INHIBITORS: FROM GLYCEMIC CONTROL TO CARDIO-RENAL PROTECTION……168-177

Larisa Manukyan, Lilit Darbinyan, Karen Simonyan, Vaghinak Sargsyan, Lilia Hambardzumyan.
PROTECTIVE EFFECTS OF CURCUMA LONGA IN A ROTENONE-INDUCED RAT MODEL OF PARKINSON'S DISEASE: ELECTROPHYSIOLOGICAL AND BEHAVIORAL EVIDENCE……178-184

Asmaa Abdulrazaq Al-Sanjary.
MATERNAL AND NEONATAL OUTCOME ACCORDING TO THE TYPE OF ANESTHESIA DURING CAESAREAN SECTION…185-189

Aliyev Jeyhun Gadir Ogli.
THE INCIDENCE OF RESISTANCE TO ANTI-TUBERCULOSIS DRUGS AMONG DIFFERENT CATEGORIES OF TUBERCULOSIS PATIENTS IN THE REPUBLIC OF AZERBAIJAN……190-193

Kabul Bakytkhan, Bakhyt Malgazhdarova, Zhadyra Bazarbayeva, Nurzhamal Dzhardemaliyeva, Assel Zhaksylykova, Raikhan Skakova, Rukset Attar.
THE ROLE OF THE VAGINAL MICROBIOTA IN THE PATHOGENESIS OF PRETERM PREMATURE BIRTH IN WOMEN WITH IC: A SYSTEMATICREVIEW……194-202

Petrosyan T.R.
BIOTECHNOLOGICALLY PRODUCED NEUROSTIMULANTS MAY CONTRIBUTE TO PROLONGED IMPROVEMENTS IN MOTOR PERFORMANCE: A NARRATIVE REVIEW……203-209

GEORGIAN MEDICAL NEWS
No 4 (361) 2025

EFFECTS OF HYPERBARIC, HYPEROXIA, PRESSURE AND HYPOXIA ON CD38 AND CD157 EXPRESSION IN ISOLATED PERIPHERAL BLOOD MONOCYTES: IN VITRO STUDY

Zainab N. Al-Abady[1]*, Nawal K. Jabbar[1], Sundus K. Hamzah[2], Mohammed N. Al-Delfi[3].

[1]*Department of Chemistry, College of Science, University of Al-Qadisiyah, Iraq.*

[2]*Department of Chemistry, College of Education, University of Al-Qadisiyah, Iraq.*

[3]*Ministry of Education General Directorate of Al-Qadisiyah Education, Diwaniyah, Iraq.*

Abstract.

Background: Oxygen therapy, utilizing both normal and elevated pressures, is a standard treatment for a range of medical conditions. Given that administered oxygen impacts the entire body, including blood constituents, this research examines how different oxygen and pressure environments influence gene expression in human peripheral blood monocytes.

Methods: The treatment of isolated PBM with hyperbaric oxygen (HBO), hyperoxia, elevated pressure and hypoxia were performed. In addition, the expression of different Monocytes surface epitopes (CD38 and CD157 expression) were examined by qPCR technique. Normoxic culture media served as a positive control.

Results: The impact of 90-minute exposures to hyperbaric oxygen, hyperoxia, and hypoxia on CD38 and CD157 expression in monocytes was investigated. Compared to normoxic controls, both hyperbaric oxygenation and hyperoxia significantly decreased ($p < 0.05$) CD38 and CD157 expression. Notably, CD157 expression exhibited a greater reduction under hyperbaric oxygenation than CD38. Conversely, hypoxia induced a significant increase in CD38 expression, while simultaneously reducing CD157 expression relative to normoxia.

Conclusions: Changes in oxygen levels and pressure, specifically through hyperbaric oxygen, hyperoxia, and hypoxia treatments, demonstrably alter monocyte behavior and the expression of surface epitopes. These alterations could play a significant role in conditions where monocytes are implicated. The data aligns with existing research highlighting the influence of oxygen tension on cellular proliferation and protein production. Consequently, these findings underscore the potential importance of controlled oxygen administration, whether normobaric or hyperbaric, in clinical settings.

Key words. Hyperbaric oxygen therapy, hypoxia, pressure, CD38, CD157, peripheral blood monocytes.

Introduction.

CD38, a cell surface protein and CD marker [1], exhibits both enzymatic and receptor roles [2,3]. As a receptor, it participates in activation and proliferation signaling, and facilitates leukocyte adhesion to the endothelium through CD31 binding [4]. The receptor functions of CD38 are well-documented across various cell types [5]. Functioning as a multi-purpose ectoenzyme, CD38 fits with the adenosine diphosphate (ADP) ribosyl cyclase (ARC) enzyme family [6]. Its enzymatic activities include the conversion of NAD to nicotinic acid adenine dinucleotide phosphate (NAADP) and cyclic adenosine diphosphate ribose (cADPR), as well as the hydrolysis of NAD to ADP-ribose [7]. In mammals, CD38 is classified within the NAD hydrolase/ARC group. This gene family generates both soluble enzymes, such as those found in Aplysia and sea urchin, and membrane-bound enzymes, including CD38 and CD157 in mammals [8]. CD157, another mammalian member of the CD38 family, is a 42-45 kDa cell surface protein [9]. Both CD38 and CD157 are glycoproteins with a polypeptide core consisting of 280-300 amino acids [10], and the CD38 gene is located on chromosome 4 [11].

CD157, or BST1, is a cell-surface protein that does double duty. It's a receptor and an enzyme that handles β-NAD+, a member of the ADP-ribosyl cyclases family, and a key player in calcium regulation [12]. While first identified in bone marrow and myeloid cells, it's actually found in many places. Because it affects immune responses, people are looking into it as a drug target [13]. It shows up in bone marrow precursors [14], and in a range of white blood cells, including neutrophils [15], basophils, monocytes [16], macrophages [17], and plasmacytoid dendritic cells [18]. Endothelial cells, important for immune cell traffic, also express it, indicating a role in inflammation [19]. Beyond that, CD157 impacts cell adhesion and movement, and is associated with worse prognoses in some cancers [20].

CD38's involvement in a wide array of cells, tissue, and diseases positions it as a potential therapeutic target, prompting extensive research into its transcriptional regulation. A variety of signaling molecules, notably cytokines (IFN-α, -β, -γ, IL-2, IL-4, TNF-α, IL-13, and Th2 cytokines) and hormones (estradiol-17β, glucocorticoids), have been identified as key regulators of CD38 expression [21-27]. Studies have demonstrated that pro-inflammatory cytokines (IFN-γ and IL-2) specifically drive CD38 transcription in monocytes and related cell lines (U937, THP-1) [28]. The transcriptional control of CD38 is further influenced by compounds such as isonicotinic acid [29], 1α,25-dihydroxy vitamin D3 [30], and ATRA [31], while DMSO has been reported to have no effect [32]. Certain flavonoids, like kuromanin and luteolin, also contribute to the regulation of CD38 transcription [33]. Finally, the expression of CD38 by its substrate, NAD, has been recently confirmed [34,35]. This study demonstrated that CD38 expression can be influenced by modulating NAD levels. Identifying effective regulators of CD38 mRNA expression could provide a valuable clinical application, particularly for patients with CD38+ subsets. While previous research has identified various regulators of CD38 expression, primarily at the mRNA level, the impacts of hyperbaric oxygen therapy (HBO), hyperoxia, pressure, and hypoxia on the in vivo regulation of CD38/CD157 gene expression have not been previously investigated.

The use of HBO has become a staple in the treatment of compromised bone structures, particularly when faced with persistent infections such as osteomyelitis and the challenges posed by bone necrosis, especially following radiation exposure [36-38]. The fundamental principle behind HBO involves placing patients in a pressurized chamber where they inhale pure oxygen. This process leads to a significant elevation in the oxygen levels reaching compromised tissues [39]. This surge in oxygen delivery is not merely a passive phenomenon; it actively facilitates the body's natural healing mechanisms. Specifically, it stimulates the generation of new vasculatures, a process known as angiogenesis, and modulates the immune response, both of which are crucial for tissue repair and regeneration [40]. It's a well-established fact that bone cells exhibit a profound sensitivity to fluctuations in oxygen tension. Under conditions of hypoxia, or low oxygen availability, there is a distinct shift in cellular activity, favoring the breakdown of bone tissue, a process mediated by osteoclasts, while simultaneously suppressing the activity of osteoblasts, the cells responsible for bone formation [41,42].

While previous investigations have demonstrated the capacity of HBO to stimulate osteoblast activity, thereby promoting bone formation [43,44], a critical gap in our understanding persists. We lack comprehensive information regarding the precise mechanisms by which HBO influences gene expression within human immune cells during the course of treatment. This absence of knowledge is particularly concerning given the potential implications for inflammatory bone diseases, where immune cell activity plays a pivotal role. Furthermore, while HBO is employed to address necrotic skeletal disorders, it's equally important to acknowledge that hypoxia is hallmark feature of numerous skeletal pathologies characterized by unnecessary osteoclast formation and subsequent bone resorption [45,46]. Existing research has primarily focused on elucidating the effects of HBO on osteoclast differentiation and activity, and has sought to determine whether HBO offers a superior therapeutic approach compared to simple elevations in oxygen levels, known as hyperoxia, or the application of pressure alone [47]. However, the molecular mechanisms through which HBO orchestrates changes in gene expression remain largely unexplored. To address these critical clinical and molecular questions, the current study was designed to meticulously evaluate the effects of HBO, hyperoxia, and elevated pressure on the expression of CD38 and CD157 genes in human peripheral blood mononuclear cells (PBMCs). These experiments were conducted under both normoxic, or normal oxygen, and hypoxic, or low oxygen, conditions, providing a comprehensive assessment of the cellular responses to these varying environmental factors.

Materials and Methods.

Cell Culture: Adhering to established ethical guidelines, healthy volunteers have given blood samples via venipuncture, with heparin added as an anticoagulant. The collected blood was subsequently diluted with an equivalent volume of unsupplemented α-MEM medium. Mononuclear cells were then isolated via density gradient centrifugation. Specifically, 15 mL of the diluted blood was carefully layered onto 25 mL of Histopaque-1077 (Sigma-Aldrich, UK) and subjected to centrifugation at 700 ×g for 30 minutes at 4°C (Figure 1). The monocyte-containing layer (buffy coat), was collected and washed with 10 mL of unsupplemented α-MEM, followed by a second centrifugation at 400 ×g for 10 minutes at 4°C. The resulting cell pellet was then resuspended in a culture medium supplemented with 10% FCS, and red blood cells were using a 10% acetic acid solution.

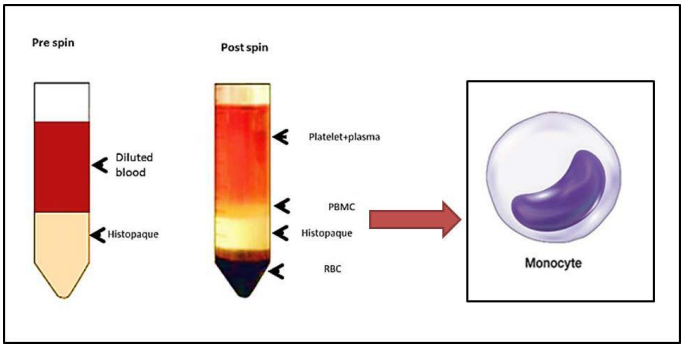

Figure 1. *Simple diagram to show isolation of Peripheral Blood Monocyte cells (PBMC) from whole blood.*

Cells were subjected to either hypoxic (2% O2) and normoxia (21% O2) conditions by placement in hermetically sealed chambers. These chambers were filled with the designated gas mixtures for a 90-minute period, subsequently sealed, and maintained at 37°C (Figure 2). For exposures to hyperbaric oxygen (HBO (97.9% O2, 2.1% CO2, 2.4 ATA), or pressure (2.4 ATA, 8.8% O2, 2.1% CO2, and 89.1% N2) and hyperoxia (95% O2, 5% CO2, 1 ATA)), cells were transferred to stainless steel hyperbaric chambers. These chambers underwent a four-minute purging with the required gas mixtures, followed by a two-minute pressurization to 2.4 ATA. Cell cultures were then exposed to the specified conditions (HBO, pressure, or hyperoxia) for 90 minutes. Following this, peripheral blood mononuclear cell (PBMC) experiments were concluded, and samples were collected for gene expression analysis.

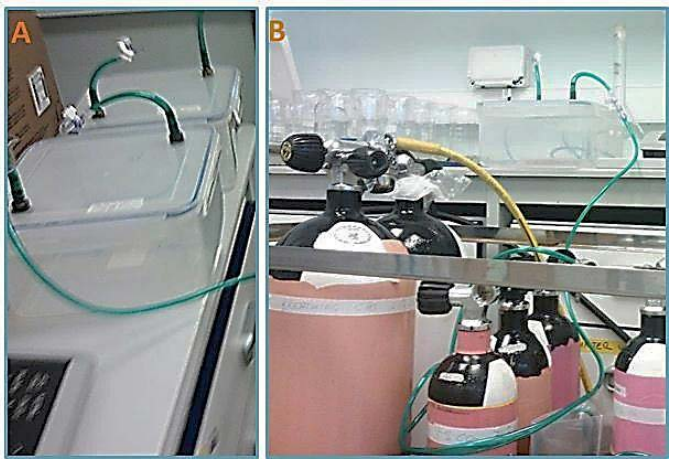

Figure 2. *(A) boxes and (B) Oxygen cylinders used in normoxia, hypoxia and hyperoxia trials.*

Quantitative RT-PCR: To quantify the expression levels of CD38 and CD157 genes, quantitative polymerase chain reaction (qPCR) was employed, utilizing the ΔΔCT method. Total RNA

was extracted with RNA kit (Sigma Genelute), and the resulting RNA was then converted to cDNA using the ImPromII Reverse Transcription System (Promega, Southampton, UK). The qPCR reactions were carried out on a StepOne PCR system (Applied Biosystems, Paisley, UK), with SYBR green serving as the detection reagent for the amplified PCR product. The forward and reverse primer sets used (Table 1).

Table 1. *Primer designed for the study.*

Genes		Primers	Size	Product (bp)
GAPDH	F	CCCACTCCTCCACCTTTGAC	20	100
	R	CTGTTGCTGTAGCCAAATTCGT	22	
CD38	F	GCACCACCAAGCGCTTTC	18	100
	R	TCCCATACACTTTGGCAGTCTACA	24	
CD157	F	GGGAAGGCAGCATGAAAGTC	20	105
	R	GGTCCACGCACTGTAAGAGCTT	22	

For this process, an initial 2-minute period at 94°C was implemented, then followed by 40 cycles. Each cycle included 30 seconds at 94°C, 30 seconds at 60°C, and 30 seconds at 72°C. The resulting gene expression values were adjusted using GAPDH as a baseline, and the data was displayed as a comparison to the control. The effect of 90-minute exposures to either hyperbaric oxygen (HBO), high oxygen (hyperoxia), or increased pressure on gene expression was evaluated. Cells were cultured under normal oxygen levels (21% O2, 1 ATA) or were exposed for 90 minutes each day to one of the following: HBO (97.9% O2, 2.4 ATA), hyperoxia (95% O2, 1 ATA), or increased pressure (8.8% O2, 2.4 ATA).

Statistical analysis: Outcomes are reported as the mean ± SEM of three independent experiments, each with eight replicate wells per condition. Statistical significance was defined as a p-value below 0.05 when compared to the normoxic control, the gene expression by PCR were represented as fold of change relative to the housekeeping gene.

Results.

In the current study (Table 2) presents the relative expression levels of CD38 and CD157 in monocytes isolated from healthy individuals subjected to different oxygenation conditions: normoxia, hyperoxia, hyperbaric oxygen (HBO), and pressure. The mean ± SEM (Standard Error of the Mean) are provided for both CD38 and CD157 expression. This data highlights the differential response of CD38 and CD157 expression in monocytes to oxygenation changes.

Table 2. *Relative expression of CD38 and CD157 in monocytes from healthy individuals under different oxygenation conditions.*

	Normoxia	Hyperoxia	HBO	Pressure	P value
CD38 Relative Expression (Fold of change)					
Mean ± SEM	1 ± 0	0.28±0.06	0.156±0.055	0.7±0.1826	0.06
CD157 Relative Expression (Fold of change)					
Mean ± SEM	1 ± 0	0.277±0.043	0.086±0.054	0.465±0.035	0.0001

CD38 and CD157 Relative Expression Under HBO, Hyperoxia and Pressure.

CD38 Relative Expression: The highest expression is seen under normoxic conditions (1±0), with reduced expression under hyperoxia (0.28±0.06), HBO (0.156±0.055), and varying expression under pressure (0.7±0.1826). The p-value of 0.0537 suggests the differences are not statistically significant ($p>0.05$).

Table 3 summarizes the results of Tukey's multiple comparisons test, analyzing the relative expression of CD38 in monocytes across different oxygenation conditions: normoxia, hyperoxia, hyperbaric oxygen (HBO), and pressure. The adjusted p-values and significance levels are shown for each comparison. The p-values indicate no statistically significant differences between any of the oxygenation conditions in the expression of CD38.

Table 3. *Tukey's multiple comparisons test for CD38 expression under different oxygenation conditions.*

Tukey's multiple comparisons test	Summary	Adjusted P Value
Normoxia vs. Hyperoxia	ns	0.1171
Normoxia vs. HBO	ns	0.0666
Normoxia vs. Pressure	ns	0.5843
Hyperoxia vs. HBO	ns	0.9625
Hyperoxia vs. Pressure	ns	0.3391
HBO vs. Pressure	ns	0.1787

CD157 Relative Expression: Similar to CD38, normoxia shows the highest expression (1±0). Expression decreases under hyperoxia (0.277±0.043) and HBO (0.086±0.054), with a moderate increase under pressure (0.465±0.035) when compared to HBO and hyperoxia. The p-value of 0.0003 indicates a highly significant difference (***).

Table 4 presents the results of Tukey's multiple comparisons test, evaluating the relative expression of CD157 in monocytes under normoxia, hyperoxia, hyperbaric oxygen (HBO), and pressure. The summary shows the level of significance for each comparison, and the adjusted p-values are provided. The results indicate that significant differences exist between normoxia and the other conditions (hyperoxia, HBO, and pressure), as well as between HBO and pressure. However, no significant differences were observed between hyperoxia and HBO or hyperoxia and pressure.

Table 4. *Tukey's Multiple Comparisons Test for CD157 Expression under Different Oxygenation Conditions.*

Tukey's multiple comparisons test	Summary	Adjusted P Value
Normoxia vs. Hyperoxia	***	0.0007
Normoxia vs. HBO	***	0.0003
Normoxia vs. Pressure	**	0.0021
Hyperoxia vs. HBO	ns	0.0806
Hyperoxia vs. Pressure	ns	0.0845
HBO vs. Pressure	**	0.0079

CD38 and CD157 Relative Expression Under Hypoxia: Table 5, illustrates the relative expression levels of CD38 and CD157 in monocytes from healthy individuals under normoxic and hypoxic conditions. mean±SEM (Standard Error of the

Mean) presented for each marker. This data suggests that there is no significant variation in CD38 and CD157 expression in monocytes between normoxic and hypoxic conditions.

Table 5. *Relative Expression of CD38 and CD157 in Monocytes from Healthy Individuals under Normoxia and Hypoxia.*

	Normoxia	Hypoxia	P value
CD38 Relative Expression (Fold of change)			
Mean±SEM	1±0	1.2±0.3	0.08
CD157 Relative Expression (Fold of change)			
Mean±SEM	1±0	0.8±0.1	0.65

CD38 Relative Expression: CD38 expression remains stable under normoxia (1 ± 0) but shows a slight increase under hypoxia (1.2 ± 0.3). The p-value of 0.5736 indicates no significant difference between the two conditions (ns). CD157 Relative Expression: Under normoxia, the expression is 1 ± 0, while under hypoxia, it slightly decreases (0.8 ± 0.1). The p-value of 0.1835 suggests no significant difference between normoxia and hypoxia (ns). When oxygen levels are low, it's generally understood that typical cells switch their energy production from using oxygen to a process called lactic acid fermentation (68), rather than relying on oxidative phosphorylation. Consequently, it's reasonable to expect that gene activity would be altered in these circumstances. Specifically, under 2% oxygen (hypoxia), we observed an increase in CD38 gene expression, while CD157 gene expression decreased. Taken together, these new findings provide strong evidence that low oxygen levels significantly impact the expression of CD38 and CD157 in monocytes from peripheral blood.

Discussion.

CD38 and its counterpart CD157 (BST-1), which are adjacent gene copies on human chromosome 4 (4p15), are members of a gene family that encodes proteins that regulate cell interactions through two-way signals. The CD157 gene, spanning over 35 kb, is situated very near its paralog CD38 and is constructed from nine exons. The significant evolutionary preservation of CD38 and CD157 is evident in the comparable length of exons 2-8 and the consistent positioning of intron insertions. Both proteins exhibit dual roles, functioning as receptors and ectoenzymes, and participate in intricate processes related to signal transduction and cellular homeostasis. CD38 and CD157 have transitioned from simple leukocyte activation markers to multifaceted molecules implicated in both health and disease [48]. The relationship between CD38 or CD157 and human diseases has been reviewed in [49]. Future studies should investigate their potential as targets for in vivo therapeutic strategies and as modulators of the immune response.

The data of the presented aligns with earlier research that highlighted the influence of oxygen concentration on cell cycle progression and protein production [50]. While hyperbaric oxygenation was explored as a possible stimulator of cell proliferation and differentiation in promyelocytic leukemia, a study involving 72-hour exposures to hyperbaric oxygen and oxygen revealed a decrease in CD13 and CD38 expression following hyperbaric treatment [50].

Notably, most studies believed that cellular and molecular mechanism through which hyperbaric oxygen therapy (HBO), hyperoxia or pressure regulate gene expression is unclear. However, other studies suggest it might be through HBO rapidly delivers oxygen to areas of ischaemic tissue damage by elevating plasma oxygen concentration [51]. The resulting rise in oxygen levels is thought to aid tissue repair through a complex interplay of factors, including changes in how blood vessels react, the creation of new blood vessels, the production of free radicals, the creation of cytokines, and the shifting of immune responses [51]. It's possible that HBO, by encouraging capillary growth, could directly initiate CD38 gene expression in previously oxygen-deprived regions. Similarly, it could also directly enhance CD157 expression. Therefore, this study seeks to determine whether HBO has a direct influence on monocyte markers under both normal and low-oxygen conditions.

Research has consistently demonstrated the positive impact of hyperbaric oxygen therapy (HBO) on bone health [52-56], leading to its use in promoting healing in conditions such as osteonecrosis, bone grafts, and dental implants [57-59]. It has been observed that daily HBO exposure accelerates the process of osteoblast differentiation, indicated by increased levels of type I collagen and Runx-2 mRNA during early culture stages. Notably, HBO exhibited a stronger influence on examined biomarkers compared to isolated increases in oxygen or pressure [51], a finding corroborated by our present study. Conversely, environments characterized by high oxygen levels or increased pressure alone may not significantly alter CD38 expression to the same extent as HBO. In fact, investigations into the effects of hyperoxia on human cells are scarce; however, a prior report indicated that hyperbaric oxygen induces cell death in Jurkat and HL60 cells, both spontaneously and in response to chemotherapy [60]. Other investigations have explored hyperoxia as a potential treatment for cancer [61,62], yet there is a lack of research examining its impact on CD38 expression in human cells, or that of pressure alone. However, in our study, we observed that both HBO and hyperoxia had a more significant effect on CD38 expression compared to CD157.

CD157, as a homologue to CD38, shows a similar response to the pressure and different oxygenation conditions, this is further confirmed previous studies which demonstrate the role of oxygen tension in the regulation of cell cycle and protein expression [50]. However, the mechanism to regulate CD157 expression in primary human monocytes exposed to different oxygenation environments, still under investigations.

The oxygen level of 2% hypoxia was intentionally chosen, as it aligns with prior publications showing that this concentration supports cell survival in culture [63]. These results could indicate a potential correlation between reduced oxygen availability and gene regulation in human monocytes. Studies examining the influence of low oxygen conditions on gene expression, particularly CD38, are scarce. However, it's widely recognized that hypoxia, a reduction in oxygen availability, significantly contributes to various disease processes, including ischemic stroke and tumor development [64]. Cells subjected to hypoxia possess the ability to survive and acclimate to this oxygen-deficient environment. This adaptation often involves the activation of specific genes, which serve to mitigate or counteract the detrimental effects of hypoxia on cellular function [65]. Research has demonstrated a notable link between hypoxia

and CD38 activity, though not necessarily CD38 expression, across various cell types and disease conditions. As an example, alterations in CD38 activity have been observed in connection with hypoxic pulmonary vasoconstriction (HPV) [66]. Another recent study showed inhibiting hypoxia and glycolysis impairs B-acute lymphoblastic leukemia-initiating cells providing a therapeutic benefit in xenotransplantation systems, these findings provide a rationale for therapeutic targeting of hypoxia in leukemia [67].

Conclusion.

The results obtained indicate there were no significant shifts in the alterations of CD38 and CD157 under hypoxic settings. This contrasts with hypoxia, which was found to stimulate CD38 expression while simultaneously suppressing CD157. The current study could provide valuable insights for future investigations, particularly those exploring the regulatory mechanisms of CD38 and its related gene, CD157, under varying oxygen and pressure conditions. This knowledge may be applicable to targeted therapies in diseases such as leukemia or other conditions associated with CD38.

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