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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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IMMUNE RESPONSE OF CULTURED MONOCYTES OF ATHEROSCLEROTIC PATIENTS RECEIVING STATIN THERAPY

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Abstract.

Aim: The current study was aimed to evaluate the immune response of monocytes/macrophages derived from atherosclerotic patients receiving hydrophilic and lipophilic statins and without lipid-lowering therapy, in order to evaluate the effect of statins on the inflammatory status of circulating monocytes.

Materials and methods: Three groups of 20 patients with atherosclerosis of the coronary arteries were included in the study: patients receiving atorvastatin or rosuvastatin therapy for at least 12 months before inclusion in the study and participants without statin therapy within a year before the inclusion in the study. CD14+ monocytes were derived from the whole blood of study participants by immunomagnetic separation. The isolated cells were cultured for 7 days under inflammatory stimulation with LPS and without stimulation. The level of basal, LPS-stimulated and re-stimulated secretion of inflammatory cytokines TNF-α and IL-1β was determined by ELISA.

Results: The significantly lower basal secretion of TNF-α was revealed in atorvastatin and rosuvastatin groups in comparison with statin-free group ($p=0.003$; $p<0.001$); the basal secretion of IL-1β was lower only in rosuvastatin recipients ($p=0.020$). LPS-stimulated secretion of TNF-α wasn't significantly different in all groups while secretion of IL-1β was significantly reduced in both atorvastatin and rosuvastatin groups ($p=0.002$; $p=0.001$). The re-stimulated secretion of TNF-α was significantly lower in rosuvastatin recipients ($p=0.031$); the effect of statins on re-stimulated secretion IL-1β wasn't revealed. The correlation analysis revealed the association of total cholesterol and LDL serum levels with basal secretion of TNF-α and IL-1β.

Conclusions: Thus, the study demonstrated the significant decrease of inflammatory cytokines secretion by cultured monocytes of patients with coronary atherosclerosis receiving statin therapy. The most prominent effect was observed in rosuvastatin recipients. The reduction of the TNF-α and IL-1β secretion by monocytes correlated with low levels of total cholesterol and LDL.

Key words. Atherosclerosis, statins, monocytes, macrophages, inflammation, cytokines.

Introduction.

Numerous studies have proven the important role of innate immune cells in the control of inflammation and abnormal lipid metabolism which are the key events in atherosclerosis development, the primary basis of cardiovascular disease due to their interaction with pattern-recognition receptors and production of various inflammatory mediators [1]. Innate immune cells express Toll-like receptors that recognize molecules released by damaged/necrotic cells, that stimulate the activation of the canonical nuclear factor kappa-B (NF-κB) pathway and therefore the induction of pro-inflammatory mediator secretion and production of reactive oxygen species. This leads to expression of adhesion molecules, accumulation of circulating monocytes in arterial wall and their differentiation into macrophages which are the major cells in atherogenesis [2]. The relationship between macrophage polarization and the progression of atherosclerosis have been demonstrated in a number of studies. It was established that atherosclerotic plaques contain both M1 and M2 macrophages, and pro-inflammatory M1 macrophages predominate in progressing atherosclerotic lesions while anti-inflammatory M2 macrophages are the most common during atherosclerosis regression [3]. Pro-inflammatory activation of circulating monocytes that differentiate into macrophages in the area of atherosclerotic lesions may be an important mechanism for the development of chronic inflammation in the pathogenesis of atherosclerosis. At the same time, it's known that the mechanisms of immune tolerance protect tissues from damage by high cytokine concentrations, which develops in response to pathogen-associated molecular patterns such as lipopolysaccharide (LPS). Endotoxin tolerance represents the response of immune cells to repeated pathogen exposure associated with a decreased cytokine secretion [4]. In this regard, the impaired endotoxin tolerance is considered as a mechanism of chronic inflammation development [5]. It has been shown that macrophages obtained from LPS-stimulated monocytes in patients with subclinical atherosclerosis demonstrate increased secretion of pro-inflammatory cytokines associated with atherosclerosis in carotid arteries [6]. Preparations of the 3-hydroxy3-methyl-glutaryl-CoA reductase inhibitor group (statins) are the most widely used anti-atherosclerotic therapeutics and possess a number of pleiotropic effects that slow the progression of atherosclerotic lesions in arterial wall in addition to their lipid-lowering effectiveness [7,8]. In particular, experimental and clinical studies have demonstrated the improvement of endothelial function, immunomodulatory, antithrombotic antioxidant, and anticancer effects of statins [9,10]. It was shown in several studies that statin therapy led to a decrease in the number of macrophages differentiated into the inflammatory phenotype [11]. Despite the fact that the pleiotropic effect of statins is widely discussed in modern literature, the mechanisms of the anti-inflammatory effects of statins in terms of innate immune cells still need to be studied in more depth. The aim of this research was to investigate the immune response of monocytes/macrophages in patients with atherosclerosis of coronary arteries receiving therapy with lipophilic and hydrophilic statins, as well as in patients with atherosclerosis not receiving lipid-lowering therapy.

Materials and Methods.

The study included three groups of study participants with atherosclerosis of coronary arteries confirmed by the results of coronary angiography:

group 1: patients receiving atorvastatin therapy for at least 12 months prior to inclusion in the study, n=20.

group 2: patients receiving rosuvastatin therapy for at least 12 months prior to inclusion in the study, n=20.

group 3: patients not receiving statin therapy for a year prior to inclusion in the study, n=20.

Exclusion criteria were type 2 diabetes mellitus, cancer, uncontrolled hypertension, decompensated renal or hepatic insufficiency, chronic heart failure. The study was conducted in accordance with the 1975 Helsinki Declaration and its revised version of 2013. The study protocol was approved by the Local Ethics Committee of the E.I. Chazov National Medical Research Center of Cardiology, Ministry of Health of the Russian Federation on February 28, 2022, protocol No. 277. All participants provided written informed consent prior to inclusion in the study. The following cardiovascular risk factors were assessed: arterial hypertension, smoking, hyperlipidemia, body mass index (BMI), and the presence of CVD in close relatives under the age of 60. Blood lipid profile parameters (total cholesterol, high-density lipoprotein cholesterol (HDL, LDL), and triglycerides) were determined by standard laboratory methods. Ultrasound duplex scanning of the carotid arteries was performed to determine carotid atherosclerosis. The SYNTAX score was calculated based on the results of the coronary angiography according to the generally accepted method, and the scores were reviewed by at least two expert physicians [12].

Circulating monocytes were obtained from whole blood of the study participants by gradient centrifugation in a Ficoll gradient followed by immunomagnetic separation of CD14+ monocytes with columns and paramagnetic nanoparticles (Miltenyi Biotec Inc., USA). The isolated cells were cultured in two wells of a culture plate at a rate of 500,000 cells per well in X-VIVO medium (Lonza Inc., Germany). In well 1, no proinflammatory stimulation was performed; the basal non-stimulated secretion of inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β was assessed in 24 hours of incubation. In well 2, proinflammatory stimulation of cells was performed with lipopolysaccharide (LPS) at a concentration of 1 μg/ml for 24 h to assess LPS-stimulated secretion, then the cells were cultured for 5 days without inflammatory stimulation and the second stimulation with LPS at a concentration of 1 μg/ml for 24 h was performed to assess the immune response of macrophages to repeated stimulation. The concentration of proinflammatory cytokines TNF-α and IL-1β in the samples of culture fluid was determined by enzyme immunoassay using commercial kits (R&D Systems Inc., USA).

The SPSS 27.0 software package (SPSS, USA) was used for statistical analysis of the obtained results. To test the type of distribution, the Shapiro-Wilk's W test was used. The Mann-Whitney U-test was used to assess differences in clinical and laboratory characteristics between the groups of study participants and to compare the levels of inflammatory cytokines secretion. The data are presented as the mean value and standard deviation, Mean (SD). Pearson correlation analysis was performed to assess the association between the inflammatory response of monocytes/macrophages and traditional cardiovascular risk factors in study participants. Significance was defined at the 0.05 level of confidence.

Results.

Clinical and laboratory characteristics of study participants are presented in Table 1. The conventional cardiovascular risk factors such as age and male gender, BMI, blood pressure, family history of CHD, smoking, and blood lipids levels didn't differ significantly between the groups of the study participants receiving atorvastatin and rosuvastatin during a year before the inclusion in the study. The group of patients receiving atorvastatin differed significantly from the statin-free group in terms of total cholesterol serum level, p=0.001. The group of patients receiving rosuvastatin differed significantly from the statin-free group in terms of the number of male participants, p=0.001. The patients in all groups had low or intermediate severity of coronary artery disease according to SYNTAX score and increased BMI indicating the overweight of study participants.

Table 1. *Clinical and laboratory characteristics of study participants.*

	Group without statins	**Atorvastatin group**	**Rosuvastatin group**
Age, years	63.1 (7.8)	60.1 (6.2)	62.6 (4.5)
Male gender	9 (45%)	10 (50%)	16 (80%)*
Body mass index, kg/м^2	26.8 (3.9)	28.0 (2.2)	25.2 (2.0)
Blood pressure, mmHg	126(31)/80(11)	129(15)/80(11)	116(23)/76(7)
Smoking	6 (30%)	5 (25%)	4 (20%)
Family history of CHD	9 (45%)	8 (40%)	9 (45%)
Syntax score	22.2 (2.3)	22.4 (2.4)	21.3 (2.2)
cIMT, mm	0.825 (0.157)	0.799 (0.179)	0.809 (0.161)
Total cholesterol, mmol/l	5.6 (0.7)	4.0 (0.7)*	4.7 (1.1)
Triglycerides, mmol/l	1.3 (0.9)	1.1 (0.6)	1.4 (0.5)
LDL, mmol/l	3.6 (0.7)	2.8 (0.7)*	3.1 (0.9)
HDL, mmol/l	1.4 (0.3)	1.5 (0.4)	1.3 (0.4)

Data presented as mean value and standard deviation (Mean (SD)).

**, significant difference in comparison with control group without statin therapy, p<0.05*

CHD: coronary heart disease; cIMT: carotid intima-media thickness; HDL: high density lipoproteins; LDL: low density lipoproteins.

Basal, LPS-stimulated and re-stimulated secretion of pro-inflammatory cytokines TNF-α and IL-1β was measured to analyse the pro-inflammatory activation and immune memory of circulating monocytes. Figure 1 demonstrates the levels of TNF-α secretion by cultured monocytes/macrophages of study participants receiving atorvastatin and rosuvastatin therapy and without lipid-lowering treatment. The basal secretion of TNF-α was 220 (95) pg/ml in the group without statins, 128 (86) pg/ml in atorvastatin group, and 64 (32) pg/ml in rosuvastatin group. It was shown that non-stimulated basal secretion of TNF-α was significantly higher in the group without statins in comparison with groups of atorvastatin and rosuvastatin (p=0.003 and p<0.001, respectively). The secretion of TNF-α in primary culture of monocytes under LPS-stimulated conditions increased significantly in all groups and was 4861 (2560) pg/ml in the group without statins, 3939 (1717) pg/ml in atorvastatin group, and 3680 (2002) pg/ml in rosuvastatin group, the difference between groups wasn't significant. Re-stimulated secretion of TNF-α was 117 (56) pg/ml in the group without statins, 113 (52) pg/ml in atorvastatin group, and 82 (42) pg/ml in rosuvastatin group, the significant difference between statin-free group and rosuvastatin group was revealed (p=0.0031).

Figure 2 demonstrates the levels of IL-1β secretion by cultured monocytes/macrophages of study participants. The basal secretion of IL-1β was 136 (108) pg/ml in stat ins-free group, that was significantly higher than in rosuvastatin group 72 (37) pg/ml (p=0.020), in atorvastatin group the basal secretion of IL-1β was 107 (55) pg/ml that wasn't significantly different in comparison with statin-free group. LPS-stimulated secretion of IL-1β in primary culture of monocytes was significantly reduced in atorvastatin and rosuvastatin groups, 1061 (736) pg/ml (p=0.002) and 1004 (743) pg/ml (p=0.001), respectively, in comparison with IL-1β secretion value 1841 (720) pg/ml in the group without statins. The value of re-stimulated IL-1β secretion was 99 (112) pg/ml in the group without statins, 113 (58) pg/ml in atorvastatin group, and 81 (21) pg/ml in rosuvastatin group, the difference between study groups wasn't significant.

Correlation analysis was performed to evaluate the association of immune response of monocytes with conventional cardiovascular risk factors. The relationship of blood lipids levels with basal secretion of studied inflammatory cytokines was observed. Figures 3 and 4 demonstrate the correlation of TNF-α and IL-1β by cultured monocytes with total cholesterol and LDL levels in blood in total group of study participants.

The secretion of TNF-α correlated significantly with total cholesterol serum level, r=0.433, p=0.001, and LDL serum level, r=0.367, p=0.005, respectively. The secretion of IL-1β correlated significantly with total cholesterol serum level, r=0.304, p=0.018, and LDL serum level, r=0.422, p=0.001, respectively. However, when studying the association of

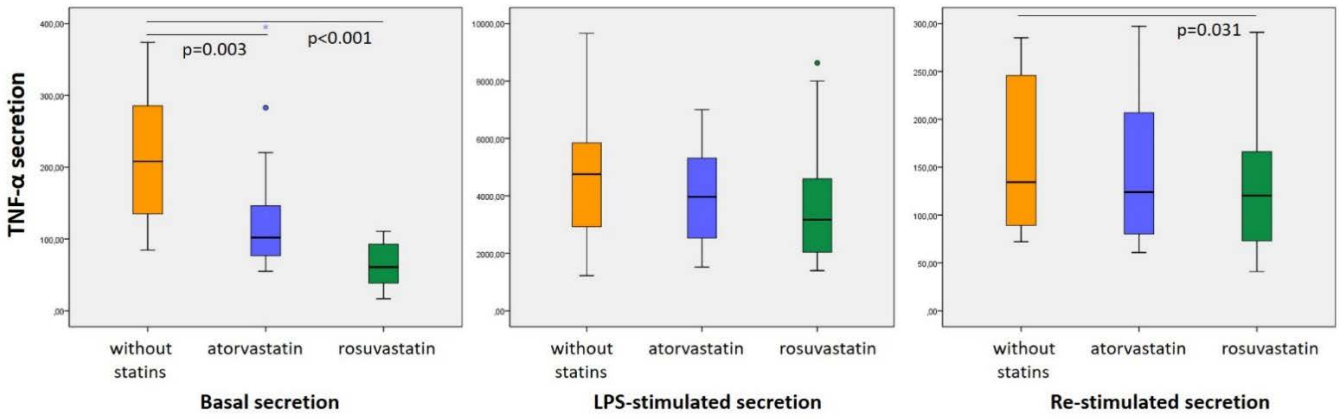

Figure 1. *TNF-α secretion by cultured monocytes/macrophages of study participants. LPS – lipopolysaccharide, p – significance value of difference in comparison with statin-free group.*

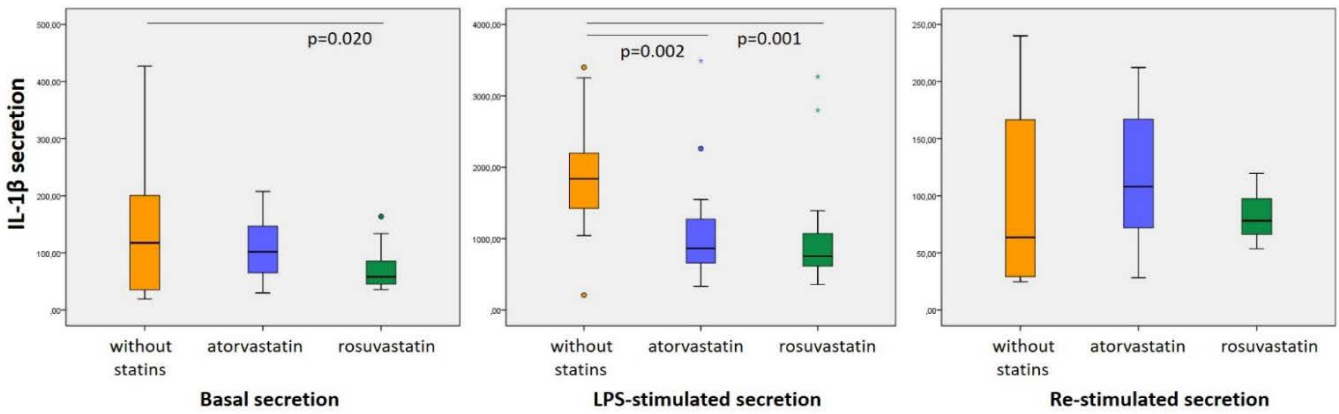

Figure 2. *IL-1β secretion by cultured monocytes/macrophages of study participants. LPS – lipopolysaccharide, p – significance value of difference in comparison with statin-free group.*

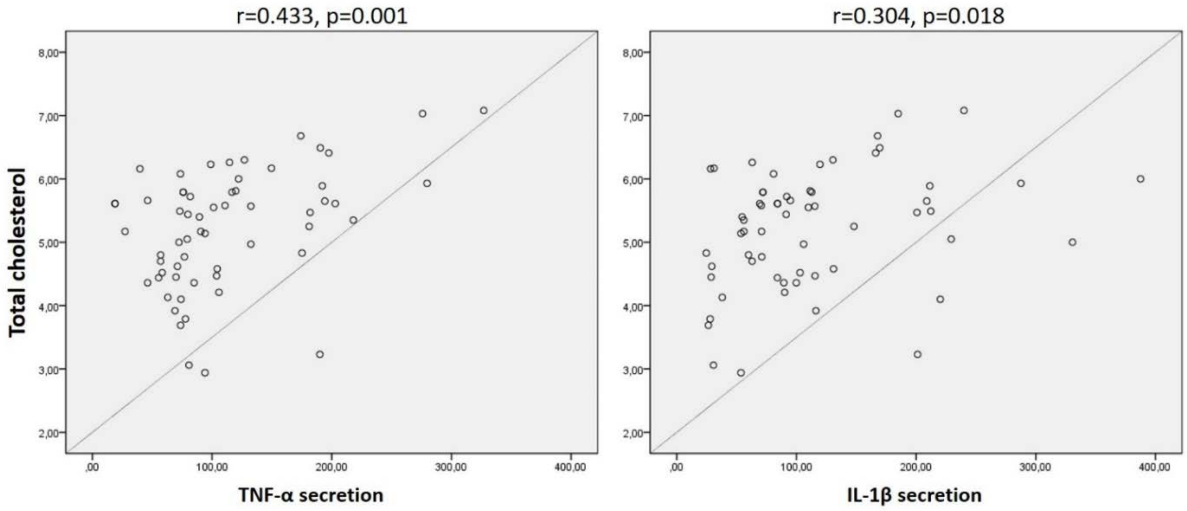

Figure 3. *The correlation of total cholesterol level in blood serum with basal secretion of TNF-α and IL-1β by cultured monocytes of study participants.*

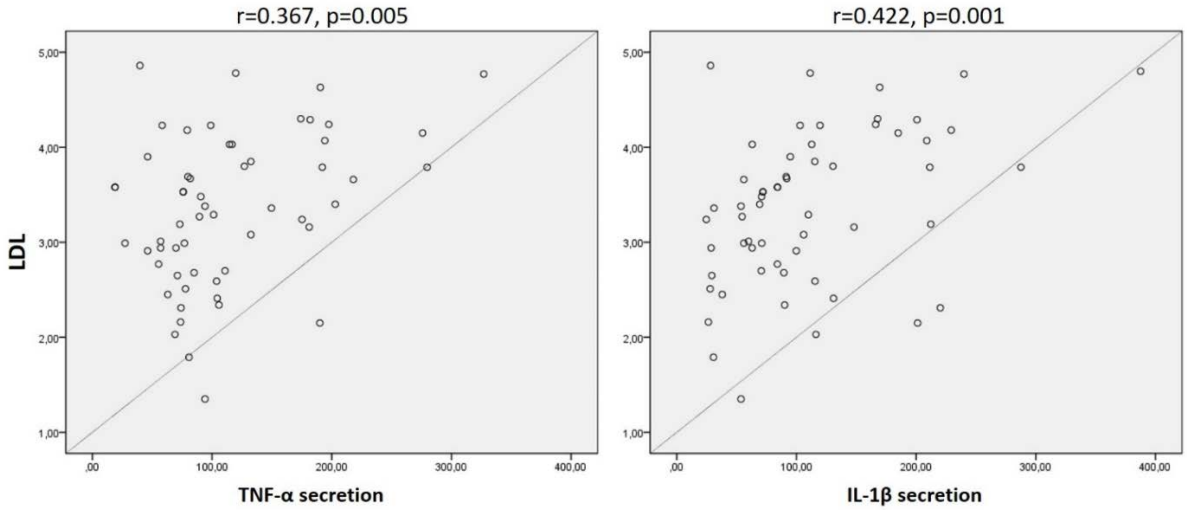

Figure 4. *The correlation of LDL level in blood serum with basal secretion of TNF-α and IL-1β by cultured monocytes of study participants. LDL, low-density lipoproteins.*

the monocyte immune response with clinical and laboratory characteristics of study participants in separate groups receiving atorvastatin, rosuvastatin, and not receiving statins, the correlation did not reach statistical significance. No association of pro-inflammatory secretion levels with other clinical and laboratory parameters of study participants was revealed.

Discussion.

The results of the present study demonstrate the anti-inflammatory efficacy of statins, which is expressed in the statistically significant suppression of the secretion of pro-inflammatory cytokines by cultured monocytes/macrophages in patients with coronary atherosclerosis which was the most effective in the rosuvastatin group. Another study demonstrated that rosuvastatin administration led to significant increase of the anti-inflammatory mediators IL-10 and chemokine (C-C motif) ligand 18 secretion by cultured human peripheral blood mononuclear cells (PBMCs). It was also shown that M1 macrophages cultured using supernatant that was used to culture M2 macrophages could significantly inhibit TNF-α and MCP-1 secretion [13]. The comparison of the effectiveness of lipophilic and hydrophilic statins in terms of the inflammatory cytokines secretion in in vitro model revealed that atorvastatin suppressed the immune response of cultured monocytes more effectively than rosuvastatin. However, the study was conducted on the primary culture of monocytes-macrophages obtained from healthy donors and cytokine secretion was assessed after incubation of cells with statins, that is, this method does not allow analysing inflammatory activation of monocytes in patients with atherosclerosis [14].

Numerous studies are devoted to investigating the pathogenetic mechanisms of anti-inflammatory effects of statins in cell and animal models. In particular, rosuvastatin inhibited LPS-induced production of proinflammatory cytokines TNF-α, IL-6, IL-1β in RAW 264.7 macrophages by preventing the activation of NF-κB [15]. Anti-inflammatory effect of rosuvastatin may be related

to reactivation of AMP-activated protein kinase α (AMPKα) pathway, a significant signalling pathway related to cellular energy balance, that was observed to be a major regulator of physiological processes such as inflammation, since rosuvastatin administration was resulted in increased ratio of phosphorylated AMPK to total AMPKα as well as decreased the inflammatory cytokines production [16]. One of the possible mechanisms of the anti-inflammatory action of statins is the inhibition of the NOD-like receptor protein 3 (NLRP3) inflammasome, a key source of cytokines of IL-1 family. It was shown that treatment with atorvastatin led to a decrease of the NLRP3 expression in mice [17]. In another study atorvastatin treatment resulted in reduction of inflammatory cytokines IL-1β, IL-18, IL-6, and TNF-α secretion along with suppression of TLR4/NF-κB and NLRP3 inflammasome pathways in cell culture model [18]. Rosuvastatin was also shown to downregulate the NLRP3 inflammasome expression and its downstream mediators IL 1β and IL 18 in PBMCs ytes of patients with stable angina pectoris and acute myocardial infarction [19]. However, another comparative study has shown that atorvastatin was more effective in terms of NLRP3 inflammasome inhibition while rosuvastatin had no impact on the levels of NLRP3 inflammasome, IL-1β and IL-18 production by PBMCs of patients with coronary artery disease [20].

This study indicates that rosuvastatin exhibits superior anti-inflammatory effects compared to atorvastatin. The differences in the metabolic effects of these preparations may be explained by the structural changes which cause the hydro- or liposolubility. The solubility of statins depends on the presence/absence of polar moieties on the largely hydrophobic backbones [21]. Rosuvastatin is a hydrophilic statin that restrict its ability to cross the phospholipid bilayer of the cell membranes. At the same time, hydrophilic preparations can be excreted without undergoing any transformation but possess higher hepatoselectivity and characterized by faster renal excretion.

Numerous studies demonstrate the ameliorating effect of statins on the progression of carotid and coronary atherosclerosis [22]. Statin therapy is associated with decreased mortality as well as improved outcomes after carotid and coronary revascularization [14]. In this study, the groups of study participants receiving atorvastatin and rosuvastatin didn't have significant difference with control group in terms of indicators of carotid and coronary atherosclerosis presented in Table 1 such as cIMT and Syntax score. The current study was cross-sectional, so the association of atherosclerosis development and immune status of monocytes under statin administration condition wasn't assessed. The study had some other limitations. Firstly, the immune response of cultured monocytes was investigated in terms of only two pro-inflammatory cytokines while a wider range of studied cytokines would allow characterizing the immune response of circulating monocytes in patients with atherosclerosis in more details. In addition, a larger sample size would allow a more reliable evaluation of cytokines secretion levels since in some points the results do not reach statistical significance. Finally, the study didn't examine the possible mechanisms of the effect of statins on the immune status of monocytes.

Conclusion.

The results of the present study demonstrate the anti-inflammatory efficacy of statins, expressed in decreased secretion of pro-inflammatory cytokines TNF-α and IL-1β by cultured monocytes/macrophages of patients with coronary atherosclerosis receiving atorvastatin and rosuvastatin therapy, compared with patients without statin therapy. Moreover, the reduction of pro-inflammatory cytokines secretion was associated with lower levels of blood lipids, in particular, total cholesterol and LDL. The most pronounced and statistically significant decrease in the secretion of TNF-α and IL-1β was observed in the group of patients receiving rosuvastatin. Thus, rosuvastatin can be considered as the most preferred preparation for pathogenetic therapy and prevention of atherosclerosis, however, additional studies with a larger number of participants and a wider range of cytokines are required.

Author Contributions: Conceptualization, T.V.K. and I.Y.Y.; methodology, Y.V.M. and A.M.M.; software, A.M.M.; validation, Y.V.M. and A.M.M.; formal analysis, I.Y.Y. and T.V.K.; investigation, A.M.M. and Y.V.M.; resources, M.V.L. and T.B.A.; data curation, M.V.L. and T.B.A.; writing - original draft preparation, T.V.K. and N.V.E.; writing - review and editing, T.V.K. and N.V.E.; visualization, T.V.K. and N.V.E.; supervision, M.V.L. and I.Y.Y.; project administration, Y.V.M.; funding acquisition, T.V.K. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate.

The study was performed in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of the Petrovsky National Research Center of Surgery. Informed consent was obtained from all subjects involved in the study.

Data Availability.

Data are available from the corresponding author upon request.

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Conflicts of Interest.

The authors declare no conflict of interest.

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