GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 12 (345) Декабрь 2023

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 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.

GEORGIAN MEDICAL NEWS
No 12 (345) 2023

Содержание:

GEORGIAN MEDICAL NEWS
No 12 (345) 2023

EXERCISE AND MICRORNA

Mukaddes Pala.

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Abstract.

Physical activity stimulates numerous structural, metabolic, and morphological adaptations. These adaptations are vital for maintaining human health throughout life. Developments in molecular biology, biochemistry, and bioinformatics, along with exercise physiology have identified many signaling pathways, and transcriptional and translational processes responsible for exercise-related adaptations. The molecular mechanisms underlying the beneficial effects of exercise are not fully understood. Recently, the focus has been on microRNAs (miRNAs). They are small noncoding RNA molecules that negatively modulate gene expression and are involved in fundamental biological processes. This review describes miRNAs whose activities change in the heart, skeletal muscle, and circulation due to exercise. In addition, miRNAs with altered activity may be parameters adaptation to exercise, preventing injuries, and monitoring health status.

Key words. Exercise, miRNAs, heart, skeletal muscle, circulating miRNAs.

Introduction.

Exercise:

Physical activity causes a worldwide reduction in lifestyle-related diseases such as cardiovascular diseases, metabolic diseases, and diabetes [1]. High physical activity and cardiorespiratory endurance are associated with a reduced risk of cardiovascular disease and mortality [2-4]. Low aerobic capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease [2,5,6]. The maximum amount of oxygen consumed (VO2max) determines cardiorespiratory endurance [2,7-11]. Additionally, the level of physical activity also increases cardiorespiratory endurance [12-14].

Exercise provides many benefits to the organism in both health and disease. Endurance exercise increases VO2max, lipid profile, endothelial function, capillaries, mitochondria, and metabolic enzymes in different organs and systems [15-18]. Studies have focused on the adaptations that occur in the cardiovascular system and skeletal muscle [7,11,19,20]. A regularly implemented exercise program improves both systolic and diastolic function in the heart and increases cardiac output [21-24]. The effects of exercise on cardiomyocytes are a shortening in the length of cardiomyocytes and an increase in contraction-relaxation ratios [25]. Aerobic exercise not only improves cardiac functions but also provides benefits to skeletal muscle. Exercise can prevent skeletal muscle atrophy, increase type I fiber distribution, and improve metabolic status [26].

In recent years, studies at the molecular level have begun to better understand the benefits of exercise by identifying intracellular signaling pathways that mediate physiological adaptations caused by acute and chronic exercise. Studies have identified signaling pathways that cause heart and skeletal muscle abnormalities, and metabolic enzymes and proteins involved in calcium processing were identified as promising targets [25,27-29].

MicroRNAs (miRNAs):

MiRNAs, non-coding RNAs, were discovered in the early 1990s. miRNAs control the expression of the gene pool in a sequence-specific manner and provide post-transcriptional regulation [30-33]. miRNAs regulate gene expression at the post-transcriptional level by either inhibiting protein synthesis or causing degradation of messenger RNA (mRNA) [30].

Dr. Victor Ambros and Dr. Gary Ruvkun discovered the first miRNA gene, lin-4 while examining post-embryonic development events in the nematode C. elegans in 1993 [34,35]. The Lin-4 gene inhibits protein synthesis by binding to 3' UTR (non-translated region) of mRNA [36,37]. Another miRNA gene, let-7, was discovered in the same nematode. Let-7 is a gene that promotes the transition from the late larval stage to the adult stage [38]. Subsequently, homologs of the let-7 gene appeared in the human and Drosophila genomes [39]. Small RNAs from flying animals, worms, and humans cloned. Over 100 new weak non-coding RNAs have been reported [40]. Based on these results, miRNAs control various cellular adaptive processes such as differentiation, proliferation, apoptosis, and metabolism [30,33,41].

Biogenesis of miRNAs:

Biogenesis of miRNAs begins with the transcription of miRNA genes (Figure 1). miRNAs are transcribed by RNA polymerase II in the nucleus and form primary transcripts (pri-miRNA) containing cap and polyadenyl structures [42]. pri-miRNAs fold to form a hairpin structure, which causes incomplete base pairing. pri-miRNAs are enzymatically cleaved by nuclear microprocessor complexes called Drosha, which are RNAse III endonucleases. Then, Drosha binds double-stranded RNA (known as the DiGeorge critical region 8 (DGCR8) protein), to form preliminary-miRNAs (pre-miRNAs) of 70-100 nucleotides in the hairpin structure [43]. Pre-miRNAs are transported from the nucleus to the cytoplasm via RANGTP and exportin 5 transporters. Pre-miRNAs are cleaved by Dicer, another RNAse III enzyme. Temporary duplexes of 18-24 nucleotides formed from pre-miRNAs via Dicer [44]. RNA-induced silencing complex (RISC) related to miRNA containing Argonaute protein added to this duplex structure [45]. At this stage, one of the double-stranded miRNAs is selected as mature, while the other is called the star chain and is rapidly degraded [46].

Mature miRNAs negatively regulate gene expression. miRNAs carry out this regulation within the cell by either suppressing translation or causing mRNA to be degraded [47].

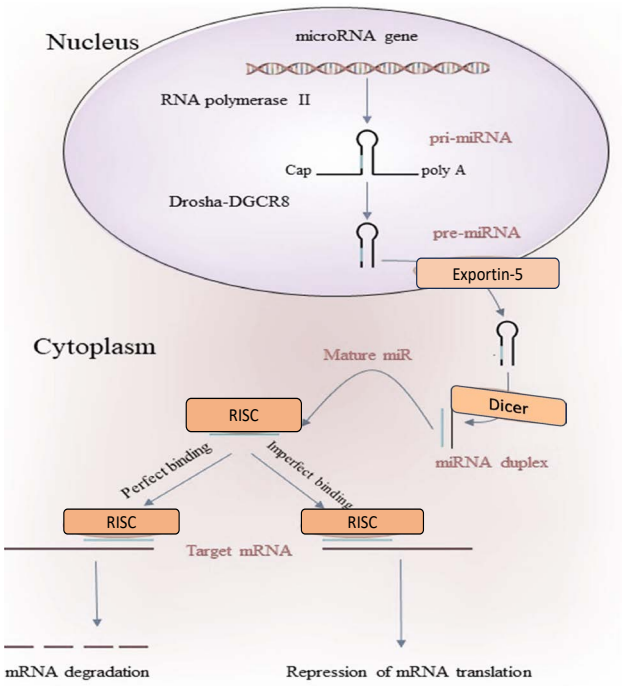

Figure 1. *Biogenesis of MiRNAs (42).*

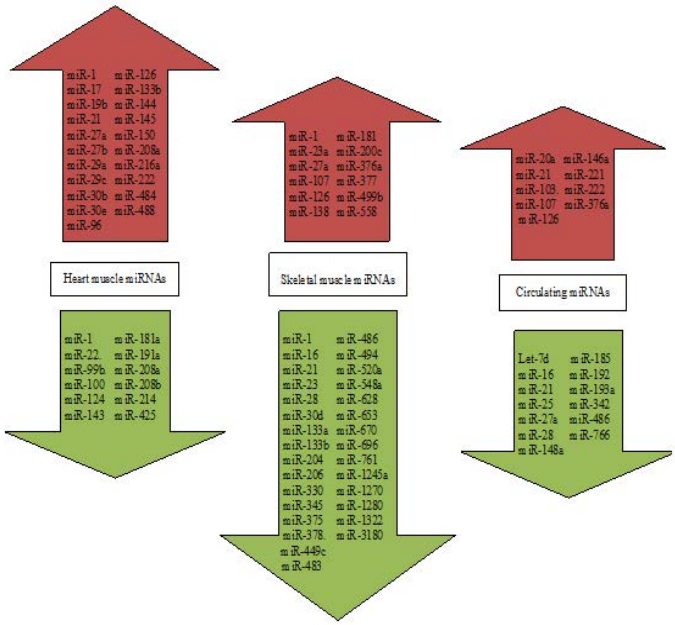

Figure 2. *miRNAs are up-regulated and down-regulated in different tissues with exercise (50).*

MiRNAs in Regulating Gene Expression.

Under normal homeostatic conditions, miRNAs regulate gene expression posttranscriptionally. The regulatory functions of miRNAs become more significant when exposed to stress or during disease processes [48].

Determination of target genes of miRNAs occurs according to base pairing. miRNAs have more than one target gene. Several databases determine the target genes of miRNAs and the signaling pathways in which these genes are involved [49]. miRBase and Kyoto Encyclopedia of Genes and Genomes (KEGG) are the most common databases (https://www.miRBase.org, https://www.genome.jp).

MiRNAs, which have increased in importance recently, are predicted as potential biomarkers in adaptive changes that occur in response to exercise [50].

MiRNAs in Exercise:

MiRNAs are necessary for cardiac [51-54] and skeletal muscle [55,56] hypertrophy, angiogenesis [57,58] atherosclerosis [59], neuron regeneration [60], and metabolism [61,62] which are adaptation processes to exercise. Additionally, miRNAs have significant roles in acute [63-66] and chronic [67-69] endurance exercise, resistance exercise [70,71] marathon runners, treadmill [72] or swimming exercise [51,53,54,57,58] models (in studies conducted in experimental animals and the general population) [53,58,61]. miRNAs are up-regulated and down-regulated in different tissues (cardiac muscle, skeletal muscle, and circulation) with exercise (Figure 2).

Cardiac Muscle Specific miRNAs:

In recent years, using large-scale screening methods, it has been shown that miRNAs, long non-coding RNAs, and other RNA molecules are involved in different processes in the heart [73]. MiRNAs associated with embryonic heart development in the fruit fly D. melanogaster identified [74-78]. The miR-1 gene is responsible for myocardial development in D. melanogaster [76,77]. In addition, miRNAs expressed in the heart play a role in heart remodeling, dilated cardiomyopathy, and triggering heart failure during embryonic heart development [74,75]. miRNAs are involved in several physiological [51,53,54,57,58] and pathological [72,73,79-86] conditions. Cardiac miRNA expression levels are associated with the development of cardiac stress and cardiac hypertrophy due to pressure overload [79-81,87], myocardial infarction, and [85] end-stage heart failure in humans [73,88,89].

Aerobic exercise causes left ventricular hypertrophy. Several experimental models, treadmill, running, and swimming, are being created to demonstrate the beneficial effects of exercise [25,90]. However, there are significant differences in the interpretation of the changes that occur with the application of these experimental models. Experimental studies have demonstrated the effects of exercise on the heart.

Athlete's Heart:

An athlete's heart is generally a benign increase in heart mass. This increase in the athlete's heart indicates physiological adaptation to chronic exercise. Cardiac hypertrophy (CH) occurs in response to exercise, protects the heart, improves cardiac functions, and prevents heart failure. Moreover, it is significant to identify the molecular mechanisms responsible for the transition from cardiac hypertrophy to heart failure [91].

The Swedish clinician Henschen made about the athlete's heart in 1890 [92]. There were identified different forms of CH in athletes by Mongaroth et al. in 1975 [93].

miRNAs contributing to aerobic exercise-induced physiological cardiac remodeling (in swimming exercise: miRNA-1, -21, -27a/b, -29a/c, -30e, -99b, -100, -124, -126, -133a /b, -143, -144, -145, -208a and -222, and in running exercise: miRNA-1, -26, -27a, -133, -143, -150, and -222) were identified [91].

Skeletal Muscle Specific miRNAs:

Skeletal muscle is a highly plastic organ that can change its phenotype in response to external stimuli such as neuromuscular activity, mechanical load, and nutrition. miRNAs are involved in the regulation of myogenesis and muscle metabolism. Many miRNAs are ubiquitously expressed, while others are tissue specific. Both categories of miRNAs play a significant role in the development and function of muscle tissue [94].

The most abundant miRNAs in muscle tissue, generally called myomiRs, work as modulators in the proliferation, differentiation, metabolism, and hypertrophy of skeletal and cardiac muscle. The myomiR family includes miR-1, miR-133a, miR-133b, miR-206, miR-208a, miR-208b, miR-486, and miR-499 [95]. Most myomiRs are expressed in the heart and skeletal muscle, except miR-208a, which is heart-specific, and miR-206, which is specific to skeletal muscle [96].

Specific miRNAs can exert their effects on many target mRNAs. Moreover, each mRNA gene can be targeted by more than one miRNA. For this reason, identifying biologically important target genes is extremely important in miRNA research. Numerous biological targets have been reported for muscle-specific miRNAs. A comprehensive overview of MyomiRs and their molecular targets has been published in a study by Horak and colleagues [97].

The Regulatory Role of MyomiRs in Skeletal Muscle:

Myo-miRs have significant roles in regulating the functions of skeletal muscle. MyomiRs are muscle-specific miRNAs that regulate myoblast proliferation and differentiation. During muscle cell differentiation, the changes occur in the expressions of miR-1, miR-133a, miR-133b, miR-206, miR-486, and miR-499. Myo-miRs miR-1, miR-206, and miR-486 promote myoblast differentiation, and miR-133a increases myoblast proliferation [98,99]. Myo-miRs regulate skeletal muscle hypertrophy and participate in the regulation of muscle fibers [100,101]. Expression of the beta-myosin heavy chain gene, which enables the development of slow-twitch type I muscle fibers, is associated with increased expression levels of miR-206, miR-208b, and miR-499. Expression of miR-208b and miR-499 helps distinguish fast-twitch and slow-twitch skeletal muscle phenotypes [102]. The regeneration process of muscle fibers is associated with an increased distribution level of miR-206, which can regulate a retrograde signaling pathway necessary for neuromuscular interactions and is an indicator of motor innervation [103,104].

MyomiRs miR-1 and miR-206 were proven to be upregulated after injury and promote muscle regeneration by affecting Pax 7 [105]. myomiRs are dysregulated in many human muscle diseases [106]. One study showed that miR-1, miR-133, and miR-206 expressions changed in Duchenne and Becker muscular dystrophy patients [107]. In another study, the upregulation of miR-206 coincided with the progression of amyotrophic lateral sclerosis [108]. Compared with healthy skeletal muscle tissue, miR-1, miR-133a, miR-133b, and miR-206 expression downregulated in rhabdomyosarcoma tumor tissues [109,110]. Decreased miR-1 expression level appeared to correlate with worsened muscle function in patients with chronic obstructive pulmonary disease [111]. The effect of inactivity on myomiR expression showed that seven days of bed rest caused miR-1 and miR-133a to be downregulated [112].

The Effect of Exercise on miRNA Expression in Skeletal Muscle:

Skeletal muscle is a highly plastic tissue that can change its phenotype in response to neuromuscular activity. Several studies have investigated changes in the expression of myomiR modulated by exercise of varying intensity and mode using muscle biopsy techniques. The first study showing that myomiR expression in human skeletal muscle responds to exercise was carried out by Nielsen et al. [68]. Researchers evaluated myomiR expression levels in samples obtained from the Vastus Lateralis after acute endurance exercise. They found that before a 12-week endurance exercise program, miR-1 and miR-133 expression levels increased significantly. In addition, during the rest period after the exercise program, miR-1, miR-133a, miR-133b, and miR-206 levels were downregulated compared to the levels before starting endurance exercise [68].

Russell et al. revealed that an acute endurance cycling exercise upregulated miR-1, miR-133a, and miR-133b, while ten days of endurance exercise led to upregulation of miR-1 and downregulation of miR-133b [113]. In a study evaluating the effects of resistance exercise on the expression of skeletal muscle miRNAs, 56 young men performed resistance exercise five days a week for 12 weeks [55]. Twenty-one miRNAs were identified in biopsy samples taken from vastus lateralis. Distribution patterns of miR-26a, miR-29a, miR-378, and miR-451 were shown to be associated with changes in functional hypertrophy and could also distinguish low and high responders to resistance exercise. Interestingly, the expression levels of myomiRs appeared unaffected after this specific resistance exercise program. In elderly participants, 12 weeks of resistance exercise resulted in downregulation of miR-1 [71]. miRNAs, whose expression changes with muscle atrophy, may play a role in age-related skeletal muscle loss [114].

Until recently, muscle tissue samples were taken to evaluate miRNA expression profiles obtained using invasive muscle biopsy techniques. This invasive technique caused discomfort to the study participants [50].

The tissue-specifically expressed miRNAs in plasma, serum, and other biological fluids have led to an intense search and identification of circulating miRNAs that can be useable as fingerprints of various physiological and pathological states. miRNAs, whose circulating activities are determined depending on the applied exercise model, can be used as biomarkers for exercise physiology. Additionally, circulating miRNAs may be involved in gaining more information about the molecular control of exercise adaptation [50].

Circulating miRNAs in exercise:

The discovery of miRNAs in body fluids in 2008 became an important research topic. Circulating miRNAs are in plasma, urine, cerebrospinal fluid, saliva, platelets, erythrocytes, and nucleated blood cells. They are resistant to boiling, low or high

pH, prolonged exposure to room temperature, and repeated freeze-thaw [115,116].

Circulating miRNAs are present in low concentrations in the circulation. They are degraded in the blood by RNase. Therefore, by understanding the mechanisms that ensure the release and protection of miRNAs, more detailed information about the biological properties of miRNAs can be obtained [115,116]. miRNAs are packaged in various microparticles (exosomes, microvesicles, and apoptotic bodies) or RNA-binding proteins (Argonaute 2) or lipoprotein complexes (high-density lipoprotein: HDL) to protect them from degradation. El-Hefnay et al. reported for the first time that RNAs in plasma were incorporated into protein or lipid vesicles to protect them from degradation. Exosomes are small vesicles of 50-100 nm in size, originating from the endosome and released from cells when multivesicular bodies (MVB) fuse with the plasma membrane. Microparticles (MPs) are submicron membrane vesicles (0.1–1 μm) released on cell activation or apoptosis. Apoptotic bodies, the largest microparticles, 0.5-2 μm in size, are released by all cell types during the late stages of apoptosis [117]. There are different hypotheses regarding the storage sites of miRNAs, their release, and uptake by recipient cells. According to one of these hypotheses, miRNAs are stored in lipid vesicles, and miRNAs released after apoptotic cell death accumulate in atherosclerotic lesions. miRNAs can be recruited into microparticles, mesenchymal stem cells, and recipient cells such as monocyte-endothelial cells. Then, miRNAs regulate gene expression through the release of miRNA-containing microparticles [117].

Circulating miRNAs are considered clinical biomarkers for diseases because they are stable in the blood [118]. In a case-control study conducted with a 10-year observation period, several circulating miRNAs were identified (let-7d-5p, let-7g-5p, miR-26a-5p, miR-29c-3p, miR-103a-3p, miR-106a-5p, miR-148b-3p, miR-151a-5p, miR-424-5p, miR-660-5p). Thus, miRNAs predict future fatal myocardial infarction in healthy individuals [50].

miRNAs can be usable to assess cardiovascular disease risk, stratify individuals at high risk, optimize treatment strategies, and understand the underlying biology. Plasma profiles of specific miRNAs involved in angiogenesis, inflammation, hypoxia/ischemia, and skeletal and cardiac muscle contraction during exercise were examined by Baggish et al. [119]. Expression profiles of circulating miRNAs were measured before and after a long-term aerobic exercise program and at rest. The expression of three different exercise-responsive miRNAs was evaluated. There is a linear correlation between miR-146 expression level, one of these miRs, and VO2max is an aerobic performance parameter [119].

In studies evaluating the effect of marathon running on circulating miRNA expression, miRNAs upregulated in all studies, except one study focusing on inflammatory miRNAs [119-125].

In the study examining the effects of acute endurance exercise on miRNA expression levels in plasma, 724 miRNAs were evaluated. They identified changes in the expression of 188 miRNAs in plasma [62]. Researchers suggested that the observed increase in myomiRs was due to selective secretion rather than passive release caused by muscle damage [62].

A study examining the expression profiles of 720 miRNAs in serum before treadmill exercise showed that miR-210, miR-21, and miR-222 levels were discriminatory between those with low and high VO2max and that miR-210 could be used as a biomarker of aerobic fitness [69].

Aoi et al. stated that c-miR-486 levels decreased significantly after acute and chronic aerobic exercise and negatively correlated with VO2 max [67].

A recent study investigating whether high-intensity interval exercise is superior to high-intensity continuous exercise showed that circulating miRNAs have the same expression pattern in these two types of exercise [126].

In a study evaluating the effect of circulating miRNAs on resistance exercise, there were no changes in the expression of circulating muscle-specific miRNAs after acute resistance exercise [70].

The profiles of myomiRs were altered in both muscle tissue and blood plasma of an elderly cohort that underwent five months of resistance exercise [127]. miR-499, expressed in plasma and muscle, was identified as the most sensitive marker in knee extensor strength with resistance exercise [127].

In a study investigating whether circulating miRNA levels differ in elite male athletes performing endurance and strength exercises; plasma levels of miR-21, miR-221, miR-222, and miR-146a were significantly higher in endurance athletes than in strength athletes [128].

Circulating miR-21, which responds differently to exercise, has been implicated as a well-known oncomiR affecting tumor development pathways [129].

In a study of changes in the leukocyte methylome after a sprint interval exercise, miR-21 and miR-210 were found to be downregulated [130].

The influence of cycling ergometer exercise on the expression level of c-miRNAs in neutrophils was investigated by Radom et al. Short-term aerobic exercise altered the expression of 38 miRNAs out of 826 miRNAs entities represented on the chip [65].

Physical activity is positively associated with longer leukocyte telomere length [131,132]. The effect of acute treadmill exercise on the expression of telomeric genes and miRNA levels in white blood cells was investigated by Chilton and colleagues [133]. The expression of 56 miRNAs changed after exercise. miR-186, miR-181, miR-15a, and miR-96 were upregulated 60 min after exercise. In addition, in silico analyses have shown that potential targets of these miRNAs are telomeric genes [131,132].

Conclusion.

In recent years, the number of research on miRNAs has increased dramatically. miRNAs are involved in the physiological adaptation to exercise, such as skeletal muscle and cardiomyocyte hypertrophy, mitochondrial biogenesis, vascular angiogenesis, and metabolic processes.

Exercise causes physiological stress and tissue damage. During the recovery process after exercise, cellular activation that leads to repair is also triggered. Study results show that numerous tissue-specific miRNAs are released into the circulation during and after exercise. miRNA expression pattern varies depending

on the type and intensity of exercise. Circulating miRNAs can be used as biomarkers because they are easy to collect samples and are stable in body fluids. Also, miRNAs with altered activity may be parameters adaptation to exercise, preventing injuries, and monitoring health status.

Funding.

None.

Ethical Approval.

This item is not applicable for this review study.

Informed Consent.

This item is not applicable for this review study.

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