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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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# ENDOTHELIAL GLYCOCALYX AND ATHEROSCLEROSIS: FROM MOLECULAR MECHANISMS TO THERAPEUTIC OPPORTUNITIES

**Kaibkhanov Ulukhan K.[1], Konyshev Mikhail V.[1], Ovsienko Aleksei A.[1], Khromov Artur M.[1], Glushets Daria D.[1], Molchanova Maria N.[1], Meilikhovich Sofia A.[1], Kopitko Olga N.[1], Solomonenko Andrey V.[1], Mamedova Roksana G.[1], Larina Anna D.[1], Boyko Valeria[1], Kutenko Anna I.[1], Gaponova Natalia A.[1], Ermolenko Ekaterina V.[2]**

*[1]North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russia*

*[2]Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia*

## Abstract.

The endothelial glycocalyx is a highly dynamic, carbohydrate-rich layer that lines the luminal surface of blood vessels and plays a fundamental role in vascular homeostasis. Although once considered a passive structural barrier, it is now recognized as a critical regulator of endothelial permeability, mechanotransduction, leukocyte adhesion, and thrombosis. Its degradation has been implicated as a pivotal event in the initiation and progression of atherosclerosis. This review synthesizes current evidence on the structure, physiological functions, mechanisms of degradation, and clinical significance of the endothelial glycocalyx in the context of atherosclerosis. We also highlight diagnostic approaches and emerging therapeutic strategies aimed at glycocalyx preservation and restoration. A growing body of evidence demonstrates that glycocalyx degradation precedes overt endothelial dysfunction and facilitates lipid infiltration, immune cell recruitment, and thrombogenic transformation of the vascular surface. Multiple triggers, including pro-inflammatory cytokines, oxidative stress, disturbed shear stress, and metabolic derangements, contribute to the loss of glycocalyx integrity. Clinical studies have identified circulating glycocalyx fragments as biomarkers of vascular damage and cardiovascular risk. Experimental and early clinical data suggest that interventions such as glycosaminoglycan supplementation, enzyme inhibition, antioxidant therapy, and lifestyle modification can restore glycocalyx structure and function. Preservation of the endothelial glycocalyx represents a promising therapeutic frontier in the prevention and treatment of atherosclerosis. Continued advances in glycocalyx imaging, molecular profiling, and targeted interventions are expected to redefine vascular risk stratification and foster the development of glycocalyx-centered therapies.

**Key words.** Endothelial glycocalyx, atherosclerosis, vascular homeostasis, endothelial dysfunction, shear stress, inflammation, oxidative stress, glycosaminoglycans, mechanotransduction, cardiovascular disease.

## Introduction.

The endothelial glycocalyx has emerged as a critical yet often overlooked component in vascular biology and pathophysiology. This fragile, carbohydrate-rich layer lining the luminal surface of the vascular endothelium serves as the first line of interaction between blood and the vessel wall, making it a key player in vascular homeostasis [1,2].

In recent years, mounting evidence has highlighted the pivotal role of the glycocalyx in the pathogenesis of atherosclerosis – the leading cause of cardiovascular morbidity and mortality worldwide [3]. The integrity of this delicate structure appears fundamental to preventing the cascade of events that culminate in atherosclerotic plaque formation, while its degradation facilitates disease progression through multiple interconnected mechanisms [4,5].

This comprehensive review synthesizes current knowledge regarding the glycocalyx's structure, functions, and its increasingly recognized significance in atherosclerotic disease, with an emphasis on potential therapeutic implications and future research directions.

### Structure and composition of the endothelial glycocalyx.

The glycocalyx represents a highly sophisticated biological interface composed of a mesh-like network of macromolecules extending from the apical surface of the endothelium into the vascular lumen [1]. This structure, measuring between 0.2 to 2 μm in thickness depending on the vascular bed, comprises several key components that work in concert to maintain vascular health [6].

At its core, the glycocalyx consists of membrane-bound proteoglycans anchored to the endothelial cell membrane. These proteoglycans feature a protein core from which glycosaminoglycan (GAG) chains extend outward into the vascular lumen [7]. The principal proteoglycans include syndecans and glypicans, which serve as the scaffolding for the attachment of various GAG chains [8]. Among these GAGs, heparan sulfate predominates, constituting approximately 50-90% of the total GAG content, followed by chondroitin sulfate and, to a lesser extent, dermatan sulfate [9]. Another critical component is hyaluronan (hyaluronic acid), a high molecular weight, non-sulfated GAG that weaves through this network, providing structural support and contributing significantly to the volume of the glycocalyx [10].

Complementing these structural elements are glycoproteins, notably selectins, integrins, and members of the immunoglobulin superfamily, which facilitate cell-cell interactions and signaling [11]. The glycocalyx further incorporates plasma proteins, lipoproteins, and soluble GAGs, creating a dynamic layer that constantly exchanges components with the bloodstream [2].

This composition allows the glycocalyx to adapt to changing physiological conditions while maintaining its essential functions in vascular homeostasis. The spatial arrangement of these components creates a mesh with small pores that functions as a molecular sieve, regulating the passage of molecules based on their size, charge, and structural configuration [12].

The structural integrity of the glycocalyx is maintained through a delicate balance of continuous synthesis and shedding, influenced by various factors including hemodynamic

forces, inflammatory mediators, and metabolic conditions [13]. This dynamic nature allows the glycocalyx to respond to physiological needs while maintaining its protective functions.

Understanding this complex architecture is essential for appreciating how disruptions in glycocalyx integrity contribute to atherosclerosis pathogenesis, as will be explored in subsequent sections.

**Physiological functions of the glycocalyx in vascular health.**

The endothelial glycocalyx executes multiple crucial functions that collectively preserve vascular homeostasis and protect against atherosclerosis [14]. First and foremost, it serves as a selective permeability barrier, regulating the transport of molecules between the bloodstream and the subendothelial space [15]. This barrier function is particularly important in preventing the transcytosis of atherogenic lipoproteins, especially low-density lipoprotein (LDL), into the vessel wall – a critical initiating event in atherosclerosis [16]. The glycocalyx achieves this through both size exclusion and electrostatic repulsion, as its negative charge repels similarly charged particles including many plasma proteins and lipoproteins [17].

As demonstrated in the research by Mitra and colleagues, the glycocalyx plays an indispensable role in mechanotransduction – the conversion of mechanical stimuli into biochemical signals [4]. When blood flows across the endothelium, the glycocalyx senses and transmits shear stress to the endothelial cytoskeleton, triggering signaling cascades that lead to the production of vasoactive substances, particularly nitric oxide (NO) [18]. This mechanotransduction function is vital for maintaining vascular tone and ensuring appropriate vasodilation in response to increased blood flow [19]. Additionally, the mechanosensing properties of the glycocalyx help establish flow-dependent atheroprotective gene expression patterns in regions of laminar flow, while disturbed flow patterns in areas prone to atherosclerosis development fail to elicit these protective responses [20].

Another critical function of the glycocalyx, as elucidated by Ferreira and colleagues, involves the regulation of leukocyte and platelet adhesion to the endothelium [21]. Through both physical and electrostatic mechanisms, the intact glycocalyx prevents unnecessary cellular adhesion by masking endothelial surface adhesion molecules like selectins, integrins, and immunoglobulins [22]. This anti-adhesive property inhibits inflammatory cell recruitment and platelet aggregation – key processes in atherosclerotic plaque formation and progression [23].

The glycocalyx also modulates inflammatory responses by binding and sequestering chemokines and cytokines, thereby controlling their availability and activity [24]. It serves as a repository for growth factors and enzymes, including lipoprotein lipase, which is crucial for triglyceride metabolism, and superoxide dismutase, which provides antioxidant protection [25].

The glycocalyx further participates in maintaining the anticoagulant state of the vascular endothelium by binding anticoagulant molecules like antithrombin III and tissue factor pathway inhibitor, while also supporting the activity of endothelial thrombomodulin [26].

Sembajwe and colleagues have demonstrated the glycocalyx's role in regulating endothelial cell volume and function through interactions with sodium ions [27]. The negatively charged glycosaminoglycans within the glycocalyx create a sodium buffer barrier that helps maintain proper sodium gradients across the endothelial membrane. This function is particularly relevant given the association between high sodium intake and cardiovascular disease risk [28].

Table 1 summarizes the key physiological functions of the endothelial glycocalyx, which collectively contribute to vascular homeostasis and protect against atherosclerosis.

Collectively, these physiological functions establish the glycocalyx as an essential guardian of vascular health, with its disruption potentially initiating or accelerating the pathogenesis of atherosclerosis [29]. The subsequent sections will explore how glycocalyx degradation contributes to atherogenesis and the potential therapeutic implications of targeting this structure in cardiovascular disease prevention and treatment.

**Glycocalyx degradation: a critical early event in atherogenesis.**

The degradation of the endothelial glycocalyx represents a pivotal early event in the pathogenesis of atherosclerosis, occurring well before histologically detectable changes manifest in the vessel wall [30]. Multiple pathophysiological mechanisms contribute to glycocalyx disruption, each potentially serving as an initiating factor in the atherosclerotic cascade.

Table 2 provides an overview of the primary mechanisms driving glycocalyx degradation in atherosclerosis, including the roles of oxidative stress, inflammation, disturbed shear stress, and hyperglycemia. These factors collectively impair the integrity of the glycocalyx, leading to increased endothelial permeability and the initiation of atherogenesis.

Inflammatory mediators play a predominant role in glycocalyx degradation [31]. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interferon-gamma (IFN-γ) stimulate endothelial cells to release enzymes that degrade glycocalyx components [32]. These enzymes include heparanase, which cleaves heparan sulfate chains; hyaluronidase, which degrades hyaluronan; and matrix metalloproteinases, which break down core proteins of proteoglycans [33]. The inflammatory environment created by these cytokines further promotes ongoing glycocalyx shedding, establishing a detrimental feedback loop that progressively diminishes glycocalyx integrity [34].

Oxidative stress represents another significant contributor to glycocalyx damage, as detailed by Valera and colleagues [35]. Reactive oxygen species (ROS) directly depolymerize glycocalyx components, particularly hyaluronan, and activate redox-sensitive enzymes that further degrade glycocalyx structures [36]. The sources of these ROS include NADPH oxidases, mitochondrial respiratory chain complexes, and uncoupled endothelial nitric oxide synthase (eNOS), all of which can be activated under conditions associated with atherosclerosis risk, such as dyslipidemia, hyperglycemia, and hypertension [37].

Hemodynamic factors significantly influence glycocalyx integrity [38]. Regions of the vasculature exposed to disturbed blood flow, such as arterial bifurcations and curvatures – which

***Table 1.*** *Physiological functions of the endothelial glycocalyx.*

| Function | Description |
|---|---|
| **Selective permeability barrier** | Regulates transendothelial transport of macromolecules and lipoproteins (e.g., LDL) through size exclusion and electrostatic repulsion. |
| **Mechanotransduction** | Senses hemodynamic shear stress and mediates intracellular signaling pathways, including activation of endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO). |
| **Leukocyte and platelet repulsion** | Prevents excessive adhesion of leukocytes and platelets by masking endothelial cell adhesion molecules (e.g., selectins, integrins). |
| **Anti-inflammatory buffering** | Binds and sequesters pro-inflammatory cytokines and chemokines, modulating their bioavailability and activity, thus controlling endothelial inflammation. |
| **Anticoagulant regulation** | Facilitates the presentation of anticoagulant proteins, including antithrombin III, thrombomodulin, and tissue factor pathway inhibitor (TFPI), thereby maintaining an anti-thrombotic state. |
| **Sodium buffering** | Regulates endothelial sodium gradients through glycosaminoglycan interactions, contributing to endothelial cell volume regulation and barrier function. |
| **Reservoir for enzymes and growth factors** | Serves as a storage site for enzymes, such as lipoprotein lipase, and antioxidants, including superoxide dismutase (SOD), which protect the endothelium from oxidative damage. |

***Table 2.*** *Mechanisms of endothelial glycocalyx degradation in atherosclerosis.*

| Mechanism of degradation | Triggers | Molecular players | Impact on glycocalyx |
|---|---|---|---|
| **Oxidative stress** | Reactive oxygen species (ROS) | NADPH oxidases, eNOS, mitochondrial dysfunction | Depolymerization of hyaluronan and heparan sulfate |
| **Inflammation** | Pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ) | Heparanase, hyaluronidase, matrix metalloproteinases (MMPs) | Cleavage of GAGs and proteoglycans |
| **Disturbed shear stress** | Flow disturbance in bifurcations and curvatures | Altered shear stress-mediated signaling pathways | Thinning of the glycocalyx and increased permeability |
| **Hyperglycemia** | Elevated blood glucose levels | Non-enzymatic glycation, upregulation of heparanase | Glycocalyx glycation and structural damage |

***Table 3.*** *Role of the glycocalyx in atherosclerosis across disease stages.*

| Atherosclerosis Stage | Glycocalyx Changes | Clinical Signs | Therapeutic Goals |
|---|---|---|---|
| **Early Stage** | Decrease in glycocalyx thickness, increased permeability | Mild inflammation, early endothelial activation | Protect glycocalyx, antioxidants |
| **Middle Stage** | Glycocalyx disruption, loss of barrier function | Local inflammation, immune cell activation | Restore barrier function, inflammation control |
| **Late Stage** | Complete degradation, loss of protective properties | Increased permeability, lipid accumulation, foam cell formation | Structural restoration, anti-atherogenic drugs |

coincidentally represent predilection sites for atherosclerosis – exhibit thinner glycocalyx coverage compared to areas of laminar flow [39]. The mechanistic link between disturbed flow and glycocalyx thinning involves altered shear stress-mediated signaling, increased local oxidative stress, and reduced synthesis of glycocalyx components [40]. This relationship between flow patterns and glycocalyx integrity helps explain the focal nature of atherosclerotic lesion development within the vasculature [20].

Metabolic disorders significantly impact glycocalyx health [41]. Hyperglycemia, as occurs in diabetes mellitus, accelerates glycocalyx degradation through multiple mechanisms, including increased oxidative stress, non-enzymatic glycation of glycocalyx proteins, and upregulation of heparanase expression [42]. Dyslipidemia, particularly elevated levels of oxidized LDL, also promotes glycocalyx shedding by inducing endothelial activation and inflammation [43].

As established in the research by Sembajwe and colleagues, sodium homeostasis plays a crucial role in glycocalyx maintenance [27]. High sodium intake can disrupt the glycocalyx by altering its electrostatic properties and promoting osmotic damage. This sodium-glycocalyx interaction may partially explain the association between high salt consumption and increased cardiovascular risk [28].

The degradation of the glycocalyx has profound consequences for endothelial function and atherogenesis [5]. Loss of glycocalyx thickness and density impairs its barrier function, allowing increased permeation of atherogenic lipoproteins into the subendothelial space [44].

Glycocalyx disruption also compromises mechanotransduction, resulting in reduced production of nitric oxide and diminished flow-mediated vasodilation [45]. Furthermore, a damaged glycocalyx exposes previously masked endothelial adhesion molecules, facilitating leukocyte recruitment and platelet adhesion – critical steps in atherosclerotic plaque formation [23]. The compromised anti-inflammatory and anticoagulant properties of a degraded glycocalyx further contribute to a pro-atherogenic environment within the vessel wall [46].

Following glycocalyx degradation, a cascade of pathophysiological events accelerates the development of complex atherosclerotic lesions. Table 3 presents a summary of how glycocalyx degradation progresses across the different stages of atherosclerosis, detailing the loss of barrier function and its contribution to lipid accumulation, immune cell recruitment,

and thrombotic processes that lead to plaque formation. This progression underscores the importance of glycocalyx integrity in the early stages of atherosclerosis and suggests potential therapeutic approaches to target its preservation.

The recognition of glycocalyx degradation as an early and potentially reversible event in atherogenesis provides a compelling rationale for therapeutic strategies aimed at preserving or restoring glycocalyx integrity, as will be discussed in subsequent sections of this review.

**Glycocalyx dysfunction and the progression of atherosclerotic lesions.**

Following initial glycocalyx degradation, a cascade of pathophysiological events ensues that drives the progression of atherosclerotic lesions [3]. Understanding these sequential processes illuminates how glycocalyx dysfunction contributes to the development of complex atherosclerotic plaques and their associated complications.

With the barrier function of the glycocalyx compromised, LDL particles more readily penetrate the endothelium and accumulate in the subendothelial space [16]. Once trapped within the arterial wall, these lipoproteins undergo oxidative modification, generating oxidized LDL (oxLDL) – a potent trigger for further endothelial activation and inflammation [47]. The degraded glycocalyx also fails to bind and sequester protective factors such as antioxidant enzymes, exacerbating oxidative stress within the developing lesion [36].

The exposure of endothelial adhesion molecules, previously masked by an intact glycocalyx, facilitates the recruitment of circulating monocytes to the vessel wall [22]. These monocytes adhere to the activated endothelium, transmigrate into the subendothelial space, and differentiate into macrophages that engulf oxLDL, transforming into foam cells – the hallmark cellular component of early atherosclerotic lesions [48]. The impaired anti-inflammatory properties of the damaged glycocalyx further contribute to the propagation of local inflammation, creating a self-perpetuating cycle of immune cell recruitment and activation [24].

Ferreira and colleagues have elucidated a critical interplay between glycocalyx degradation and von Willebrand Factor (vWF) exposure in the progression of atherosclerosis [21]. An intact glycocalyx normally conceals vWF, preventing inappropriate platelet adhesion. However, when the glycocalyx is compromised, vWF becomes exposed on the endothelial surface, promoting platelet binding and subsequent release of pro-inflammatory and pro-fibrotic mediators that accelerate lesion development [49]. This glycocalyx-vWF interaction appears particularly significant in regions of disturbed flow, where both glycocalyx thinning and elevated vWF expression coincide.

The progression from early to advanced atherosclerotic lesions involves the proliferation and migration of vascular smooth muscle cells (VSMCs) from the media to the intima [50]. The degraded glycocalyx contributes to this process by failing to sequester growth factors and matrix metalloproteinases that promote VSMC migration and proliferation. Additionally, the compromised mechanotransduction function of the glycocalyx alters gene expression patterns in both endothelial cells and VSMCs, favoring a synthetic, proliferative phenotype that contributes to intimal thickening and plaque expansion [18].

As atherosclerotic lesions advance, neovascularization occurs within the plaque, providing another route for inflammatory cell infiltration [3]. The endothelium of these intraplaque microvessels exhibits defective glycocalyx coverage, making them particularly leaky and prone to intraplaque hemorrhage – a feature associated with plaque instability and increased risk of rupture [51]. The compromised anti-thrombotic properties of the degraded glycocalyx further heighten the risk of thrombotic complications following plaque rupture or erosion [26].

Valera and colleagues have demonstrated that glycocalyx dysfunction not only contributes to initial lesion development but also influences plaque composition and stability [35]. Areas with more severely degraded glycocalyx tend to develop plaques with larger lipid cores, thinner fibrous caps, and more extensive inflammation – all characteristics of vulnerable plaques prone to rupture and thrombosis [52].

Interestingly, the relationship between glycocalyx dysfunction and atherosclerosis progression appears bidirectional [4]. While glycocalyx degradation promotes atherogenesis, the inflammatory and oxidative environment within developing plaques further compromises glycocalyx integrity in adjacent endothelium, creating a vicious cycle that accelerates disease progression [5]. This interplay helps explain why atherosclerosis, once initiated, tends to progress and expand within affected vascular regions [53].

Understanding the central role of glycocalyx dysfunction in atherosclerotic lesion progression underscores the potential therapeutic value of interventions aimed at preserving or restoring glycocalyx integrity throughout the disease course [54]. The following sections will explore current evidence regarding such therapeutic strategies and their potential impact on atherosclerosis prevention and treatment.

**Diagnostic assessment of glycocalyx integrity in atherosclerosis.**

The recognition of glycocalyx degradation as a critical factor in atherosclerosis has spurred interest in developing methods to assess glycocalyx integrity for diagnostic and prognostic purposes. Various approaches have been developed, each with specific advantages and limitations for clinical and research applications [55].

Direct visualization of the glycocalyx presents significant challenges due to its fragile nature and susceptibility to damage during tissue preparation. However, advanced microscopy techniques including electron microscopy, confocal microscopy, and two-photon laser scanning microscopy have enabled researchers to visualize the glycocalyx in experimental settings [56]. These methods have revealed crucial insights into glycocalyx dimensions and structure, demonstrating reduced glycocalyx thickness in atheroprone regions and in the presence of cardiovascular risk factors [39]. The main limitation of these approaches is their invasiveness and inapplicability to routine clinical assessment.

For clinical evaluation, several less invasive techniques have emerged. Sidestream darkfield imaging allows visualization of the microcirculation, including the glycocalyx, in accessible

vascular beds such as the sublingual microvasculature [57]. This technique estimates glycocalyx thickness by measuring the perfused boundary region (PBR) – the distance between the red blood cell column and the endothelium. An increased PBR suggests a thinner or more permeable glycocalyx. Studies have demonstrated correlations between increased PBR measurements and cardiovascular risk factors, making this a promising tool for clinical glycocalyx assessment [58].

Glycocalyx degradation results in the shedding of its components into the circulation, creating the opportunity to use circulating glycocalyx constituents as biomarkers [59]. Syndecan-1, hyaluronan, heparan sulfate, and chondroitin sulfate levels in plasma have been investigated as indicators of glycocalyx status. Elevated levels of these markers in circulation reflect ongoing glycocalyx shedding and have been associated with various cardiovascular conditions, including atherosclerosis, myocardial infarction, and heart failure [60]. The advantage of these biomarkers lies in their relatively straightforward measurement using standard laboratory techniques, although their specificity for vascular-derived glycocalyx components remains a limitation.

Functional assessment of the glycocalyx can be performed through vascular permeability studies [15]. The ratio of glycocalyx volume to total vascular volume can be estimated by measuring the difference in distribution volumes of glycocalyx-permeable tracers (like dextran 40) versus glycocalyx-impermeable tracers (like labeled red blood cells). This approach provides insights into glycocalyx barrier function rather than just its physical dimensions.

Emerging technologies include contrast-enhanced ultrasound with microbubbles to assess glycocalyx permeability and magnetic resonance imaging with specialized contrast agents targeting glycocalyx components [61]. These methods hold promise for non-invasive assessment of glycocalyx integrity in specific vascular beds, including coronary arteries.

The integration of glycocalyx assessment into cardiovascular risk prediction models represents an evolving area of research [55]. Studies have begun to explore whether markers of glycocalyx degradation provide incremental prognostic information beyond traditional risk factors for atherosclerotic cardiovascular events. Early data suggest that elevated levels of circulating glycocalyx components may identify individuals at higher risk for adverse cardiovascular outcomes, potentially informing more targeted preventive interventions [60].

Despite these advances, several challenges remain in the clinical assessment of glycocalyx integrity. These include standardization of measurement techniques, determination of reference ranges for glycocalyx parameters in diverse populations, and validation of glycocalyx-based measurements as surrogate markers for cardiovascular outcomes. Additionally, the heterogeneity of glycocalyx structure and function across different vascular beds complicates the extrapolation of findings from accessible sites to atherosclerosis-relevant arteries [14].

The continued refinement of these diagnostic approaches holds significant promise for early identification of glycocalyx dysfunction, potentially allowing for earlier intervention before atherosclerotic lesions become established. Furthermore, reliable glycocalyx assessment methods would facilitate the evaluation of therapeutic strategies targeting glycocalyx restoration, as will be discussed in the following section.

**Therapeutic strategies targeting the endothelial glycocalyx in atherosclerosis.**

The emerging role of the endothelial glycocalyx as a key regulator of vascular homeostasis and atherogenesis has prompted the development of therapeutic strategies aimed at its preservation or restoration. These interventions target both the structural components of the glycocalyx and the molecular mechanisms underlying its degradation. Below, we outline the principal approaches currently under investigation, supported by experimental and early clinical data.

One of the most studied therapeutic approaches involves the supplementation or replacement of glycosaminoglycans (GAGs), the major structural elements of the glycocalyx. Sulodexide, a mixture of fast-moving heparin and dermatan sulfate, has demonstrated the ability to restore glycocalyx thickness, reduce endothelial permeability, and attenuate inflammation in both in vitro and in vivo models [26,29,55]. In early clinical studies, sulodexide was associated with improved vascular function and reduced albuminuria, especially in patients with diabetes and chronic vascular disease [29,60]. Its mechanisms include suppression of heparanase activity and stabilization of endothelial tight junctions.

Multiple enzymes contribute to glycocalyx breakdown during inflammation and oxidative stress, including heparanase, hyaluronidase, and matrix metalloproteinases (MMPs) [31-34]. Inhibition of these enzymes represents a rational strategy to prevent glycocalyx loss. For example, heparanase inhibitors such as modified heparins and PI-88 have shown efficacy in reducing endothelial permeability and leukocyte adhesion in experimental models of atherosclerosis [33]. Similarly, broad-spectrum MMP inhibitors help preserve proteoglycan core structures and limit cytokine-induced glycocalyx shedding [31].

Oxidative stress is a major driver of glycocalyx degradation through direct damage to hyaluronan and heparan sulfate, as well as activation of sheddases [35-37]. Antioxidants such as vitamin C, N-acetylcysteine, and superoxide dismutase mimetics have been shown to preserve glycocalyx structure and barrier function in preclinical models [4,36]. These agents also enhance nitric oxide bioavailability and mitigate inflammatory responses, thereby indirectly stabilizing the endothelial surface [18,36].

The sphingosine-1-phosphate (S1P) signaling pathway has gained attention for its role in maintaining endothelial integrity. Agonists of the S1P1 receptor, such as SEW2871 and CYM5442, promote cytoskeletal stabilization, reduce endothelial permeability, and support glycocalyx regeneration [27]. These effects are mediated by the activation of Rac1 signaling and increased expression of endothelial junctional proteins. While current data are mostly preclinical, the mechanistic rationale is strong, particularly in inflammatory and ischemic vascular injury settings [27,55].

Non-pharmacological strategies also play an essential role in protecting the glycocalyx. Sodium restriction has been shown to preserve the electrostatic properties of the GAG matrix, as excessive salt intake leads to glycocalyx thinning and impaired

endothelial function [27,28]. Moreover, glycemic control in diabetic patients correlates with reduced glycocalyx shedding, likely due to the suppression of hyperglycemia-induced oxidative and enzymatic damage [42]. Regular aerobic exercise, weight reduction, and Mediterranean-style diets also contribute to vascular health through indirect effects on glycocalyx preservation [6,29].

Preserving the endothelial glycocalyx offers a multifaceted approach to interrupting early atherogenic processes. While most therapies remain in the experimental stage, growing mechanistic insight and advances in non-invasive glycocalyx assessment support further translational research. Ultimately, glycocalyx-targeted strategies may complement existing lipid-lowering and anti-inflammatory treatments to more comprehensively address cardiovascular risk.

## Conclusion.

The endothelial glycocalyx has transitioned from a structural curiosity to a central player in cardiovascular pathophysiology. This review consolidates compelling evidence that glycocalyx integrity is essential for preserving endothelial function, regulating vascular permeability, and maintaining anti-inflammatory and antithrombotic properties of the endothelium. Its early degradation initiates a cascade of events leading to lipid accumulation, immune cell adhesion, and thrombosis – hallmarks of atherosclerosis. Furthermore, the glycocalyx emerges as a promising diagnostic and therapeutic target, with measurable biomarkers and emerging interventions aimed at its protection or regeneration.

Despite significant advancements, challenges remain in standardizing glycocalyx measurements and translating findings into clinical practice. Future research should prioritize integrative strategies combining molecular profiling, non-invasive diagnostics, and personalized therapies to fully harness the potential of glycocalyx-targeted approaches. Protecting the endothelial glycocalyx may prove to be a cornerstone in the next generation of strategies against atherosclerotic cardiovascular disease.

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