




## REVIEW PAPER

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# The significance of glycocalyx in medicine

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## ABSTRACT

**Introduction.** The glycocalyx is a gel-like layer covering the membrane of many cells, especially cells of epithelial tissue. It consists of membrane-bound proteoglycans, glycosaminoglycan chains, glycoproteins, and adjacent proteins. Glycocalyx is necessary in maintaining the permeability of vessels, modulation of inflammatory responses and interactions between cells. It is also involved in cell adherence, mobility, mechanotransduction, regulation of the cell cycle and cell. Abnormalities in the structure and function of the glycocalyx underlie many diseases and disorders such as dry eyes disease, diabetes and its complications as well as sepsis.

**Aim.** In this review, we present the current view on the role of glycocalyx in human diseases.

**Material and methods.** This review was performed according to latest literature from the following databases: EBSCO, PubMed, Science Direct, and Springer Link.

**Analysis of the literature.** Pathological mechanisms such as disruption of the glycocalyx barrier and decreased hydration of the ocular epithelial surface cause dry eye disease. During hyperglycaemia, glycocalyx dysfunction occurs, which leads to its dysfunction and activation of the prothrombotic system. Moreover, the increase in the concentration of hyaluronidase leads to increase in the plasma hyaluronan levels and promotion of endothelial dysfunction. Additionally, degradation of glycocalyx in sepsis prevails over increased synthesis of its components strongly favors its enhanced enzymatic degradation.

**Conclusion.** A better understanding of glycocalyx impairment in disease could alter therapeutic strategies to improve patient outcomes.

**Keywords.** disease, glycocalyx degradation, glycosaminoglycans, hyperglycemia, medicine

## Introduction

The glycocalyx is a carbohydrate-rich layer that covers the membrane of many cells, especially cells of epithelial tissue. It was first described on the surface of endothelial cells by Danielli in 1940.<sup>1</sup> Glycocalyx is necessary

in maintaining the proper permeability of blood vessels and modulates interactions between blood cells and endothelium, and is also involved in cell adherence, mobility, mechanotransduction, regulation of the cell cycle and proliferation of normal cells.<sup>2</sup> Moreover, glycocalyx

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participates in immunological processes by modulating inflammatory responses by binding cytokines and weakening their binding to cell membrane receptors. In addition, it is known to be involved in the process of angiogenesis and metastasis.<sup>3</sup>

The biochemical composition of glycocalyx depends on the type of cell, type of tissue and the prevailing mechanical and physicochemical conditions, but its main building blocks are proteoglycans and glycoproteins. Proteoglycans have long and unbranched carbohydrate chains consisting of core proteins that covalently link to at least one molecule of glycosaminoglycans (GAG). GAGs are linear polysaccharides made up of repeating disaccharide units with N-acetylated or N-sulfated hexosamine or uronic acid (glucuronic acid or iduronic acid) or galactose. The dominant GAG group is heparan sulfate, which has numerous sulfate groups, which accounts for 50–90% of GAG. The second most common GAG in the glycocalyx of endothelial cell is chondroitin sulfate/dermatan sulfate.<sup>4</sup> The presence of heparan sulfate and chondroitin sulfate is estimated to have a typical ratio of 4:1 for the endothelium.<sup>5</sup> Proteoglycans show great structural diversity as they can contain GAGs of various numbers and chain lengths, which are further modified by repeating disaccharides forming a complex pattern of sulfate groups and a different core protein structure. The core proteins of proteoglycans, mainly syndecan and glypican, are linked to the cell membrane by a glycosylphosphatidylinositol anchor or a transmembrane protein domain.<sup>6</sup> On the other hand, glycoproteins are composed of a protein to which usually straight-chain oligosaccharides are covalently attached, usually consisting of several monosaccharide residues (N-acetylhexosamine, galactose or mannose). The major glycoproteins of the glycocalyx include selectins, integrins, and other adhesion molecules such as intercellular adhesion molecules 1 and 2, and thrombocyte/endothelial adhesives.<sup>7,8</sup> Additionally, other molecules are attached to the glycocalyx, including growth factors and their receptors, coagulation inhibitors, lipoprotein lipase and low-density lipoproteins, and plasma and extracellular matrix proteins.<sup>6</sup> Research by Kabedev and Lobaskin shows that changes in glycocalyx glycan density determine its resistance to slight deformation, which also prevents stress transfer to the cell membrane.<sup>9</sup>

The thickness of the glycocalyx layer also depends on the type of cell and the diameter of the vessels, but measurements with an atomic force microscope revealed that on the surface of the endothelium the structure is about 0.3–1  $\mu\text{m}$ .<sup>10</sup> Nevertheless, Ebong et al. using transmission electron microscopy observed that the glycocalyx on the surface of the endothelium lining the bovine aorta can be as much as 11  $\mu\text{m}$  thick.<sup>11</sup>

Pathological breakdown of glycocalyx occurs in response to many factors including mechanical cell stress, endotoxins, pro-inflammatory cytokines such as tumor

necrosis factor alpha, reactive oxygen species, and hyperglycemia.<sup>12,13</sup> Abnormalities in the structure and functioning of the glycocalyx underlie many diseases and disorders such as dry eyes disease, diabetes and its complications as well as sepsis.

## Aim

In this review, we present the current view on the role of glycocalyx in human diseases

## Material and methods

This review was performed according to latest literature from the following databases: EBSCO, PubMed, Science Direct, and Springer Link.

## Analysis of the literature

### *Dry eyes disease*

Dry eye disease is a common and multifactorial disease with a high prevalence worldwide. In the apical part of the eye epithelium there are microfolds covered with glycocalyx, whose main function is to increase the surface area. Glycocalyx protects the surface of epithelial cells against chemical and mechanical damage, and also prevents the penetration of pathogens into the eye, reduces friction during blinking and maintains the hydrophilic surface of the eye. Pathological mechanisms such as disruption of the glycocalyx barrier and decreased hydration of the ocular epithelial surface cause dry eye disease.<sup>14</sup>

Research indicates that transmembrane mucins and galectin-3 play a key role in the glycocalyx epithelial barrier and are essential for maintaining proper hydration of the eye epithelium. The very large glycans in transmembrane mucus are necessary to keep the eye surface wettable due to their very high water-holding capacity. Among them, three main mucins can be distinguished – MUC1, MUC4 and MUC16. *In vitro* studies show that MUC1 serves as an anti-adhesion and signaling molecule. In turn, MUC4 is involved in proliferation signaling by activating the ErbB2 tyrosine kinase receptor. MUC16, which is the largest membrane-bound mucin, plays a key role in the formation of the protective shell.<sup>15,16</sup> It has also been shown that the reduction or alteration of the chemical composition of the glycocalyx on the surface of the eye may be one of the factors contributing to the dryness of the eyes associated with the use of soft contact lenses.<sup>17</sup>

### *Diabetes and its complications*

One of the diseases in which the glycocalyx plays an important and confirmed role is diabetes. With this disease, there is a marked increase in the risk of developing vascular complications. Vascular complications developing on a micro and macro scale lead to a deterioration of the comfort and quality of life as well as a shortened life expectancy of patients.<sup>18</sup> An early symptom of dam-

age to blood vessels is an increase in their permeability, which results in the disruption of their physiological functions.<sup>19,20</sup> This leads to the onset of albuminuria and the development of cardiac complications.<sup>12</sup> Under physiological conditions, the glycocalyx protects cells from direct contact with blood. During hyperglycaemia, glycocalyx dysfunction occurs, which leads to its dysfunction and activation of the prothrombotic system.<sup>21</sup> In patients with type 1 diabetes, the volume of glycocalyx is reduced by 50% within 6h after induction of acute hyperglycaemia.<sup>22</sup> The loss of glycocalyx is directly related to the increase in the concentration of hyaluronidase what leads to increase in the plasma hyaluronan levels and promotion of endothelial dysfunction.<sup>23</sup> Moreover, hyperglycemia changes the phenotype of fibroblasts which are more elongated but less motile and less contractile than healthy dermal fibroblasts. It is caused by formation of larger focal adhesions stabilized by a glycocalyx as well as associated with increased expression of the cell surface glycoprotein MUC16.<sup>24</sup> Additionally, recent study by Wadowski et al. indicated that the loss of glycocalyx dimensions is correlated with increasing level of glycosylated hemoglobin.<sup>25</sup>

Research was conducted to confirm the hypothesis of possible beneficial effects that restoration of glycocalyx volume may have in the context of preventing the development of diabetes complications. It was examined whether there was a reduction in the amount of glycocalyx in patients with type 2 diabetes and whether oral administration of glycosaminoglycan precursors improved the activity of glycocalyx. Ten men with type 2 diabetes and ten control group were included in the study, in whom the level of glycocalyx was determined before and 2 months after the administration of one of GAGs – sulodexide at a dose of 200 mg/day. The conducted research has shown that in the case of patients with type 2 diabetes, the activity of glycocalyx in relation to healthy people was impaired. This group of patients also experienced an increase in vascular permeability (increased albuminuria).<sup>26</sup> GAGs such as sulodexide act at multiple levels: they promote glycocalyx reconstitution, control glycocalyx degrading enzymes, exert anti-inflammatory effects and have anti-apoptotic and anti-senescence effects on endothelial cells.<sup>27</sup>

The kidneys of people with diabetes are characterized by glomerular hypertrophy, thickening of the basement membrane, and damage to endothelial cells and glycocalyx. Even in the case of microalbuminuria, a reduced amount of glycocalyx and the enzyme heparinidase, responsible for the breakdown of GAGs, were engraved.<sup>28,29</sup>

The hyperglycemia present in diabetes causes the production of reactive oxygen species as well as vascular endothelial growth factor and angiotensin II.<sup>30,31</sup> These substances reduce the selectivity of the barrier as a result of the weakening of the action of superoxide dismutase, the function of which is the decomposition of the super-

oxide anion. Such oxidative stress damages the glycocalyx and impairs filtration.<sup>32</sup> As the disease progresses, the amount of protein in the urine increases – podocytes are damaged, and angiotensin II, along with increased glucose levels, weakens the production of proteoglycans by podocytes.<sup>33-35</sup> More and more active nephrons are lost, causing the remaining nephrons to become overloaded and hypertrophied, followed by interstitial tissue fibrosis and renal dysfunction.<sup>33</sup> As a result, anemia, secondary hyperparathyroidism, bone mineralization disorders, and soft tissue calcification appear.<sup>36</sup>

In improving the health of people with cardiovascular diseases, related to type II diabetes, exercise and a low-salt diet can help. This helps to maintain a “thick layer” of the endothelial glycocalyx which is important in preventing clotting.<sup>37</sup> With the increase of physical activity, increases heart rate, and the rate of blood flow in blood vessels. This favors the transport of Na<sup>+</sup> ions from the endothelial glycocalyx. Due to the action of electrostatic forces, the space between red blood cells, the glycocalyx of the endothelium, increases.<sup>38,39</sup> The charge of erythrocytes is negative, and along with the removal of sodium cations (supplied, among others, with NaCl salt) from the glycocalyx, the total charge is more negative and repulsion increases.<sup>40</sup>

### Sepsis

Sepsis is an ominous clinical manifestation of a severe generalized infection leading to systemic multiorgan sequelae such as hypotension, acute respiratory distress syndrome, renal failure, and lactic acidosis, among others. Glycocalyx is also used effectively as a biomarker for sepsis. During the initial development of sepsis, it is damaged.<sup>41,42</sup> The fact that the degradation of glycocalyx in sepsis prevails over increased synthesis of at least one of its components strongly favors its enhanced enzymatic degradation. It is carried out by sheddases, a disintegrin and metalloproteinases, matrix metalloproteinase, heparanase-1, and hyaluronidases.<sup>43-45</sup> As a result, the level of circulating glycocalyx components such as syndecans, heparan sulfates and hyaluronic acid increases. Their level is measured, on the basis of which the developing pathogenic process can be determined. Despite the accumulated knowledge regarding the important roles of the glycocalyx, the relationship between derangement of the endothelial glycocalyx and severity of sepsis has not been adequately elucidated.<sup>46</sup>

### Conclusion

Over the past two decades, glycocalyx has attracted more and more attention from scientists, and its role in health and disease has been intensively studied. However, despite the well-described pathological sequelae that follow glycocalyx damage, there are few reports of therapeutic strategies targeting impairment of the glycocalyx structure and function.

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