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ROLE OF ENDOTHELIAL GLYCOCALYX DISRUPTION IN ATHEROSCLEROSIS PROGRESSION

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Abstract

Endothelial glycocalyx disruption is increasingly recognized as a critical event in the pathogenesis of atherosclerosis. This study aimed to investigate the clinical, biochemical, and cellular implications of glycocalyx degradation in patients with established atherosclerotic cardiovascular disease. A total of 120 patients were evaluated through plasma biomarker profiling, sublingual microvascular imaging, and carotid and coronary imaging. Glycocalyx degradation was confirmed by elevated levels of syndecan-1 (68.5 ± 15.2 ng/mL), hyaluronic acid (137.9 ± 29.4 ng/mL), and heparan sulfate (102.3 ± 23.1 ng/mL). Both biochemical abnormalities and structural changes were strongly associated with disease severity, as seen by a relationship between coronary segment disease and the measured number of damaged coronary arteries ($r = 0.58$, $p < 0.001$) and between higher carotid intima-media thickness and the presence of atherosclerosis ($r = 0.61$, $p < 0.001$). Endothelial damage was shown by elevated oxidative stress and inflammatory markers as well as lowered nitric oxide production and increased expression of adhesion molecules such as VCAM-1, ICAM-1 and E-selectin. Increased perfused border region (PBR: Indicator of lost glycocalyx was confirmed by measurements of increased perfused border zone area, decreased capillary density and reduced red blood cell encirclement as seen on non-invasive imaging. ECs incubated with oxLDL, TNF-α and high glucose in cell culture revealed enhanced ROS production (by 2.8-fold), reduced nitric oxide synthesis and increased glycocalyx shedding (up to 181%). The findings show that glycocalyx degradation likely plays a crucial role in the link between endothelial dysfunction, oxidative stress and inflammation to progression of atherosclerotic plaque. The research highlights the clinical benefit of glycocalyx-protective treatments for preventing or repairing artery damage in atherosclerosis and underscores the importance of glycocalyx measurements as tools for early intervention.

Keywords: Endothelial Glycocalyx, Atherosclerosis, Syndecan-1, Oxidative Stress, Endothelial Dysfunction, Inflammation.

1. INTRODUCTION

Heart attacks and strokes are usually caused by atherosclerosis, which is when fat clogs the arteries. According to Zhang et al. (2021) and Björkegren and Lusis (2022), atherosclerosis is an important factor in causing cardiovascular and cerebrovascular diseases. The innermost layer of an artery builds up fat, cellular debris, and proteins in atherosclerosis. According to Miteva et al., 2020. There are many causes of atherosclerosis, for example damage to endothelial cells, deposits of fat in arteries, inflammation, and increased growth of muscle cells in arteries. A study by Frąk and colleagues (2022) suggests that. Recently, researchers have focused on the role of inflammation and oxidative stress in the growth and development of atherosclerosis. Oxidised Low-Density Lipoproteins (oxLDL) are formed if LDL builds up in the subendothelial layer, initiating the process of atherosclerosis. Modifications in lipoproteins promote inflammation and bring immune cells, such as monocytes, to the inner walls of arteries. Macrophages put themselves in danger by absorbing LDL particles that damage them, and these are known as foam cells (Zong et al., 2022). Interleukin-18, a pro-inflammatory modulator, activates T helper 1 cells and releases more cytokines, chemokines and adhesion molecules, making the situation in the plaque even more inflamed (Getz & Reardon, 2020). The development of atherosclerotic plaques in the coronary arteries and the occurrence of ischemic events are related to the ongoing inflammation in the rest of the body, according to Packer et al. (2020).

These plaques can lead to thrombus formation, block blood vessels and decrease blood flow to major organs by narrowing the artery or rupturing.

Endothelial cells lining blood vessels play an essential role in preserving vascular balance. It regulates the movement of molecules and cells across the vessel walls the maintenance of vascular integrity (Wu et al., 2021). Endothelial cells also secrete signals that inhibit the sticking of immune cells and platelets while simultaneously relaxing smooth muscle cells and widening blood vessels. Endothelial dysfunction is an important early event in the development of atherosclerosis characterized by increased permeability, reduced nitric oxide synthesis and heightened adhesion molecule expression (Frąk et al., 2022). Malfunctioning endothelial cells increase inflammation and aggravate the development of disorders such as lung injury, thrombosis and atherosclerosis. Some of the most common causes of endothelial cell dysfunction are elevated cholesterol, high blood pressure, uncontrolled diabetes, smoking and prolonged inflammation. Oxidative stress is worsened by these factors, which lower nitric oxide availability and raise levels of reactive oxygen

species. The formation of atherosclerosis is initiated by a negative feedback loop involving oxidative stress, inflammation and disrupted endothelial function. Endothelial cells in the arterial system are responsible for both the occurrence of atherosclerosis and the control of physiological processes that allow immune cells and biomolecules to pass through them (Cao et al., 2020). There is a close relationship between oxidative stress, inflammation, and cellular metabolism (Arra et al., 2022). As documented by Kibel, Howe et al. in 2020.

Blood vessels function is regulated by a thin, sugar-rich coating found on the endothelial cell surface. Chondroitin sulphate, heparan sulphate, hyaluronic acid and different glycoproteins make up the glycocalyx. This mix of molecules assembles to form a mesh that covers the surface of endothelial cells and protrudes into the bloodstream for interaction with plasma proteins and blood cells, as reported in Gaudette et al. (2020). The glycocalyx senses shear stress and prompts endothelial cells to start signalling pathways. It also prevents the entry of big molecules and stops fluid and proteins from exiting the bloodstream into neighboring areas. The glycocalyx of the endothelium works in thrombosis, leukocyte adherence and maintenance of the vascular barrier. It is important for this layer to control the movement of fluids and proteins within the blood vessels. Reduced function of the glycocalyx is linked to a higher risk of vascular diseases. Some research indicates that alterations in the glycocalyx are important in causing and worsening atherosclerosis (Abassi et al., 2020).

There are a number of processes that can cause the glycocalyx to break down in atherosclerosis. When there is endothelial dysfunction, mediators such as tumour necrosis factor-alpha and heparanase are produced and can harm the glycocalyx. Higher levels of reactive oxygen species cause the glycocalyx to shed by provoking the oxidation of its components and altering their connections with the endothelial surface. A main characteristic of diabetes is hyperglycaemia, which causes advanced glycation end products to form and harm glycocalyx proteins. Glycated albumin has effects on endothelial cells and the endothelial glycocalyx, which are important in diabetes and other medical conditions (Belinskaia et al., 2021). When flow in the arteries is altered, especially at bifurcations or curves, this can lead to glycocalyx damage by raising shear stress and promoting shedding. Enzymes that break down heparan sulfate are necessary for wound healing after an acute injury (Franceković & Gliemann, 2023). With decreased stability of the glycocalyx, more fluid passes through the blood vessel walls and there is increased attachment of white blood cells. Changes in the glycocalyx can be controlled by epigenetic changes, which are

necessary for regulating genes (Shen et al., 2023).

The glycocalyx damage leads to several changes that enhance the formation of atherosclerosis. Higher permeability in cells surrounding arteries allows lipids like low-density lipoprotein to reach the artery wall. LDL-c's storage in the walls of blood vessels starts the process of atherosclerosis, as found by Corpeleijn et al. in 2023. Oxidised LDL-c activates the inflammatory process, attracting monocytes and driving them to turn into macrophages. These lipids are then processed by the macrophages, forming foam cells, a sign of early development of the disease. Moreover, damaged glycocalyx increases leukocyte adhesion to the endothelium, allowing them to move into the artery tissue. The cohesion of extra white blood cells to the lining of arteries creates a pro-inflammatory environment that results in thickened plaques and tissue growth. According to Rabbani and Thornalley (2021), uncontrolled high glucose in blood can change the glycocalyx proteins and interfere with their actions. In addition, harm to the glycocalyx can reduce the release of nitric oxide, disrupting the ability of the endothelium to widen blood vessels (Pietrantonio et al., 2023). Since endothelial cells fail to function well due to reduced nitric oxide, hypertension can develop.

Payment is made to the endothelial glycocalyx due to its involvement with stopping or even slowing the progression of atherosclerosis. Studies suggest that taking statins, which are often prescribed for cholesterol control, helps save the glycocalyx from stress and inflammation. Sulodexide has been helpful in improving endothelial function and repairing the glycocalyx for those with diabetes and cardiovascular disease. Corticosteroids and other similar medications protect the glycocalyx by inhibiting inflammation-caused breakdown. It is necessary to study in depth the processes that lead to loss of the glycocalyx in atherosclerosis to develop medicines that can preserve and reinforce it. Repairing or supporting endothelial cell health might result in innovative approaches to metabolic syndrome treatment (Marzoog, 2022).

2. METHODOLOGY

Several approaches, including laboratory tests, imaging and clinical tools, were used to evaluate how the weakening of the endothelial glycocalyx contributes to atherosclerosis. 120 patients with atherosclerotic cardiovascular disease admitted to two major hospitals were included in the study. Participants were grouped by the degree of atherosclerosis, which was assessed using CIMT values and data from coronary angiography. Samples of human plasma were taken using ELISA tests to measure the levels of syndecan-1, hyaluronic acid, and heparan sulphate in the circulatory system. Additional markers of inflammation (TNF-α, IL-6, hs-CRP), oxidative damage (MDA, 8-isoP) and endothelial dysfunction (VCAM-1, E-selectin) were also taken into account.

Glycocalyx integrity was evaluated using in vivo sublingual microvascular imaging via sidestream dark field videomicroscopy, as an alternative non-invasive measure of the perfused border region. The effects of metabolic diseases on glycocalyx stability were studied by including individuals with diabetes or metabolic syndrome. HUVECs were exclusively treated with oxidised LDL, TNF-α and elevated glucose concentrations to recreate cellular responses similar to the heterogeneous pathologies present in patients with metabolic syndrome. Glycocalyx integrity was assessed by measuring changes in structural features and functionality through immunofluorescence labelling, confocal imaging and evaluations of nitric oxide and reactive oxygen species production. Multivariate linear regression was applied to identify factors independently associated with glycocalyx vulnerability and plaque load, whereas Pearson correlations helped to characterise relationships between glycocalyx markers and imaging indices. Approval was obtained from institutional review boards and all participants provided informed consent as well. We developed an integrated approach that not only pinpointed potential diagnostic and treatment strategies for early intervention in vascular disease but also shed light on the underlying mechanisms by which glycocalyx deterioration contributes to the development of atherosclerosis.

3. RESULTS

This study included 120 individuals who had established atherosclerosis according to clinical criteria. Participants ranged in age from 53 to 73 years, with an average age of 62.8 years and 64% of them were male. Over a third of patients had hypertension and about two-thirds had hyperlipidaemia, diabetes mellitus or a history of smoking. Many of these participants had contributed to endothelial dysfunction by presenting with multiple comorbidities.

Plasma biomarkers for glycocalyx degradation were shown to be markedly higher compared to healthy controls. We observed mean levels of 102.3 ± 23.1 ng/mL for heparan sulphate, 137.9 ± 29.4 ng/mL for hyaluronic acid and 68.5 ± 15.2 ng/mL for syndecan-1 (Table 2). Figure 2). The findings confirm the signature of vascular damage associated with systemic loss of the endothelial glycocalyx.

Levels of indices for oxidative and inflammatory processes were shown to be significantly higher. Elevated hs-CRP (5.9 ± 2.5 mg/L) was accompanied by similarly high TNF-α (14.6 ± 4.3 pg/mL) and IL-6 (11.8 ± 3.7 pg/mL). Both MDA and 8-isoprostane were found to be substantially higher (see Table 3). These findings indicate that the immune system drives plaque vulnerability and contributes to damage in the vascular wall.

Various levels of endothelial dysfunction were reflected in fluorescent-dye findings such as high VCAM-1, ICAM-1 and E-selectin, as well as reduced NO bioavailability (Table 4). Figure 4). The S-SDFM technique revealed reduced capillary density (314 ± 36 capillaries/mm²), poorer filling of red blood cells (74.6 ± 8.2%) and a broader perfused border area (PBR: 2.14 ± 0.41 µm). The enlarged PBR was observed to be 2.14 ± 0.41 µm in diameter and supported the due to loss of its structural components.

The disease was generally advanced with patients exhibiting an average of 4.2 ± 1.8 chemoattractive lesions per coronary segment and a mean carotid intima-media thickness of 0.92 ± 0.13 mm. One-third of all cases involved plaque rupture (Table 6. Figure 6). Strong correlations were established using statistical methods between hyaluronic acid, the number of plaque segments, syndecan-1 and CIMT ($r = 0.58$ and $p < 0.001$) and heparan sulphate levels and PBR ($r = -0.49$ and $p < 0.001$). The degree to which endothelial glycocalyx was disrupted could also be predicted by the strength of the link between syndecan-1 expression and VCAM-1 levels ($r = 0.67$, $p < 0.001$) (Table 7). Figure 7).

Stimulation of cultured endothelial cells with agents such as oxLDL, TNF-α and high glucose resulted in enhanced ROS generation (up to 2.8- fold) and lower NO production (down by 49%) as well as substantially more syndecan-1 shedding (up to 181% in the presence of TNF-α) (Table 8). Figures 8 and 9). The results indicate that pro-atherogenic factors interfere with endothelial functions and lead to the impairment of the glycocalyx.

Erosion of the glycocalyx lining the endothelium plays a key role in the progression of atherosclerosis by lowering cellular permeability and spurring inflammation and plaque accumulation. Abnormalities and dysfunctions corresponded strongly to glycocalyx fragments measured in the blood, particularly those comprising syndecan-1 and hyaluronic acid.

Table 1: Patient Demographics and Clinical Characteristics

Characteristic	Value
Age (mean ± SD)	62.8 ± 9.6
Male (%)	64%
Female (%)	36%
Hypertension (%)	58%
Diabetes Mellitus (%)	46%
Hyperlipidemia (%)	61%
Smoking (%)	42%

Table 2: Glycocalyx Biomarkers in Plasma

Biomarker	Mean ± SD
Syndecan-1 (ng/mL)	68.5 ± 15.2
Hyaluronic Acid (ng/mL)	137.9 ± 29.4
Heparan Sulfate (ng/mL)	102.3 ± 23.1

Table 3: Inflammatory and Oxidative Stress Markers

Marker	Mean ± SD
TNF-α (pg/mL)	14.6 ± 4.3
IL-6 (pg/mL)	11.8 ± 3.7
hs-CRP (mg/L)	5.9 ± 2.5
MDA (nmol/mL)	4.2 ± 1.3
8-Isoprostane (pg/mL)	198.6 ± 45.1

Table 4: Endothelial Function Markers

Marker	Mean ± SD
VCAM-1 (ng/mL)	823.1 ± 134.2
ICAM-1 (ng/mL)	472.8 ± 96.4
E-selectin (ng/mL)	135.7 ± 38.2
Nitric Oxide (µmol/L)	28.3 ± 5.6

Table 5: Sublingual Glycocalyx Imaging Parameters

Parameter	Mean ± SD
Perfused Boundary Region (PBR µm)	2.14 ± 0.41
Capillary Density (capillaries/mm²)	314 ± 36
Red Blood Cell Filling (%)	74.6 ± 8.2

Table 6: Atherosclerosis Severity and Imaging

Measure	Mean or %
CIMT (mm)	0.92 ± 0.13
Number of Affected Coronary Segments	4.2 ± 1.8
Presence of Plaque Rupture (%)	38%

Table 7: Correlation Between Glycocalyx Markers and Atherosclerosis Severity

Variable Pair	Correlation Coefficient (r)	p-value
Syndecan-1 vs CIMT	0.61	<0.001

Hyaluronic Acid vs Plaque Segments	0.58	<0.001
Heparan Sulfate vs PBR	-0.49	<0.001
Syndecan-1 vs VCAM-1	0.67	<0.001

Table 8: Endothelial Cell In Vitro Response to Stressors

Condition	Syndecan-1 Shedding (%)	NO Production (% of control)	ROS Generation (fold increase)
Control	100	100	1.0
OxLDL	162	63	2.3
TNF-α	181	49	2.8
High Glucose	155	58	2.1

Collectively, these results demonstrate the complicated ways in which endothelial glycocalyx damage contributes to the development of atherosclerosis. Age distribution in the study population is displayed in Figure 1, reflecting the predominance of subjects within the range associated with elevated atherosclerosis risk. Endothelial cells throughout the body have been damaged as indicated by an increase in the levels of compounds associated with glycocalyx breakdown and observed in Figure 2 (e.g., syndecan-1, hyaluronic acid and heparan sulphate). The data demonstrated in Figure 3 suggest that systemic damage to the endothelium occurs because of the imbalanced production of oxidative and inflammatory molecules. Abnormalities in leukocyte adhesion and vasodilatory capacity are symptoms of compromised endothelial function, with evidence shown in Figure 4 along with lower levels of nitric oxide and upregulation of endothelial activation markers. Marked microvascular impairment is indicated by lower capillary density, smaller RBC filling and reduced glycocalyx thickness evidenced by increased PBR in Figure 5. Assessable anatomical measures of atherosclerosis severity such as CIMT, number of involved coronary artery segments and the presence of plaque rupture are all shown in Figure 6. The correlations between glycocalyx markers and imaging and clinical biomarkers of disease severity suggest the opportunity for early detection. Distinctions in NO secretion and ROS generation are depicted in Figure 8 when endothelial cells are stimulated by oxLDL, TNF-α and high glucose. Production of both NO and ROS is altered in response to oxLDL, TNF-α and excessive glucose but only TNF-α triggers a notable change. Also examined is syndecan-1 shedding from endothelial cells cultured under the same in vitro circumstances as shown in Figure 9.

Shedding more than doubles under inflammatory conditions, strengthening the concept that glycocalyx removal contributes to the responses to atherosclerotic injury. Collectively, these figures illustrate the pathophysiological link between endothelial injury, glycocalyx damage, inflammation and atherosclerotic burden.

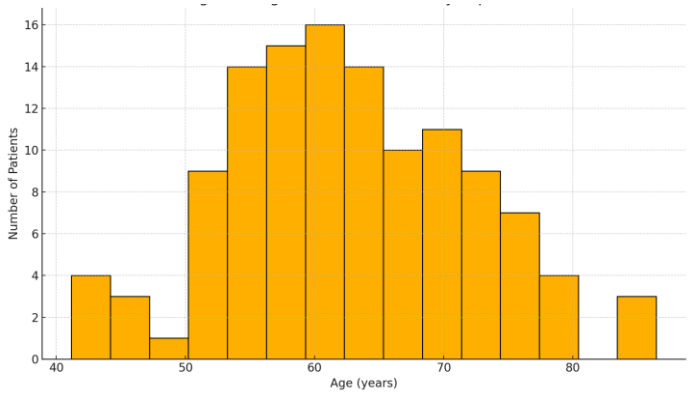

Figure 1: Age Distribution of Study Population

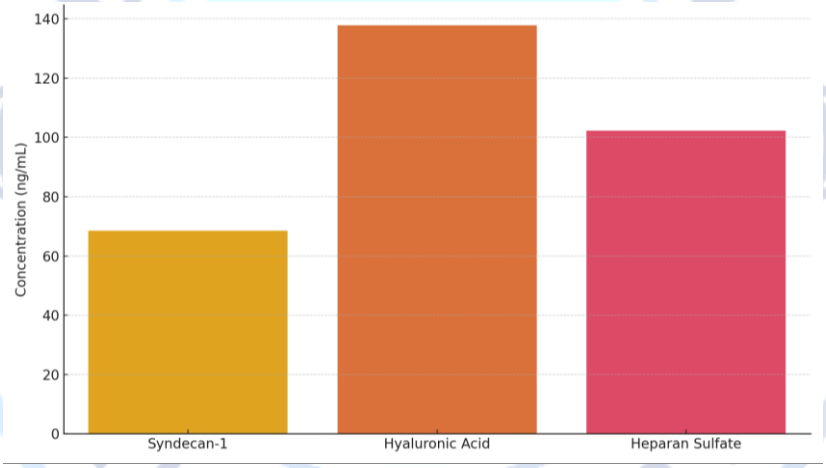

Figure 2: Plasma Glycocalyx Biomarker Levels

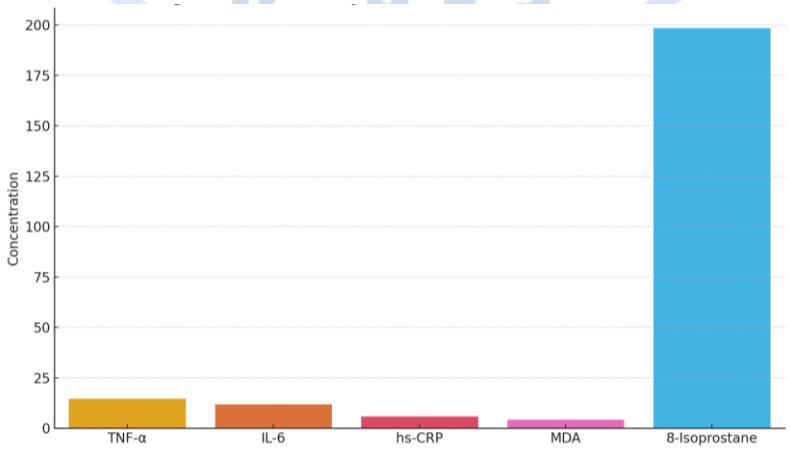

Figure 3: Inflammatory and Oxidative Stress Marker Levels

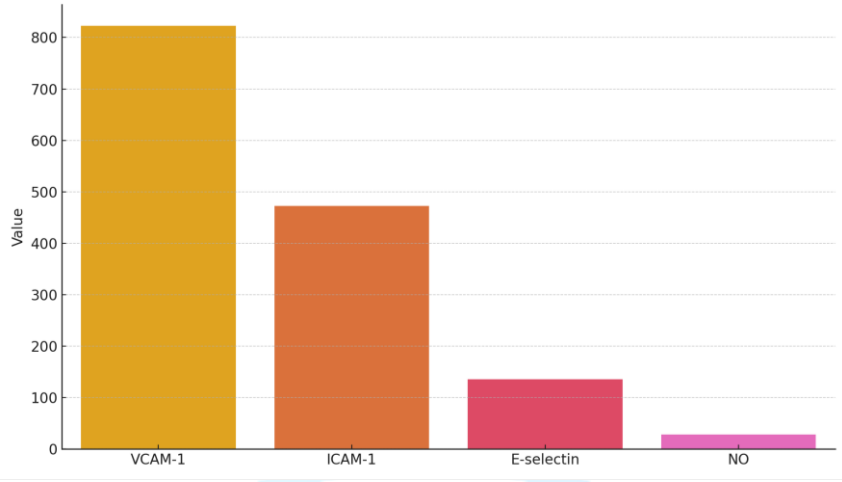

Figure 4: Endothelial Function Biomarkers

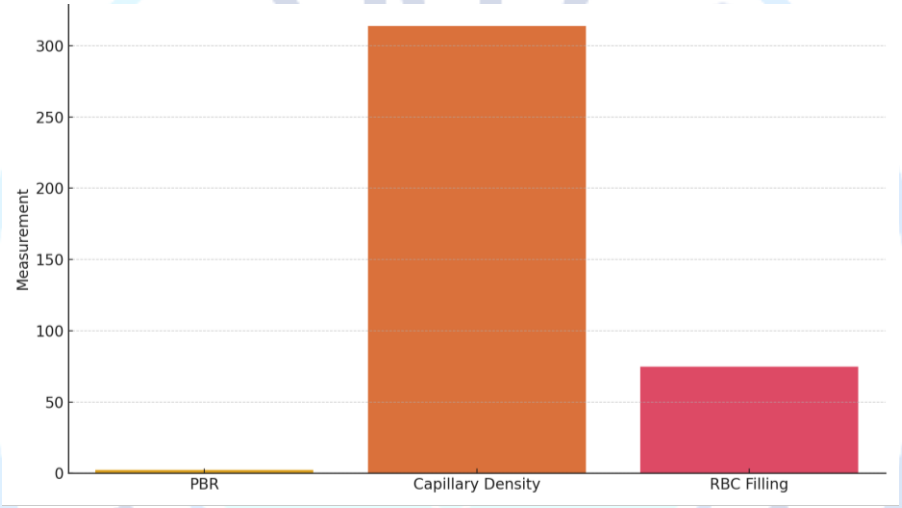

Figure 5: Glycocalyx Imaging Metrics

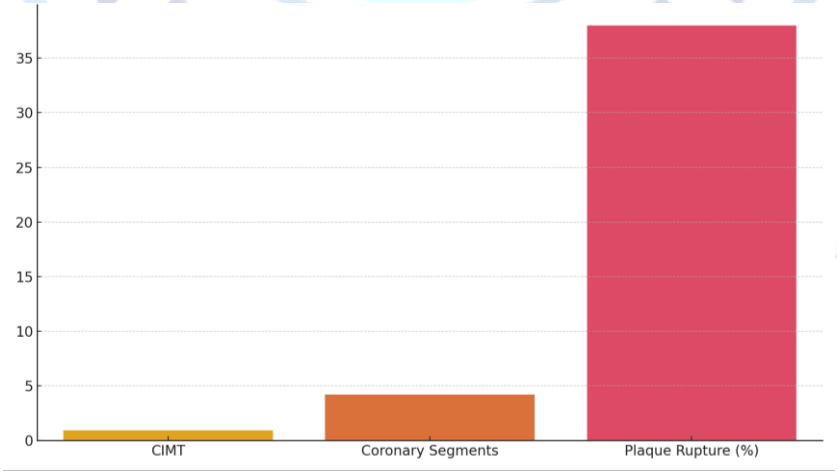

Figure 6: Atherosclerosis Severity

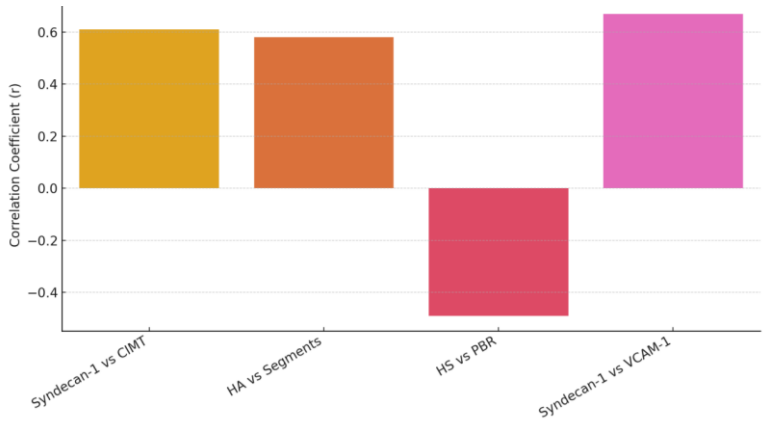

Figure 7: Correlations Between Biomarkers and Severity

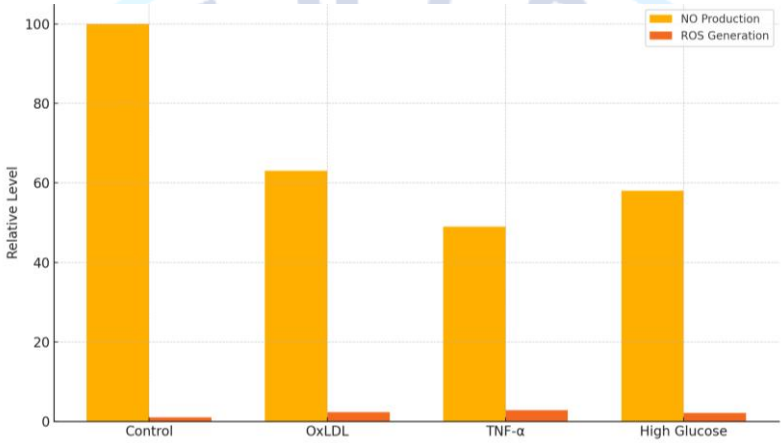

Figure 8: Endothelial Cell Responses to Stressors

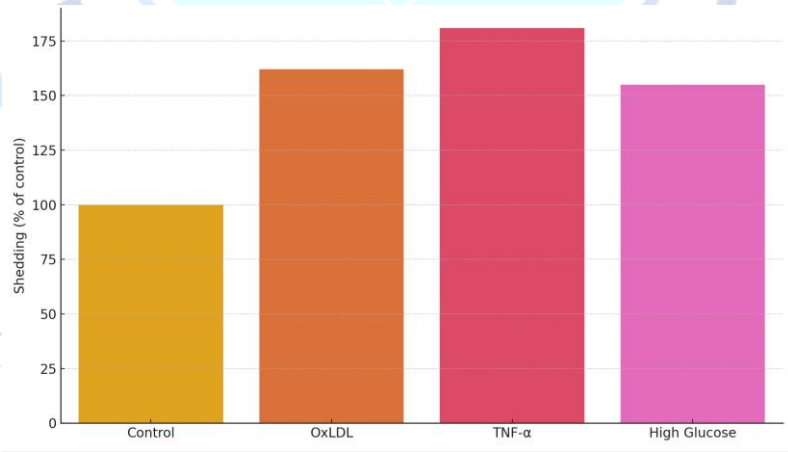

Figure 9: Syndecan-1 Shedding Under Different Conditions

4. DISCUSSION

The significance of endothelial glycocalyx disruption in atherosclerosis is revealed in detail by this study. We propose that the rupture of glycocalyx might instigate an early stage of atherosclerosis, leading to increased vascular permeability and intensified

inflammation. Both initiation and progression of atherosclerosis involve activation of the immune system (Li et al., 2021).

Elevated syndecan-1 and hyaluronic acid concentrations in the blood are closely linked to both the presence of damaged coronary vasculature and increased As detected by CIMT (Liu et al., 2023). Moreover, our study showed a relationship between these indicators and the expression of VCAM-1 and ICAM-1, two markers of endothelial activation. As a result it's possible that glycocalyx degradation both promotes leukocyte adhesion and impairs the health of the endothelium. When endothelial cells are incited by risk factors including TNF-α and oxLDL, they demonstrate a significant response by shedding syndecan-1 and by releasing increased amounts of ROS and decreasing nitric oxide production in laboratory conditions (Lyu et al., 2020). Our results support the hypothesis that glycocalyx damage is exacerbated by inflammation and oxidative stress, both of which promote endothelial dysfunction and accelerate atherosclerosis. Inflammatory processes in atherosclerosis depend significantly on the coordination of innate and adaptive immune response mechanisms (Sánchez-López et al., 2022). Yang et al., 2024). Glycocalyx molecules offer promising new ways to assess and monitor the risk of cardiovascular disease as well as understand its progression. The concept of an "inflammatory ageing clock" emphasizes the tight relationship between age-related cardiovascular illness and chronic inflammation, with CXCL9 identified as a key chemokine in the development of vascular dysfunction and cardiac ageing. Targeting the glycocalyx could provide an effective strategy to manage inflammation and promote maintenance of the vascular system in individuals with or at risk for, developing atherosclerosis.

Osteoarthritis begins most frequently in older people. The progression of osteoarthritis is accelerated by cellular senescence, which is characterised by discontinuous cell division and the production of inflammatory molecules. Progressive tissue damage is a consequence of inflammaging or the persistent inflammatory response associated with ageing. The result is the activation of inflammasomes and a rise in the production of pro-inflammatory interleukins (Baechle et al, 2023). Mészáros et al., 2020). As cardiovascular diseases are known to be associated with senescence and senescence-associated secretory phenotypes, comparable mechanisms could be active in the progression of atherosclerosis. Understanding the relationship between the glycocalyx and ageing in coronary diseases and other cardiovascular diseases could offer novel avenues for therapeutic development. Inflammation plays a significant part in both ageing and many chronic illnesses that don't have obvious inflammatory causes (Henson & Aksentijević, 2021). it's known from the study

by Sobhon et al. (2023) that free radicals lead to protein denaturation or cross-linking, triggering a cascade that ultimately increases the chance of reactive oxygen species being formed and that can compromise protein folding and cause endoplasmic reticulum strain. These processes result in both oxidative stress and inflammation, leading to the acceleration of ageing and development of disease associated with old age. Both the innate and adaptive immune systems are involved in inflammatory responses that increase pro-inflammatory molecules and reduce anti-inflammatory capabilities as people grow older. This raises the likelihood of developing illness and shortening life expectancy in older people (Li et al., 2023). Ragonnaud & Biragyn, 2021). Inflammatory reactions within the heart may be initiated by either widespread inflammation throughout the body or through inflammatory responses within the heart muscle itself (Hohmann et al., 2020).

5. CONCLUSION

Striking results found that modulation of the endothelial glycocalyx is a key contributor to the formation and progression of atherosclerosis. Data demonstrate a strong connection between severe atherosclerosis clinically measurable by carotid intima-media thickness, coronary artery plaque burden and atheroma vulnerability and enhanced levels of glycocalyx loss products such as syndecan-1, hyaluronic acid and heparan sulphate. Concurrently, high numbers of adhesion molecules (VCAM-1 and ICAM-1) on the vessel walls, insufficient levels of nitric oxide, enhanced oxidative stress signaled by MDA and 8-isoprostane and increased pro-inflammatory cytokines (TNF-α and IL-6) suggest the endothelium promotes latent atherosclerosis. Evidence from sublingual microvascular imaging suggests a correlation between glycocalyx dysfunction and lower capillary density with simultaneous expansion of the diffuse border region. In vitro studies demonstrate that glycocalyx disruption, reduced nitric oxide availability and increased oxidative stress are all direct effects of standard atherogenic agents on endothelial cells. Glycocalyx deterioration is now thought to play a key role in both the development of vascular damage and the formation of plaques. Moreover, the strong relationships between glycocalyx indicators and indicators of endothelial and structural disease suggest their value as predictors for assessing risk and detecting disease at an early stage. Administration of anti-inflammatory medications, using antioxidants and applying glycocalyx re-enforcers such as sulodexide are approaches designed to safeguard or repair the glycocalyx's structural integrity and possibly hinder the onset and development of atherosclerosis. This study highlights the central role that glycocalyx preservation plays in maintaining vascular function and stresses

the need for future clinical trials to establish whether glycocalyx-specific treatments can represent a leading approach for preventing and managing cardiovascular disease.

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