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Review Article

The potential involvement of glycocalyx disruption in abdominal aortic aneurysm pathogenesis ☆

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ABSTRACT

Background: Abdominal aortic aneurysm is a weakening and expansion of the abdominal aorta. Currently, there is no drug treatment to limit abdominal aortic aneurysm growth. The glycocalyx is the outermost layer of the cell surface, mainly composed of glycosaminoglycans and proteoglycans.
Objective: The aim of this review was to identify a potential relationship between glycocalyx disruption and abdominal aortic aneurysm pathogenesis.
Methods: A narrative review of relevant published research was conducted.
Results: Glycocalyx disruption has been reported to enhance vascular permeability, impair immune responses, dysregulate endothelial function, promote extracellular matrix remodeling and modulate mechanotransduction. All these effects are implicated in abdominal aortic aneurysm pathogenesis. Glycocalyx disruption promotes inflammation through exposure of adhesion molecules and release of proinflammatory mediators. Glycocalyx disruption affects how the endothelium responds to shear stress by reducing nitric oxide availabilty and adversely affecting the storage and release of several antioxidants, growth factors, and antithromotic proteins. These changes exacerbate oxidative stress, stimulate vascular smooth muscle cell dysfunction, and promote thrombosis, all effects implicated in abdominal aortic aneurysm pathogenesis. Deficiency of key component of the glycocalyx, such as syndecan-4, were reported to promote aneurysm formation and rupture in the angiotensin-II and calcium chloride induced mouse models of abdominal aortic aneurysm.
Conclusion: This review provides a summary of past research which suggests that glycocalyx disruption may play a role in abdominal aortic aneurysm pathogenesis. Further research is needed to establish a causal link between glycocalyx disruption and abdominal aortic aneurysm development.

1. Introduction

Abdominal aortic aneurysm (AAA) is a condition characterized by the weakening and expansion of the abdominal aorta and currently there are no established drug therapies to limit AAA growth or rupture [1–3]. The only current treatment for AAA is surgical repair [1]. Open surgical repair involves dissecting out the aneurysm neck and the distal arteries, temporarily clamping these vessels and replacing the weakened aneurysm sac with a prosthetic graft [1]. This major operation has a perioperative mortality of 2 to 5% and can be associated with other major complications [1,4]. The more modern minimally invasive surgical method involves endovascular repair, whereby covered stents are placed percutaneously from the groin inside the weakening aorta [5]. Endovascular aneurysm repair aims for blood flow to occur through the stent grafts and not leak into the remaining aneurysm sac [5]. Unfortunately in approximately 20% of patients blood continues to leak into the aneurysm sac after endovascular repair and this can lead to continued aneurysm expansion and later rupture [2,5]. Previous randomized controlled trials indicate that neither open nor endovascular AAA repair reduces mortality in people with small aneurysms (<55 mm) [6,7]. Thus, patients with

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small AAA (<55 mm men; <50 mm women) are simply monitored by imaging surveillance and surgery is only indicated if patients become symptomatic or the aneurysm expands to ≥55 mm in men and ≥50 mm in women [8]. Due to continued aneurysm growth, however, up to 70% of small aneurysms ultimately undergo surgical repair and thus drug therapies are needed to limit AAA growth and reduce the risk of AAA rupture [9]. Surveys of patients and health professionals indicate that the absence of drugs to limit AAA growth and shrink the aneurysm is their number one research priority [10,11]. The lack of treatment options negatively impacts patients with small AAAs or those who are unfit for surgery [1,9]. Collaborative research across multiple disciplines in the past three decades has significantly advanced the understanding of aneurysm development, suggesting that alterations in hemodynamic stress and aberrant vascular remodeling are significant factors in the development and progression of AAA [2–4,12,13]. AAA development involves upregulation of adhesion molecules and chemokines, inflammatory cell infiltration, vascular smooth muscle cells (VSMC) apoptosis, oxidative stress, extracellular matrix (ECM) remodeling, angiogenesis, and intraluminal thrombus formation [2–4,12,13]. This article focuses on the potential role of dysfunction of the glycocalyx (GC) in AAA pathogenesis.

2. Glycocalyx physiology

The GC is a dynamic brush-like coating on the surface of mammalian cells and is mainly composed of glycoproteins and glycolipids [14–18]. The endothelial GC (eGC) is a proteoglycan complex, composed of core proteins called syndecans and glypicans in addition to polymers of glycosaminoglycans (GAGs), such as heparan sulfate (HS), chondroitin sulfate (CS), and hyaluronans (HA) [14–18]. The eGC covers the luminal surface of the endothelial cell (EC) layer and maintains vascular permeability [14–18]. Various enzymes, such as superoxide dismutase, xanthine oxidoreductase and lipoprotein lipase, and coagulation inhibitors like antithrombin III and several growth factors, are stored and regulated by the GC [14–18]. The eGC acts as a potent mechanosensor by transducing blood flow stimulated shear stress to the cytoskeleton within EC and regulating nitric oxide (NO) dependent vascular functions [16,17]. Local microenvironment influences the interactions between GAGs and proteins, while composition and characteristics of GAGs are actively controlled by EC through continuous metabolic turnover [14–20]. Therefore, an intact eGC acts to inhibit thrombosis, inflammation, and atherosclerosis.

Endothelial GC disruption can be prompted by hemodynamic stress, proinflammatory mediators, and matrix degradation, stimulated by matrix metalloproteinases (MMPs), heparanase, hyaluronidase, lipopolysaccharide, and serine proteases, such as thrombin [16–28]. GC degradation can lead to release of mutually interconnected mediators that may create a self-perpetuating cycle of endothelial dysfunction and GC disruption [16–18]. The properties of the GC components have divergent characteristics depending on whether they are membrane bound or degraded into fragments [16,20,28]. The intact GC has anti-inflammatory properties while in contrast degraded fragments promote inflammation and endothelial dysfunction [16,17,20,28].

3. Potential association of glycocalyx disruption and abdominal aortic aneurysm

Evidence for a potential role of GC disruption in AAA pathogenesis comes from the findings of several previous studies summarized in Table 1 [30,33–37]. Examination of human AAA samples has suggested substantial changes in the GC in aneurysm tissue as compared to abdominal aortic samples from individuals with no AAA [29,30]. These differences include reduced content of HS, CS, and HA in the GC within human AAA tissue compared to normal aortic samples [28]. Syndecans play a key role in regulating several vascular functions, while their expression and shedding is associated with vascular inflammation [18,20,25,31–35]. Chronically accelerated syndecan-1 shedding has been suggested to generate a sustained proinflammatory and proteolytic environment which promotes AAA formation in the angiotensin II-induced mouse model [33]. In contrast, syndecan-2 has been reported to be abundantly expressed in the later stages of angiotensin II-induced AAA and was suggested to be a component of the reparative process aimed to maintain vascular integrity [33]. Syndecan-1 deficiency has been reported to promote AAA formation in both the elastase perfusion and angiotensin II-induced mouse models [34]. Aneurysms were reported to have marked protease activity, inflammatory cell infiltration and elastin degradation in both mouse models [34]. Downregulation in the expression of syndecan-4 has also been reported in both human AAA samples and a mouse model of AAA [35]. Deficiency in syndecan-4 has been reported to promote angiotensin II-induced AAA formation and rupture, possibly by transforming VSMCs to a synthetic phenotype [35]. Degradation of other components of the GC has also been implicated in AAA pathogenesis in rodent models [36,37]. Inhibition of hyaluronidase has been reported to inhibit calcium chloride ($CaCl_2$)-induced AAA formation in mice [36]. While HA fragmentation has been reported in samples from $CaCl_2$-induced AAAs and implicated in stimulating cluster of differentiation 44-driven inflammation [36]. HS levels have been reported to be low, while expression of heparanase has been found to be high within human AAA samples as compared with control aortic tissue [37]. It should be noted that the previous research summarized above focuses on components of the GC but these proteins are also expressed in other tissues and thus it remains unclear whether disruption of the GC specifically is involved in AAA pathogenesis [15–20].

In order to be confident of a role of GC damage in AAA pathogenesis, it would be ideal to investigate the effect of GC disruption specifically, but currently techniques to achieve this are unclear. Furthermore, it is acknowledged the human studies outlined above were performed in tissue samples from large AAAs, so the findings may be attributable to the secondary effects of vascular remodeling rather than causal in the initiation of AAA development. The animal models of AAA have a number of limitations [38]. For example, the $CaCl_2$ model has limited aortic expansion which usually occurs over 2 weeks after induction and this model does not exhibit aortic rupture typical of human AAA [38]. The angiotensin II model simulates aortic dissection and false rather than true aneurysm formation found in human AAA [38]. Aortic expansion is limited to approximately 4 weeks in the elastase model and aortic rupture does not occur [38]. The β-aminopropionitrile fumarate-elastase model holds promise in better simulating human AAA pathology and aneurysm growth but has not been the focus of GC studies as yet [38]. Future research using other animal models may provide outcomes with greater relevance to human AAA.

Important risk factors for human AAA, include hypertension, smoking, dyslipidemia, advanced age and obesity, which have also been implicated in GC damage [39–42]. These risk factors could possibly contribute to the GC disintegration which subsequently affects the vascular integrity of the abdominal aorta, as highlighted in Table 2 [43–48]. The relationship between these overlapping risk factors, GC disintegration and AAA development requires further investigation.

Human observational and animal model studies suggest that metformin limits growth of AAA, although this needs to be confirmed in randomized clinical trials [49]. It is possible that metformin may act to maintain GC integrity but this has not been investigated as yet [50].

Table 1
Association of glycocalyx disruption with mechanisms implicated in abdominal aortic aneurysm pathogenesis.

Samples/model used	Study aims	Findings	References
Human AAA tissues and control normal aortic samples	GAGs characterization	GAGs (HA, HS, CS) content in AAA was reduced as compared to normal aortic samples	[30]
Ang-II AAA model in ApoE knockout mice Human AAA tissue	Analysis of syndecans expression	Accelerated syndecan-1 shedding is associated with inflammatory responses and proteolytic activities. Syndecan-2 was expressed in the later stages of AAA as a reparative process	[33]
Ang-II and elastase perfusion model in ApoE/syndecan-1 deficient double knockout mice	Investigation of the effect of syndecan-1 deficiency	Syndecan-1 deficiency promoted AAA formation in both the elastase and Ang-II mouse models. Syndecan-1 deficient macrophages contributed to AAA severity	[34]
Human AAA tissue Ang-II AAA model in ApoE and syndecan-4 double knockout mice	Investigation of the effect of syndecan-4 deficiency	Syndecan-4 downregulated in human AAA samples. In an experimental mice model, syndecan-4 deficiency promoted AAA formation and rupture. Syndecan-4 deficiency led to transformation of VSMCs from a contractile to a synthetic phenotype	[35]
$CaCl_2$ AAA mice model	Investigate effect of hyaluronidase inhibitor	Inhibition of hyaluronidase suppressed AAA progression	[36]
Human AAA and normal aorta tissue	Characterization of HS and heparanase	HS levels reduced but heparanase levels increased in AAA compared to normal aortic samples. Heparanase proposed to have a role in AAA formation via ECM degradation	[37]

AAA, abdominal aortic aneurysm; Ang-II, angiotensin II; ApoE, apolipoprotein E; $CaCl_2$, calcium chloride; CS, chondroitin sulfate; ECM, extracellular matrix; GAGs, glycosaminoglycan; HA, hyaluronic acid; HS, heparan sulfate; VSMCs, vascular smooth muscle cells.

Table 2
Risk factors overlapping between glycocalyx disruption and abdominal aortic aneurysm pathogenesis.

Risk factor	Study investigation	Findings	References
Hypertension	Evaluation of GC damage using cationized ferritin binding analysis on capillary EC in the hypothalamus of SHR	Damage to the GC was identified in brain slices. GC damage was responsible for hypertension-induced blood brain barrier dysfunction	[43]
Atherogenesis	Examination of the GC in the carotid arteries of ApoE*3-Leiden mice fed with an atherogenic diet	GC thickness decreased at sites prone to atherogenesis	[44]
Smoking	Investigation of GC restoration during a 3-month smoking cessation program involving 188 current smokers randomized to varenicline or nicotine replacement therapy	Smoking cessation therapy resulted in restoration of GC	[45]
Hyperuricemia	Investigation of GC shedding in oxonic rich diet-induced hyperuricemic rats and cultured human umbilical vein EC	Uric acid induced EndoMT in cultured EC via ROS generation and GC shedding. Uric acid promoted EC phenotypic switch through oxidative stress and GC shedding	[46]
Advanced age	Investigation of GC thickness in - young and old mice - human sublingual microvasculature	GC thickness was decreased in older age. Microvascular dysfunction associated with advanced age may accelerate the risk of CVD	[47]
Obesity	Investigation of GC damage in skeletal muscle using high-fat diet induced obese mice	Early GC damage and glucose intolerance in mouse model suggests a potential link between GC and impaired insulin action in obesity	[48]

ApoE, apolipoprotein E; CVD, cardiovascular disorders, GC, glycocalyx; EC, endothelial cell; EndoMT, endothelial-to-mesenchymal transition; ROS, reactive oxygen species; SHR, spontaneously hypertensive rats.

The primary biomarkers for GC integrity include fragments of syndecans, HS, HA, and CS [15–20]. Elevated levels of shed HS, HA, CS, and syndecans may signify GC disruption, which could also be observed in AAA patients and used as biomarkers [15–20]. However, larger rigorously designed biomarker studies are needed in which findings are validated in multiple cohorts, assay methods used are reproducible and adjustment for confounding factors is included [16].

3.1. Glycocalyx disruption may aggravate vascular inflammation

Vascular inflammation has been proposed to play a key role in AAA pathogenesis [2–4,12,13]. An early event in vascular inflammation is leukocyte tethering to endothelial adhesion molecules [12,20]. Under physiological conditions, the GC shields adhesion molecules within its framework, acting as protective barrier limiting exposure of the adhesion molecules to leukocytes, as shown in Fig. 1 [14–21].

The GC stores and regulates several enzymes, chemokines, and cytokines, and thus GC degradation can induce dysregulation of these bioactive molecules [16–20]. GC disruption is regarded as an initial step in inflammation by exposing adhesion molecules promoting platelet and leukocyte tethering to the endothelium and releasing pro-inflammatory cytokines (Fig. 1) [16–20,28,51].

HS acts as a ligand for L-selectin that is responsible for regulating leukocyte rolling [18–20,52]. In a study in which wounds were induced in diabetic rats, HS downregulated the nucleotide-binding domain, leucine-rich repeat containing protein 3 (NLRP3) inflammasome mediated immune response [53]. Similarly, HA in its polymerized state of high molecular weight-HA possesses anti-inflammatory properties as it regulates cluster of differentiation 44 receptor interactions and limits immune cell infiltration [20,36]. In an osteoarthritis murine model, high molecular weight-HA downregulated Toll-like receptor (TLR)-mediated immune response and reduced levels of proinflammatory cytokines and MMPs [54]. CS has also been reported to limit tumor necrosis factor-alpha-induced EC and monocyte activation and reduce proinflammatory mediator release in obese mice and human cells *in vitro* [55]. Syndecans exhibit protective properties against inflammation by binding and regulating several ligands, including cy-

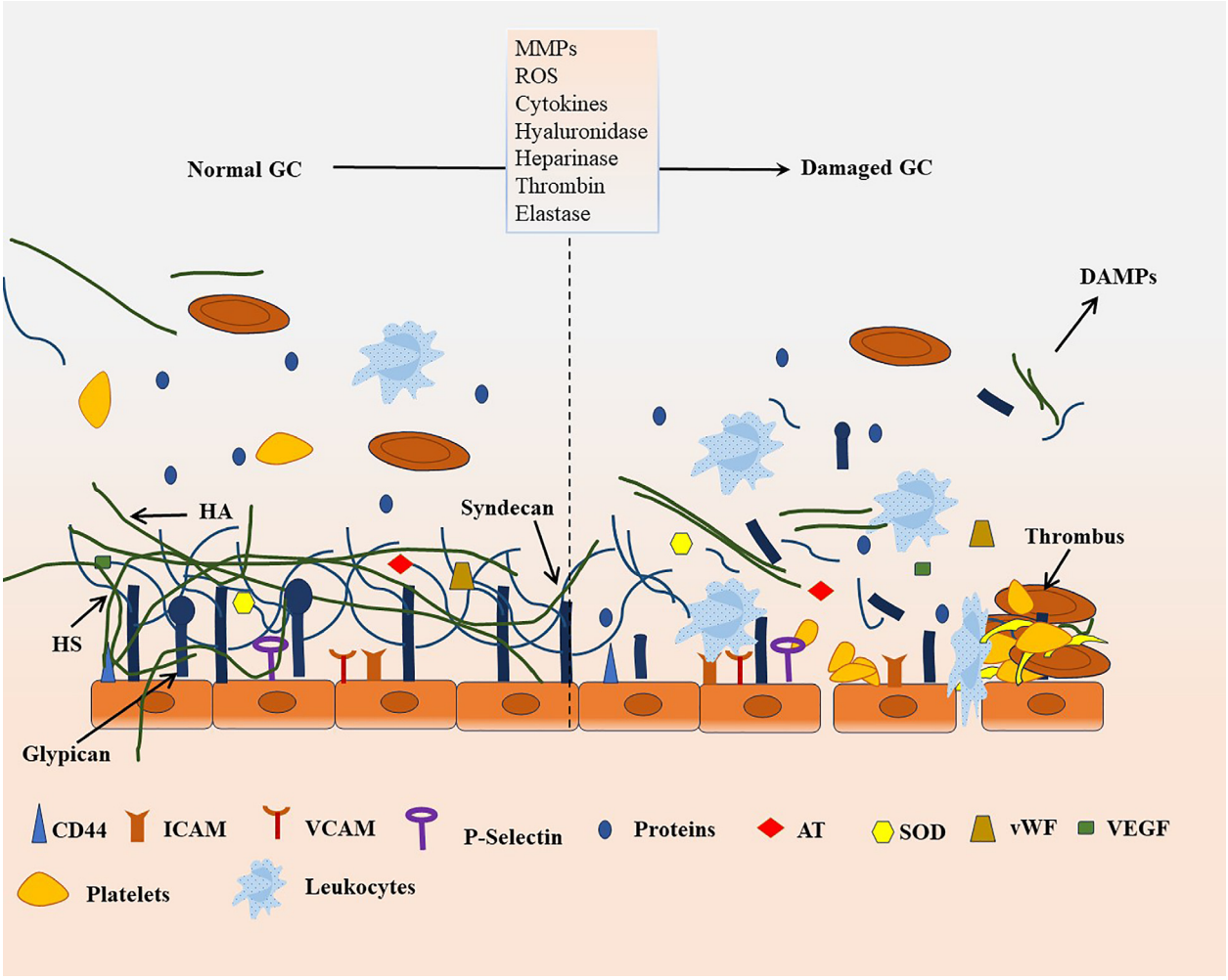

Fig. 1. Comparison of normal GC and disrupted GC. A visual illustration showing the contrasting effects of a healthy and damaged GC on cell adhesion. In the normal state (left), the intact GC covers adhesion molecules, acting as a protective barrier and limiting leukocyte and platelet adhesion to the cell surface. However, in the disrupted state (right), the collapsed or damaged GC exposes adhesion molecules, leading to enhanced leukocytes and platelets adhesion. AT, antithrombin; CD44, cluster of differentiation 44; CS, chondroitin sulfate; DAMPs, damage-associated molecular patterns; ECM, extracellular matrix; GC, glycocalyx; HA, hyaluronic acid; HS, heparan sulfate; ICAM, intercellular adhesion molecule; MMPs, matrix metalloproteinases; ROS, reactive oxygen species; SOD, superoxide dismutase; SS, shear stress; TLRs, toll-like receptors; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

tokines, chemokines, and proteases (e.g., MMP, neutrophil elastase and cathepsin G) [20,25,31–35]. Syndecan-1 deficient mice have elevated inflammation as compared to wild type controls [33–35]. These studies suggest that intact components of the GC have anti-inflammatory properties.

In contrast released fragments of GC appear to act as damage-associated molecular pattern signals to activate the innate immune system [18,20]. In murine and human samples, HS fragments released from the damaged GC can potentiate inflammation by binding to TLRs and activating the nuclear factor-kappa B pathway which induces cytokine release [56]. HS fragments shed from the GC accelerate leukocyte and platelet activation through stimulating intercellular adhesion molecule and vascular cell adhesion molecule upregulation [18,20,52,57]. Similarly, several studies have confirmed the proinflammatory nature of low-molecular weight-HA in both human and murine cell lines resulting in alveolar macrophages activation and increased chemokine gene expression [58]. Similarly, low-molecular weight-HA shed following GC degradation leads to TLR activation and stimulated nuclear factor-kappa B and subsequently upregulates cytokine expression [59]. Furthermore, syndecan fragments have been suggested to be useful as a biomarker for inflammation [60]. Overall, these studies suggest that GC disruption might potentially stimulate vascular inflammation relevant to AAA pathogenesis, as illustrated in Fig. 2 [16–20,51,61]. It should be acknowledged these studies have been largely in laboratory models of diseases other than AAA.

3.2. Glycocalyx disruption may alter mechanotransduction

Biomechanical stress is a key means of signal transduction in healthy blood vessels and changes in biomechanical forces implicated in development of vascular disease [62]. A potential link between endothelial nitric oxide synthase (eNOS) uncoupling and AAA was demonstrated in experimental research, as angiotensin II infusion resulted in a significantly higher incidence of AAA formation and rupture in eNOS preuncoupled hyperphenylalaninemia-1 mice than wild type animals [63]. Furthermore, shear stress may upregulate vascular inflammation, oxidative stress and ECM degradation, all implicated in AAA pathogenesis [2–4,12,13,64].

The eGC plays a crucial role in maintaining proper eNOS function and NO bioavailability. Under normal conditions, the intact GC converts hemodynamic effects into biochemical signals that regulate vascular tone [17,21–24]. The GC responds to shear stress by influencing mechanotransduction pathways and regulating NO production through alterations in the presentation and availability of cell surface receptors and ligands [16,17,21–24,65–75]. Dysfunc-

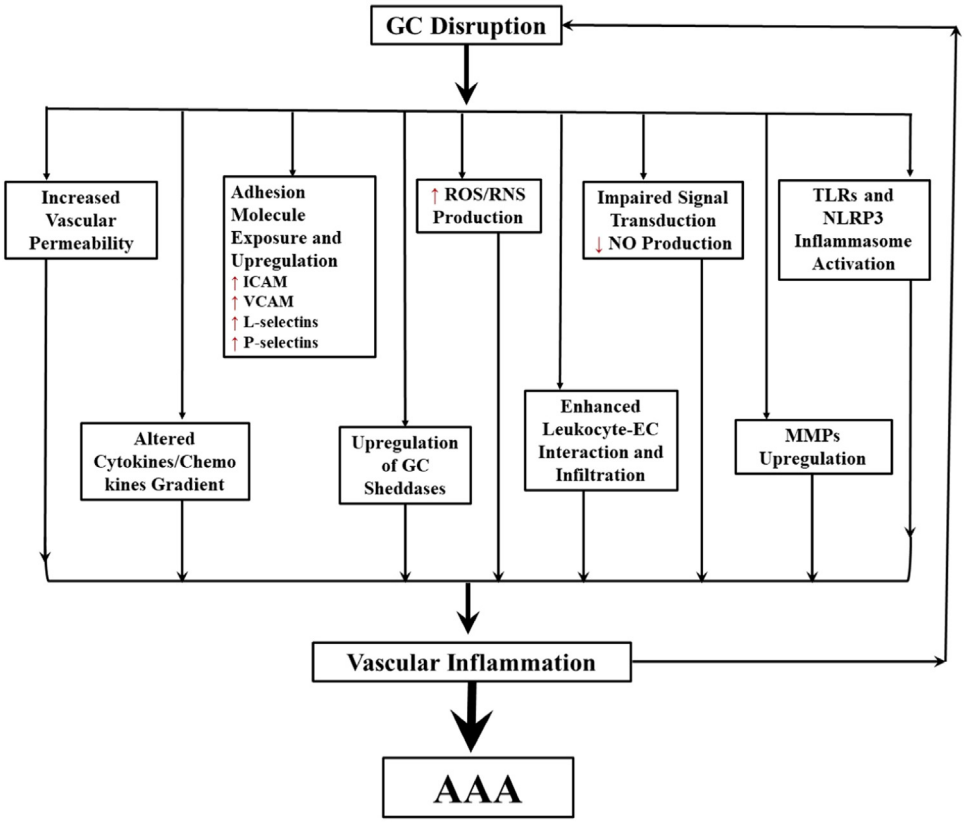

Fig. 2. Potential impact of GC damage on vascular inflammation and possible role in AAA formation. This figure illustrates how GC damage may induce events that contribute to vascular inflammation and could be involved in AAA pathogenesis. AAA, abdominal aortic aneurysm; GC, glycocalyx; EC, endothelial cells; ICAM, intercellular adhesion molecule; MMPs, matrix metalloproteinases; NLRP3, nucleotide-binding domain, leucine-rich repeat containing protein 3; NO, nitric oxide; RNS; reactive nitrogen species; ROS, reactive oxygen species; TIMPs, tissue inhibitors of metalloproteinases; TLR, toll-like receptor; VCAM, vascular cell adhesion molecule.

tion of the GC disrupts mechanosensing and affects cytosolic calcium levels, eNOS activity, and various signaling molecules, such as tyrosine kinases [16,17,21–24,65–75]. Studies have shown that HS and HA are potent mechanosensors, as removal of these GC components through enzyme degradation resulted in decrease or complete block of NO production [68–72]. HA helps in NO production by directly activating eNOS in response to shear stress [71]. In porcine femoral arteries, enzymatic HA removal suppressed shear stress responsive NO bioavailability [71]. Heparanase and hyaluronidase induced GC degradation has been reported to block shear stress stimulated NO production in bovine aortic EC culture [68–71]. Similarly, enzymatic degradation of GC resulted in decreased NO production from rat abdominal aortic samples exposed to high shear stress *in vitro* [65]. The GC component glypican-1 has been reported to influence NO production [73,74]. Deficiency of glypican-1 has been reported to reduce eNOS activation in response to shear stress [73,74]. Tarbell and Pahakis [75] have suggested that shear stress signals in a different way in a damaged compared to an intact GC. Based on this past research, it can be proposed that GC disruption may change how hemodynamic forces influence the abdominal aorta, possibly playing a role in AAA initiation. Further research is needed to test this hypothesis.

3.3. Glycocalyx disruption may induce oxidative stress

Oxidative stress is linked to elevated levels of reactive oxygen species (ROS) and reactive nitrogen species and has been implicated in AAA pathogenesis [2–4,12,13,76].

Antioxidants like superoxide dismutase and xanthine oxidoreductase are present within the GC [16]. GC dysfunction may lead to loss of protective effects of these antioxidants and result in elevated levels of ROS, leading to endothelial dysfunction [16–20,71]. As noted above, GC disruption can reduce NO production which can promote generation of ROS [16–18,67–71,75]. Enzymatic removal of GC components (HS and sialic acid) of femoral arteries in pigs has been reported to decrease eNOS activity and increase ROS levels [71]. *In vitro* studies in hamster cremaster muscles demonstrate that exposing ECs to oxidized low density lipoprotein leads to both ROS generation and GC disruption [77]. These studies provide some preliminary evidence that GC disruption and ROS generation are frequent concurrent events of relevance to AAA pathogenesis.

3.4. Glycocalyx disruption may promote vascular smooth muscle cells dysregulation

Disrupted communication between ECs and VSMCs has been implicated in AAA and atherosclerosis pathogenesis [2–4,12-13,78,79]. VSMCs isolated from human and animal model AAA samples illustrate reduced proliferation and increased apoptosis, compared to control samples [2–4,12,13,35,78,79].

Several growth factors, including tissue growth factor-β, vascular endothelial growth factor receptor (VEGF), and fibroblast growth factor, which participate in the healthy functioning of VSMCs are anchored on GC components [16]. The GC also influences the distribution and activation of VSMCs linked integrin receptors, thereby controlling downstream signaling pathways involved in proliferation, cell motility, and phenotype switching [35,79–89]. An intact GC can prevent NLRP3 associated apoptosis of VSMCs and GC damage may lead to activation of the NLRP3 inflammasome [16,20,53,79,80]. HS acts as a potent mechanosensory component of the GC which regulates shear stress induced con-

Table 3
Relevance of glycocalyx disruption in promoting thrombosis implicated in abdominal aortic aneurysm pathogenesis.

Coagulation factors	Relevance to GC damage	Outcomes	References
Adhesion molecule	Increased adhesion molecules exposure on EC surfaces	Platelets adhesion and aggregation increased	[16,105,106,111]
Tissue factors pathway inhibitors	Decreased inhibition of tissue factors	Coagulation cascade inhibition decreased	[16,105–107]
Heparin cofactor II	Decreased activation of Heparin cofactor II	Coagulation cascade inhibition decreased	[16]
Thrombomodulin	Decreased activation of protein C anticoagulant system	Coagulation cascade inhibition decreased	[61,105–106,109]
Antithrombin III	Reduced binding of antithrombin III to EC surface	Coagulation cascade inhibition decreased	[16,105–108]
vWF	vWF release	Coagulation cascade activation	[110]

GC, glycocalyx; EC, endothelial cells; vWF, von Willebrand factor.

tractile responses of VSMCs [83]. GC disruption stimulates inflammatory mediator release which can further contribute to VSMCs phenotype switching by promoting synthetic marker expression and dysregulating signaling pathways [16,20,53,79]. Degradation of the eGC may lead to decreased NO production and result in subsequent increased proliferation of VSMCs [79–84]. In shear stress exposed human umbilical VSMCs, RhoA-Rho kinase pathway mediated VSMC contraction was completely blocked due to enzymatic degradation of the GC [85]. In human VSMCs, high salt induced GC damage resulted in VSMCs remodeling and hypertrophy [84]. Furthermore, several *in vitro* studies proposed that VSMCs proliferation was manifested in syndecan-1 and HS deficient mice [87–89]. Based on these findings, it is suggested that GC damage can promote phenotypic changes in VSMCs and possibly contribute to AAA pathogenesis.

3.5. Glycocalyx disruption may exacerbate angiogenesis

Angiogenesis is implicated in AAA pathogenesis [2–4,12,13]. Angiogenesis is suggested to promote inflammation and result in ECM degradation implicated in AAA development [2–4,12,13,64,90,91]. The GC acts as an important regulator of angiogenesis as it stores and interacts with several growth factors [16,17].

GC damage can lead to enhanced angiogenesis by dysregulating growth factor binding with GAGs, changing cellular signaling and inflammatory responses [16–20,71,90–92]. HS is a critical component involved in regulating angiogenesis by modulating the binding and bioavailability of the major angiogenesis stimulant VEGF to its receptors [16,17,66–70]. Additionally, glypican-1 and syndecan-1 have been found to interact with VEGF and modulate its biological activity [16,73,93]. Heparanase induced HS removal promoted migration and angiogenesis in melanoma cells [94]. In another study, HS cleavage altered the regulation of VEGF signaling by upregulating VEGF expression in tumor cells and promoting angiogenesis [95]. Syndecan-1 shedding also promoted angiogenesis in myeloma cells [96]. The disruption of the GC may modulate VEGF signaling and angiogenesis within the aortic wall and may contribute to AAA development.

3.6. Glycocalyx disruption may aggravate extracellular matrix degradation

ECM remodeling is a critical process in AAA pathogenesis [2–4,12,13,90,97,98]. This remodeling involves the breakdown of elastin and the degradation of collagen, which are essential components maintaining the structural integrity of the artery wall [90,97,98]. Upregulation of MMPs is thought to play a crucial role in ECM degradation [2–4,12,13,97,98]. MMPs, including MMP-2 and MMP-9, are enzymes responsible for ECM remodeling by breaking down collagen and elastin [97,98]. The GC is itself a specialized ECM and interacts with ECM proteins including collagen, fibronectin, and proteases [16–20]. GC disruption has been identified as a factor that upregulates MMP expression and activity in ECs, leading to the degradation of ECM proteins and promoting inflammation [16–20,54,59,70,75]. This upregulation of MMPs can be triggered by oxidative stress and inflammation, both of which are associated with GC damage [99,100]. Additionally, shedding of the GC can downregulate tissue inhibitors of metalloproteinases in EC culture [101]. Moreover, MMPs themselves can contribute to GC degradation, creating a positive feedback loop that exacerbates the disease process [71–75,101]. It has been suggested that shedding of the GC may expose underlying ECM proteins, making them more susceptible to MMP-mediated degradation [99,100]. The continuous remodeling, driven by GC damage may contribute to the degradation of the arterial wall and AAA development.

3.7. Glycocalyx disruption may enhance thrombosis formation

Intra-luminal thrombus is a characteristic feature of AAA which is composed of red blood cells, macrophages, fibrins, and platelets, and has been implicated in AAA pathogenesis [2–4,12,13,102]. Excessive activation of neutrophil and subsequent release of neutrophil extracellular traps has been proposed to play a role in AAA formation [12].

The GC serves as anticoagulant barrier as it is a repository and interactive medium for multiple coagulation regulators and inhibitors like antithrombin III, tissue factor pathway inhibitor, heparin cofactor II, thrombomodulin, and von Willebrand factor (vWF) [16,17,27,51,103–110]. Antithrombin binds to HS while thrombomodulin that is anchored on CS can stimulate binding of procoagulants to the protein C anticoagulant system [16,61]. GC disruption triggers exposure of adhesion molecules which results in platelets adhesion and aggregation [16–20]. Additionally, GC disruption results in decreased binding of antithrombin to HS, promoting thrombosis [16,61,103–110]. In an *in vitro* study, oxidized low density lipoprotein induced GC degradation leads to accumulation and adhesion of platelets to EC [77]. GC damage induces release of proinflammatory cytokines and NO impairment which are procoagulant in nature [16–20,111]. These mechanisms highlight the potential involvement of GC disruption in inducing Intraluminal thrombus formation which has been proposed to promote AAA progression (Table 3) [16,105–111].

3.8. Critical insight

The studies outlined above do not directly establish the causal nature of GC disruption in AAA pathogenesis. Many of the studies are not undertaken in AAA disease models and thus the findings are indirect and the causal link between GC disruption and AAA formation is speculative and unproven. The GC is a protective covering which is essential for maintaining various physiological functions in the body [16–20]. Its disruption can trigger and promote several pathological processes [16–20]. Limiting GC disruption through restoration and preservation may potentially limit AAA pathogenesis but effective therapeutics to achieve this are currently unknown. Furthermore, as different components of the GC may be involved in distinct pathological processes, deciding which components to specifically target is likely to be challenging [16–20].

3.9. Limitations

This was a narrative review and while every attempt was made to include all the key studies, no systematic search of published research was performed. Thus it is possible important studies were overlooked. As noted above, currently there is no convincing data showing a causal link between GC disruption and AAA pathogenesis and further research is needed.

4. Conclusion

GC disruption leads to loss of key hemodynamic signaling, anti-inflammatory, anticoagulant and antioxidative stress functions of blood vessels. Since inflammation, oxidative stress, ECM remodeling and angiogenesis, and EC and VSMC dysfunction have been implicated in AAA pathogenesis, it is possible GC disruption may play a role in AAA formation [2–4,12,13,14–20]. Currently, however, the causal relationship between GC disruption and AAA is speculative and if proven it is unclear how GC repair could be instigated therapeutically. It is important that future GC research employs animal models representative of human AAA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

CRediT authorship contribution statement

Bibi Rabia: Writing – original draft, Visualization, Software, Methodology, Conceptualization. **Shivshankar Thanigaimani:** Writing – review & editing, Validation, Supervision, Software, Methodology, Conceptualization. **Jonathan Golledge:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

References

[1] Golledge J, Norman PE. Current status of medical management for abdominal aortic aneurysm. Atherosclerosis 2011;217(1):57–63. doi:10.1016/j.atherosclerosis.2011.03.006.

[2] Golledge J. Abdominal aortic aneurysm: update on pathogenesis and medical treatments. Nat Rev Cardiol 2019;16(4):225–42. doi:10.1038/s41569-018-0114-9.

[3] Golledge J, Muller J, Daugherty A, Norman P. Abdominal aortic aneurysm: pathogenesis and implications for management. Arterioscler Thromb Vasc Biol 2006;26(12):2605–13. doi:10.1161/01.ATV.0000245819.32762.cb.

[4] Golledge J, Thanigaimani S, Powell JT, Tsao PS. Pathogenesis and management of abdominal aortic aneurysm. Eur Heart J 2023;44(29):2682–97. doi:10.1093/eurheartj/ehad386.

[5] Antoniou GA, Antoniou SA, Torella F. Editor's choice - endovascular vs. open repair for abdominal aortic aneurysm: systematic review and meta-analysis of updated peri-operative and long term data of randomised controlled trials. Eur J Vasc Endovasc Surg 2020;59(3):385–97. doi:10.1016/j.ejvs.2019.11.030.

[6] Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346(19):1437–44. doi:10.1056/NEJMoa012573.

[7] Ulug P, Powell JT, Martinez MA, Ballard DJ, Filardo G. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev 2020;7(7):CD001835. doi:10.1002/14651858.CD001835.pub5.

[8] Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's choice—European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms [published correction appears in Eur J Vasc Endovasc Surg. 2020 Mar;59(3):494]. Eur J Vasc Endovasc Surg 2019;57(1):8–93. doi:10.1016/j.ejvs.2018.09.020.

[9] Golledge J, Moxon JV, Singh TP, Bown MJ, Mani K, Wanhainen A. Lack of an effective drug therapy for abdominal aortic aneurysm. J Intern Med 2020;288(1):6–22. doi:10.1111/joim.12958.

[10] Lee R, Jones A, Cassimjee I, Handa A. Patients' opinions regarding research and management of abdominal aortic aneurysms. Int Angiol 2017;36(6):526–30. doi:10.23736/S0392-9590.17.03889-5.

[11] Lee R, Jones A, Cassimjee I, Handa A. Oxford abdominal aortic aneurysm study. International opinion on priorities in research for small abdominal aortic aneurysms and the potential path for research to impact clinical management. Int J Cardiol 2017;245:253–5. doi:10.1016/j.ijcard.2017.06.058.

[12] Gao J, Cao H, Hu G, Wu Y, Xu Y, Cui H, et al. The mechanism and therapy of aortic aneurysms. Signal Transduct Target Ther 2023;8(1):55. doi:10.1038/s41392-023-01325-7.

[13] Li Z, Kong W. Cellular signaling in abdominal aortic aneurysm. Cell Signal 2020;70:109575. doi:10.1016/j.cellsig.2020.109575.

[14] Milusev A, Rieben R, Sorvillo N. The endothelial glycocalyx: a possible therapeutic target in cardiovascular disorders. Front Cardiovasc Med 2022;9:897087. doi:10.3389/fcvm.2022.897087.

[15] Möckl L. The emerging role of the mammalian glycocalyx in functional membrane organization and immune system regulation. Front Cell Dev Biol 2020;8:253. doi:10.3389/fcell.2020.00253.

[16] Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. Pflugers Arch 2007;454(3):345–59. doi:10.1007/s00424-007-0212-8.

[17] Fu BM, Tarbell JM. Mechano-sensing and transduction by endothelial surface glycocalyx: composition, structure, and function. Interdiscip Rev Sys Biol Med 2013;5(3):381–90. doi:10.1002/wsbm.1211.

[18] Zhang X, Sun D, Song JW, Zullo J, Lipphardt M, Coneh-Gould L, et al. Endothelial cell dysfunction and glycocalyx–a vicious circle. Matrix Bio 2018;71-72:421–31. doi:10.1016/j.matbio.2018.01.026.

[19] Constantinescu AA, Vink H, Spaan JA. Endothelial cell glycocalyx modulates immobilization of leukocytes at the endothelial surface. Arterioscler Thromb Vasc Biol 2003;23(9):1541–7. doi:10.1161/01.ATV.0000085630.24353.3D.

[20] Qu J, Cheng Y, Wu W, Yuan L, Liu X. Glycocalyx impairment in vascular disease: focus on inflammation. Front Cell Dev Biol 2021;9:730621. doi:10.3389/fcell.2021.730621.

[21] McDonald KK, Cooper S, Danielzak L, Leask RL. Glycocalyx degradation induces a proinflammatory phenotype and increased leukocyte adhesion in cultured ECs under flow. PloS one 2016;11(12):e0167576. doi:10.1371/journal.pone.0167576.

[22] Thi MM, Tarbell JM, Weinbaum S, Spray DC. The role of the glycocalyx in reorganization of the actin cytoskeleton under fluid shear stress: a "bumper-car" model. Proc Natl Acad Sci 2004;101(47):16483–8. doi:10.1073/pnas.0407474101.

[23] Yen W, Cai B, Yang J, Zhang L, Zeng M, John M, et al. Endothelial surface glycocalyx can regulate flow-induced nitric oxide production in microvessels *in vivo*. PloS one 2015;10(1):e0117133. doi:10.1371/journal.pone.0117133.

[24] Dragovich MA, Chester D, Fu BM, Wu C, Xu Y, Goligorsky MS, et al. Mechanotransduction of the endothelial glycocalyx mediates nitric oxide production through activation of TRP channels. Am J Physiol Cell Physiol 2016;311(6):C846–53. doi:10.1152/ajpcell.00288.2015.

[25] Manon-Jensen T, Multhaupt HA, Couchman JR. Mapping of matrix metalloproteinase cleavage sites on syndecan-1 and syndecan-4 ectodomains. FEBS J 2013;280(10):2320–31. doi:10.1111/febs.12174.

[26] Schmidt EP, Yang Y, Janssen WJ, Gandjeva A, Perez MJ, Barthel L, et al. The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. Nat Med 2012;18(8):1217–23. doi:10.1038/nm.2843.

[27] Chappell D, Hofmann-Kiefer K, Jacob M, Rehm M, Briegel J, Welsch U, et al. TNF-α induced shedding of the endothelial glycocalyx is prevented by hydrocortisone and antithrombin. Basic Res Cardiol 2009;104(1):78–89. doi:10.1007/s00395-008-0749-5.

[28] Sieve I, Münster-Kühnel AK, Hilfiker-Kleiner D. Regulation and function of endothelial glycocalyx layer in vascular diseases. Vascul Pharmacol 2018;100:26–33. doi:10.1016/j.vph.2017.09.002.

[29] Ghadie NM, St-Pierre JP, Labrosse MR. The contribution of glycosaminoglycans/proteoglycans to aortic mechanics in health and disease: a critical review. IEEE Trans Biomed Eng 2021;68(12):3491–500. doi:10.1109/TBME.2021.3074053.

[30] Theocharis AD, Tsolakis I, Tsegenidis T, Karamanos NK. Human abdominal aortic aneurysm is closely associated with compositional and specific structural modifications at the glycosaminoglycan level. Atherosclerosis 1999;145(2):359–68. doi:10.1016/s0021-9150(99)00117-3.

[31] Bernfield M, Götte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, et al. Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem 1999;68:729–77. doi:10.1146/annurev.biochem.68.1.729.

[32] Park PW, Reizes O, Bernfield M. Cell surface heparan sulfate proteoglycans: selective regulators of ligand-receptor encounters. J Biol Chem 2000;275(39):29923–6. doi:10.1074/jbc.R000008200.

[33] Wen J, Wang P, Smith SV, Haller CA, Chaikof EL. Syndecans are differentially expressed during the course of aortic aneurysm formation. J Vasc Surg 2007;46(5):1014–25. doi:10.1016/j.jvs.2007.06.022.

[34] Xiao J, Angsana J, Wen J, Smith SV, Park PW, Ford ML, et al. Syndecan-1 displays a protective role in aortic aneurysm formation by modulating T cell–mediated responses. Arterioscler Thromb Vasc Biol 2012;32(2):386–96. doi:10.1161/ATVBAHA.111.242198.

[35] Hu J, Li Y, Wei Z, Chen H, Sun X, Zhou Q, et al. A reduction in the vascular smooth muscle cell focal adhesion component syndecan-4 is associated with abdominal aortic aneurysm formation. Clin Transl Med 2021;11(12):e605. doi:10.1002/ctm2.605.

[36] Miyoshi T, Yonezawa T, Nakamura K, Rakugi H, Matsuoka H, Shimada K, et al. A hyaluronidase inhibitor prevents the development of experimental abdom-

inal aortic aneurysm by interfering interplay between low molecular weight hyaluronan and CD44. Circulation 2011;124:A11614.
[37] Wu J, Jing Z. Involvement of heparanase in human abdominal aortic aneurysm. Chin Med J 2002;82(20):1378–80.
[38] Golledge J, Krishna SM, Wang Y. Mouse models for abdominal aortic aneurysm. Br J Pharmacol 2022;179(5):792–810. doi:10.1111/bph.15260.
[39] Vardulaki KA, Walker NM, Day NE, Duffy SW, Ashton HA, Scott RA. Quantifying the risks of hypertension age sex and smoking in patients with abdominal aortic aneurysm. Br J Surg 2000;87(2):195–200. doi:10.1046/j.1365-2168.2000.01353.x.
[40] Golledge J, Norman PE. Atherosclerosis and abdominal aortic aneurysm: cause response or common risk factors? Arterioscler Thromb Vasc Biol 2010;30(6):1075–7. doi:10.1161/ATVBAHA.110.206573.
[41] Wang JC, Tsai SH, Tsai HY, Lin SJ, Huang PH. Hyperuricemia exacerbates AAA formation through the URAT1/ERK/MMP-9 signaling pathway. BMC Cardiovasc Disord 2023;23(1):55. doi:10.1186/s12872-022-03012-x.
[42] Sheng C, Liu T, Chen S, Liao M, Yang P. The neglected association between central obesity markers and abdominal aortic aneurysm presence: a systematic review and meta-analysis. Front Cardiovasc Med 2023;10:1044560. doi:10.3389/fcvm.2023.1044560.
[43] Ueno M, Sakamoto H, Liao Y, Onodera M, Huang CL, Miyanaka H, et al. Blood-brain barrier disruption in the hypothalamus of young adult spontaneously hypertensive rats. Histochem Cell Biol 2004;122(2):131–7. doi:10.1007/s00418-004-0684-y.
[44] van den Berg BM, Spaan JA, Rolf TM, Vink H. Atherogenic region and diet diminish glycocalyx dimension and increase intima-to-media ratios at murine carotid artery bifurcation. Am J Physiol Heart Circ Physiol 2006;290(2):H915–20. doi:10.1152/ajpheart.00051.2005.
[45] Ikonomidis I, Marinou M, Vlastos D, Kourea K, Andreadou I, Liarakos N, et al. Effects of varenicline and nicotine replacement therapy on arterial elasticity endothelial glycocalyx and oxidative stress during a 3-month smoking cessation program. Atherosclerosis 2017;262:123–30. doi:10.1016/j.atherosclerosis.2017.05.012.
[46] Ko J, Kang HA, Kim DJ, Kim MJ, Ryu ES, Lee S, et al. Uric acid induced the phenotype transition of vascular endothelial cells via induction of oxidative stress and glycocalyx shedding. FASEB J 2019;33(12):13334–45. doi:10.1096/fj.201901148R.
[47] Machin DR, Bloom SI, Campbell RA, Phuong TT, Gates PE, Lesniewski LA, et al. Advanced age results in a diminished endothelial glycocalyx. Am J Physiol Heart Circ Physiol 2018;315(3):H531–9. doi:10.1152/ajpheart.00104.2018.
[48] Eskens BJ, Leurgans TM, Vink H, Van Teeffelen JW. Early impairment of skeletal muscle endothelial glycocalyx barrier properties in diet-induced obesity in mice. Physiol Rep 2014;2(1):e00194. doi:10.1002/phy2.194.
[49] Golledge J, Moxon J, Pinchbeck J, Anderson G, Rowbotham S, Jenkins J, et al. Association between metformin prescription and growth rates of abdominal aortic aneurysms. Br J Surg 2017;104(11):1486–93. doi:10.1002/bjs.10587.
[50] Eskens BJ, Zuurbier CJ, van Haare J, Vink H, Van Teeffelen JW. Effects of two weeks of metformin treatment on whole-body glycocalyx barrier properties in db/db mice. Cardiovasc Diabetol 2013;12:175. doi:10.1186/1475-2840-12-175.
[51] Lupu F, Kinasewitz G, Dormer K. The role of endothelial shear stress on haemodynamics inflammation coagulation and glycocalyx during sepsis. J Cell Mol Med 2020;24(21):12258–71. doi:10.1111/jcmm.15895.
[52] Collins LE, Troeberg L. Heparan sulfate as a regulator of inflammation and immunity. J Leukoc Biol 2019;105(1):81–92. doi:10.1002/JLB.3RU0618-246R.
[53] Wang T, Zhao J, Zhang J, Mei J, Shao M, Pan Y, et al. Heparan sulfate inhibits inflammation and improves wound healing by downregulating the NLR family pyrin domain containing 3 (NLRP3) inflammasome in diabetic rats. J. Diabetes. 2018;10(7):556–63. doi:10.1111/1753-0407.12630.
[54] Campo GM, Avenoso A, Nastasi G, Micali A, Prestipino V, Vaccaro M, et al. Hyaluronan reduces inflammation in experimental arthritis by modulating TLR-2 and TLR-4 cartilage expression. Biochim Biophys Acta - Mol Basis Dis 2011;1812(9):1170–81. doi:10.1016/j.bbadis.2011.06.006.
[55] Melgar-Lesmes P, Garcia-Polite F, Del-Rey-Puech P, Rosas E, Dreyfuss JL, Montell E, et al. Treatment with chondroitin sulfate to modulate inflammation and atherogenesis in obesity. Atherosclerosis 2016;245:82–7. doi:10.1016/j.atherosclerosis.2015.12.016.
[56] Goodall KJ, Poon IK, Phipps S, Hulett MD. Soluble heparan sulfate fragments generated by heparanase trigger the release of pro-inflammatory cytokines through TLR-4. PloS One 2014;9(10):e109596. doi:10.1371/journal.pone.0109596.
[57] Chappell D, Dörfler N, Jacob M, Rehm M, Welsch U, Conzen P, et al. Glycocalyx protection reduces leukocyte adhesion after ischemia/reperfusion. Shock 2010;34(2):133–9. doi:10.1097/SHK.0b013e3181cdc363.
[58] Noble PW, McKee CM, Cowman M, Shin HS. Hyaluronan fragments activate an NF-kappa B/I-kappa B alpha autoregulatory loop in murine macrophages. J Exp Med 1996;183(5):2373–8. doi:10.1084/jem.183.5.2373.
[59] Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. Physiol Rev 2011;91(1):221–64. doi:10.1152/physrev.00052.2009.
[60] Bertrand J, Bollmann M. Soluble syndecans: biomarkers for diseases and therapeutic options. Br J Pharmacol 2019;176(1):67–81. doi:10.1111/bph.14397.
[61] Delgadillo LF, Lomakina EB, Kuebel J, Waugh RE. Changes in endothelial glycocalyx layer protective ability after inflammatory stimulus. Am J Physiol Cell Physiol 2021;320(2):C216–24. doi:10.1152/ajpcell.00259.2020.
[62] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular cellular and vascular behavior. J Am Coll Cardiol 2007;49(25):2379–93. doi:10.1016/j.jacc.2007.02.059.
[63] Kuhlencordt PJ, Gyurko R, Han F, Scherrer-Crosbie M, Aretz TH, Hajjar R, et al. Accelerated atherosclerosis aortic aneurysm formation and ischemic heart disease in apolipoprotein E/endothelial nitric oxide synthase double-knockout mice. Circulation 2001;104(4):448–54. doi:10.1161/hc2901.091399.
[64] Sunderland K, Jiang J, Zhao F. Disturbed flow's impact on cellular changes indicative of vascular aneurysm initiation expansion and rupture: a pathological and methodological review. J Cell Physiol 2022;237(1):278–300. doi:10.1002/jcp.30569.
[65] Liu J, Kang H, Ma X, Sun A, Luan H, Deng X, et al. Vascular cell glycocalyx-mediated vascular remodeling induced by hemodynamic environmental alteration. Hypertension 2018;71(6):1201–9. doi:10.1161/HYPERTENSIONAHA.117.10678.
[66] Zeng Y. Endothelial glycocalyx as a critical signalling platform integrating the extracellular haemodynamic forces and chemical signalling. J Cell Mol Med 2017;21(8):1457–62. doi:10.1111/jcmm.13081.
[67] Zeng Y, Zhang XF, Fu BM, Tarbell JM. The role of endothelial surface glycocalyx in mechanosensing and transduction. Adv Exp Med Biol 2018;1097:1–27. doi:10.1007/978-3-319-96445-4_1.
[68] Florian JA, Kosky JR, Ainslie K, Pang Z, Dull RO, Tarbell JM. Heparan sulfate proteoglycan is a mechanosensor on endothelial cells. Circ Res 2003;93(10):e136–42. doi:10.1161/01.RES.0000101744.47866.D5.
[69] Tarbell JM, Ebong EE. The endothelial glycocalyx: a mechano-sensor and transducer. Sci Signal 2008;1(40):8. doi:10.1126/scisignal.140pt8.
[70] Pahakis MY, Kosky JR, Dull RO, Tarbell JM. The role of endothelial glycocalyx components in mechanotransduction of fluid shear stress. Biochem Biophys Re Commun 2007;355(1):228–33. doi:10.1016/j.bbrc.2007.01.137.
[71] Kumagai R, Lu X, Kassab GS. Role of glycocalyx in flow-induced production of nitric oxide and reactive oxygen species. Free Radic Biol Med 2009;47(5):600–7. doi:10.1016/j.freeradbiomed.2009.05.034.
[72] Cosgun ZC, Fels B, Kusche-Vihrog K. Nanomechanics of the endothelial glycocalyx: from structure to function. Am J Pathol 2020;190(4):732–41. doi:10.1016/j.ajpath.2019.07.021.
[73] Ebong EE, Lopez-Quintero SV, Rizzo V, Spray D, Tarbell JM. Shear-induced endothelial NOS activation and remodeling via heparan sulfate glypican-1 and syndecan-1. Integr Biol 2014;6(3):338–47. doi:10.1039/c3ib40199e.
[74] Zeng Y, Liu J. Role of glypican-1 in endothelial NOS activation under various steady shear stress magnitudes. Exp Cell Res 2016;348(2):184–9. doi:10.1016/j.yexcr.2016.09.017.
[75] Tarbell JM, Pahakis MY. Mechanotransduction and the glycocalyx. J Intern Med 2006;259(4):339–50. doi:10.1111/j.1365-2796.2006.01620.x.
[76] Emeto TI, Moxon JV, Au M, Golledge J. Oxidative stress and abdominal aortic aneurysm: potential treatment targets. Clin Sci 2016;130(5):301–15. doi:10.1042/CS20150547.
[77] Vink H, Constantinescu AA, Spaan JJ. Oxidized lipoproteins degrade the endothelial surface layer: implications for platelet-endothelial cell adhesion. Circulation 2000;101(13):1500–2. doi:10.1161/01.cir.101.13.1500.
[78] Ailawadi G, Moehle CW, Pei H, Walton SP, Yang Z, Kron IL, et al. Smooth muscle phenotypic modulation is an early event in aortic aneurysms. J Thorac Cardiovasc Surg 2009;138(6):1392–9. doi:10.1016/j.jtcvs.2009.07.075.
[79] Méndez-Barbero N, Gutiérrez-Muñoz C, Blanco-Colio LM. Cellular crosstalk between endothelial and smooth muscle cells in vascular wall remodeling. Int J Mol Sci 2021;22(14):7284. doi:10.3390/ijms22147284.
[80] Yao Y, Rabodzey A, Dewey CF Jr. Glycocalyx modulates the motility and proliferative response of vascular endothelium to fluid shear stress. Am J Physiol Heart Circ Physiol 2007;293(2):H1023–30. doi:10.1152/ajpheart.00162.2007.
[81] Shi ZD, Abraham G, Tarbell JM. Shear stress modulation of smooth muscle cell marker genes in 2-D and 3-D depends on mechanotransduction by heparan sulfate proteoglycans and ERK1/2. PloS One 2010;5(8):e12196. doi:10.1371/journal.pone.0012196.
[82] Kang H, Fan Y, Deng X. Vascular smooth muscle cell glycocalyx modulates shear-induced proliferation migration and NO production responses. Am J Physiol Heart Circ Physiol 2011;300(1):H76–83. doi:10.1152/ajpheart.00905.2010.
[83] Ainslie KM, Garanich JS, Dull RO, Tarbell JM. Vascular smooth muscle cell glycocalyx influences shear stress-mediated contractile response. J Appl Physiol 1985;98(1):242–9. doi:10.1152/japplphysiol.01006.2003.
[84] Qiu J, Zheng Y, Hu J, Liao D, Liao D, Gregersen H, Deng X, et al. Biomechanical regulation of vascular smooth muscle cell functions: from *in vitro* to *in vivo* understanding. J R Soc Interface 2013;11(90):20130852. doi:10.1098/rsif.2013.0852.
[85] Kang H, Liu J, Sun A, Liu X, Fan Y, Deng X. Vascular smooth muscle cell glycocalyx mediates shear stress-induced contractile responses via a Rho kinase (ROCK)-myosin light chain phosphatase (MLCP) pathway. Sci Rep 2017;7:42092. doi:10.1038/srep42092.
[86] Bkaily G, Simon Y, Menkovic I, Bkaily C, Jacques D. High salt-induced hypertrophy of human vascular smooth muscle cells associated with a decrease in glycocalyx. J Mol Cell Cardiol 2018;125:1–5. doi:10.1016/j.yjmcc.2018.10.006.
[87] Fukai N, Kenagy RD, Chen L, Gao L, Daum G, Clowes AW. Syndecan-1: an inhibitor of arterial smooth muscle cell growth and intimal hyperplasia. Arterioscler Thromb Vasc Biol 2009;29(9):1356–62. doi:10.1161/ATVBAHA.109.190132.
[88] Kinsella MG, Tran PK, Weiser-Evans MC, Reidy M, Majack RA, Wight TN. Changes in perlecan expression during vascular injury: role in the inhibition

of smooth muscle cell proliferation in the late lesion. Arterioscler Thromb Vasc Biol 2003;23(4):608–14. doi:10.1161/01.ATV.0000063109.94810.EE.
[89] Tran P, Tran-Lundmark K, Soininen R, Tryggvason K, Thyberg J, Hedin U. Increased intimal hyperplasia and smooth muscle cell proliferation in transgenic mice with heparan sulfate–deficient perlecan. Circ Res 2004;94(4):550–8. doi:10.1161/01.RES.0000117772.86853.34.
[90] Mongiat M, Andreuzzi E, Tarticchio G, Paulitti A. Extracellular matrix a hard player in angiogenesis. Int J Mol Sci 2016;17(11):1822. doi:10.3390/ijms17111822.
[91] Hu Z, Cano I, D'Amore PA. Update on the role of the endothelial glycocalyx in angiogenesis and vascular inflammation. Front Cell Dev Biol 2021;9:734276. doi:10.3389/fcell.2021.734276.
[92] Fuster MM, Wang L. Endothelial heparan sulfate in angiogenesis. Prog Mol Biol Transl Sci 2010;93:179–212. doi:10.1016/S1877-1173(10)93009-3.
[93] Nagarajan A, Malvi P, Wajapeyee N. Heparan sulfate and heparan sulfate proteoglycans in cancer initiation and progression. Front Endocrinol 2018;9:483. doi:10.3389/fendo.2018.00483.
[94] Roy M, Marchetti D. Cell surface heparan sulfate released by heparanase promotes melanoma cell migration and angiogenesis. J Cell Biochem 2009;106(2):200–9. doi:10.1002/jcb.22005.
[95] Zetser A, Bashenko Y, Edovitsky E, Levy-Adam F, Vlodavsky I, Ilan N. Heparanase induces vascular endothelial growth factor expression: correlation with p38 phosphorylation levels and Src activation. Cancer Res 2006;66(3):1455–63. doi:10.1158/0008-5472.CAN-05-1811.
[96] Purushothaman A, Uyama T, Kobayashi F, Yamada S, Sugahara K, Rapraeger AC, et al. Heparanase-enhanced shedding of syndecan-1 by myeloma cells promotes endothelial invasion and angiogenesis. Blood 2010;115(12):2449–57. doi:10.1182/blood-2009-07-234757.
[97] Didangelos A, Yin X, Mandal K, Saje A, Smith A, Xu Q, et al. Extracellular matrix composition and remodeling in human abdominal aortic aneurysms: a proteomics approach. Mol Cell Proteomics 2011;10(8) M111.008128. doi:10.1074/mcp.M111.008128.
[98] Wilson WR, Anderton M, Schwalbe EC, Jones JL, Furness PN, Bell PR, et al. Matrix metalloproteinase-8 and-9 are increased at the site of abdominal aortic aneurysm rupture. Circulation 2006;113(3):438–45. doi:10.1161/CIRCULATIONAHA.105.551572.
[99] Ramnath R, Foster RR, Qiu Y, Cope G, Butler MJ, Salmon AH, et al. Matrix metalloproteinase 9-mediated shedding of syndecan 4 in response to tumor necrosis factor α: a contributor to endothelial cell glycocalyx dysfunction. FASEB J 2014;28(11):4686–99. doi:10.1096/fj.14-252221.
[100] Ali M, Mahmoud AM, Le Master E, Levitan I, Phillips SA. Role of matrix metalloproteinases and histone deacetylase in oxidative stress-induced degradation of the endothelial glycocalyx. Am J Physiol Heart Circ Physiol 2019;316(3):H647–63. doi:10.1152/ajpheart.00090.2018.
[101] Lipowsky HH. Protease activity and the role of the endothelial glycocalyx in inflammation. Drug Discov Today Dis Models 2011;8(1):57–62. doi:10.1016/j.ddmod.2011.05.004.
[102] Bontekoe J, Matsumura J, Liu B. Thrombosis in the pathogenesis of abdominal aortic aneurysm. JVS Vasc Sci 2023;4:100106. doi:10.1016/j.jvssci.2023.100106.
[103] Van Teeffelen JW, Brands J, Stroes ES, Vink H. Endothelial glycocalyx: sweet shield of blood vessels. Trends Cardiovasc Med 2007;17(3):101–5. doi:10.1016/j.tcm.2007.02.002.
[104] Noble MI, Drake-Holland AJ, Vink H. Hypothesis: arterial glycocalyx dysfunction is the first step in the atherothrombotic process. QJM 2008;101(7):513–18. doi:10.1093/qjmed/hcn024.
[105] Moore KH, Murphy HA, George EM. The glycocalyx: a central regulator of vascular function. Am J Physiol Regul Integr Comp Physiol 2021;320(4):R508–18. doi:10.1152/ajpregu.00340.2020.
[106] Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level a marker of endothelial glycocalyx degradation is associated with inflammation protein C depletion fibrinolysis and increased mortality in trauma patients. Ann Surg 2011;254(2):194–200. doi:10.1097/SLA.0b013e318226113d.
[107] Nieuwdorp M, van Haeften TW, Gouverneur MC, Mooij HL, Lieshout MV, Levi M, et al. Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation *in vivo*. Diabetes 2006;55(2):480–6. doi:10.2337/diabetes.55.02.06.db05-1103.
[108] Chappell D, Brettner F, Doerfler N, Jacob M, Rehm M, Bruegger D, et al. Protection of glycocalyx decreases platelet adhesion after ischaemia/reperfusion: an animal study. Eur J Anaesthesiol 2014;31(9):474–81. doi:10.1097/EJA.0000000000000085.
[109] Fraser DD, Patterson E, Slessarev MK, Gill SE, Martin C, Daley M, et al. Endothelial injury and glycocalyx degradation in critically ill coronavirus disease 2019 patients: implications for microvascular platelet aggregation. Crit Care Explor 2020;2(9):e0194. doi:10.1097/CCE.0000000000000194.
[110] Kalagara T, Moutsis T, Yang Y, Pappelbaum KI, Farken A, Cladder-Micus L, et al. The endothelial glycocalyx anchors von Willebrand factor fibers to the vascular endothelium. Blood Adv 2018;2(18):2347–57. doi:10.1182/bloodadvances.2017013995.
[111] Henry CB, Duling BR. TNF-α increases entry of macromolecules into luminal endothelial cell glycocalyx. Am J Physiol Heart Circ Physiol 2000;279(6):H2815–23. doi:10.1152/ajpheart.2000.279.6.H2815.