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Endothelial Glycocalyx as Biomarker for Cardiovascular Diseases: Mechanistic and Clinical Implications

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Abstract

The endothelial surface layer is covered with abundant proteoglycans, of which syndecans and glycosaminoglycans are major constituents. Among the endothelial glycocalyx (eGC) constituents, syndecan-1 (sdc1) is a main component, and an elevated serum level of sdc1 may indicate the degradation of eGC. In patients with ischemic heart disease or heart failure, elevation of serum sdc1 has been associated with worsening cardiac and renal function; however the causal relationship between degradation of eGC and clinical outcomes is unclear. Herein, we review the previous literature on eGC in cardiovascular and non-cardiovascular diseases and their clinical implications.

Keywords

endothelial glycocalyx; Cardiovascular Diseases; syndecan-1 (sdc1)

INTRODUCTION

Endothelial cells are covered with abundant proteoglycan complexes known as “endothelial glycocalyx (eGC),” which is comprised of transmembrane core proteins known as syndecans, and polymers of glycosaminoglycans such as heparin sulfate, chondroitin sulfate, and hyaluronans that branch from the highly sulfated and negatively-charged syndecan cores. Endothelial glycocalyx maintains the integrity of the interface between blood flow and endothelial surface, and prevents extravasation of salt, water and proteins. It also functions as a barrier to keep proteins or cytokines of untoward effect from direct contact to the endothelium. Adhesion of leukocytes and platelets to endothelium are attenuated in the presence of the eGC, diminishing blood coagulation [1, 2]. The eGC controls nitric-oxide mediated vasodilation by transducing shear stress to the cytoskeleton in the endothelial cells [3, 4]. Deformation of cortical cytoskeleton by such mechanotransduction is assumed to initiate the various chains of intracellular signaling as well as nitric oxide production [5–7].

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COMPLIANCE WITH ETHICS GUIDELINES

Conflict of Interest

Youn-Hyun Kim, Petra Nijst, and Kathryn Kiefer declare that they have no conflict of interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Although a growing body of evidence shows degradation of eGC leads to adverse cardiovascular events, the studies on eGC in the clinical setting remain limited. The following is a review of studies evaluating the clinical impact of measured eGC in cardiovascular and non-cardiovascular diseases and endeavor to illuminate the future direction of investigation.

Endothelial glycocalyx in non-cardiovascular disease

Inflammation—In addition to increased porosity of the eGC during mild inflammation, proteases from activated neutrophils and severely traumatized tissue promote breakdown of the eGC. The shedding of the eGC exposes intercellular adhesion molecules (ICAMs) and P-selectin underneath the glycocalyx layer. Consequently, the eGC shedding facilitates more adhesion of inflammatory cells to the endothelium, which is followed by increased endothelial permeability and propagation of inflammation [8, 9]. On the other hand, the soluble fragments from eGC appear to have opposing actions, which are spread between inflammation and contribution to immunosuppression [10]. Syndecan-1 (sdc1) is the most investigated constituent of the cell surface glycocalyx in the area of cancer prognosis and trauma related inflammation [11]. In wild-type mice, the level of inflammation due to *Pseudomonas aeruginosa* infection was more severe with a greater amount of shed sdc1, while sdc1-null mice had attenuated lung-injury. Interestingly, the protective phenotype in sdc-1-null mice was lost when isolated sdc1 ectodomains were administered, suggesting that shed sdc1 enhances bacterial virulence by a probable way of altered innate immunity [12]. In contrast, the presence of soluble sdc1 in blood accelerated removal of the tissue-bound inflammatory chemokines and resolution of the accumulated neutrophils, while multi-organ injury and lethality were attenuated with infused heparin sulfate [2, 13, 14]. Additionally, absence of sdc1 in sdc1-null mice delayed wound healing due to defected migration of keratinocytes [11, 15]. Those results suggested that soluble sdc1 shed from the cells helped recovery from systemic inflammation.

Tumors—In most tumors, reduced expression of sdc1 in epithelial-origin tumor cells was associated with less adhesion of the cells to the extracellular matrix, leading to increased cell migration/invasion, and eventually poor clinical outcomes [16, 17]. Elevated serum sdc1 in hematologic malignancies was also associated with poor prognosis [18–21]. Overexpression of sdc1 in stromal fibroblasts or shedding of sdc1 from the cells into tumor microenvironments was associated with accelerated angiogenesis and cancer progression. [16, 22–26]. Contrary to the general nature of tumor behaviors, several cancers (e.g. breast cancer, gallbladder cancer, glioma and squamous cell carcinoma of the head and neck) showed better prognosis when sdc1 was overexpressed on the cells [22]. Therefore, cellular integral membrane proteins, in conjunction with properties of the extracellular matrix and the amount of sdc1 shed in the tumor microenvironments, each interactively affect the modulation mechanism of cell migration [11].

Soluble sdc1 is thought to be a biologically active mediator of interaction between extracellular matrix and cancer cells, and may enhance migration and invasion of malignant cells [22]. Shed sdc1 can bind the same ligands of intact ectodomain and even compete with intact ectodomain to downregulate signal transduction [27]. Interestingly, soluble sdc1 may

be a potential pro-angiogenic factor. In Hodgkin's lymphoma, with high expression of heparinase, soluble sdc1 stimulated vascular endothelial growth factor (VEGF) receptors on the adjacent endothelial cells by forming a complex with VEGF [28]. In an animal study, high expression of sdc1 in stromal fibroblasts increased the density of microvasculature in the tumors, which was explained by sequestration of pro-angiogenic factors in the tumor microenvironment [29]. These findings suggested that soluble sdc1 may both promote angiogenesis [14] and may be used to treat cardiovascular diseases.

Although soluble sdc1 from the cells may switch malignant cells from proliferative to invasive phenotypes [27], it is unclear whether a high level of soluble sdc1 resulted from overproduction of sdc1 or excessive shedding from the cells. While study investigators primarily used antibodies to sdc1 ectodomains on the cell surface, antibodies to both the ectodomains and the carboxy-terminal-fragments of sdc1 are warranted to answer the question.

Endothelial glycocalyx in cardiovascular disease

Preclinical studies—Oxidized low density lipoprotein cholesterol (ox-LDL) degrades eGC and enhances adherence of leukocytes to the endothelial surface in mouse cremaster venules, [1] corresponding to the notion of endothelial dysfunction in patients with dyslipidemia. Among four subtypes of syndecan, sdc1 is the most prominent on the surface of endothelial cells [30], and the function of membrane-bound or soluble sdc1 ectodomain is increasingly investigated. Sdc1-null mice developed larger neointimal hyperplasia in injured carotid arteries, and had increased proliferation of smooth muscle cells compared to wild type mice. [31]. Reduced motility of macrophages in sdc1-null mice also appear to contribute to augmented atherosclerosis, as lymphatic clearance of sdc1 $^{-/-}$ macrophages was significantly delayed [32]. This data suggested that sdc1 restricted intimal thickening in healing arteries by inhibiting smooth muscle cell proliferation and modulation of macrophage motility.

Contradictory results regarding the influence of sdc1 on matrix remodeling of injured animal hearts also exist. In sdc1-null mice with induced myocardial infarction, enhanced endothelial adhesion and trans-endothelial migration of the inflammatory cells, as well as exaggerated adverse matrix remodeling and fibrosis, were observed [33]. The absence of sdc1 also attenuated angiotensin II-induced cardiac dysfunction and fibrosis in mice [34]. The Langendorf model of isolated guinea pig hearts demonstrated that degradation of the eGC led to reduced endothelial barrier function and extravasation of administered starch, which seems analogous to the fluid shift to the third space as observed in patients with heart failure [35–37].

Clinical studies—Various clinical studies demonstrate different effects of eGC glycosaminoglycans, depending on arteries and subfamilies of glycosaminoglycans. Heparin sulfate, the major glycosaminoglycan molecule in the eGC, decreased in human aorta as age and cholesterol contents in the aorta increased [38]. The concentration of hyaluronic acid, a minor constituent, showed a negative gradient from normal areas to atheromatous areas in the human aorta, with its biological function being a negative regulator on vascular smooth

muscle cell (VSMC) proliferation and a positive regulator of the migration [39]. One study reported that the progression of atherosclerosis was favored by an increase in chondroitin sulfate in the arterial walls [40], while another reported that serum soluble sdc1 was significantly elevated in patients with acute coronary syndrome, suggesting a contributory effect of eGC damage to atherosclerotic plaque vulnerability [41].

In a study by Ostrowski *et al.,* with acute ST segment elevation myocardial infarction, sdc1 was weakly correlated with circulating catecholamine level, with marginal association with development of heart failure (p=0.069) and no association with 30-day mortality [42]. In the same study, adrenaline was associated with both 30-day mortality and heart failure development [42]. Interestingly, there was no reported relationship between serum soluble sdc1 with peak troponin I, which could infer that eGC damage does not correlate with size of infarction, but it potentially develops prior to coronary arterial occlusion.

Several studies investigated the clinical implication of sdc1 in patients with heart failure. Bielecka-Dabrowa *et al.* assigned 120 hypertensive patients to two groups, based on the presence of heart failure and investigated C-statistics of various combinations of biomarkers for the diagnosis of heart failure [43]. In that cross-sectional analysis, syndecan-4 showed only 0.781 of area under the curve (AUC) in the receiver operation characteristics (ROC) for the diagnosis with heart failure, whereas N-terminal pro-brain type natriuretic peptide (NT-proBNP) showed 0.873 of AUC [43]. In another study by the same investigators, serum soluble syndecan-4 levels showed significant correlation with left ventricular dilation and reduced left ventricular systolic function in patients with dilated cardiomyopathy, but their causal relationship was not explained [44].

Longitudinal observational studies of patients with acute or chronic heart failure also suggest correlations to serum soluble sdc1 [45–47]. Neves *et al.* studied 201 patients with acute decompensated heart failure [46]. The ratio of patients with sdc1 >125 ng/ml and <125 ng/ml was about 1:3, and the risk of 6 month-mortality was 22.4% and 8.5%, respectively. Higher serum soluble sdc1 was also associated with more frequent renal dysfunction during hospitalization [46].

Tromp *et al.* and Meyer *et al.* both studied 567 patients with acute heart failure, by measuring sdc1 following stabilization and prior to discharge [47, 48]. The ratio of patients with sdc1 >27.7 ng/mL and sdc1 < 27.6 ng/mL was about 1:4, suggesting a rapid decrease of serum soluble sdc1 levels when compared to the previous study [46]. Through univariable analysis, doubling of sdc1 significantly increased the risk of mortality (HR=1.2) in patients with preserved ejection fraction. Interestingly, the association between sdc1 and mortality was significant in women and marginal in men [47, 48].

Demissei *et al.* also prospectively observed 2,033 patients with acute heart failure, after stabilization during hospital stay, of which 17.6% of patients died within 180 days of the study [45]. They evaluated the diagnostic accuracy of 44 biomarkers for heart failure, including sdc1. Although differences in hazard ratios of sdc1 for 30-day and 180-day mortality were significant at 1.43 and 1.27 per 1 standard deviation, their C-statistics were not as high (0.767 for 30-day mortality and 0.706 for 180-day mortality), and continuous net

reclassification improvements (cNRI) were only 0.38 and 0.24, when sdc1 was added to the conventional model [45].

Areas awaiting further investigation

Evaluation of the amount of endothelial glycocalyx *in situ*—Due to optical transparency and fragility of eGC, *in vivo* virtual characteristics were primarily inferred through existence of the "exclusion zone" of erythrocytes in the blood-perfused microvessels, which is observed with light microscopy [49, 50]. Although the elevated eGC constituents in serum (i.e. syndecan or heparan sulfate) appear to represent degradation of the eGC, methods to directly measure the actual amount of eGC were not sufficiently investigated, which may relate to the lack of clinical studies. Despite minimal investigation, several novel methods were devised to measure the amount of eGC on the endothelial surface layer *in situ*.

Direct visualization of harvested microvessels with electron microscopy is being performed. Although the *ex vivo* measurements of vessel thickness is extremely variable (0.3 μm ~ 60 μm) between studies and vessels, due to fragility and potential eGC structural loss [51], microscopic imaging modalities (confocal, multiphoton fluorescence or transmission electron microscopy) are still being used for direct visualization. In particular, rapid freezing of endothelial cells and use of a novel fixation solution, such as lanthanium (III)-nitrate/glutaraldehyde, revealed a thicker layer of eGC *ex vivo*, which was more efficacious compared to preparation with a conventional fixation method for microscopic analysis [35, 52].

Another method, known as intravital microscopy, enables observation of capillary blood flow in living animals. Bright-field and fluorescent microscopy can demonstrate the virtual diameter of capillaries *in vivo*, which are comparable to anatomical diameters [53]. Functional diameter of capillaries can also be estimated by measuring the diameter of deformed erythrocytes flowing through capillaries. Considering that capillary functional diameters are smaller than anatomical diameters, the thickness of the endothelial surface layer can be calculated from the difference. Endothelial surface layer thickness can then be used as a true interface between blood flow and the luminal surface [49]. The resolution may be enhanced with molecules that have high affinity to the glycosaminoglycan chains. [54] Using this method, significant relationships were determined between thickness of eGC in human sublingual microvasculature and cardiovascular risk factors [55, 56].

Lastly, the double tracer dilution method uses two tracers to quantify virtual volume of eGC in the circulatory system [57]. Erythrocytes labeled with sodium fluorescein, which is impermeable to the eGC, are used to quantify circulating plasma volume not included in the eGC layer. eGC-permeable tracers (e.g. dextran 40) are used to quantify total intravascular volume, which includes the eGC layer [49]. The difference between circulating plasma volume and total intravascular volume was assumed to represent the volume of the eGC [55]. Nieuwdorp *et al.* used the double tracer method to demonstrate that acute normo-insulinemic hyperglycemia reduced the systemic total eGC volume from 1.75 L to 0.8 L [58]. Despite debates on the precision [59], this method is worthy of further investigation because of limited quantitative methods for *in vivo* evaluation of total human eGC volume.

While the techniques mentioned above may be beneficial for quantitative and qualitative measurement of eGC, they do not completely represent the eGC functional aspect. The permeation rate of intravenous substance into extravascular space through endothelial layer, flow mediated vasodilation (indicative of mechano-transduction function of eGC), or grade of inflammatory reaction dependent on syndecan level, may provide more direct information regarding the functional aspect of the eGC. In general, further investigation of eGC quantitative and qualitative structural measures, in conjunction with analytical methods of function, are required.

Shedding of syndecan-1 and endothelial dysfunction in heart failure

Although new validation tests are gaining popularity in studies exploring new biomarkers, the studies mentioned above did not demonstrate high C-statistics, and the improvement of net reclassification was only moderate. [45, 47] In addition, the interpretation of the tests requires special attention because the application of C-statistics often eliminates established risk factors from new models [60, 61], and net reclassification is often positive for even weak markers, leading to overestimation of the real risk. [62–64] Conversely, the clinical value of sdc1 as a prognosticator of cardiovascular events is still unestablished. In fact, none of the novel biomarkers alone showed superiority to natriuretic peptide (e.g. BNP or NT-proBNP), although addition of novel biomarkers to the traditional diagnostic model may improve discriminative ability. [43] Therefore, considering cost-effectiveness, additional measurements of serum sdc1 may not be plausible. Perhaps, it may be worth focusing on the mechanism of how the degradation of the eGC, represented by elevated serum soluble sdc1, leads to adverse cardiovascular events or *vice versa*, rather than solely investigating sdc1 outcomes predictability.

The endothelial dysfunction and vascular permeability can be identified using flow-mediated vascular dilation (FMD) and non-invasive measurement of microvascular leakage with strain gauge plethysmography [65, 66]. Flux forces applied to core proteins on the glycocalyx are transferred and amplified in both the cells and deformed cortical cytoskeleton. This mechano-transduction is assumed to initiate the chain of intracellular signaling, such as nitric oxide production, and can be estimated by FMD [5, 6]. In a study that evaluated the relationship between FMD and serum soluble sdc1, 49 patients with untreated nephrotic syndrome and 25 healthy controls were compared. After adjustment for several clinical variables and endothelial function biomarkers (ICAM-1 and e-selectin), only sdc1 was independently associated with FMD [67]. Hyperglycemia induced reduction of the eGC volume was accompanied by impairment of FMD and activation of coagulation system, which were attenuated by infusion of N-acetylcysteine [58, 68]. These findings support the notion that damaged eGC causes endothelial dysfunction in the peripheral arteries. Additionally, previous studies demonstrate that peripheral artery vasomotor dysfunction is prevalent in patients with heart failure [65, 66, 69, 70] and that degradation of eGC appeared to contribute to worse cardiovascular outcomes in patients with heart failure [45–47]. If a temporal/causal relationship can be established among increased sdc1, endothelial dysfunction, vascular permeability, and adverse cardiovascular events in this population, then eGC will become a promising therapeutic target of heart failure.

Endothelial glycocalyx as a potential salt reservoir in heart failure—An area that requires more evaluation is the role of eGC in sodium storage. Accumulation of sodium in interstitial tissue does not necessarily require commensurate water retention [71–73]. Skin is abundant with glycosaminoglycan polymerization [74], and the modulation of intracutaneous tonicity and lymph capillary network enables skin to be a sizable reservoir of sodium without commensurate water [73]. Considering the similarities in composition of eGC to the cutaneous glycosaminoglycans and abundance on the endothelial surface, the eGC may be able to buffer excess sodium and contribute to homeostasis of the systemic volume status. Moreover, the negative charge of sulfated glycosaminoglycan polymers in eGC and their direct contact to sodium in circulating blood confers more weight to the idea of sodium buffering [75]. Siegel *et al.* used *ex vivo* human coronary arteries to suggest that blood flow causes conformational changes of negatively charged glycosaminoglycan chains from random coils to a filamentous state. The conformational change exposes intramolecular cation-binding sites to sodium ions, which allows increased sodium binding in glycosaminoglycan chains [76, 77]. Despite doubts on the accuracy, the calculated amount of sodium that can be buffered by total endothelial glycocalyx was estimated to range from 0.7 g to as much as 14 g, when the thickness of eGC is assumed to range from 0.3 μm to 60 μm [51, 78].

Additionally, the increase in endothelial permeability is another important area to be explored. Even if the buffer capacity of eGC for sodium is minimal, its role as a sodium buffer is still significant such that eGC can smoothen sharp fluctuation of intravascular sodium concentration and osmolality after a meal by binding sodium with its abundant, free negative charges. Contrary to the classical principle of Ernest Starling, in which the oncotic pressure difference between the intravascular and the interstitial tissue matters, the thin protein-free zone of eGC was suggested to play greater role in the control of vascular permeability [37]. When eGC are shed, sodium can readily enter into the intracellular space of the endothelial cells and eventually extravasate into interstitial space [3, 22, 35, 79]. Furthermore, there is evidence showing that increased permeability by perturbed eGC allows leakage of other intravascular constituents such as albumin in other organs [80–82].

Shedding and signaling mechanism of syndecan-1

So far, multiple shedding mechanisms were suggested. When colloids were infused during major surgery, the majority of infused colloids extravasated, and the eGC volume was significantly reduced regardless of the type of colloids. Although the authors suggested “wash-out” of the eGC as a shedding mechanism, it was not clarified whether the “wash-out” was induced by volume expansion or trauma from surgery [57]. In another study, patients who underwent major surgery had elevated serum sdc1. Increased production of natriuretic peptide induced by overloaded volume was thought to degrade the eGC. [35, 83].

Sodium overload *per se* can accelerate shedding of eGC without mediators. When the stiffness of eGC from a human umbilical cord artery was directly measured *ex vivo* using atomic force microscopy, increase in sodium concentration induced eGC stiffening and reduced heparin sulfate residues by 68% [84]. Meanwhile, hyperglycemia-induced reduction of the eGC volume was accompanied by impairment of flow mediated vascular diameter and

activation of the coagulation system, which were attenuated by infusion of N-acetylcysteine. Therefore, reactive oxygen generated under hyperglycemic conditions was suggested as a cause of eGC destruction, where a Toll-like receptor gene appeared to mediate the signaling [58, 68].

Syndecan, heparan sulfate and hyaluronan in plasma are consistently increased in cardiopulmonary bypass or post-cardiac arrest syndrome where ischemia and reperfusion ensue. [85, 86] Hypoxia/reoxygenation in experimental models cause similar deterioration of eGC as found in ischemia/reperfusion in humans. Hypoxia and reoxygenation lead to degradation of eGC, aided by mast cells. Tissue deoxygenation produces nucleoside adenosine and inosine from the adenine nucleotide, which stimulates mast cells to release heparinase in the granular stores [87–89].

Clinically, shedding of the eGC is well reported in systemic inflammation syndrome (i.e., sepsis, major surgery, trauma, etc.), and degraded eGC are associated with altered vascular permeability and resistance, systemic edema, hypovolemia and multi-organ dysfunction, leading to poor clinical outcomes [90, 91]. Bacterial endotoxin in sepsis is thought to initiate the endothelial perturbation in a TNF-α mediated manner [89], and reduced thickness and stiffness of eGC was demonstrated in experimental models exposed to lipopolysaccharide or TNF-α [92]. Mice deficient of the TNF-α receptor did not show reduced thickness in the endothelial surface layer, and inhibition of heparinase prevented endotoxemia-induced degradation of eGC [2].

Apart from the potential shedding mechanism mentioned above, there are many potential “sheddases,” which includes tryptase, elastase, proteinase-3, thrombin, tissue-type plasminogen activator, plasmin, cathepsin B, hyaluronidase, etc. Nevertheless, more research is required to determine which enzymes are the main degraders of eGC [30, 93]. An effective inhibitor of eGC sheddases also requires further investigation.

Potential restorer of endothelial glycocalyx—Albumin-containing solutions elicit shear stress-dependent vasodilation, consequently lower fluid flux across the vessel walls more than other types of colloid fluids. Other studies have shown that human albumin affords protection of the glycocalyx in experimental models and possesses a high affinity for the glycocalyx [36]. This was probably due to the high negative charge on the albumin molecules. The glycocalyx *in vivo* is highly enriched with cations, which are attracted by the negative charges of heparin sulfate. Hypothetically, the calcium ions on top of the endothelial surface layer, which are divalent cations with dense positive charges, attract albumin more efficiently than other cations [30, 36]. In addition to the electrostatic interaction between albumin and eGC, sphingosine-1 phosphate (S1P)-mediated restoration of the eGC was suggested. The majority of S1P is carried in serum albumin, and endothelial cells contain abundant S1P receptors. Adding S1P to the culture media of the endothelial cells inhibited shedding of sdc1 and induced recovery of the eGC [94, 95].

Apart from albumin, blood-borne proteins and glycosaminoglycan in fresh frozen plasma protected or restored eGC. Animal models with hemorrhagic shock demonstrated that infusion of fresh frozen plasma inhibited shedding of the hemorrhagic shock-induced eGC,

preserving microvascular perfusion [96–98]. Steroids also appear to have a protective effect. Preliminary data have shown that hydrocortisone could help in sustaining vascular barrier function and possibly abrogate damage of the glycocalyx, in the acute inflammatory and proteolytic situation of a myocardial infarction. [93, 99, 100]. In mouse cremaster venules, destruction of eGC by infusion of heparinase or oxidized low density lipoprotein cholesterol (ox-LDL) leads to increase in the number of adherent leukocytes to the endothelial surface, which was partially reversed by infusion of heparin sulfate. In the study, circulating heparin sulfate was suggested to reconstitute eGC [1]. Circulating shed heparin sulfate may be re-integrated into the eGC and can reconstitute the endothelial surface. Sulodexide, a mixture of natural porcine heparin and dermatan sulfates, may be also be administered to restore the eGC. In rats or mice, the restitution of damaged eGC takes several days [101], but the duration required for eGC restitution requires further clarification. In patients with heart failure, slowing of the incremental elevation in serum sdc1 may provide information on the dynamics of the eGC replenishment.

The synthesis of glycocalyx components is also affected by mechano-transduction of the fluid shear stress on the cell surface. In cultured endothelial cells, expression of heparin sulfate on the cell surface was accelerated with atheroprotective shear stress waveforms, which has relatively “high mean shear” and “no shear reversal”, whereas it was reduced with atherosclerotically prone waveform, which has “low mean shear” and “shear reversal” [102–104]. These findings may be confirmed in patients with severe left ventricular systolic dysfunction, severe aortic regurgitation, or those who are supported with extracorporeal mechanical life support, where low shear stress waveforms with shear reversal would be observed.

CONCLUSION

Although many studies proposed that endothelial dysfunction, particularly concerning the eGC, might have intervened between cardiovascular diseases and development of adverse outcomes, the number of studies on this topic are limited. The technical difficulties in evaluating the endothelial dysfunction may have created a vicious cycle of poor understanding and poor attention. Despite difficulties with visualization and volume quantification of eGC, progress in laboratory techniques has increased awareness of eGC roles in the control of endothelial dysfunction by way of shear stress transduction, control of endothelial permeability, and protection of endothelium from inflammatory cells, enzymes, or cytokines with untoward effects.

As increased serum-soluble syndecan in patients with heart failure was associated with adverse clinical outcomes, preservation of eGC is thought to have a protective effect on cardiovascular systems. However, the complexity of eGC constituents mediating a poor prognosis in this population is not well-understood. With the increasing prevalence of heart failure among ageing populations and necessity for developing diverse diagnostic and treatment methods, the role of the eGC is a fascinating and potentially beneficial area that requires further investigation. Currently, the limited number of clinical studies evaluating benefits of eGC protection urges investigators to increase exploration efforts into this emerging field.

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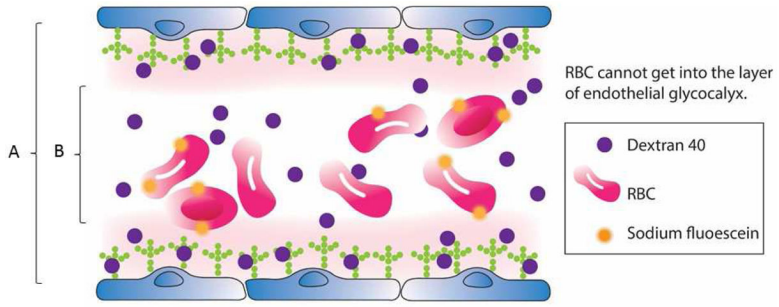

Figure 1.

Double tracer dilution method. The endothelial glycocalyx volume can be obtained by subtracting the circulating volume measured by labeled erythrocytes from the total circulation volume measured using dextran (or other tracer permeable to the glycocalyx layer).

Volume of endothelial glycocalyx = Total circulation volume measured using dextran 40 (A) – Circulation volume measured by labeled RBCs (B)

**RBC,* red blood cell

Table 1

Clinical studies that evaluated syndecan-1 as a diagnostic/prognostic factor in patients with cardiovascular disease.

Authors	Study Subject	Methods	Measurement	Outcomes	Results	Weak points
Oliveira neves et al. [46]	Brazil 201 patients, LVEF 41.5+-14.4%, ADHF	Retrospective cohort, comparison among syndecan-1, GFR and mortality	During ED admission, syndecan-1, hsCRP, ICAM-1, NO, BNP	In-hospital mortality, 6-months mortality	Syndecan-1 is associated with AKI development, associated with 6 month mortality	No functional data (e.g. FMD, association with permeability, no temporal relationship data btw syndecan and HF aggravation
Tromp J et al. [47]	Netherland, 567 patients, chronic HF	Nested cohort study of a prospective randomized study (COACH).	Before discharge, syndecan- 1NTproBNP, hsCRP, IL-6, ST-2, galectin- 3, periostin, TGFbeta	primary: all-cause mortality + rehospitalization at 18 months, Secondary: all-cause mortality at 3 yrs.	Doubling of syndecan was associated with pri/sec end points only in HFpEF (n=107), not in HFrEF(n=353), syndecan-1 associated with cardiac fibrosis markers.	Only chronic stabilized patients. Associated with only HFpEF patients. No functional data. No temporal/causal relationship
Meyer S et al [48]	Netherland, 567 patients, chronic HF	Nested cohort study of a prospective randomized study (COACH).	Before discharge, syndecan- 1NTproBNP, hsCRP, IL-6, ST-2, galectin- 3, periostin, TGFbeta	primary: all cause mortality at 3 yrs, Secondary: all-cause mortality+ rehospitalization at 18months.	Differential sex association between biomarkers and mortality, syndecan was significantly associated with mortality in women, marginally in men.	Only chronic stabilized patients. Associated with only women. No functional data. No temporal/causal relationship
Bielecka - Dabrow a et al [44]	Poland, 68 stable DCM patients	Nested cohort study of a prospective randomized study	proBNP, cystatin C, syndecan-4	Association with further cardiac function assessed by echo.	syndecan-4 are associated with future LVEF, LV dimension.	No data for CV outcomes.
Demissei et al. [45]	Netheland, 2033 acute heart failure	Prospective cohort	During admission, 44 biomarkers including syndecan-1q	time to death, rehospitalization through 30 and 180days	syndecan-1 showed significant HR of adverse events, but was not best biomarker.	No functional data. No temporal/causal relationship
Bielecka - Dabrow a et al. [43]	Poland, 120 hypertensive patients. (60 HF vs. 60 non-HF.)	Cross- sectional	Outpatients, syndecan-4, NTproBNP used for confirmation.	Accuracy of each biomarkers for diagnosis with HF.	AUC for syndecan- 4=0.781	Cross sectional. No causal relationship. No data for CV outcomes.
Ostrowsk et al. [42]	Denmark, 571 patients, STEMI	Prospective cohort	During primary PCI, adrenalin, noradrenalin, syndecan-1, soluble thrombomodulin	30day all-cause mortality CV mortality, Re-MI, HF	adrenalin was associated with 30day mortality, syndecan was marginally associated with only 30days HF admission (p=0.069)	