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REVIEW

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Human glycocalyx shedding: Systematic review and critical appraisal

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Abstracts

Background: The number of studies measuring breakdown products of the glycocalyx in plasma has increased rapidly during the past decade. The purpose of the present systematic review was to assess the current knowledge concerning the association between plasma concentrations of glycocalyx components and structural assessment of the endothelium.

Methods: We performed a literature review of Pubmed to determine which glycocalyx components change in a wide variety of human diseases and conditions. We also searched for evidence of a relationship between plasma concentrations and the thickness of the endothelial glycocalyx layer as obtained by imaging methods.

Results: Out of 3,454 publications, we identified 228 that met our inclusion criteria. The vast majority demonstrate an increase in plasma glycocalyx products. Sepsis and trauma are most frequently studied, and comprise approximately 40 publications. They usually report 3-4-foldt increased levels of glycocalyx degradation products, most commonly of syndecan-1. Surgery shows a variable picture. Cardiac surgery and transplantations are most likely to involve elevations of glycocalyx degradation products. Structural assessment using imaging methods show thinning of the endothelial glycocalyx layer in cardiovascular conditions and during major surgery, but thinning does not always correlate with the plasma concentrations of glycocalyx products. The few structural assessments performed do not currently support that capillary permeability is increased when the plasma levels of glycocalyx fragments in plasma are increased.

Conclusions: Shedding of glycocalyx components is a ubiquitous process that occurs during both acute and chronic inflammation with no sensitivity or specificity for a specific disease or condition.

1 | INTRODUCTION

The glycocalyx is a 0.2-5 μm thick layer of glycosylated proteins that covers the luminal side of the endothelium throughout the cardiovascular system (Figure 1). The layer is believed to have great functional importance to local vasodilatation, coagulation, and inflammation.[1,2]

Degradation of the endothelial glycocalyx layer ("shedding") occurs in inflammatory states, during ischemia, and after vigorous

volume loading. Such shedding is claimed to quickly change the physiology of the endothelium by obstructing local adaptation of blood flow and increasing the capillary permeability for macromolecules, which promotes hypovolemia.[3]

Given these properties, there is no wonder that the glycocalyx has received considerable attention over the past decade as demonstrated by the significant increase in publications. The majority of studies on glycocalyx shedding have been performed in laboratory animals, mostly in rats. Here, shedding of the endothelial glycocalyx seems to result primarily from metalloproteinase (MMP) activity, as inhibition of MMPs reduces endothelial glycocalyx degradation in response to inflammatory stimulation.[4-6]

Increases in circulating heparan sulfates, hyaluronan, and syndecan-1 have been reported in rat models of sepsis[7,8] and hemorrhagic shock.[9-11]

In terms of human investigations, the most common clinical study design has been to identify situations where the glycocalyx is degraded by measuring glycocalyx breakdown products in the plasma of patients. This has been done for a wide variety of conditions with the hypothesis being that the integrity of the glycocalyx can be related to changes in plasma concentrations of glycocalyx shed products.

In the discussion, we review confounding issues related to measuring plasma components assumed to represent cell-surface constituents but that have not been correlated to induce meaningful structural implications of clinical relevance.

Editorial Comment

Glycocalyx shedding during inflammatory and ischemic states, and as a response to volume loading, is an very active area of research in recent years in anesthesiology and critical care medicine. This systematic review of glycocalyx shedding provides a detailed update on the current state of knowledge on quantification of glycocalyx shedding as assessed by measurements from plasma and in vivo structural measurements. Discussion is included regarding uncertainties when interpreting plasma measurements of breakdown products from glycocalyx shedding.

2 | METHODS

To obtain a comprehensive dataset on all of the publications evaluating the human endothelial glycocalyx, a search of PubMed using the term "glycocalyx" yielded 3454 publications, returned from the earliest date in the database record, October 1958 to August 2020. The presentation adhered to the PRISMA Statement, whenever applicable.

Figure 2 represents a summary of our methodology. The first search was automated using the search terms "glycocalyx," then all abstracts were manually reviewed by one person (VP) to ensure the Methods indicated that the study was: (a) human data, (b) recorded a glycocalyx component: syndecan-1 (sdc-1), syndecan-4 (sdc-4), glypican (Gpc), heparan sulfate (HS), chondroitin sulfate (CS) or hyaluronan (HA), and (c) recorded the source (plasma, CSF, urine). Every abstract published that included the word "glycocalyx" was reviewed in detail. The methods sections were reviewed for the type of study that was performed. Review articles and manuscripts without an Abstract in English or else did not evaluate the "human" glycocalyx, "glycocalyx integrity," and/or "glycocalyx damage" were excluded.

Structural assessments of the glycocalyx were categorized as sidestream dark field (SDF) imaging, orthogonal polarization spectral (OPS) imaging, incidental dark field (IDF) imaging, bright-field imaging and erythrocyte sodium sensitivity studies. A brief explanation of each method is presented in the Appendix. SDF, OPS, and IDF are quite similar methods but with incremental refinement to improve image clarity and resolution.

Abstracts that described structural assessment of the glycocalyx using fluorescent dextrans to determine void volumes of the glycocalyx were not included in this review due to concerns raised about this methodology.[12]

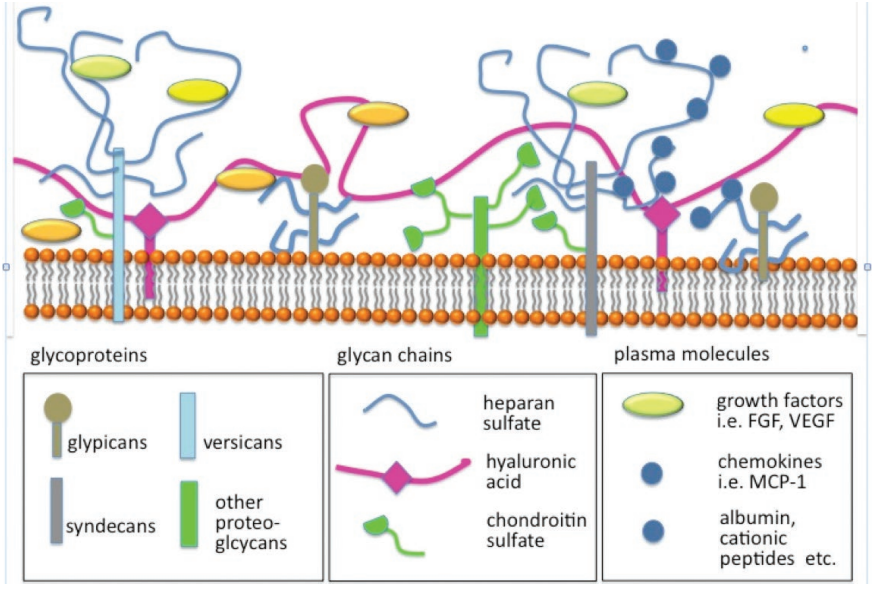

FIGURE 1 Schematic drawing of the molecular ultrastructure of the endothelial glycocalyx layer.[2] Used, by permisison, from Bertram A, Stahl K, Hegermann J, Haller H. The glycocalyx layer. In: Hahn RG, ed. Clinical Fluid Therapy in the Perioperative Setting, 2nd Ed. Cambridge: Cambridge University Press [Colour figure can be viewed at wileyonlinelibrary.com]

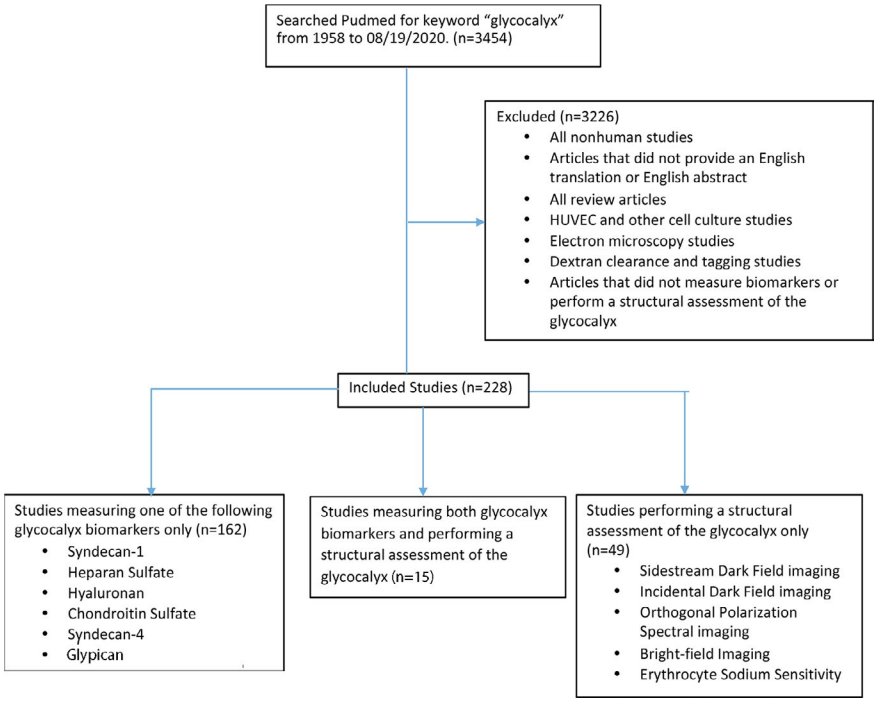

FIGURE 2 Flow-chart showing the search strategy for the systematic review [Colour figure can be viewed at wileyonlinelibrary.com]

We then categorized glycocalyx evaluation in common disease processes and organ systems studied by the authors. In doing so, we categorized common disease and syndromes as: critical illness; endocrine disease; pregnancy; surgery; healthy experimental patients; cardiovascular disease; renal disease; infectious disease; miscellaneous. From there, we identified subcategories in each category based on the models from the reviewed publications. These subcategories are given in the Tables that we chose to present our results.

After placing the reviewed publications into one of the major categories and subcategories, the publications were divided into three groups based on whether the publication investigated breakdown products, performed a structural assessment, or performed both.

The publications are listed in four tables using the following methods. We first assigned reference numbers in an ascending fashion to the models that performed an investigation of breakdown products as there were more publications that investigated this. These were assigned to Tables 1-3. We continued our reference list numerically to include the studies that performed a structural assessment. These were assigned to Table 4.

If a study performed both analysis of breakdown products and structural assessment, it was given the reference number that was labeled in Tables 1-3 and was also placed in Table 4 with the same numerical reference. We indicate an increase (+), decrease (-), or no change (0) in the glycocalyx breakdown product(s) depending on the individual study findings. Methods showing glycocalyx thickness were references as showing decrease (-), increase (+), or no change (0).

3 | RESULTS

After reviewing the 3,454 articles, secondary filters narrowed that list to 228 publications that met inclusion criteria of human studies. Of these studies, 97% measured sdc-1, HS, and/or HA. The remaining studies assessed Gpc, CS, or synd-4.

3.1 | Commonly studied glycocalyx biomarkers

Sepsis and trauma are the most frequently studied conditions and comprise about 40 studies. They usually report 3-4-foldt increased levels of glycocalyx degradation products. Exceptions are quite rare (Table 1, top). One study on encephalitis showed elevated concentrations of sdc-1 in the cerebrospinal fluid.[62] By contrast, studies of diabetes more rarely report increased concentrations of glycocalyx degradation products. Among the few studies of pregnancy, an elevation is common when complications arise, such as preeclampsia or the HELLP syndrome (Table 1, bottom).

Surgery shows a variable picture. Major surgery that involves moments of ischema and marked inflammation, such as cardiac surgery and transplantations, are most likely to show elevations of glycocalyx degradation products. The same number of studies of low-risk surgery show elevations as those that show no change or a decrease, which is the same overall picture offered by studies of healthy humans not undergoing surgery (Table 2).

Fourteen studies have measured glycocalyx degradation substances in cardiovascular disease, which is few when considering that the endothelium is part of the vascular system (Table 3, top). Heart failure and myocardial infarction show variable results. Other conditions show consistent elevations but are covered by single reports only. Renal disease shows a mixed picture, while all seven studies of infectious disease report elevations, mostly of syndecan-1. A number of other diseases in the internal medical field, such as lupus and leukemia, show consistent increases of glycocalyx degradation products. However, these conditions are mostly covered by single reports (Table 3, bottom).

TABLE 1 Changes in glycocalyx biomarker in critical illness, endocrine disease, and during pregnancy

Condition	Syndecan-1	Heparan sulfate	Hyaluronan	Source	Reference
Critical illness					
Sepsis	+			P	13-27
	+	+		P	28
	+		+	P	29,30
	-		-	P	31
		+	+	P	32,33
	+		+	P	34,36
		+	+	U	35[c]
Trauma	+			P	37-52
	+	+		P	53
	+	+	+	P	54[c]
Traumatic Brain Injury	+			P	55-58
Stroke	+			(P, CSF)	59
	0			P	60
	0	+	0	P	61[a,b,c]
Meningitis/ Encephalitis	+			P	62
	+			CSF	62
Non-septic ICU/CCU	+			P	60,63
	+	+		P	64,65
	-			P	66[a]
Endocrine disease					
Gestational diabetes	0	0	0	P	67[c]
Type 1 diabetes		x		P	68,69
Type 2 diabetes	0			P	70
		x		P	71
Pregnancy					
Preeclampsia	-			P	72,73
	+			P	74,75
			+	P	76
	-		+	P	77
	0	+	+	P	78
C section	+	+		P	79
HEELP syndrome	+	+	+	P	80

Note: (P) plasma, (U) urine, (+) increase, (-) decrease, (0) no change

[a]Measured syndecan-4; [b]Measured syndecan-2 and −3; [c]Measured chondroitin sulfate

3.2 | Rarely studied glycocalyx biomarkers

Two studies included data on plasma Gpc; one study[21] measured plasma from septic *vs* control patients and the second study[164] examined plasma glycocalyx markers (glypican and sdc-1) in relationship to forearm arterio-venous fistula failure. In sepsis, Gpc was increased along with C-reactive protein, lactate, pro-calcitonin, sdc-1, and heparin-binding protein. In the second study, there was no relationship between plasma Gpc-1 or sdc-1 *vs* fistula failure; however, HA was positively correlated with failure of the arterio-venous fistula.

The five studies that reported on plasma concentrations of CS found increasing plasma concentrations during sepsis and acute respiratory failure,[33,36] trauma,[54] ischemic stroke,[61] and gestational diabetes.[67]

The results for sdc-4 in plasma are more variable. One study found no change in sdc-4 during sepsis.[34] In a cohort of ICU patients

TABLE 2 Changes in glycocalyx biomarkers in surgical patients and healthy humans

Condition	Syndecan-1	Heparan Sulfate	Hyaluronan	Source	Reference
Surgery					
Cardiac surgery	+			P	81-88
	-			P	89-91
	0	0		P	92
	+	+		U	93
	+	+		P	94-97
	0	-	+	P	98
	+		+	P	99
	-		-	P	100
Brain surgery	+	0		P	101
Vascular surgery	-			P	102
	+	+		P	103,104
Abdominal surgery	+			P	105-107
	+	+		P	108
	0				109,110
	0	+	0	P	111
	0		0	P	112
	0	0	0	P	113,114
	-	-	+	U	114
Transplant surgery	+			P	115-117
	+	+		P	118
	+		+	P	119
	+	-			120
Thoracic surgery	+			P	121
	+	0		P	122
	+	+		P	123
Elective low-risk surgery	-			P	124
	+		+	P	125
	+	0	+	P	126
	+	0		U	126
	+	0		P	127
	0	+	-	P	128
	0	-	-	U	128
Healthy humans[b]					
	+			P	129-134
	0				135
			+	P	136,137
		+	+	P	138
			0	P	139,140
	0	0	-	P	141
	+	+	0	P	142

Note: (P) plasma, (U) urine, (+) increase, (-) decrease, (0) no change

[b]subjected to exercise, simulated altitude, hypoxia etc

composed of gastrointestinal bleed, trauma, sepsis and cardiac arrest, sdc-4 was not different between patients groups or different from controls.[24] Sdc-4 decreased in ICU patients receiving lipid emulsion infusion,[66] while an increase did occur in myocardial infarction.[151] These limited data preclude any meaningful summary from being made.

TABLE 3 Changes in glycocalyx biomarkers in cardiovascular, infectious, and renal diseases

Condition	Syndecan-1	Heparan sulfate	Hyaluronan	Source	Reference
Cardiovascular					
Cardiomyopathy	+			P	143
Heart failure	+			P	144,145
	-	+		P	146
	0		+	P	147
Myocardial infarction	+			P	148-150
	0			P	151[a],152
	+	+	+	P	
Coronary artery disease	+			P	154
	-			P	155
			+	P	156,157
Pulmonary embolism	+			P	158
Cardiac arrest	+		+	P	153,159
Renal					
Hemodialysis	+			P	160,161
	-			P	162
	+		+	P	163
	0		+	P	164
	+		+	P	165,166
Nephrotic syndrome	+				167,168
Acute kidney injury	+				169
	+	+	+		170
	-	-	-	U	170
Infectious					
	+			P	171-175
		+	+	P	176,177
	+	0	+	P	178[b]
		+		U	179,180
Miscellaneous					
Leukemia	+			P	181
Lupus	+			P	182
Kawasaki´s disease	+			P	183
	+		+	P	184
Vascular dementia			+	CSF	185
Transfusion-dependent	+			P	186-188
	+	0	0	P	189
Cirrhosis		+		P	190

Note: (P) plasma, (U) urine, (CSF) cerebrospinal fluid
(+) increase, (-) decrease, (0) no change
[a]syndecan-4 increased; [b]chondroitin sulfate increased

3.3 | Structural measurements

The most widely used method for structural studies of the endothelial glycocalyx layer is to assess its thickness in the sublingual area by side Stream Dark Field (SDF) imaging. The assumption is that shedding of the glycocalyx layer both elevates the plasma concentration of glycocalyx degradation products and causes a thinning or complete absence of this layer on the SDF image.

When sepsis has been studied by this approach, some studies have found a thinning of the glycocalyx layer while others have found no change (Table 4, top). There are two studies in stroke, and both also show a thinning.

TABLE 4 Structural measurements of glycocalyx thickness in various clinical settings. References with a lower number than 191 also report biomarkers, see Tables 1-3 for details

Condition	SDF	OPS	IDF	Other	Vascular bed	Ref.	Biomarker
Critical illness							
Sepsis	0				SL	191,192	
	-				SL	193-196	
				(-) Bright-field	SL	197	
Trauma			-		SL	38	sdc-1 +
Stroke	-				SL	198,199	
Non-septic ICU			-		SL, conjunctiva	63	sdc-1 +
	0					66	sdc-1 +
Endocrine disease							
Type 2 diabetes	+				SL and retinal	71	sdc-1 -
	+				SL	200	
	-				SL	202,203	
Type 1 diabetes		-			SL	68	sdc-1- HS- HA -
	-				SL	204,205	
Pregnancy							
Preeclampsia	-				SL	78	sdc-1- HS + HA +
Surgery							
Cardiac	-				SL	96,206,207	sdc-1 + HS +
	-				Skin	208	
Transplant surgery	-				Peritubular	118	sdc-1 + HA +
Elective low risk surgery	-				SL	209,210	
Neurosurgery	-					211	
				(-) Bright-field microscopy	SL	212	
Healthy humans[a]		-			SL	213	HS - HA -
				(-) Bright-field microscopy	Labial	214	
	+				SL	215-217	
	0				SL	218	HA +
	-				SL	219	
Cardiovascular							
Heart failure	-				SL	220	
	0				SL	221	
Hypertension	-				SL	222-224	
Coronary artery disease	-				SL	225,226	
	0				SL	227,228	
Pulmonary Artery Hypertension	0				SL	229	
Miscellaneous							
Hemodialysis				(+) sodium sensitivity	N/A	230	
				(-) sodium sensitivity	N/A	231	
	0				SL	232	sdc-1
Transfusion dependent	-				SL	189	sdc-1 + HA - HS -

(Continues)

TABLE 4 (Continued)

Condition	SDF	OPS	IDF	Other	Vascular bed	Ref.	Biomarker
Infection	-				Buccal	177	HS + HA +
	0				SL	233	
Antiphospholipid syndrome	-				SL	234	sdc-1+

Note: (SL) sublingual, (+) thickening, (-) reduction, (0) unchanged thickness

[a]subjected to exercise, simulated altitude, hypoxia etc

Trauma and a stroke have been studied with Incidental Dark Field (IDF) imaging, and both show a thinning of the glycocalyx layer. Most studies of diabetes and all studies in major surgery also show thinning (Table 4, middle). The thickness of the glycocalyx in diabetes has also been studied with a third method, Orthogonal Polarization Spectral (OPS) imaging.

The results in healthy humans are quite mixed, while seven of the eight studies of cardiovascular conditions show thinning of the glycocalyx layer (Table 4, bottom).

Assessment of the glycocalyx thickness was made along with biomarker measurements in 15 studies of which 9 showed a correlation (60%). These studies can be found in Table 4.

4 | DISCUSSION

Quantification of glycocalyx shedding has become a common and expedient method to assess the integrity of the endothelial glycocalyx in human disease models. The number of publications increase at a high rate and involve many areas of human medicine. Sdc-1, HS, and HA are most commonly measured in humans, while Gpc, CS, and sdc-4 have been more rarely assessed. The many observational studies performed show that shedding of endothelial surface proteins is a common and ubiquitous occurrence during both acute and chronic inflammation. Less frequently, the thickness of the glycocalyx has been assessed by specialized imaging methods.

For anesthetists, the importance of the glycocalyx has been perceived to be functional and prognostic. The inflammation induced by trauma and major surgery triple the plasma concentrations of several molecules present in the glycocalyx, which has been attributed to endothelial injury. More pronounced elevations, averaging 15 times of baseline, has been reported after surgeries associated with ischema, such as cardiac surgery.[105]

The common pattern is that several glycocalyx biomarkers become elevated, but in some studies only sdc-1 was increased and not HS.[101,122,126,178,189] This is surprising since syndecan-1 carries predominantly HS on its core protein and both markers would be expected to be correlated in plasma concentrations. However, this finding might be due to analytical error since syndecan-1 is stable in saved samples over time while heparan sulfate is more fragile, in particular if not consistently stored at −70°C until analyzed. Conversely, two studies reported a decrease in sdc-1 but an increase in HS or HA.[77,146]

Elevated plasma concentrations of glycocalyx degradation products are clearly related to poor prognosis in severe disease, such as trauma[44,47] and sepsis.[29,105,196,235] However, our review still shows a paucity of data that links changes in plasma concentrations with quantitative physiological or pathological processes in humans. The sensitivity or specificity for examining glycocalyx fragments in plasma has not been demonstrated. A few studies show reductions in glycocalyx thickness but none of these studies make direct measurements of the functional consequences of such changes. Based on the Revised Starling Principle, glycocalyx shedding should increase the capillary permeability of macromolecules such as albumin, which reduces the plasma volume. We have found no studies in humans supporting that capillary permeability is increased when the plasma levels of glycocalyx fragments are increased. In fact, there is evidence that demonstrates no change in vascular permeability.[65,109,236]

These uncertainties are unfortunate because clinical recommendations are frequently based on assumed connections of pathophysiological events involving the glycocalyx. For example, warnings have been given during the past decade that acute hypervolemia causes glycocalyx shedding and implicate that colloid fluids quickly lose most of their volume enhancing effect.[237–240] Recent studies show no shedding from hypervolemia during surgery. These include cholecystitis, appendectomy,[109] hysterectomy,[112] and lengthy abdominal surgery.[128] Elevation of the sdc-1 and HA levels has been reported after correction for plasma dilution,[126] but the validity of such corrections is unproven due to a lack of pharmacokinetic characteristics for these substances.

Animal studies show that the glycocalyx layer might become degraded within 10 minutes, while restoration requires up to one week provided the shedding stimulus is removed.[241] In the rat lung restoration even occurs within 24 hours, but the recovery is dependent on the expression of the fibroblast growth factor receptor which is inhibited by sepsis.[242] These rates cannot be uncritically extrapolated to humans due to interspecies differences in metabolic rate and substrate turnover time.[243]

The metabolism of these compounds is very complicated, and with much of the elimination normally taking place in the liver. The kidneys are usually not considered to be of importance, but urinary concentrations actually do not deviate much from the plasma concentrations. A recent report highlighted the kidney as a source of elimination by measuring sdc-1, HS, and HA over 5 hours in healthy volunteers and post-surgical patients.[170] The renal clearance of

sdc-1 suggested that the entire plasma pool of free sdc-1 would be completely excreted within 15 hours and that a 6-fold variability in plasma concentration could be explained by acute changes in renal function and not due to increased shedding.

Glycocalyx constituents are assumed to stem from the endothelium despite being widely expressed in the body. Protein expression of sdc-1 is abundant in the liver, digestive tract, kidney, urinary bladder, and bone marrow, but hardly at all in muscle, adipose tissue, tongue, and skin. Protein expression for HS is found in muscle and occurs in the cytoplasma of many cell types, as well as in the interstitial matrix.[244] It is often assumed that measured plasma constituents are uniformly derived from the luminal side of the endothelium throughout the vascular tree but, in fact, we do not know from where in the body they originate. This fact constitutes a bias in the present review, as authors being aware of the widespread distribution of glycosaminoglycans in the body may not always use manuscript titles and search terms that refer to the glycocalyx.[235]

We believe that direct measurement of perfused boundary region (PBR) in the microcirculation is, at present, the best method to assess degradation of the glycocalyx. The sublingual vessels have been used as an easily accessible vascular bed to determine the PBR, which is used a surrogate for glycocalyx thickness. In one study, sdc-1 was elevated but there were no changes in the PBR and glycocalyx dimensions obtained through structural imaging; Is the vascular endothelium the source, and do all vascular beds and endothelium contribute equally to shedding? Such questions are relevant because there are a number of human sepsis studies where sublingual PBR has no correlation with a variety of microvascular hemodynamic parameters.[189,195] Specifically, PBR was not correlated with sublingual microvascular parameters including perfused vessel density, proportion of perfused vessels or microvascular flow index in resuscitated sepsis.[196] Likewise, PBR did not correlate with microvascular parameters in normodynamic *vs* hyperdynamic shock and there was limited correlation between the sublingual circulation and gut microcirculation in sepsis.[189,245] Finally, this lack of correlation was reported following transfusion and use of activated protein C in septic patients.[23,144] In summary, the current data show only a weak correlation between glycocalyx thickness and with structural microcirculatory indices during sepsis.

There is widespread acceptance of the glycocalyx as a permeability barrier. The original publication that gave rise to the glycocalyx' role as a permeability barrier came from Adamson who measured the hydraulic conductivity (L_p) of frog mesenteric microvessels before and after pronase treatment.[246] Pronase is a broad-spectrum protease that was presumed to significantly degrade the glycocalyx off the surface of the mesenteric vessels. Adamson reported that pronase digestion of glycocalyx increased L_p by 2.5-fold and calculations estimated that glycocalyx accounted for 60% of hydraulic resistance to water flow across the capillary wall. However, increased capillary leakage of fluid or albumin resulting from increased plasma levels of sdc-1 and HS in humans has not been possible to demonstrate in volunteers and in surgical patients.[65,109,110,236] Similarly, Ince *et al* and colleagues found no change in vascular barrier to fluid distribution despite increases in plasma sdc-1 and HA in hemorrhaged rats.[247] They also demonstrated that normovolemic hemodilution-induced glycocalyx shedding in rats does not alter vascular permeability to dextrans, albumin or plasma.[248]

In chronic diseases, compensatory responses may offset changes in shedding or expression. For example, in one study assessment of the glycocalyx by SDF imaging showed no significant difference in glycocalyx dimensions between patients with and without cardiovascular disease.[227] However, two studies have reported elevations in sdc-1 and HA in patients with cardiovascular disease.[159,184] Support for compensatory reaction(s) can be inferred from an in vivo study of the glycocalyx in sdc-1 knock-out (KO) mice where Savery et al used micro-particle velocimetry to determine the presence of a hydrodynamically significant cell surface layer.[249] They observed no difference in wild-type vs. sdc-1 KO mice and concluded that sdc-1 was not necessary for the existence of an endothelial glycocalyx. Their limited analysis, however, could not rule out altered expression of other glycocalyx components in the sdc-1 KO. Consider that in cultured endothelial cells, knock down the sdc-1 gene resulted in increased mRNA for Gpc-1, sdc-4, sdc-4, and for a series of enzymes involved in heparan sulfate biosynthesis.[250]

Langford and colleagues examined the effect of mutated glucosaminoglycan attachment sites on the core protein of syndecan-1 on invasive cell function.[251] To their surprise, cells that expressed a modified syndecan with reduced glucosaminoglycan attachment sites on the core protein displayed no change in total cell surface heparan sulfate. This means the cells had compensatory responses to maintain a constant amount of HS on their surface to preserve function. If similar responses occur in vivo it is not surprising that sdc-1 KO mice have a normal glycocalyx. Evaluation of a single parameter then seems to be insufficient to make conclusion(s) about the composition, 3-dimensional structure, or functional consequences to the glycocalyx.

If we were to assume that all the data in Table 1 was free from publication bias and issues of renal clearance, the preponderance of data suggests that the glycocalyx is damaged during a wide variety of insults, as shedding increased in 96% of all published reports. If this percentage is valid, then what is the usefulness of a biomarker that increases ubiquitously across many disease states? Although uncertain, we suggest that an increase of five times the baseline in acute disease or trauma might be accepted as evidence of release of glycocalyx degradation products from somewhere in the body. Smaller changes might be due to short-term fluctuations in metabolism and urinary excretion.

5 | CONCLUSION

The utility of measuring glycocalyx breakdown products in the plasma as biomarkers with a predictive value for determining a specific disease or the progression of a disease is unproven. Shedding of glycocalyx components is a ubiquitous process that occurs during both acute and chronic inflammation with no sensitivity or specificity

for a specific disease or condition. Uncertainties related to proteoglycan expression levels, turnover rate, shedding, renal clearance and lack of correction for hemodilution cast doubts on many of the reported alterations in glycocalyx breakdown products measured in plasma. There is only a moderately good correlation between plasma concentration and the structural assessment of glycocalyx thickness (60% agreement), which further questions the utility of measuring plasma glycocalyx components as a surrogate for structural and functional alterations. Finally, compensatory expression of glycocalyx constituents may offset the loss of specific components in order to maintain structural integrity.

CONFLICT OF INTEREST

None.

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APPENDIX

The following methods have been used to assess the thickness of the glycocalyx layer in vivo.

Bright-field imaging	Microcirculation is illuminated with visible light, positioned at a long working distance from the tissues and projected at angles between 45 and 90 degrees from the tissue surface. Reflected image is projected through a lens for direct viewing or capture by a camera. Provides relatively low resolution.
Orthogonal polarization spectral (OPS) imaging	Microcirculation is illuminated with polarized green light. Reflected light from the tissue surface is captured and quantified. Emission and reflected light travel through the same tube thus method is sensitive to internal reflectance. Signal processing includes filtering of reflected polarized light to improves visualization of underlying vessels.[252]
Sidestream dark field (SDF) imaging	Developed as a refinement to OPS. Uses light emitting diodes (LEDs; 530 nm) tuned to absorption by hemoglobin. LEDs are arranged concentrically around a center sensing tube and are placed in contact with tissue. Light paths for excitation and emission are different thus reducing internal interference and providing clearer images.[253]
Incidental dark field (IDF) imaging	Similar to SDF, but IDF illuminates tissue using a non-homogenous field. Incident illumination is projected at a very low angle relative to the tissue surface. Increased signal sensitivity, greater field of view and improved optical resolution contributes to enhance image quality.[254]
Erythrocyte sodium sensitivity test (ESST)	Based on the principle that the red blood cell glycocalyx and vascular endothelial glycocalyx are in direct contact. Loss of the endothelial glycocalyx increases drag forces on the RBC surface and damages the RBC glycocalyx. This damage can be assessed and quantified by salt-sensitive sedimentation rates of the RBC. Studies have shown a correlation between EC glycocalyx thickness and RBC sedimentation rates.[255,256]