7-24-2018

Underappreciation of Endothelial Glycocalyx

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Introduction

While most clinicians have a basic understanding of the human body's "pumps and pipes," many do not know that blood vessels contain a special protective layer called the endothelial glycocalyx. Its unique composition and function make it important to more than several pathophysiologic processes in the body.

When the endothelial glycocalyx is damaged, the luminal side of the endothelium is no longer protected and complications can occur. There are four main identifiable reasons that contribute to the degradation of the glycocalyx and surprisingly, all are very common among those who are critically ill.

This structure is worth discussing because it ultimately dictates the severity of hemodynamic compromise that can occur once the glycocalyx is degraded. By avoiding damage, the hope is that both morbidity and mortality can be reduced.

Pathophysiologic Process

Composition:

The endothelial glycocalyx is a slimy, gel-like substance in the shape of thin, hair-like projections on the inside of the lumen wall in blood vessels (see figure 1).

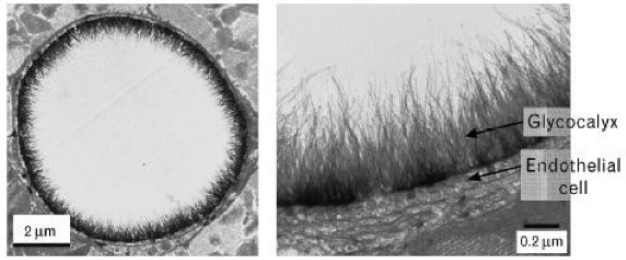
It is primarily made up of glycoproteins and proteoglycans. Glycoproteins are proteins that have carbohydrate groups attached to a polypeptide chain while proteoglycans are proteins bonded to glycosaminoglycan groups. Without plasma constituents binding to the glycocalyx such as albumin, the glycocalyx has no active physiologic role.

Once the structure binds plasma constituents, like albumin to its surface, they together form the active endothelial surface layer. The surface has a net negative charge and repels other negatively charged molecules as well as red and white blood cells along with platelets (Alphonsus & Rodseth, 2014).

How It Helps:

- Regulates vascular permeability by acting as a double barrier to large and small molecules
- Regulates vascular tone
- Protects endothelial cells from shear stress
- Prevents adhesion of white blood cells and platelets to vessel wall
- Docks coagulation enzymes creating antithrombotic effect in vasculature
- Allows red blood cells to flow smoothly through vessel (Biddle, 2014)

Figure 1. Microscopy of vessel lumen with enlargement of glycocalyx. Source: (Roberson & Watton, 2013)



Damaged Endothelial Glycocalyx Worsens Patient Outcomes

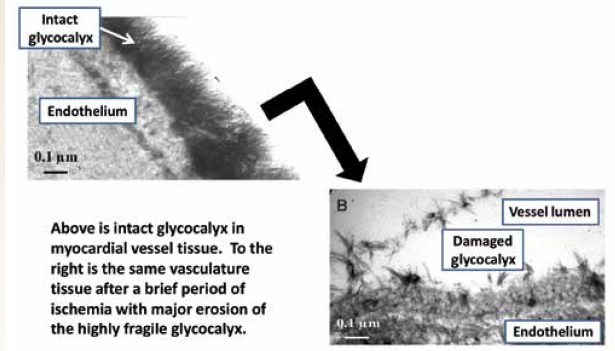
Signs and symptoms of a damaged glycocalyx include:

- Capillary leak
- Edema
- Increased inflammation
- Platelet aggregation
- Hypercoagulability
- Loss of vascular tone

(Biddle, 2014)

Lab data that shows an elevation in serum glycocalyx shedding positively correlates with a worsened clinical outcome in critical illness (Colbert & Schmidt, 2016). When the glycocalyx is damaged, parts of the structure are broken down and the flow of blood releases these parts into circulation(see figure 2).

Figure 2. Microscopy before and after ischemia has damaged the glycocalyx . Source: (Biddle, 2014)



Above is intact glycocalyx in myocardial vessel tissue. To the right is the same vasculature tissue after a brief period of ischemia with major erosion of the highly fragile glycocalyx.

Lab Testing & Treatment

Using glycocalyx degradation as a marker for severity of endothelial damage and/or critical illness may be a potential laboratory value of merit. It may also be a new screening tool for sepsis (Martin, Koczera, Zechendorf, & Schuerholz, 2016). Currently, there is not enough research to demonstrate its routine use. Point-of-care testing may be worth further research.

Microcirculation-protective therapies like steroids, colloids, vasopressors, and anticoagulants were initially thought to protect the glycocalyx, however, outcomes in clinical trials have shown no therapeutic benefit (Colbert & Schmidt, 2016). Currently, there are no recommended treatments other than treating the underlying cause.

Main Culprits

Ischemia

Without oxygen, the glycocalyx begins to degrade and shed its full, thick coat. The vessels that supply blood to the heart as well as the vessels that supply blood to the central nervous system are particularly more sensitive to ischemia (see figure 2). Once shedding starts, leukocyte and platelet adhesion to the epithelial surface exacerbates the injury (Biddle, 2014). Higher concentrations of serum glycocalyx components have been noted particularly in peripheral arterial surgery and coronary artery bypass surgery (Alphonsus & Rodseth, 2014).

Inflammation

Inflammatory mediators, such as cytokines, in trauma and septic patients degrade the glycocalyx. The cleavage of the glycocalyx renders the endothelium bare; this contributes to capillary leakage (Chen, 2016a). Also, shearing stress to the endothelium causes release of nitric oxide which in turn causes vasodilation of blood vessels. This is one reason why septic patients are profoundly hypotensive in addition to the hypovolemia caused by fluid leaking out into the interstitial space. Serum levels of glycocalyx degradation in septic patients are correlated with worse outcomes (Chen, 2016b).

Hypervolemia

By administering too much IV fluid, preload of the heart increases. As the right atria and left ventricle begin to stretch, natriuretic peptides are released and activate metalloproteinases that digest the glycocalyx. This is especially true if the IV fluid is albumin and the patient is normovolemic prior to the infusion since albumin is made up of larger molecules and stays in the intravascular space longer (Chappell & Jacob, 2014; O'Connor & Prowle, 2015)

Hyperglycemia

Elevated blood glucose, especially in type-1 diabetic patients, degrades the glycocalyx. Research has shown that type-1 diabetics have half the thickness of a normal glycocalyx when compared to non-diabetic counterparts (Alphonsus & Rodseth, 2014). Even in healthy, non-diabetics, 6 hours of hyperglycemia degrades the systemic glycocalyx by 50% (Biddle, 2014).

Implications

Despite the lack of treatment options to reduce the severity of damaged endothelial glycocalyx, understanding its purpose and the negative consequences it can have will allow clinicians to avoid exposing their patients to the main culprits of degradation.

Future research should be focused on point-of-care lab testing and effective microcirculation-protective therapies.

Conclusion

The glycocalyx is an underappreciated component of the endothelial vascular layer that resides within the lumen of blood vessels. Due to its sensitive nature, every effort to protect its structure should be utilized.

By avoiding ischemia, hypervolemia, inflammation, and hyperglycemia, the risk of capillary leak, edema, and other complications can be avoided. Analyzing the microcirculation is a promising new way to detect early dysfunction and improve the outcomes for those who are critically ill.

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