

The role of the endothelial glycocalyx in the pathogenesis of atherosclerosis: a new frontier in cardiovascular health

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Much recent work on the pathogenesis of atherosclerosis has focused on the “response to injury theory”. In brief, the theory holds that atherosclerosis may be understood as an inflammatory response to insults occurring to the endothelium.¹

When the endothelium is healthy atherosclerosis does not occur. When the endothelium is damaged, it produces surface-adhesion molecules causing monocytes and t-lymphocytes to stick to its surface, which then penetrate the endothelium into intima. As low density lipoprotein (LDL) particles follow the path, they enter the intima and begin to oxidize. This sets the stage for foam cell formation and plaque development. The resulting plaque then builds up and, when internally inflamed or externally eroded, can be a threat to rupture its contents into the arterial flow, potentially triggering a blood clot that if large enough or not lysed quickly enough can occlude the artery to various degrees causing anything from mild to devastating downstream ischemia. Indeed, it is the clotting in response to plaque disruption, not the plaque accumulation in the arteries per se that poses the real threat. 75% of heart attacks occur at arteries that are less than 50% blocked, while mild plaquing escapes traditional stress tests 80% of the time.

Needless to say, this means that merely measuring the serum levels of LDL and HDL is inadequate to assess event risk. To interrupt the cycle, clinicians need to be primarily concerned with the health of the endothelium.

The injury-response theory is gaining widespread acceptance, but it begs an important question: What causes the injury to the endothelium in the first place? Multiple candidates have been cited such as:

- Direct trauma causing physical injury
- Turbulence in the blood flow, for example at artery bifurcations
- Excessive blood glucose levels
- Circulation of free radicals

- TMAO (trimethylamine-N-oxide)
- Higher than normal concentrations of LDL or VLDL
- High blood pressure
- Circulating toxins
- Deterioration of the NO system

All of these explanations have value, but they miss a critical factor in endothelial health which merits more attention than it has received in the current literature. That factor is the endothelial glycocalyx.

The Endothelial Glycocalyx

Popular accounts of the endothelium inaccurately describe it as “the inner lining” of the blood vessels. Here’s Wikipedia:

“Endothelium is a type of epithelium that lines the interior surface of blood vessels and lymphatic vessels, forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall.”

What’s missing from these accounts is the glycocalyx, a slippery smooth gel coating of the endothelium that positions an additional layer between the endothelium and the circulating blood. This is the true interface. In other words, it’s the endothelial glycocalyx—not the endothelial cells themselves—that has (or should have) direct contact with the circulating fluids and particles.

When we help doctors explain the endothelial glycocalyx to patients, we sometimes liken it to the non-stick surface of a frying pan. The analogy is useful because it highlights the protective function of this important structure. A healthy glycocalyx ensures that LDL particles “slip by” without contacting the endothelium. Conversely, when the endothelial glycocalyx is compromised (which happens very easily) the endothelium becomes susceptible to injury impairment and LDL penetration.

Important clinical implications follow. To prevent atherosclerosis, we must protect the endothelium from injury and preserve its vital functions. To protect endothelial function, we must support its *existing natural protection*, the endothelial glycocalyx. In layman’s terms: if you want to stop food sticking to your saucepan, take care of the non-stick coating! If you want the infrastructure of the endothelium to work you need to protect its surface.

A Closer Look at the Glycocalyx

The endothelial glycocalyx is a thin gel-like layer that coats the entire luminal side of the vascular endothelium. It is a meshwork mainly of glycoproteins, proteoglycans and glycosaminoglycans at a thickness of approximately 1 μm magnitude.²⁻⁴ Syndecans and glypicans are the core proteins of heparan sulfate (a glycosaminoglycan) proteoglycans bound to endothelial cells identified in the glycocalyx. Glycoproteins such as selectins and integrins are also anchored on endothelial cells while some other soluble proteins and proteoglycans simply dock in glycocalyx.⁵

Extensive research has revealed the importance of glycocalyx-mediated endothelial function in vascular and microvascular health.

For example, the endothelial glycocalyx:

- Regulates vascular permeability and fluid balance due to the large size and negative charge of glycosaminoglycans.^{6,7}
- Provides a physical barrier against inadvertent adhesion of platelets and leukocytes to the vascular wall.⁸
- Regulates coagulation as many of mediators of coagulation pathway are buried inside the glycocalyx under normal physiological condition.⁵

Most intriguingly, the glycocalyx is found to be a mechano-sensor and -transducer of the shear-force inside blood vessels.³ The signal is believed to be transduced to endothelial nitric oxide synthase (eNOS) via heparan sulfate in the glycocalyx to either up- or down-regulate the synthesis of nitric oxide (NO) in response to the blood flow.^{9,10}

Figure 1 below illustrates the chemical structure of the endothelial glycocalyx and its signal transduction to eNOS and subsequently sGC (soluble guanylyl cyclase) to induce smooth muscle relaxation via shear stress.

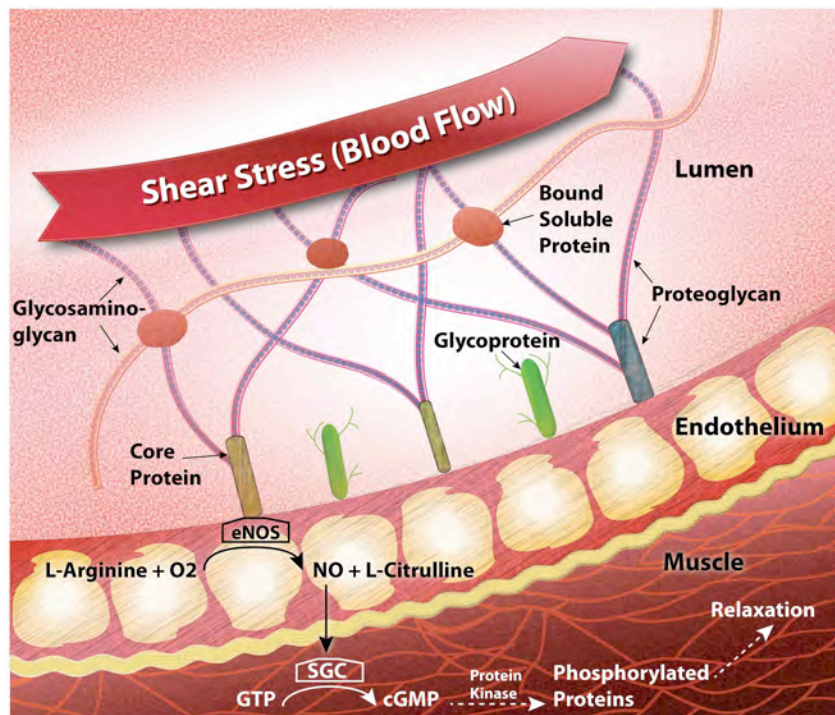


Figure 1. Structure of the endothelial glycocalyx and its activation of vascular muscle relaxation via NO in response to increased shear force

Damage to the Endothelial Glycocalyx

The endothelial glycocalyx is a delicate structure and can be damaged by several common mechanisms involved in the pathogenesis of atherosclerosis. These include high blood glucose,¹¹ oxidative stress,¹² and inflammation.⁴ It is known that high-sugar diets, cigarette smoking, stress, and aging can all degrade the glycocalyx.

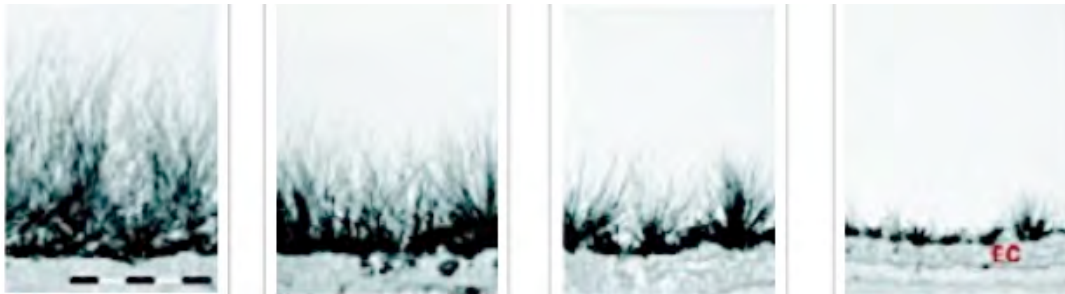
Hyperglycemia is a major cause for disruption of the endothelial glycocalyx.^{11,13} In fact individuals with hyperglycemia and diabetes are known to have less endothelial glycocalyx.¹⁴ Such a change may explain the endothelial dysfunction and increased microvascular permeability that lead to major complications in the diabetic population.^{15,16}

There are several other disease conditions identified so far to be associated with a compromised endothelial glycocalyx:

- Coronary heart disease¹⁷
- Renal diseases¹⁸

- Lacunar stroke (a small vessel disease)¹⁹
- Severe trauma²⁰

These electron-microscope images show the deterioration of the endothelial glycocalyx:



Clinical Interventions

Given the vital role the endothelial glycocalyx plays in the pathology of many vascular and micro-vascular related diseases, it has naturally become a target for pharmaceutical intervention.^{21,22} However, glycocalyx drug development is still in its infancy and no substantial progress has been made to date.²³

A dietary supplement has been tested and shown to have measurable benefits for a compromised glycocalyx in healthy subjects. Brand-named Arterosil, its primary ingredient is rhamnan sulfate derived from rare marine algae. Rhamnan sulfate has a similar chemical structure to heparan sulfate found abundantly in the human endothelial glycocalyx, and may exert its bioactivity by regenerating the glycocalyx.

In an early clinical trial, the positive impact on the glycocalyx was established by measuring recovery of RHI (reactive hyperemia index) in 20 healthy human subjects following a high-sugar, high-fat meal. Results were compared with and without consumption of Arterosil. The study confirmed a significant improvement in glycocalyx RHI recovery with the supplement.

Important safety data were obtained for complete metabolic panel (CMP), thyroid stimulating hormone (TSH), complete blood count (CBC), and partial thromboplastin time (PTT) from the trial. No significant changes were observed for any of these tests after 4 weeks of Arterosil supplementation. There was also no serious adverse event reported during the study and the product was well tolerated by all subjects.

The Glycocalyx and Arterial Elasticity: A New Frontier

The clinical significance of arterial elasticity is well established: Central arterial stiffness has been shown to be an independent predictor of cardiovascular morbidity and mortality.²⁴ While the prognostic value of this measure is widely accepted, the causes of arterial stiffness are still subject to debate. Some research suggests that the issue is not limited to the larger arteries themselves, but may extend to the microvascular system.²⁵ Other studies indicate the role of endothelial function in determining the degree of arterial elasticity.²⁶

One useful contribution to this debate may prove to be a new focus on the endothelial glycocalyx. Because the glycocalyx serves to protect the integrity of the endothelium, and hence of the arterial wall, it stands to reason that a healthy glycocalyx might be associated with good arterial elasticity.

We conducted a pilot study to test patients for arterial elasticity — among other markers — before and after the consumption of Arterosil.

Nineteen healthy human subjects (11 females age 22 to 64 and 8 males age 30 to 60) were randomly recruited for the single blinded clinical study, which was conducted at an independent cardiology center on the Baylor Medical Campus in Plano, Texas. Their vascular health condition was evaluated utilizing MaxPulse, an FDA approved Class II device (The Cardio Group, 6440 N. Central Expressway, Suite 100, Dallas, TX 75206). The MaxPulse utilizes accelerated plethysmography technology with data being gathered by way of a finger probe. This technology, also known as pulse wave analysis, includes multiple factors including wave type, arterial elasticity, eccentric constriction and remaining blood volume valuations.

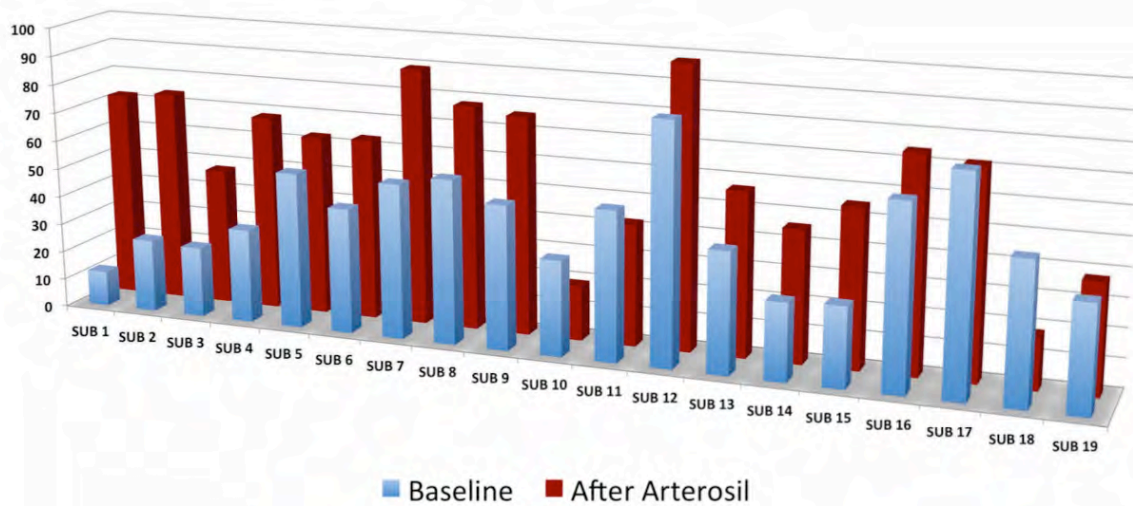
In this study, the baseline reading was taken at approximately 2 hours (+/- 30 minutes) post consumption of a breakfast of the subjects' choice. Immediately after the baseline reading one capsule of ArterosilHP* was swallowed. A post-dose reading was taken every 30 minutes for 3 hours, for a total of 7 readings (baseline, 30 min, 60 min, 90 min, 120 min, 150 min & 180 min +/- 5 minutes). The patients were kept in a quiet ambient environment. No food or liquid (other than small amounts of water as needed) was consumed during the 3 hour testing period.

The results are summarized in the table below:

Arterial Elasticity by Subject

Average increase: 89.6%

($p = .0081$)



In sum, 78.9% of subjects experienced an increase in arterial elasticity. The average percentage increase in arterial elasticity was 89.6% ($p = .0081$). The mean time to maximum increase was 118 minutes. There was concurrent improvement in remaining blood volume and eccentric contraction.

In this preliminary study, we were able to demonstrate that Arterosil improves arterial elasticity in healthy human subjects. It is likely this acute beneficial effect is a result of improved glycocalyx and its mediated endothelial functions. These new data are in agreement with our previous findings that Arterosil helps regenerate the endothelial glycocalyx and restore compromised endothelial functions. Clearly there is a need for further studies to validate these early results.

We know that arterial stiffness indicates adverse changes of blood vessel structure and function, and poses a significant threat to patients' cardiovascular health.²⁷ If it transpires that rebuilding the glycocalyx has a rapid and positive impact on arterial elasticity, this could suggest a valuable clinical intervention, both for patients presenting disease conditions and for those seeking preventative care.

About the Primary Author

Dr. Derrick DeSilva is a practicing internist with a wide range of medical interests. He serves as Senior Attending Staff at the Department of Medicine, Raritan Bay Medical Center (RBMC) in Perth Amboy, New Jersey. He also serves on the teaching faculty of the JFK Medical Center in Edison, New Jersey. Dr. DeSilva serves as Chairman of the Planning Committee for the Age Management Medicine Group (AMMG) and is a Past President of the American Nutraceutical Association. He has been a recipient of the Alan Mintz Award for Excellence in Clinical Age Management Medicine, and he has received the Best Doctor Award by Castle Connolly for the past 15 consecutive years. Dr. DeSilva is host of "Ask the Doctor" on WCTC Radio, a medical correspondent for Cablevision (News 12 New Jersey) and host of "12 to Your Health".

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