What is “new” in preventive cardiology/ Glycocalyx

Stephen W. Parcell, ND

Learning Objectives



WHAT IS A GLYCOCALYX?



WHEN/WHY IS IT RELEVANT?



WHAT ARE THE COMPONENTS OF THE GLYCOCALYX?



WHAT ROLE DOES THE ENDOTHELIAL GLYCOCALYX PLAY AND ARTERIAL DISEASE AND HYPERTENSION



WHAT FACTORS DAMAGE THE GLYCOCALYX?



WHAT DIET AND LIFESTYLE INTERVENTIONS HELP RESTORE THE GLYCOCALYX?



WHAT NATURAL MOLECULES CAN BE USED?

What is the endothelial glycocalyx (eGC)

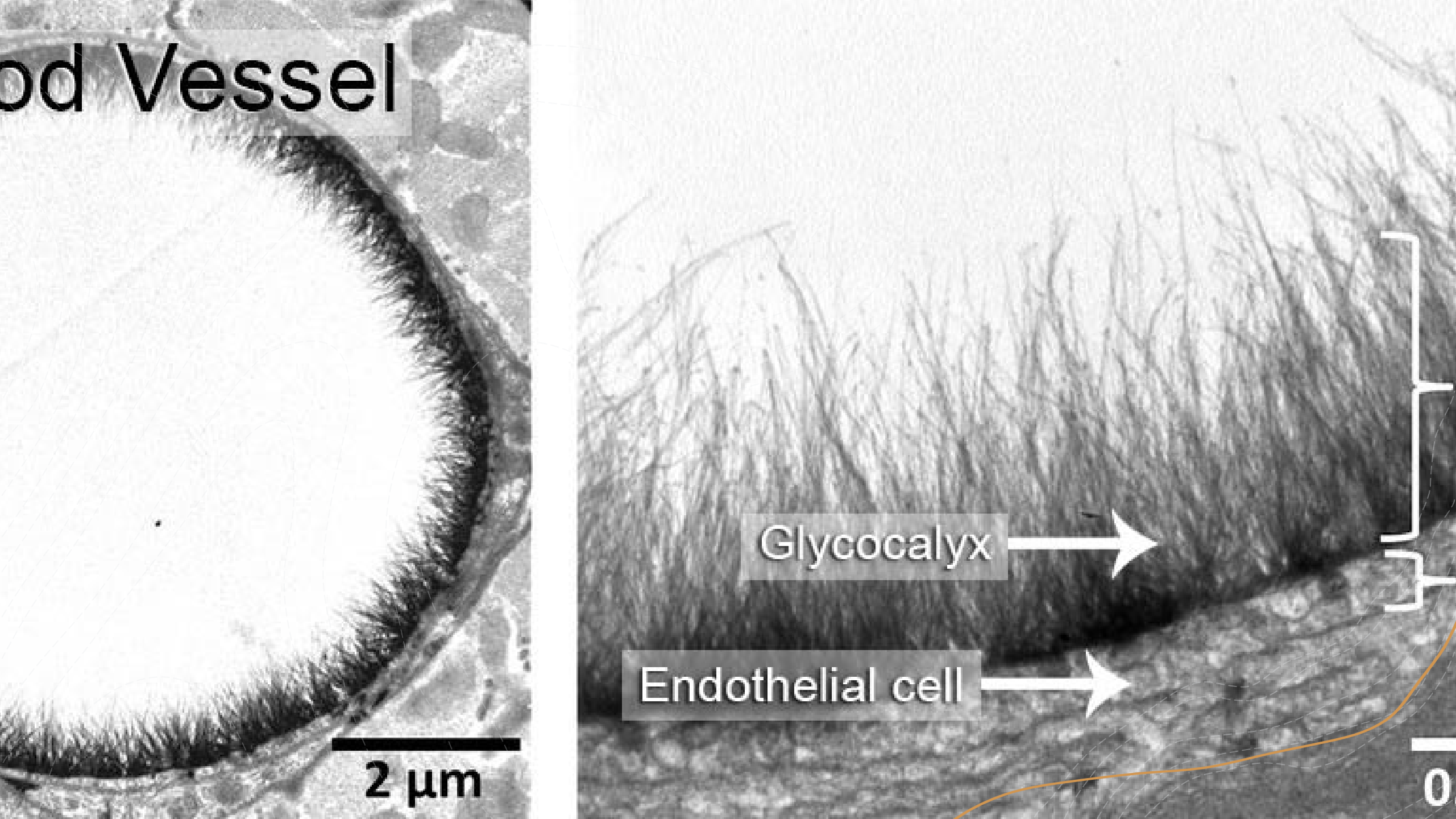
All cells even bacteria have this protective (gel) lining made of long chains of carbohydrates and proteins. Our interest here is the vascular endothelial glycocalyx.

Similar to structured water (negative charge). Mixture of proteoglycans, glycosaminoglycans, and glycoproteins

It is found in arteries, veins and capillaries. The eGC has a negative charge. It's "non-stick" surface helps maintain endothelial function including arterial elasticity and healthy blood pressure. Researchers now consider the endothelial glycocalyx as a first line of defense against vascular diseases.

I used to say that the endothelium is the first-line of defense but now I call the endothelium the second line of defense.

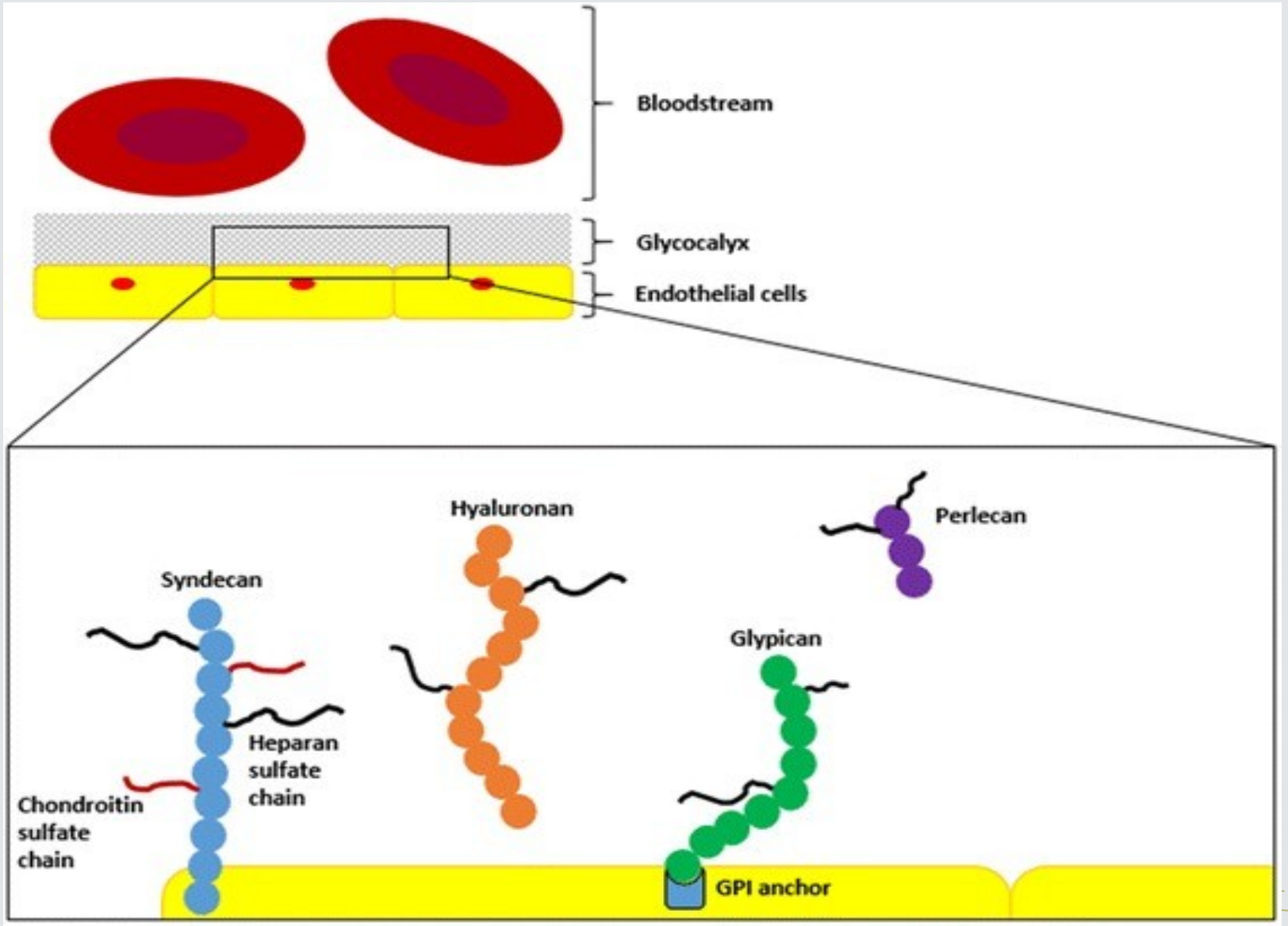
It is a central regulator of vascular function

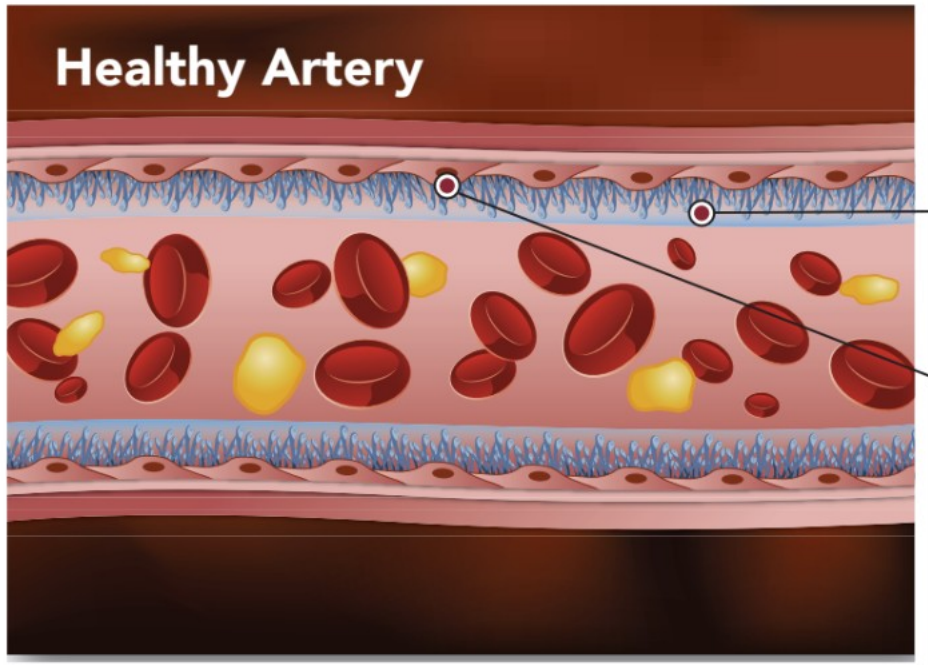

od Vessel
2 µm
Glycocalyx
Endothelial cell

The eGC has various functions

Cell recognition	Cell adhesion	Protection	A barrier that controls permeability of molecules, LDL etc
Controls nitric oxide release, vascular tone and vasodilation	Contains enzymes, plasma and more	Maintains arterial flexibility/ controls vascular aging	Glycocalyx thickness correlates with eGC integrity and function. Reduced thickness has been observed in inflammatory disorders in humans and is associated with vessel dysfunction

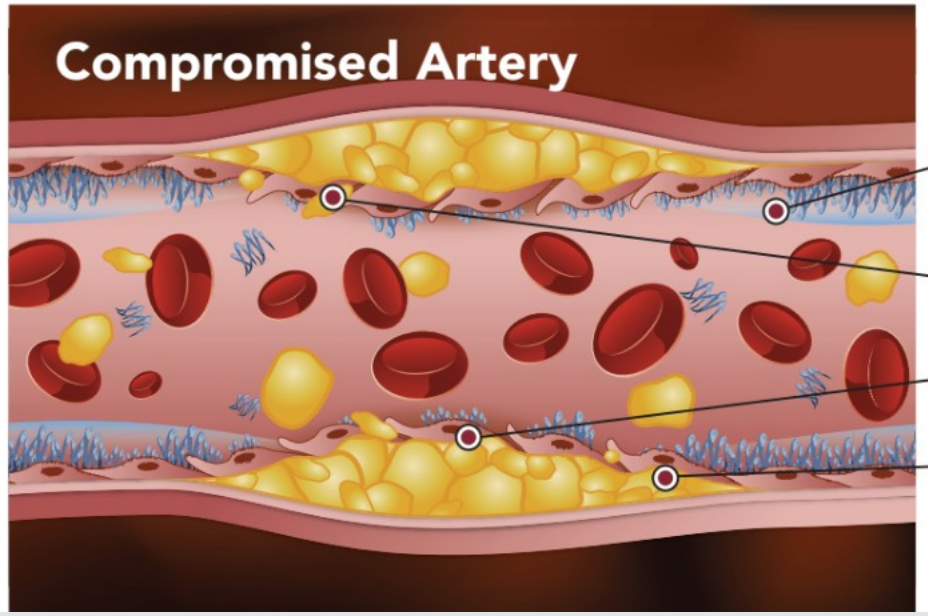
Function	Reference
Forms the interface between the vessel wall and the bloodstream	Reitsma et al. 2007 [5]
	Alphonsus and Rodseth 2014 [10]
Maintains the colloid osmotic gradient of the vascular barrier	Rehm et al. 2007 [12]
Acts as a barrier to:	
vascular exchange of water and solutes	Reitsma et al. 2007 [5]
leukocyte–endothelium adhesion	Henry and Duling 1999 [13]
	Lipowsky et al. 2011 [14]
	Constantinescu et al. 2003 [15]
	Becker et al. 2015 [19]
Acts as a sieve for plasma proteins	Vink and Duling 2000 [16]
	Lipowsky et al. 2011 [14]
Provides binding sites for everal molecules, including:	
antithrombin III	Alphonsus and Rodseth 2014 [10]
tissue factor pathway inhibitors	Reitsma et al. 2007 [5]
lipoprotein lipase	Kolářová et al. 2014 [18]
vascular endothelial growth factor	
fibroblast growth factor	
extracellular superoxide dismutase	
hyaluronic acid molecules	
Acts as a shear stress sensor and regulator of mechanotransduction	Reitsma et al. 2007 [5]
	Florian et al. 2003 [17]
	Yen et al. 2014 [20]
	Becker et al. 2015 [19]


Bloodstream
Glycocalyx
Endothelial cells
Hyaluronan
Perlecan
Syndecan
Glypican
Heparan sulfate chain
Chondroitin sulfate chain
GPI anchor



Endothelial glycocalyx protects artery walls, allowing blood to flow freely

Artery wall is compact, deterring penetration



Protective glycocalyx layer is destroyed

Fats penetrate endothelium

Endothelium is compromised

Artery wall becomes slack and weak

Nitric oxide (O=N)

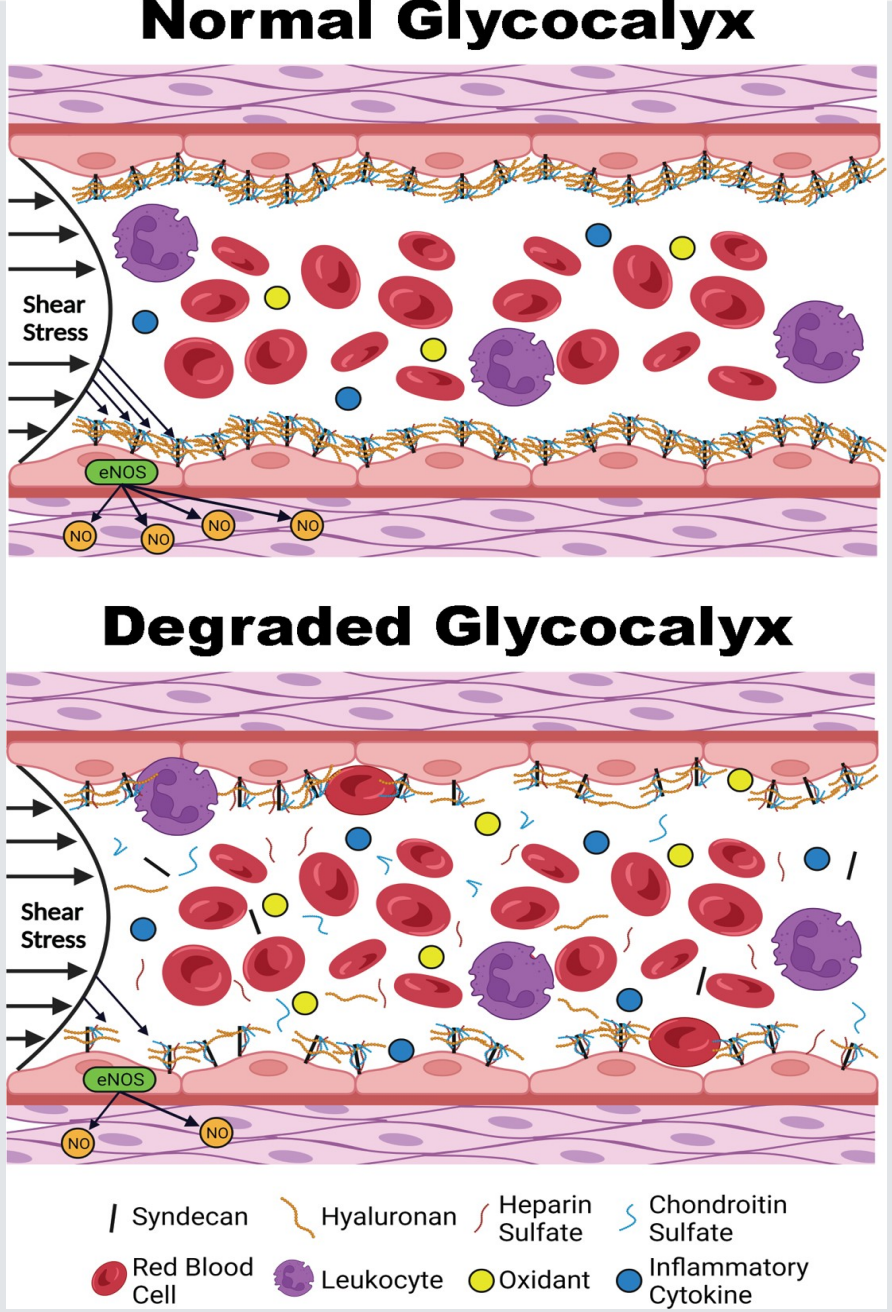
Decreased IC calcium=relaxation

NO interacts with vascular smooth muscle cells and activates soluble guanylate cyclase (sGC), which converts guanosine-triphosphate (GTP) to cyclical guanosine-monophosphate (cGMP). This leads to activation of protein kinase G (PKG)and subsequently **decreases intracellular calcium levels**, causing relaxation of smooth muscle cells and vasodilation.

Shear stress stimulates NO

NO>sGC>GTP>cGMP>PKG= **vasodilation**

The eGC mechanotransduces shear stress to the endothelium, which ALSO promotes nitric oxide-mediated vasodilation. Shear stress is bad if it is degraded. In its degraded state, components of the eGC can be found in the blood, and this is how damage is measured.



MACHIN DR, SABOURI M, ZHENG X, DONATO AJ. THERAPEUTIC STRATEGIES TARGETING THE ENDOTHELIAL GLYCOCALYX. CURR OPIN CLIN NUTR METAB CARE. 2023 NOV 1;26(6):543-550.

We have known about this since 1970 why is it “new” in Cardiology?



A GROWING BODY OF EVIDENCE SHOWS DEGRADATION OF EGC LEADS TO ADVERSE CARDIOVASCULAR EVENTS



THE VARIOUS ROLES THE GLYCOCALYX PLAYS ARE MORE WELL UNDERSTOOD NOW BY THE SCIENTIFIC COMMUNITY.



STRATEGIES (“DRUGS”) ARE BEING DEVELOPED FOR RESTORING IT.



COVID RESEARCH

Age degrades eGC

A study found that glycocalyx thickness in the sublingual microcirculation was 33% lower in older human participants (average age 60 ± 2 years) compared to younger participants (average age 29 ± 1 years).

Older individuals exhibited a 10–22% greater PBR, indicating a more penetrable and thus degraded eGC.

Perfused microvascular density was 18% lower, and red blood cell (RBC) fraction was 5% lower in older participants, suggesting compromised microvascular function associated with glycocalyx degradation.

MACHIN DR ADVANCED AGE RESULTS IN A DIMINISHED ENDOTHELIAL GLYCOCALYX. AM J PHYSIOL HEART CIRC PHYSIOL. 2018 SEP 1;315(3):H531-H539. DOI: 10.1152/AJPHEART.00104.2018. EPUB 2018 MAY 11.

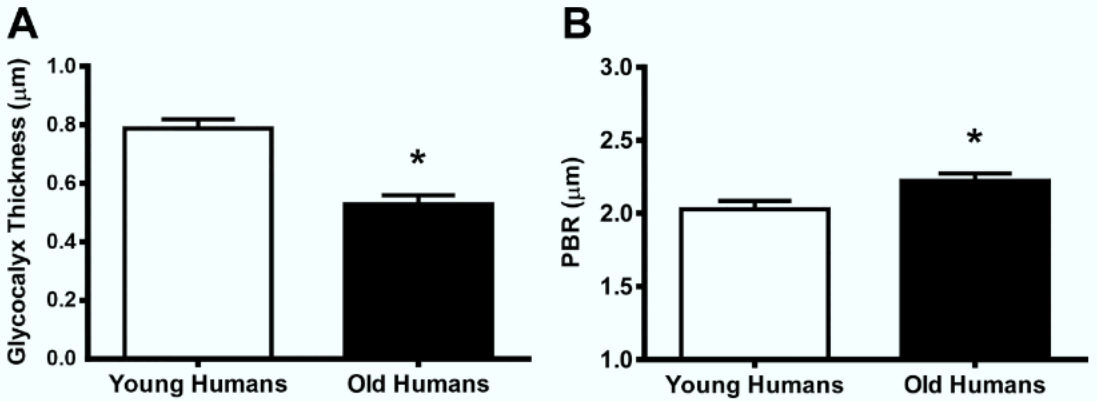


Fig. 4. Glycocalyx thickness (*A*) in sublingual microvessel segments (5–8 μm) and perfused boundary region (PBR; *B*) in sublingual microvessel segments (5–25 μm) of younger and older human participants ($n = 30$ participants/group). *$P < 0.05$, significant difference vs. younger participants. All data are means ± SE.

Thus, further study is warranted to determine if a diminished glycocalyx is a risk factor for age-related chronic diseases, as well as to determine if the glycocalyx is a potential therapeutic target to prevent these age-related chronic diseases.

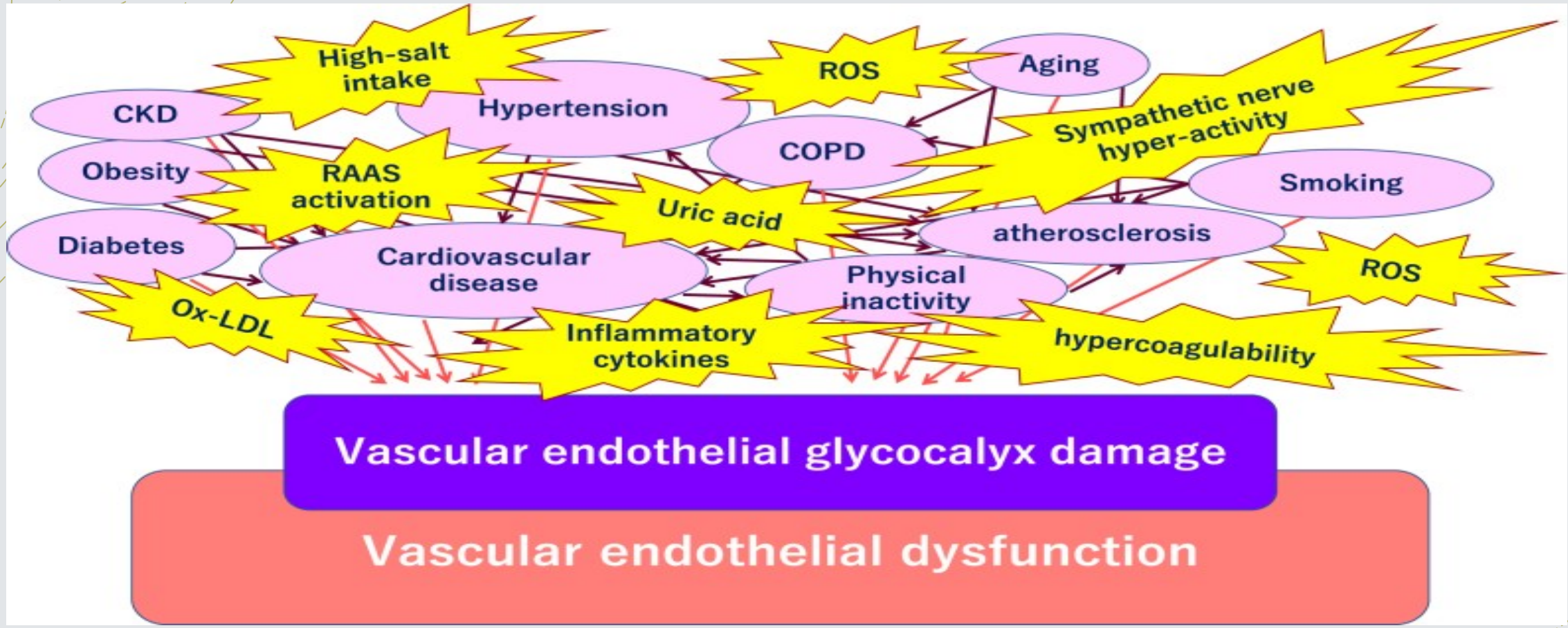
In addition to diminished glycocalyx thickness, PBR, a marker of glycocalyx barrier function, was higher in older mice and in older humans, indicating a greater ability of RBCs to penetrate the glycocalyx. PBR is derived using an automated capture and analysis system that examines RBC positioning in thousands of microvessel segments over the course of several

37), our use of an automated capture and analysis system provides an alternative approach to objectively measure age-related microvascular perfusion in a large number of microvessel segments while simultaneously measuring the glycocalyx. We observed lower perfused microvascular density and RBC fraction in older mice and humans compared with their younger counterparts. The difference in perfused microvascular density between young and old groups was primarily due to a higher density of the smallest perfused microvessel segments in both young mice and humans.

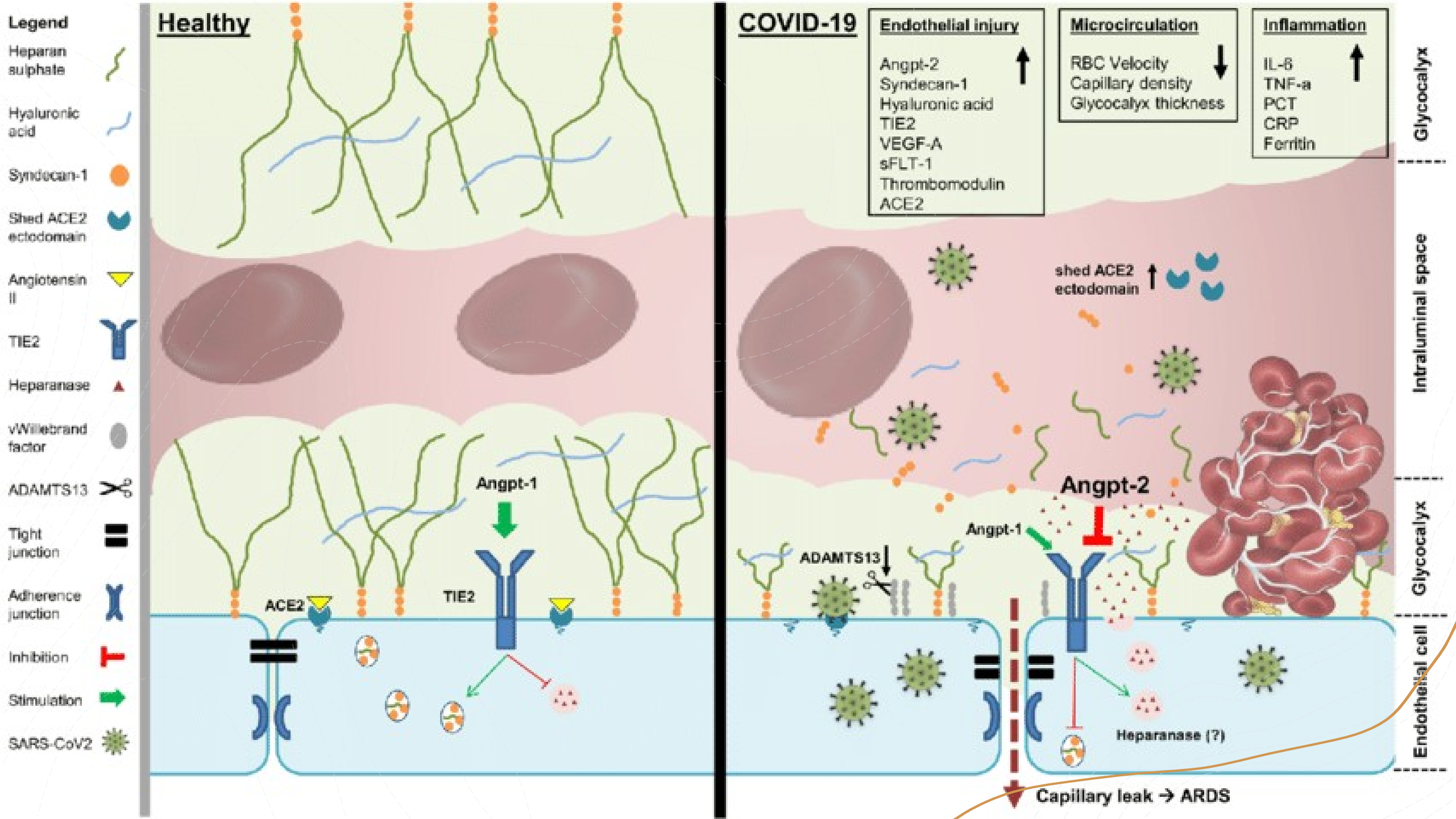
What damages the glycocalyx

- When the glycocalyx is damaged endothelial dysfunction results leading to less resiliency against OXSTRESS, inflammation and disease
- General inflammation (high hsCRP from obesity, poor diet)
- Diabetes
- Kidney disease
- Stroke
- Cancer
- Infections, sepsis, COVID-19
- High blood pressure
- High cholesterol
- Oxidative stress, smoking, pollution, excessive exercise
- Activation of the renin angiotensin system, this leads to vasoconstriction and HTN
- Trauma
- Elevated stress hormones but probably not cortisol
- Obesity
- Alcohol
- Excessive salt consumption >1,500 mg
- Aging
- Hyaluronidase

A few more things



+ Yamaoka-Tojo M. Endothelial glycocalyx damage as a systemic inflammatory microvascular endotheliopathy in COVID-19. Biomed J. 2020 Oct;43(5):399-413.


Legend
Heparan sulphate
Hyaluronic acid
Syndecan-1
Shed ACE2 ectodomain
Angiotensin II
TIE2
Heparanase
vWillebrand factor
ADAMTS13
Tight junction
Adherence junction
Inhibition
Stimulation
SARS-CoV2
Healthy
Angpt-1
TIE2
ACE2
COVID-19
Endothelial injury
Angpt-2
Syndecan-1
Hyaluronic acid
TIE2
VEGF-A
sFLT-1
Thrombomodulin
ACE2
Microcirculation
RBC Velocity
Capillary density
Glycocalyx thickness
Inflammation
IL-6
TNF-a
PCT
CRP
Ferritin
shed ACE2 ectodomain
Angpt-2
Angpt-1
ADAMTS13
Heparanase (?)
Capillary leak → ARDS
Glycocalyx
Intraluminal space
Glycocalyx
Endothelial cell

A Damaged/Disorganized Glycocalyx Induces Endothelial Dysfunction and ASVD:



In a healthy vascular endothelial cell covered with enough glycocalyx, the cells are **well organized** and have good vascular endothelial functions including production of nitric oxide (NO), anticoagulant factors and antioxidant balance.

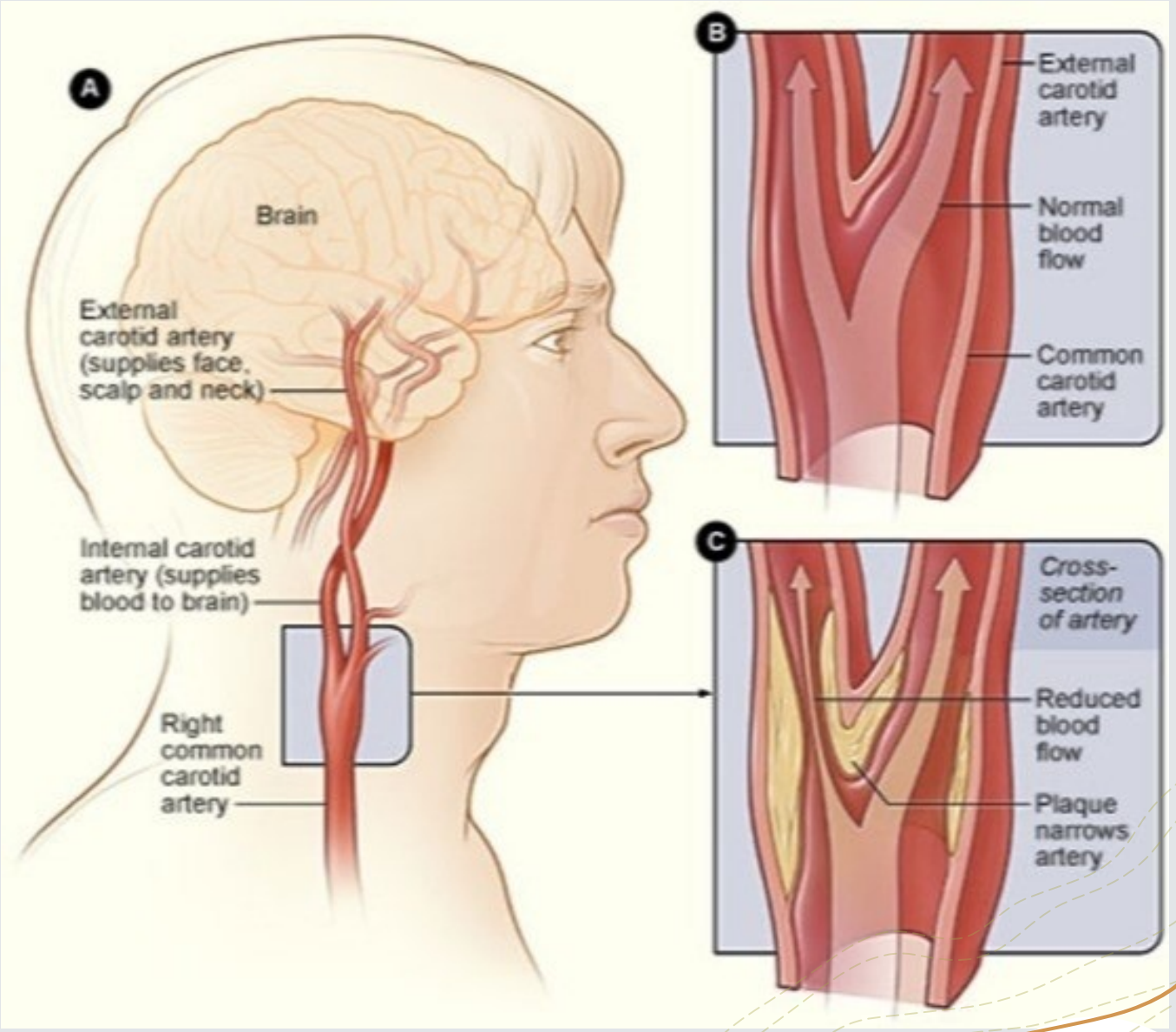


Accumulation of oxidized lipoproteins (OXLDL) in the vessel wall first occurs at sites of endothelial dysfunction, characterized by increased endothelial cell layer permeability, impaired cellular communication and vessel tone, complement activation, leukocyte adhesion, platelet aggregation and alteration of the glycocalyx.



Most atherosclerotic lesions develop in areas subjected to **turbulent or reduced flow** like bifurcations, curvatures and branching points. Disturbed or reduced flow profiles are known to damage the endothelial glycocalyx. **This is why plaque develops in the proximal left anterior descending and carotid artery internal and external bifurcations**.

Lesions develop in areas subjected to **turbulent, low shear or reduced flow** like bifurcations, curvatures and branching points.

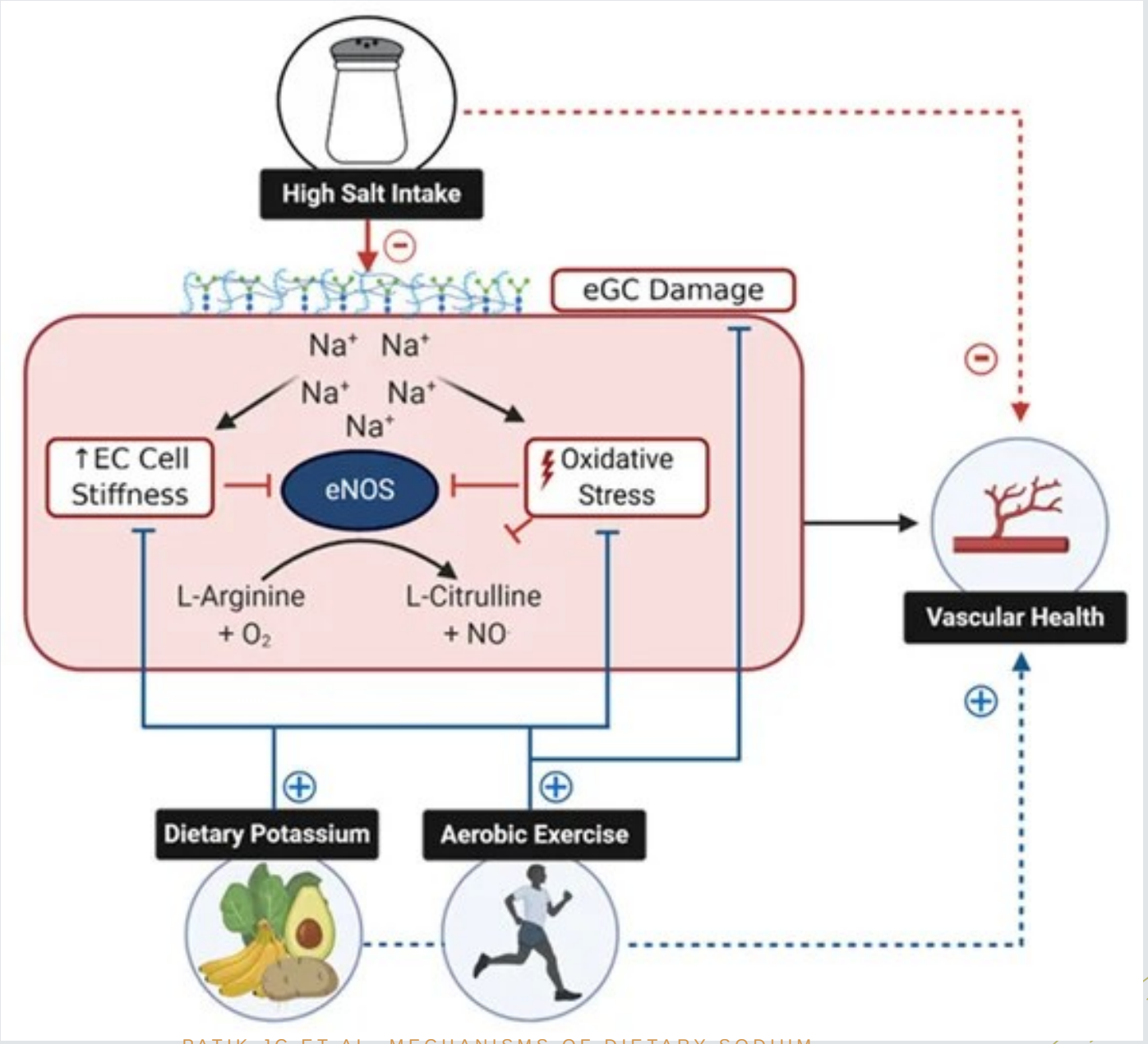


Sodium

The endothelial cells with excessively degraded glycocalyx from excess sodium overload are unable to produce sufficient nitric oxide due to the reduced activation of endothelial nitric oxide synthase.

The damage to the eGC induced by high salt intake occurs more with chronic salt overload as opposed to acute salt loading.

SEMBAJWE LF, SSEKANDI AM, NAMAGANDA A, MUWONGE H, KASOLO JN, KALYESUBULA R, NAKIMULI A, NAOME M, PATEL KP, MASENGA SK, KIRABO A. GLYCOCALYX-SODIUM INTERACTION IN VASCULAR ENDOTHELIUM. NUTRIENTS. 2023 JUN 25;15(13):2873.



PATIK JC,ET AL. MECHANISMS OF DIETARY SODIUM-INDUCED IMPAIRMENTS IN ENDOTHELIAL FUNCTION AND POTENTIAL COUNTERMEASURES. NUTRIENTS. 2021; 13(1):270. HTTPS://DOI.ORG/10.3390/NU13010270

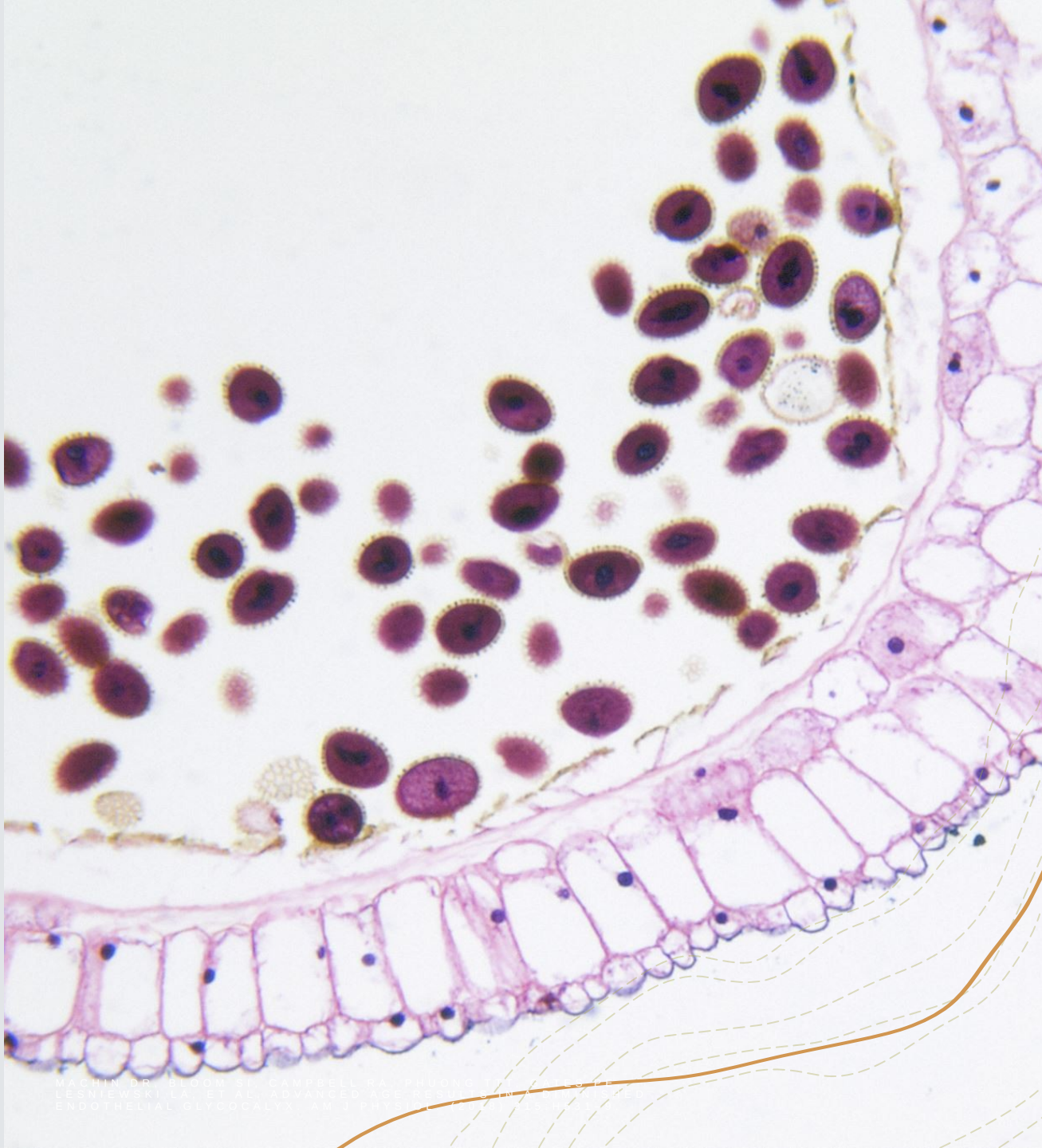
Hyaluronidase

- Hyaluronidase is an enzyme used to improve the absorption and dispersion of parenterally administered fluids, drugs, and contrast agents. Early research into hyaluronidase identified it as a "spreading factor" which allowed for increased permeability of the connective tissue. Hyaluronidase has been used in surgical settings for at least the past 60 years to improve the diffusion of local anesthetics.
- Damage by hyaluronidase treatment can be partially recovered by acute infusion of hyaluronan and chondroitin sulfate.

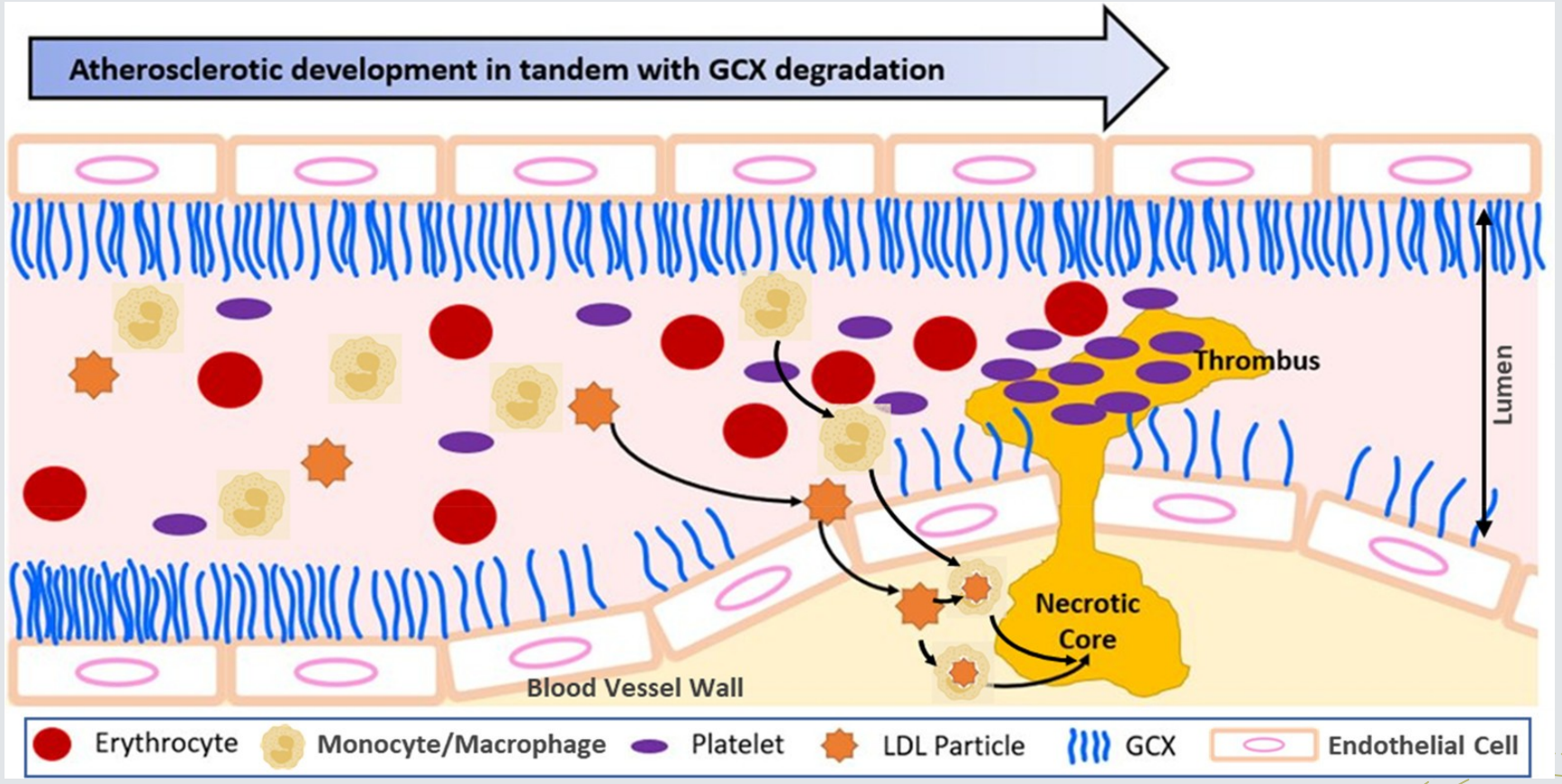
HENRY C.B., DULING B.R. PERMEATION OF THE LUMINAL CAPILLARY GLYCOCALYX IS DETERMINED BY HYALURONAN. AM. J. PHYSIOL. 1999;277:H508–H514.

Vascular aging

- Vascular aging is a risk factor associated with increased vessel stiffness. This causes microvascular dysfunction, impaired blood flow and reduced capillary density. Glycocalyx health tends to degenerate with age.
- A reduction of the endothelial glycocalyx thickness of ~30% was observed in humans with a mean age of 60 years compared to 30-year-old individuals.
- *



Atherosclerosis



Hypertension

Hypertension Damages the Glycocalyx:

Increased Shear Stress & Mechanical Damage

Chronic high blood pressure exerts **excessive mechanical force** on the endothelium, physically disrupting the delicate glycocalyx layer.

Oxidative Stress & Inflammation

Hypertension is associated with **increased reactive oxygen species (ROS)** and inflammation, which degrade glycocalyx components like **heparan sulfate and syndecans**.

Endothelial Dysfunction & Reduced Nitric Oxide (NO)

NO is essential for glycocalyx maintenance, but in hypertension, **NO production is impaired**, leading to a weakened and more permeable endothelial layer.

Increased Vascular Permeability & Stiffness

A damaged glycocalyx allows **more proteins, immune cells, and oxidized LDL** to penetrate the endothelium, promoting **atherosclerosis and vascular stiffening**.

What can be done to repair and protect the EGC?

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Regeneration and Assessment of the Endothelial Glycocalyx To Address Cardiovascular Disease

Selina Banerjee, John G. Mwangi, Theodora K. Stanley, Ronodeep Mitra, and Eno E. Ebong*

Cite this: *Ind. Eng. Chem. Res.* 2021, 60, 48, 17328–17347

Publication Date: November 24, 2021

https://doi.org/10.1021/acs.iecr.1c03074

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Industrial & Engineering Chemistry Research

PDF (15 MB)

SUBJECTS: Peptides and proteins, Regeneration, Rodent models,

Treatments linked with protection of the glycocalyx

Treatment **Reference**

1. **Hydrocortisone** (if low) Chappell et al. 2007, 2009b, 2010
2. Antithrombin Chappell et al. 2009a, 2009b, 2010
3. Protein C Marechal et al. 2008
4. **Nitric oxide** Bruegger et al. 2008
5. **Hyaluronic acid and chondroitin sulphate** (Endocalyx) Henry and Duling 1999
6. Sulodexide Broekhuizen et al. 2010
7. Lidoflazine Flameng et al. 1983 and
8. Albumin Jacob et al. 2006, 2009
9. Hydroxethyl starch Rehm et al. 2004; Jacob et al. 2006
10. **N-acetylcysteine** Nieuwdorp et al. 2006
11. **Metformin** E skens et al. 2013
12. **Antioxidants from food and supplements**
13. **Allopurinol** (Blocks uric acid production)
14. **Rosuvastatin** (Crestor) Meuwese et. al. J Lipid Res. 2009 Jan;50(1):148-53.
15. **Nutraceutical:** (animal studies but limited human data) Reiger et al Int J Mol Sci. 2022 Dec 8;23(24):15520.
16. **Nutraceutical:** (human studies, green seaweed species, **rhamnan sulfate (RS))**
17. **Fucoidan** Yuan L, er al. ERJ Open Res. 2022 May 3;8(2):00652-2021
18. **Hawthorne**
19. Get younger ☺

NAC: Mitigating and preserving

NAC Mitigates Glycocalyx Damage Under Hyperglycemic Conditions.

NAC replenishes intracellular glutathione and directly scavenges ROS, mitigating oxidative stress-induced damage to the glycocalyx.

By reducing oxidative stress, NAC helps maintain the expression of key glycocalyx proteoglycans like syndecan-1 and glypican-1.

NAC suppresses the expression of MMP-9, an enzyme that degrades glycocalyx components, thereby preventing glycocalyx shedding.

A 2023 study investigated the effects of NAC on EGCX damage in human heatstroke (HS) models. Significant shedding of the glycocalyx was observed, evidenced by decreased syndecan-1 expression and increased plasma levels of syndecan-1 and hyaluronic acid indication damage to EGLYC. Pretreatment with NAC alleviated these changes, preserving the glycocalyx structure and reducing the release of glycocalyx components into the plasma.

PENG N, ET AL. ENDOTHELIAL GLYCOCALYX INJURY IS INVOLVED IN HEATSTROKE-ASSOCIATED COAGULOPATHY AND PROTECTED BY N-ACETYLCYSTEINE. FRONT IMMUNOL. 2023 JUN 6;14:1159195.

Nanomechanics and Sodium Permeability of Endothelial Surface Layer Modulated by Hawthorn Extract WS 1442

Wladimir Peters[1]*, Verena Drueppel[1], Kristina Kusche-Vihrog[1], Carola Schubert[2], Hans Oberleithner[1]

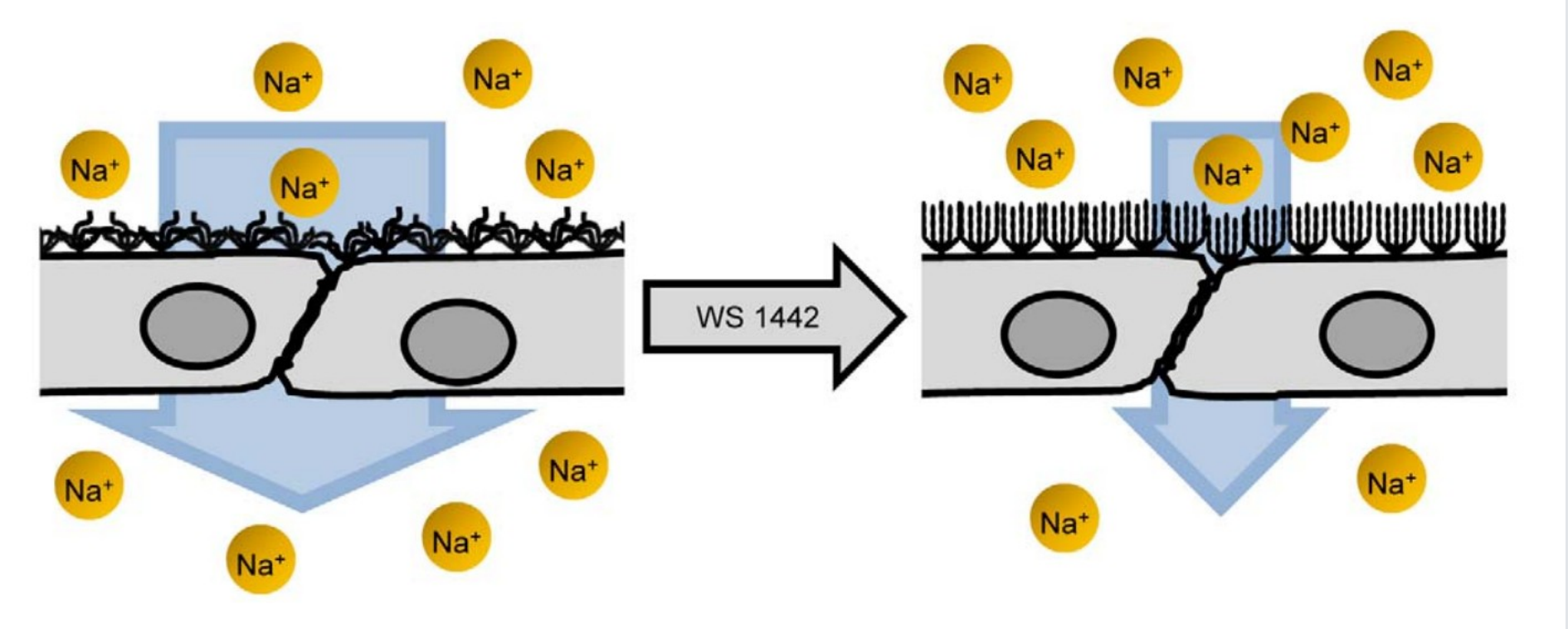
1 Institute of Physiology II, University of Münster, Münster, Germany, **2** Institute of Gender in Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany

Abstract

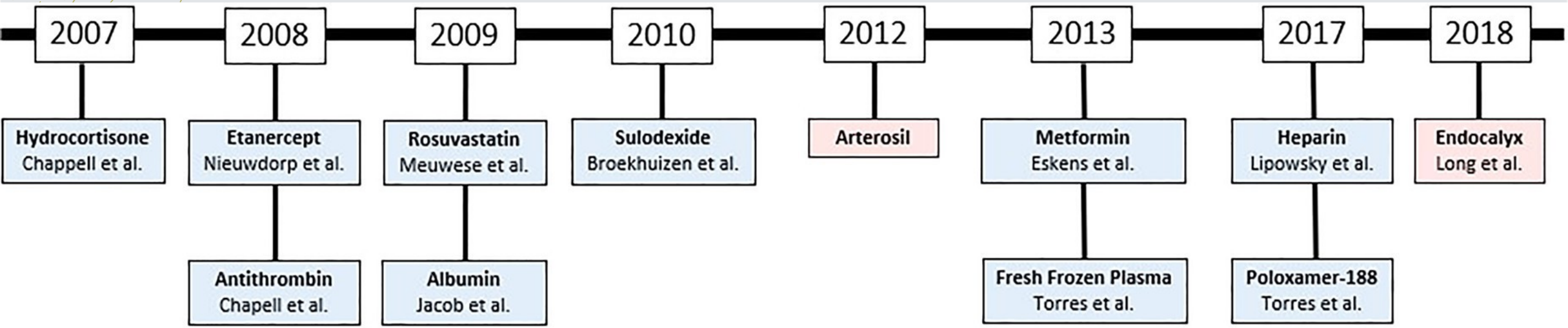
The endothelial glycocalyx (eGC) plays a pivotal role in the physiology of the vasculature. By binding plasma proteins, the eGC forms the endothelial surface layer (ESL) which acts as an interface between bloodstream and endothelial cell surface. The functions of the eGC include mechanosensing of blood flow induced shear stress and thus flow dependent vasodilation. There are indications that levels of plasma sodium concentrations in the upper range of normal and beyond impair flow dependent regulation of blood pressure and may therefore increase the risk for hypertension. Substances, therefore, that prevent sodium induced endothelial dysfunction may be attractive for the treatment of cardiovascular disease. By means of combined atomic force - epifluorescence microscopy we studied the impact of the hawthorn (*Crataegus* spp.) extract WS 1442, a herbal therapeutic with unknown mechanism of action, on the mechanics of the ESL of *ex vivo* murine aortae. Furthermore, we measured the impact of WS 1442 on the sodium permeability of endothelial EA.hy 926 cell monolayer. The data show that (i) the ESL contributes by about 11% to the total endothelial barrier resistance for sodium and (ii) WS 1442 strengthens the ESL resistance for sodium up to about 45%. This mechanism may explain some of the vasoprotective actions of this herbal therapeutic.

The results showed that hawthorn extract (WS 1442) leads to a softer and higher ESL accompanied by a reduction in sodium influx

Model explaining the effect of Hawthorne extract the conformation of the endothelial surface layer. The ESL can exist in a more densely packed state or in a more loosely packed state. The functional parameters of the ESL, such as e.g. the sodium permeability, strongly depend on the state of the ESL. Hawthorne extract induced a transition from the densely packed to the loosely packed state.



PETERS ET AL. NANOMECHANICS AND SODIUM PERMEABILITY OF ENDOTHELIAL SURFACE LAYER MODULATED BY HAWTHORN EXTRACT WS 1442. PLOS ONE. 2012;7(1):E29972.


2007
Hydrocortisone
Chappell et al.
2008
Etanercept
Nieuwdorp et al.
Antithrombin
Chapell et al.
2009
Rosuvastatin
Meuwese et al.
Albumin
Jacob et al.
2010
Sulodexide
Broekhuizen et al.
2012
Arterosil
2013
Metformin
Eskens et al.
Fresh Frozen Plasma
Torres et al.
2017
Heparin
Lipowsky et al.
Poloxamer-188
Torres et al.
2018
Endocalyx
Long et al.

Studies on rhanman sulphate

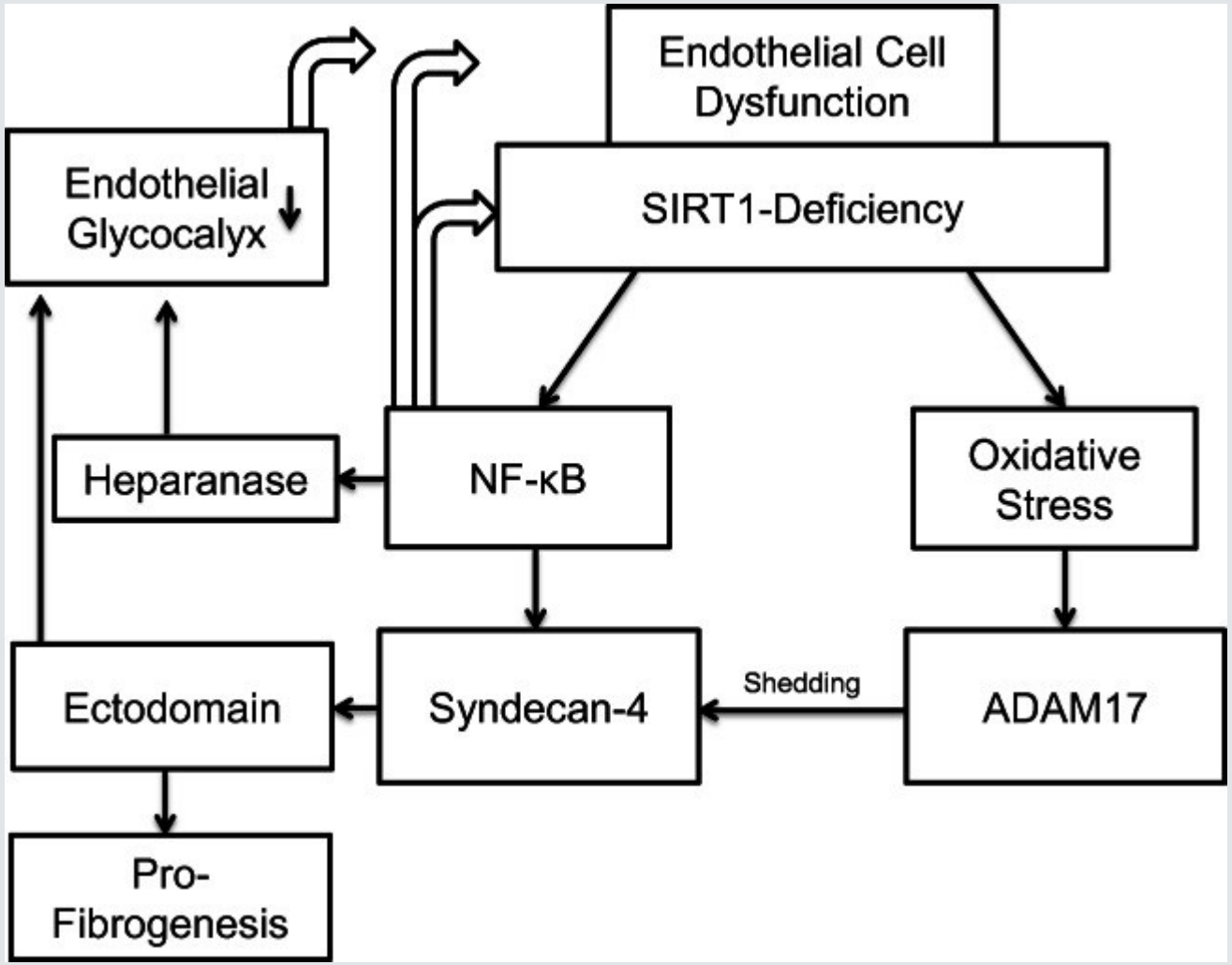
+ **The Studies: Overview**
+ **1. MRI Carotid Plaque Regression Study**, Hospitals in Beijing—Human Proof-of-Concept Pilot Finding: Significant reduction of lipid-rich necrotic core (LRNC) of carotid atherosclerotic plaque
+ **2. Plaque Reduction Retrospective Case Study**, Private Practice—True North Center for Functional Medicine Finding: Significant reduction of artherosclerotic plaque.
+ **3. Arterial Plaque Study**, Drexel University—Animal Study Finding: Rhanman sulfate extract significantly reduced plaque in the aorta and aortic root.
+ **4. Glycocalyx Regeneration Study**, Chinese Academy of Sciences—Cellular Study Finding: Repairs and regenerates glucose-impaired endothelial glycocalyx
+ **5. Leukocyte Adhesion Study**, Maastricht University—Animal Study Finding: Prevents the increase of leukocyte adhesion caused by enzymatic removal of the endothelial glycocalyx
+ **6. Arterial Elasticity Study**, Baylor Heart Institute Campus—Human Study Finding: Improved endothelial function—arterial elasticity increased by an average of 89.6%
+ **7. Hypertension Study**, The Hypertension Research Institute (Mark Houston, MD)—Human Study Finding: Significantly lowered diastolic blood pressure
+ **8. Diabetic Neuropathy Study**, The Hypertension Research Institute (Mark Houston, MD)—Human Study Finding: Improved objective and subjective measures of neuropathy.

SIRT-1 and 2 activators

Natural Compounds:	
Resveratrol	• Found in red wine and grapes. • First identified as a SIRT1 activator. • Improves metabolic health and extends lifespan in some organisms.
Quercetin	• A flavonoid with antioxidant properties. • Weak SIRT1 activator.
Fisetin	• Another flavonoid with potential SIRT1-modulating activity.
Piceatannol	• A resveratrol analog with potential SIRT1 activity.

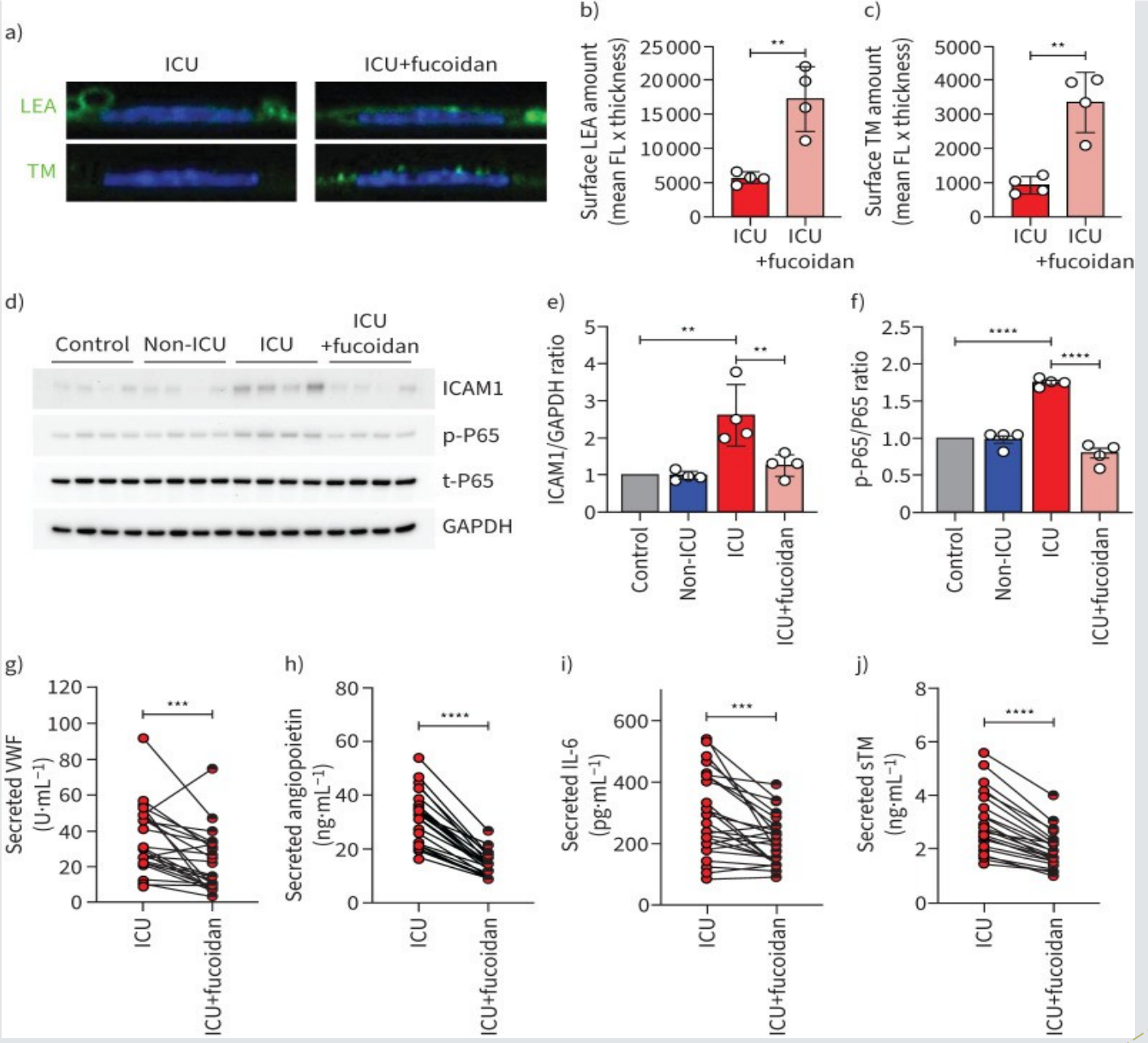
GERTZ M., NGUYEN G.T., FISCHER F., SUENKEL B., SCHLICKER C., FRÄNZEL B., TOMASCHEWSKI J., ALADINI F., BECKER C., WOLTERS D., ET AL. A MOLECULAR MECHANISM FOR DIRECT SIRTUIN ACTIVATION BY RESVERATROL. PLOS ONE. 2012;7:E49761

Sirtuin deficiency. Sirtuins are a family of enzymes that are **NAD$^+$** or **ADP-r dependent**. They regulate a wide range of cellular processes, especially those related to **aging, metabolism, and stress resistance**.



LIPPHARDT M, SONG JW, GOLIGORSKY MS. SIRTUIN 1 AND ENDOTHELIAL GLYCOCALYX. PFLUGERS ARCH. 2020 AUG;472(8):991-1002.

Fucoidan (brown seaweed) **restores glycocalyx thickness** on human pulmonary microvascular endothelial cells (HPMECs) and reduces endothelial activation.



YUAN L, CHENG S, SOL WMPJ, VAN DER VELDEN AIM, VINK H, RABELINK TJ, VAN DEN BERG BM. HEPARAN SULFATE MIMETIC FUCOIDAN RESTORES THE ENDOTHELIAL GLYCOCALYX AND PROTECTS AGAINST DYSFUNCTION INDUCED BY SERUM OF COVID-19 PATIENTS IN THE INTENSIVE CARE UNIT. ERJ OPEN RES. 2022 MAY 3;8(2):00652-2021

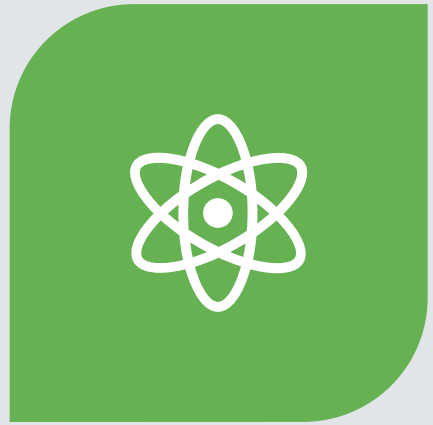
NAC



VASCULAR ENDOTHELIUM IS ACTIVATED IN NON-INSULIN DEPENDENT DIABETES.



NAC CAN TREAT THIS.



DECREASES VCAM (VASCULAR CELL ADHESION MOLECULE)

MASHA A., BROCATO L., DINATALE S., MASCIA C., BIASI F., MARTINA V. N-ACETYLCYSTEINE IS ABLE TO REDUCE THE OXIDATION STATUS AND THE ENDOTHELIAL ACTIVATION AFTER A HIGH-GLUCOSE CONTENT MEAL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS. J. ENDOCRINOL. INVESTIG. 2009;32:352–356.

Uric Acid: Allopurinol

A 2019 study published in Kidney International investigated the effects of uric acid (UA) on endothelial cells and the potential protective role of allopurinol. The researchers found that elevated UA levels induced oxidative stress, leading to shedding of the glycocalyx in human umbilical vein endothelial cells. In hyperuricemic rats, increased plasma levels of syndecan, a marker of glycocalyx degradation were observed.

Treatment with allopurinol ameliorated these effects, reducing oxidative stress and preserving the glycocalyx structure.

Allopurinol functions as a xanthine oxidase inhibitor, thereby reducing the production of reactive oxygen species (ROS) associated with UA metabolism. By mitigating oxidative stress, allopurinol helps maintain the integrity of the endothelial glycocalyx, preventing its degradation and the subsequent endothelial dysfunction.

KO J, KANG HJ, KIM DA, KIM MJ, RYU ES, LEE S, RYU JH, RONCAL C, JOHNSON RJ, KANG DH. URIC ACID INDUCED THE PHENOTYPE TRANSITION OF VASCULAR ENDOTHELIAL CELLS VIA INDUCTION OF OXIDATIVE STRESS AND GLYCOCALYX SHEDDING. FASEB J. 2019 DEC;33(12):13334-13345.

Would tart cherry also work?

Animal Study on Tart Cherry Juice and XO Activity

A study published in Malaysian Journal of Nutrition investigated the effects of tart cherry juice on serum uric acid levels and hepatic XO activity in normal and hyperuricemic rats. The results showed that **tart cherry juice significantly reduced serum uric acid levels** in hyperuricemic rats and inhibited hepatic XO activity. Additionally, tart cherry juice increased total antioxidant capacity and decreased malondialdehyde levels, indicating reduced oxidative stress.

In Vitro Study on Sour Cherry Extracts

A study published in Frontiers in Nutrition analyzed the XO inhibitory activity of various sour cherry cultivars. The study found that all tested **sour cherry extracts exhibited XO inhibitory activity. The inhibitory activity was positively correlated with the total phenolic and flavonoid content of the extracts**.

Study on Montmorency Tart Cherry Extract

Research published in *Food Chemistry* examined the inhibitory effects of Montmorency tart cherry extract on key enzymes related to inflammation and oxidative stress. **The study reported that the extract exhibited moderate XO inhibitory activity, along with significant inhibition of cyclooxygenase-1 and lipoxygenase enzymes**.

Glycosaminoglycans

A mixture of **chondroitin sulfate (CS)** and **hyaluronic acid (HA)** effectively restored the structure of the eGC in both in vivo (Syrian golden hamsters) and in vitro (human umbilical vein endothelial cells) models.

Given individually they did not work…only together.

SELINA BANERJEE, JOHN G. MWANGI, THEODORA K. STANLEY, RONODEEP MITRA, AND ENO E. EBONGREGENERATION AND ASSESSMENT OF THE ENDOTHELIAL GLYCOCALYX TO ADDRESS CARDIOVASCULAR DISEASE INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH 2021 60 (48), 17328-17347

Green tea

- In a rat model of angiotensin-II-induced hypertension, the administration of green tea extract restored endothelium vasodilatation through antioxidant mechanisms



ANTONIOS M., MONTEMURRO D., BOLOGNESE G., DI PASCOLI M., PIVA G., GRECO F., STICCHI D., GIULIANI L., SARRISA S., ROSSI G.P. PREVENTION OF HYPERTENSION, CARDIOVASCULAR DAMAGE, AND ENDOTHELIAL DYSFUNCTION WITH GREEN TEA EXTRACTS. AM. J. HYPERTENS. 2007;20:1321–1329. DOI:10.1016/J.AMJHYPER.2007.08.006.

Fucoidan

Fucoidan, a sulfated polysaccharide derived from brown seaweed, has been shown to preserve and protect the **endothelial glycocalyx (eGC)** through multiple mechanisms, particularly in conditions associated with oxidative stress and inflammation.



Fucoidan

Supplementation has been observed to **restore the thickness of the eGC** in both in vitro and in vivo models. For instance, a study demonstrated that a dietary supplement containing fucoidan significantly improved baseline eGC thickness in endothelial cells and increased eGC dimension.

Fucoidan acts as a **heparan sulfate mimetic, inhibiting the activity of heparanase**—an enzyme responsible for degrading heparan sulfate components of the glycocalyx. By preventing this degradation, fucoidan helps maintain the structural integrity of the eGC .

Fucoidan has been shown to **reduce endothelial activation by modulating inflammatory signaling pathways.** Specifically, it inactivates the NF-κB signaling pathway, leading to decreased expression of intercellular adhesion molecule 1 (ICAM-1) and other pro-inflammatory markers, thereby protecting the endothelial barrier function .

By restoring the glycocalyx and reducing inflammation, fucoidan contributes to the recovery of endothelial barrier integrity. This effect has been particularly noted in studies involving endothelial cells exposed to serum from patients with conditions like COVID-19, where fucoidan treatment led to significant improvements in barrier function.

YUAN L, ET AL. HEPARAN SULFATE MIMETIC FUCOIDAN RESTORES THE ENDOTHELIAL GLYCOCALYX AND PROTECTS AGAINST DYSFUNCTION INDUCED BY SERUM OF COVID-19 PATIENTS IN THE INTENSIVE CARE UNIT. ERJ OPEN RES. 2022 MAY 3;8(2):00652-2021.

Treat low cortisol?

Hydrocortisone reduced coronary resistance, vascular permeability, tissue edema, the release of lactate, uric acid, purines, and histamine, which were accompanied by severe degradation induced by TNF-α.

Studies are mainly on ischemia-reperfusion injury

CHAPPELL D, HOFMANN-KIEFER K, JACOB M, REHM M, BRIEGEL J, WELSCH U, CONZEN P, BECKER BF. TNF-ALPHA INDUCED SHEDDING OF THE ENDOTHELIAL GLYCOCALYX IS PREVENTED BY HYDROCORTISONE AND ANTITHROMBIN. BASIC RES CARDIOL. 2009 JAN;104(1):78-89.

Summary

Many of the risk factors that increase damage to the glycocalyx can be controlled and treated

Target nitric oxide and treat hypertension

Anyone with hypertension **or** over 50 needs glycocalyx support

Do eGC risk assessment (age, weight, exercise, diet, ox stress)

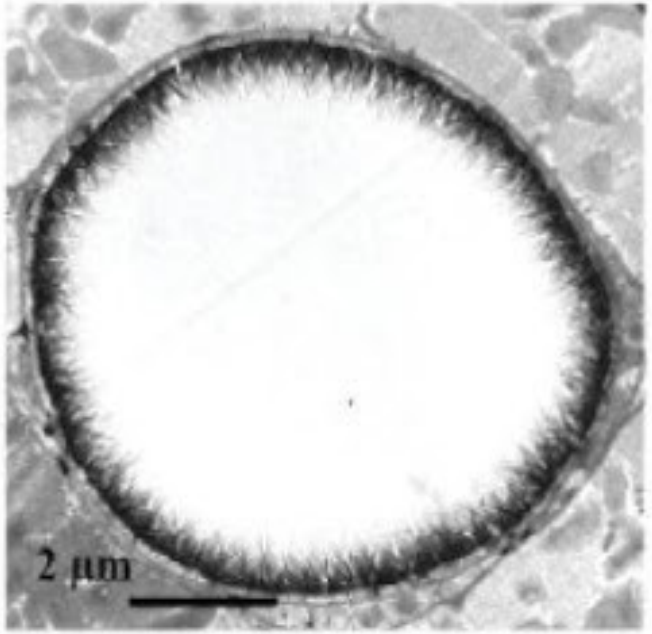
Need a healthy lifestyle and whole foods diet with plenty of plants. Also consider sleep, exercise, stress control etc.

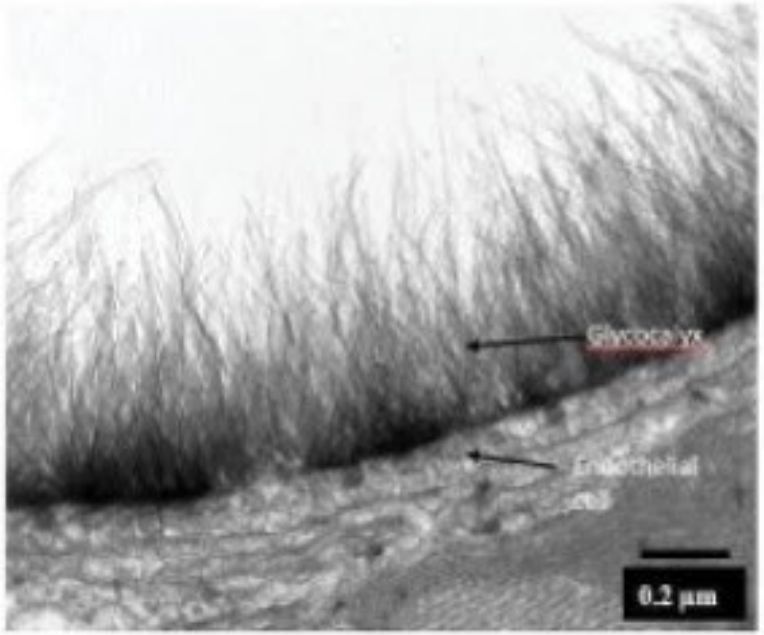
Human studies exist…**nutraceuticals exist**

Control salt and blood pressure/avoid dehydration (RAAS activation)

Multiple naturopathic treatment options exist

Explain it to pts and show images





van den Berg, Vink & Spaan, Circulation Research 2003, 92: 592-594

(LEFT) Cross-section of a capillary blood vessel in a rat heart muscle shows extensive dimension of the glycocalyx in a healthy blood vessel.

(RIGHT) High magnification showing the dimension of the glycocalyx is several fold the thickness of the endothelium.