

Glikokaliks: Yapı ve Fonksiyonu

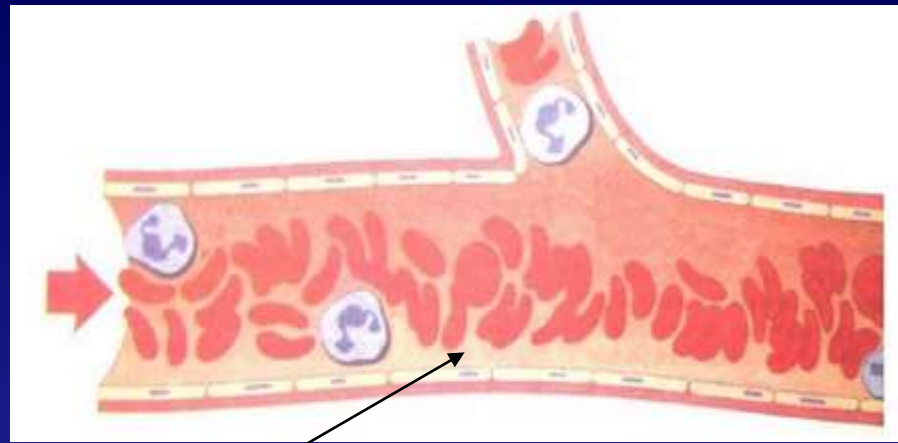


Doç.Dr. Uğur AKSU

İstanbul Üniversitesi Fen Fakültesi Biyoloji Bölümü

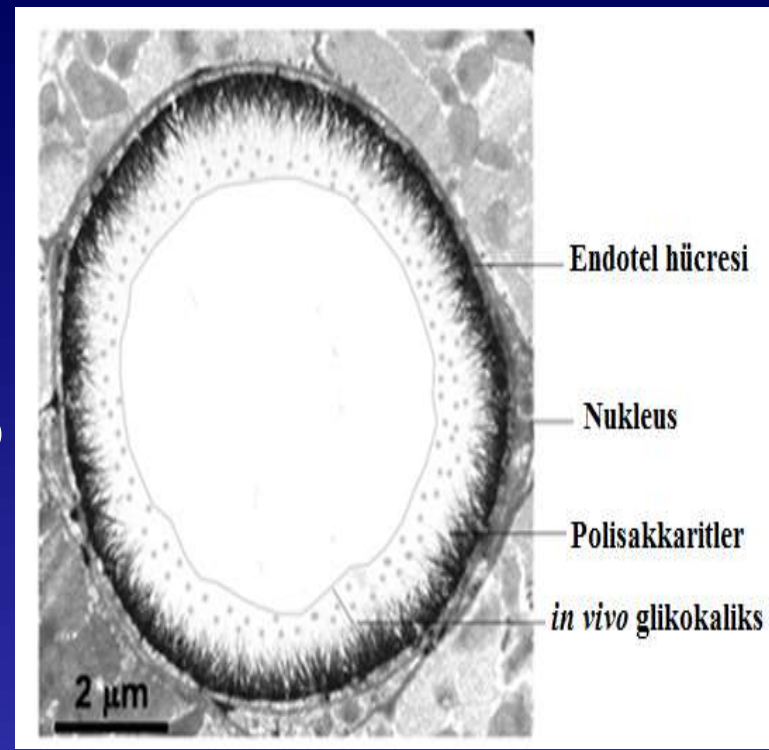
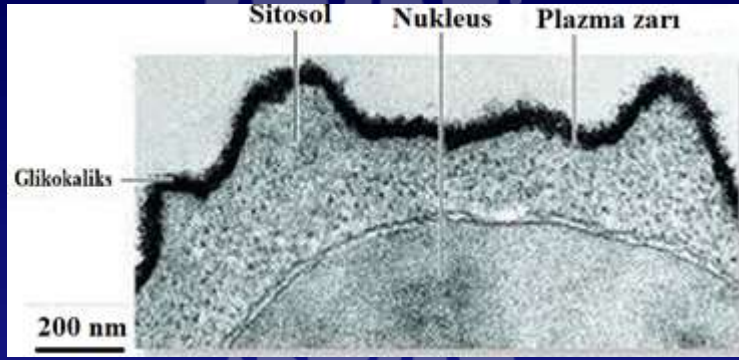
Akış:

- Genel bilgi
- Yapı
- Fonksiyon
- Hasarı yapan nedir?
- Nasıl korunur?
- Sonuç

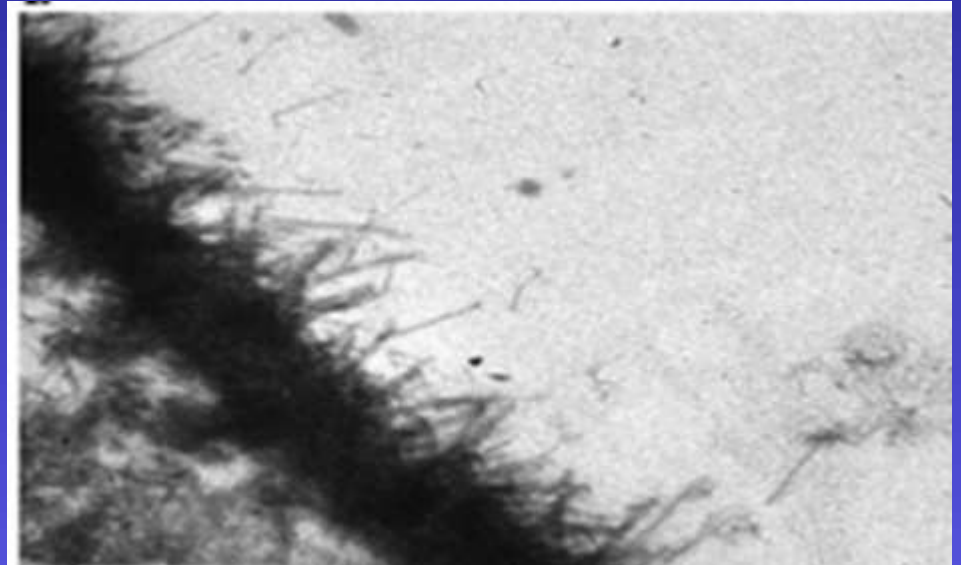
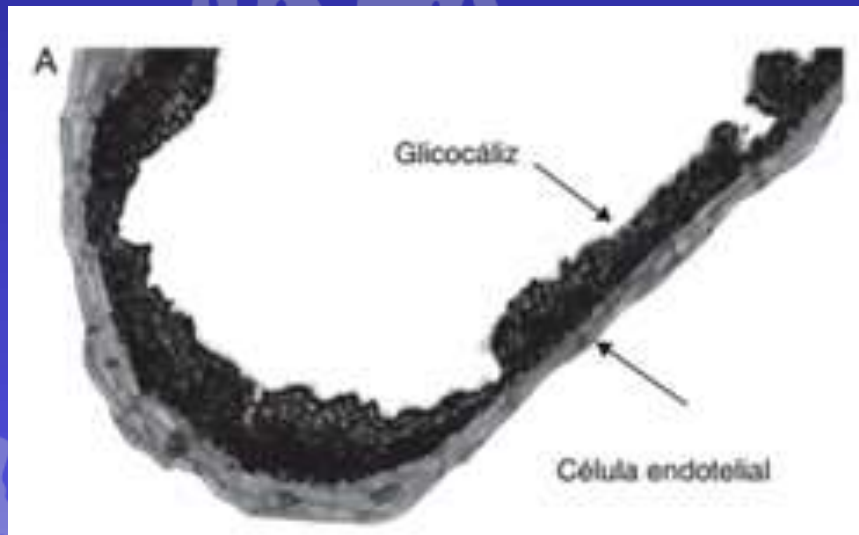


Sadece sıvı mı?
Gizli koruyucu bir jel mi?





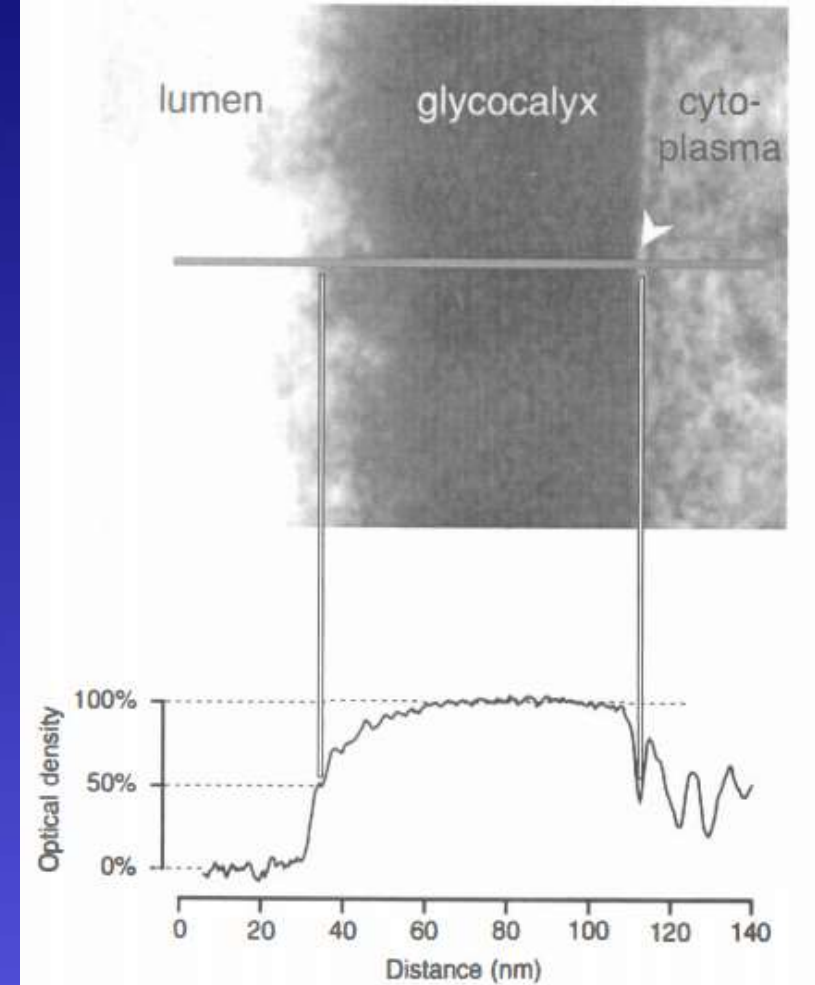
- Karmaşık bir fırça görünümüne sahip
- Endotelden daha kalın olan
- Damar duvarının bir parçası
- Damar duvarının kendisi üretir.



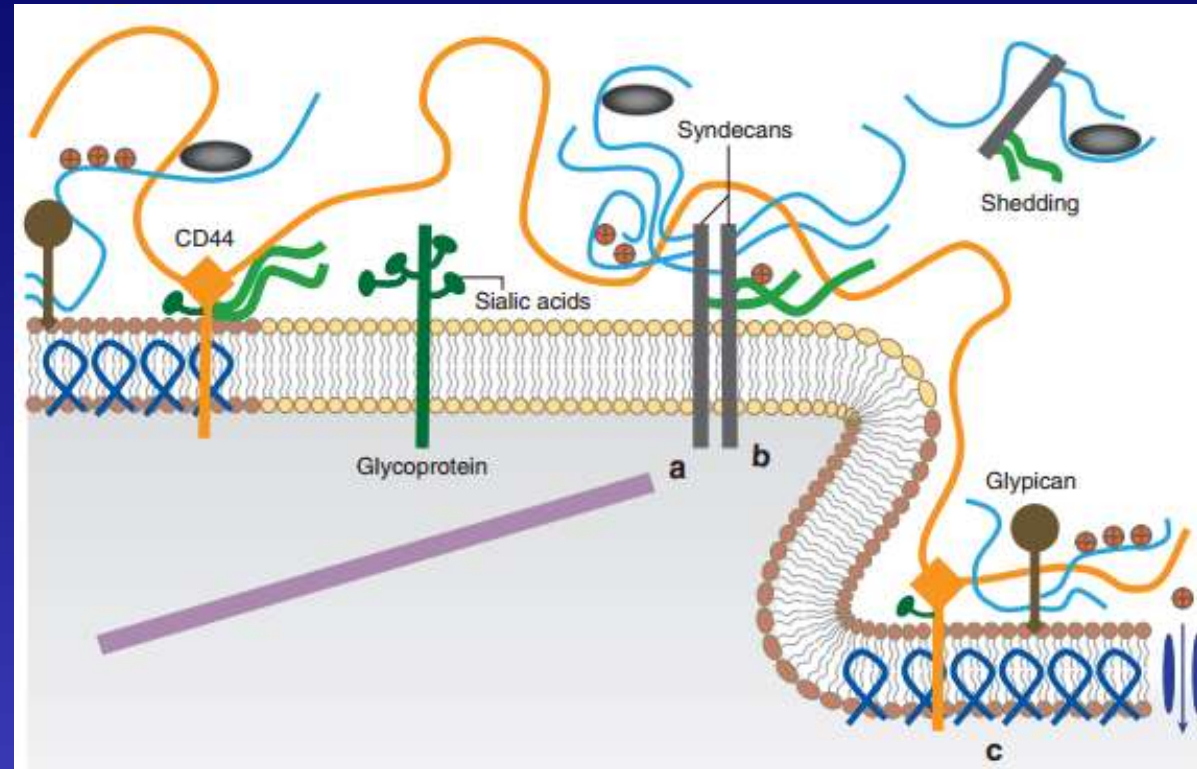
Ve Őuanki tanımlama:

Glikokaliks

- Endotelin l mene bakan y z n  saran, zara baęlı proteoglikanlar ve glikoproteinlerden oluŐan bir aędır.
- Hem endotel hem de plazmadan t revlenmiŐ  oz n r molek ller bu  rg  sisteme dahildir.



Glikokaliks bileşenleri



- Proteoglikanlar

- Sialoproteinler

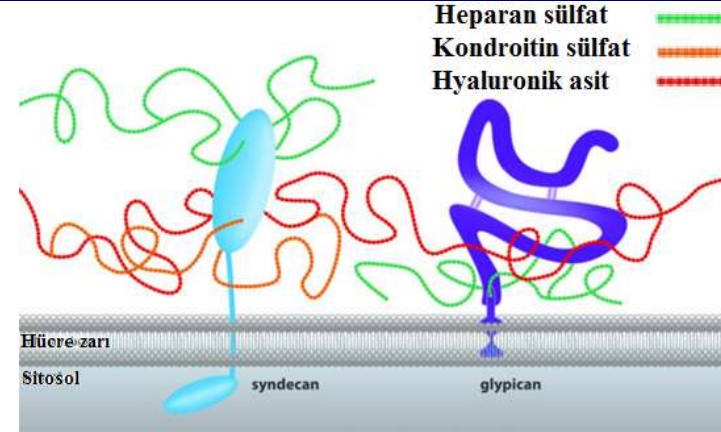
- Absorplanmış bileşenler (albumin vs.)

Proteoglikanlar:

– Ana protein bileşeni

Table 1 Characteristics of proteoglycan core proteins in the vascular endothelial glycocalyx

Core protein group	Core protein size (kDa)	Number of subtypes	Number of GAG-chains linked	Type of GAG-linked
Syndecan	19–35	4	5	HS/CS
Glypican	57–69	6	3	HS/CS
Perlecan	400	1	3	HS/CS
Versican	370	1	10–30	CS/DS
Decorin	40	1	1	CS/DS
Biglycan	40	1	2	CS/DS
Mimecan	35	1	2–3	KS



Membrane-spanning

GPI-anchor

Secreted

Secreted

Secreted

Secreted

Secreted

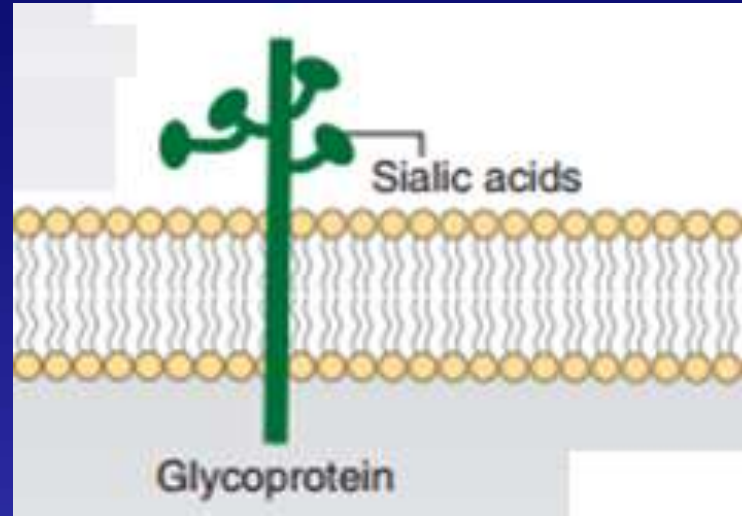
– Yan zincir (GAG)

Table 2 Composition of the disaccharides of various glycosaminoglycan chains

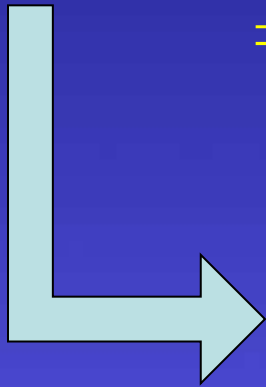
	Heparan sulfate	Chondroitin sulfate	Dermatan sulfate ^a	Hyaluronan	Keratan sulfate
Uronic acid	GlcA(2S) IdoA(2S)	GlcA	GlcA IdoA(2S)	GlcA	Gal(6S)
Disaccharide link	1β4	1β3	1β3	1β3	1β4
Hexosamine	GlcNAc(NS)(3S)(6S)	GalNAc4S ^a GalNAc6S ^a	GalNAc(4S)(6S)	GlcNAc	GlcNAc(6S)
Polymerization link	1β4	1β4	1β4	1β4	1β3

Glikozaminoglikanlar (GAG) aniyonik yükten sorumludur.

Sialoproteinler: Neurominik asit taşıyan ve oldukça fazla bulunan bir bileşen



Sialik asit + glikoproteinler
= sialoproteinler



- *9C'lu bir monosakkarit türevidir
- *mannozamin ve pirüvattan türer
- *net negatif yüke katkısı oldukça fazladır.

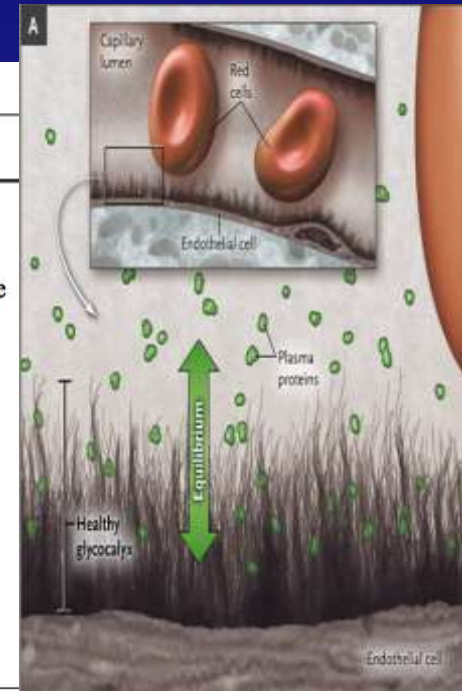
Absorplanmış bileşenler:

- Albumin

Table 3 Molecules dependent on interaction with the endothelial glycocalyx for proper functioning

Interacting molecule	Primary function in vasculature
Antithrombin III	Potent inactivator of pro-coagulant proteases such as thrombin, factor Xa and factor IXa; activity enhanced by heparin or heparan sulfate
Heparin cofactor II	Inactivator of the procoagulant protease thrombin; activated by dermatan sulfate in the endothelial glycocalyx
TFPI	Anticoagulant protein blocking activated factor VII and X
LPL	Enzyme involved in breakdown of low density lipoproteins
LDL	Transports cholesterol and triglycerides through the circulation
VEGF	Potent stimulator of angiogenesis, production of which is triggered by hypoxia
TGFβ1/2	Growth factor known to mediate in a lot of signaling pathways, including smooth muscle cell differentiation and vascular tone and reactivity
FGF(r)	Growth factor (receptor) involved in endothelial cell proliferation and angiogenesis
Ec-SOD	Extracellular quencher of reactive oxygen species
IL 2, 3, 4, 5, 7, 8, 12, RANTES	Chemotaxis of leukocytes to the subendothelium; involved in arrest and diapedesis

TFPI Tissue factor pathway inhibitor, *LPL* lipoprotein lipase, *LDL* low density lipoprotein, *VEGF* vascular endothelial growth factor, *TGFβ1/2* transforming growth factor β1 or β2, *FGF(r)* fibroblast growth factor (receptor), *ec-SOD* extracellular superoxide dismutase, *IL* interleukin, *RANTES* Regulated on Activation, Normal T Expressed and Secreted—also known as chemokine CCL5



İnflamasyon



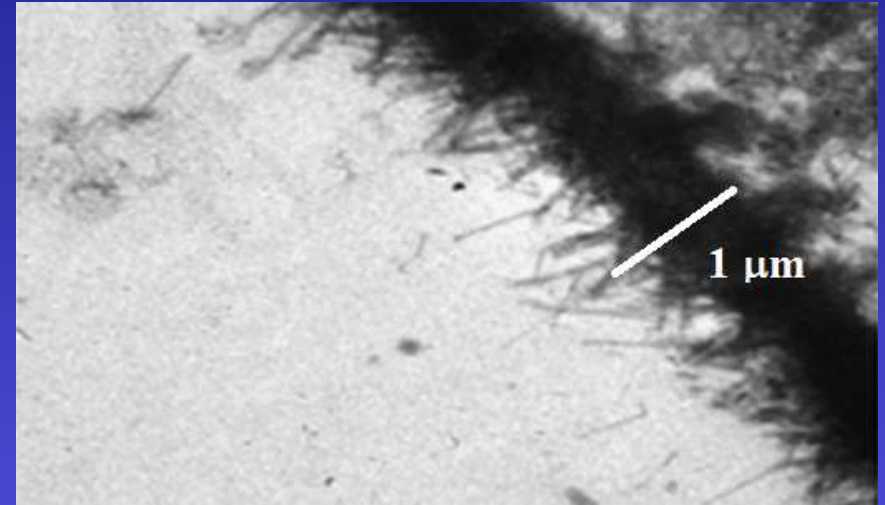
Yıkım



Shear stres



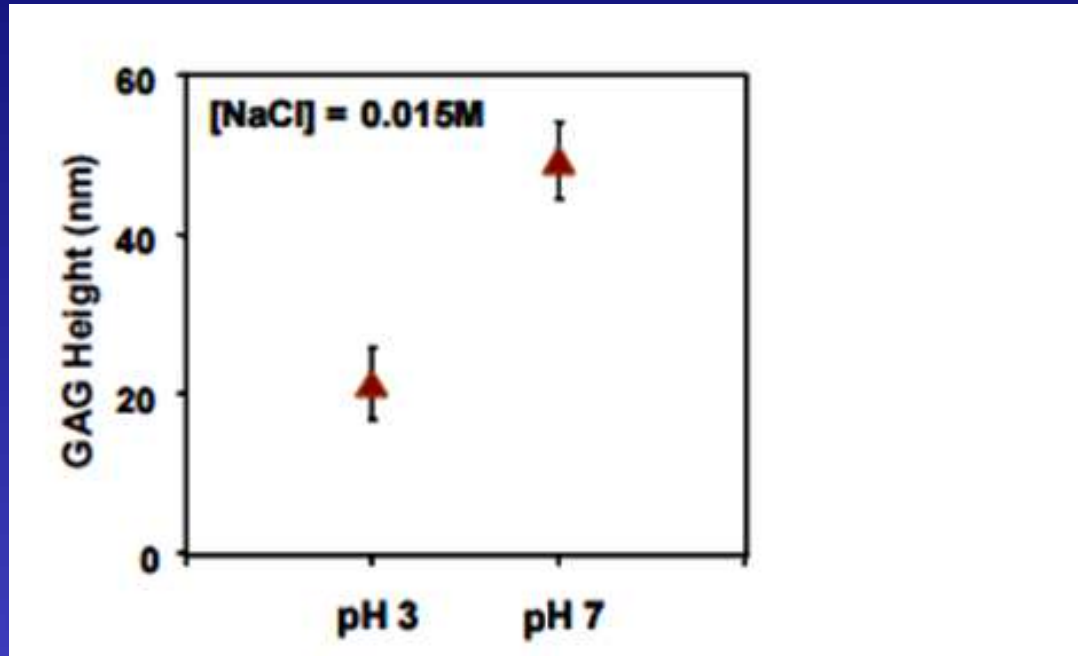
Sentez



Ann N Y Acad Sci. 1995 Jan 17;748:543-54.

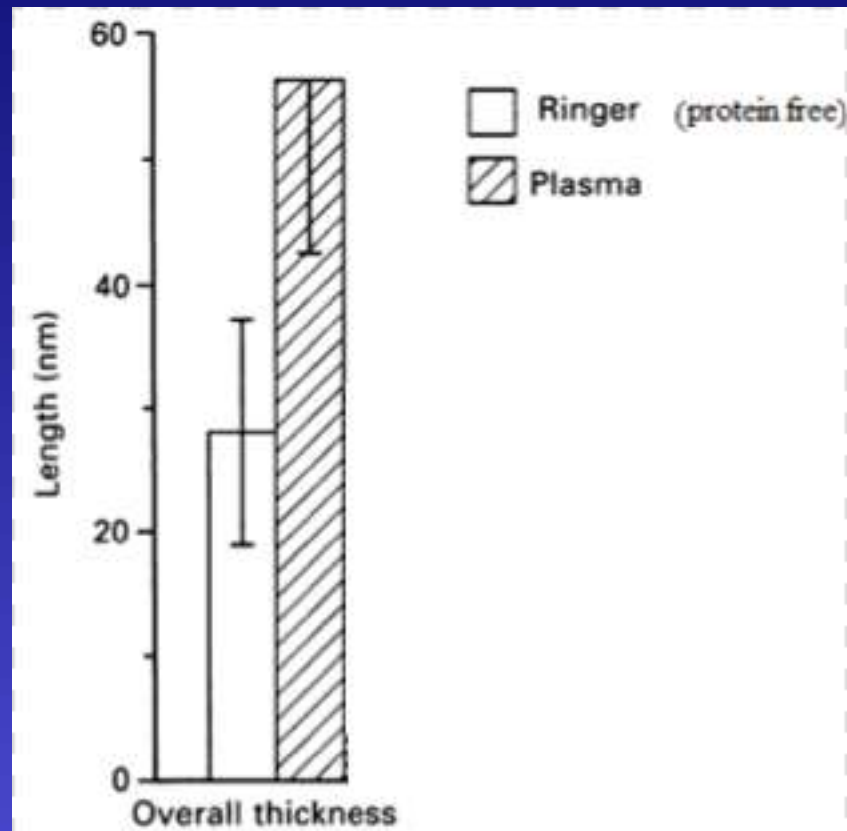
Am J Physiol Heart Circ Physiol 2004; 286: H1672–1680.

Lokal iyonik güç ve pH glikokaliksin esnekliğini etkilemektedir.

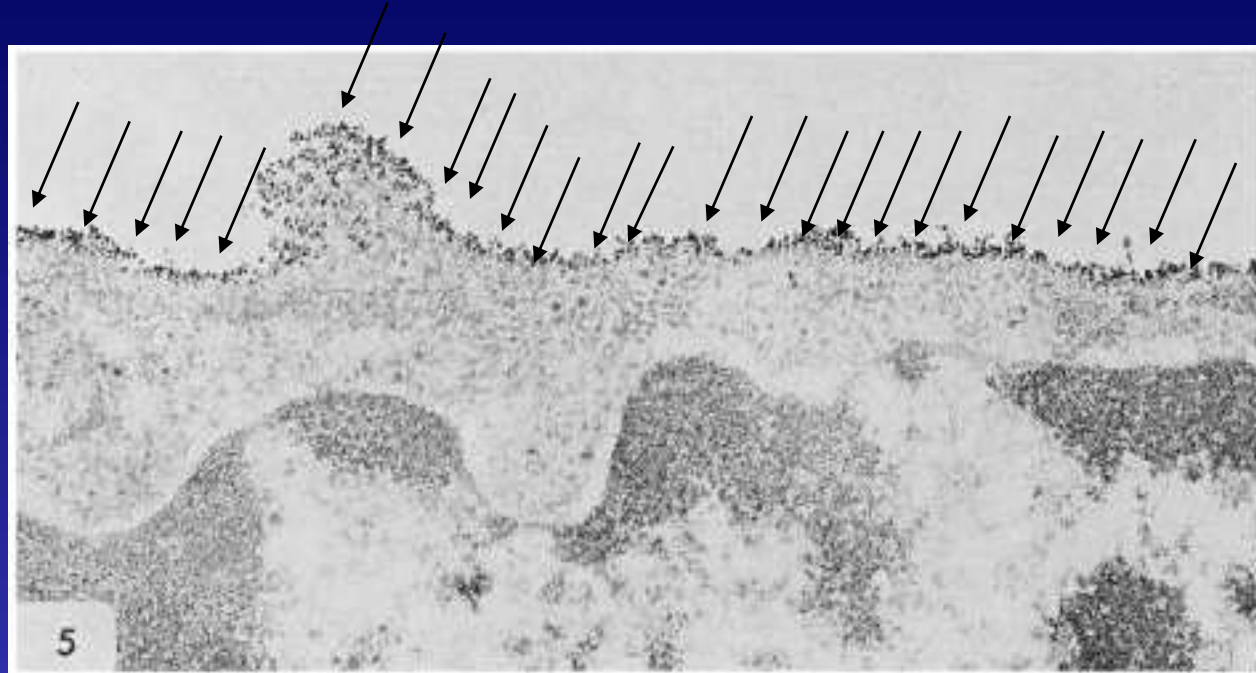


GAG'lar kendi uzunluğunun yaklaşık iki katına çıkabilir.

GAG'ların proteinler ile ilişkisi yapısını etkiler.



GK fonksiyon: Akan hücrelerin sürtünme etkisinden endoteli korumak



Katyonik ferritinin bağlandığı bölgeler

Table I: Binding of CF on membranes of vascular endothelium and RBCs of guinea pigs and rabbits[#]

	Ferritin particles/micron ²	
	Guinea pig	Rabbit
Endothelial cells	2600	2500

[#] Number of ferritin particles counted per micron² on micrographs (x 75,000) of tangentially sectioned membranes of guinea pig and rabbit endothelium and red blood cells.

Eritrosit membranında katyonik ferritin bağlanması

- Hücrelerin endotele yapışmaması
- Aglutinasyonun engellenmesi

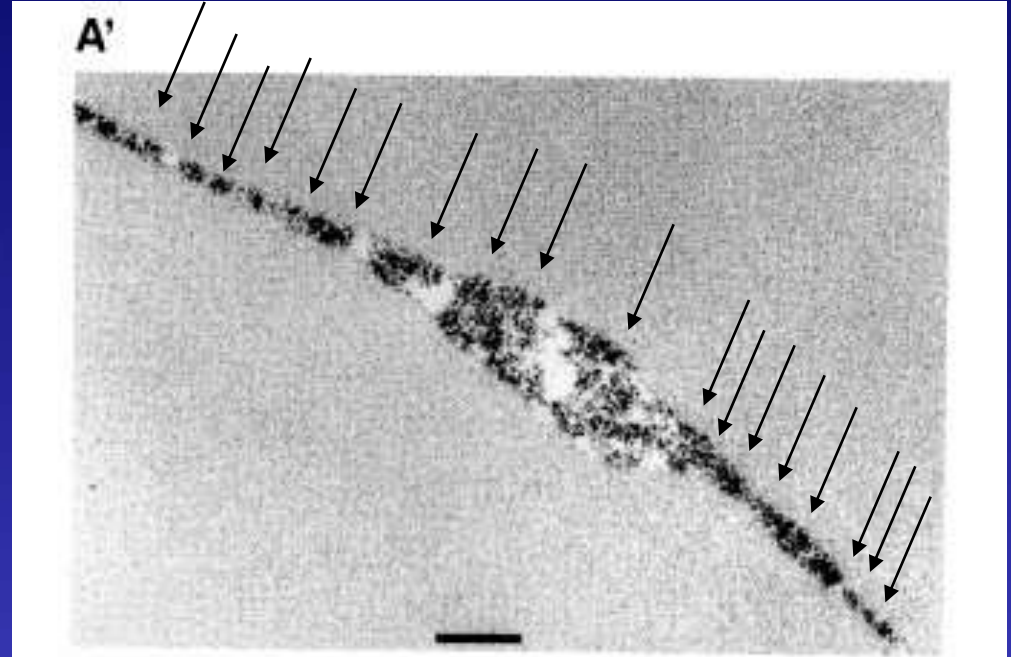
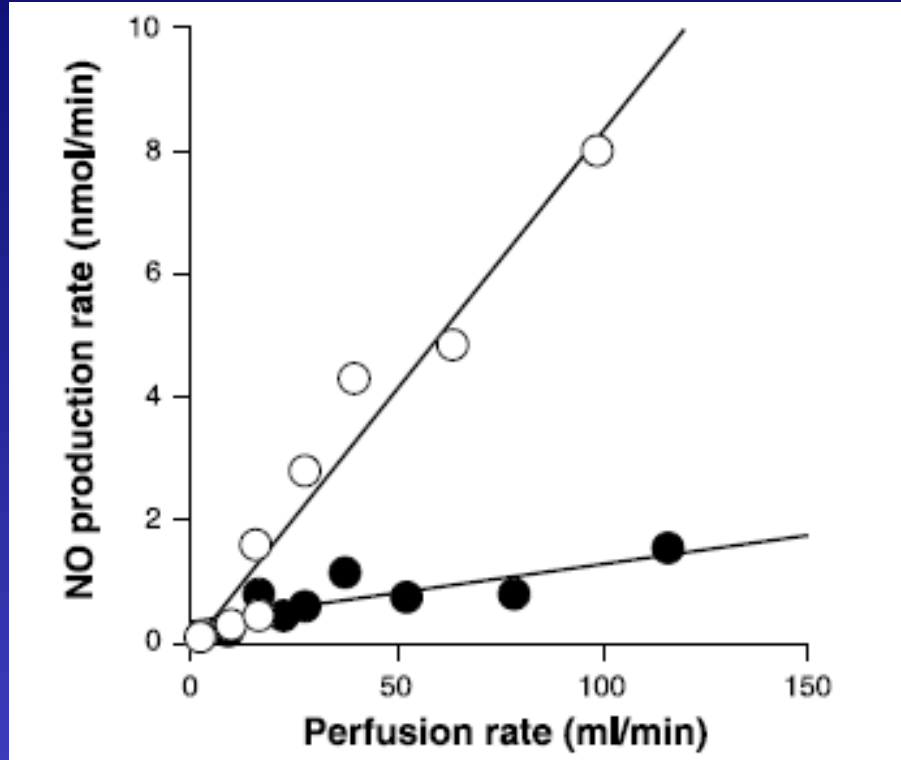


Fig. 4. Transmission electron micrographs of ultrathin sections of human RBC surface. Washed cells were incubated in medium containing CF (200 $\mu\text{g}/\text{ml}$) at 37°C for 5 min and washed twice with PBS. CF-labeled cells were prepared as described in Materials and Methods (A). Scale bar = 1 μm . (A') shows partial extension of (A). Scale bar = 100 nm.

GK fonksiyon: Shear stres bilgisi endotele glikokaliks aracılıđıyla aktarılmaktadır.

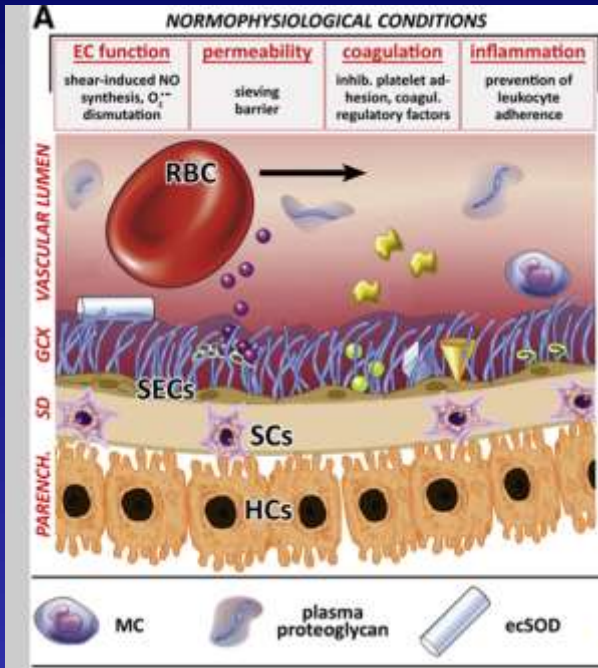


Kontrol damar

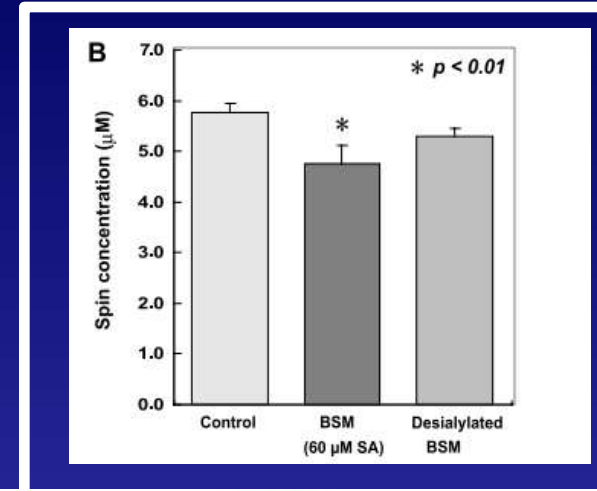
Hyaluronidaz uygulanmış damar

Vasküler tonus ve endotel fonksiyonuna aracılık

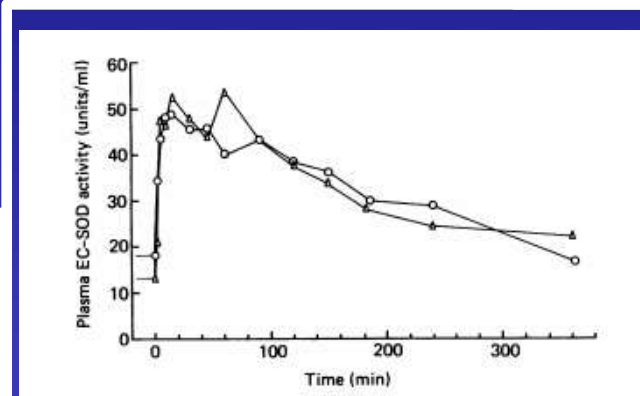
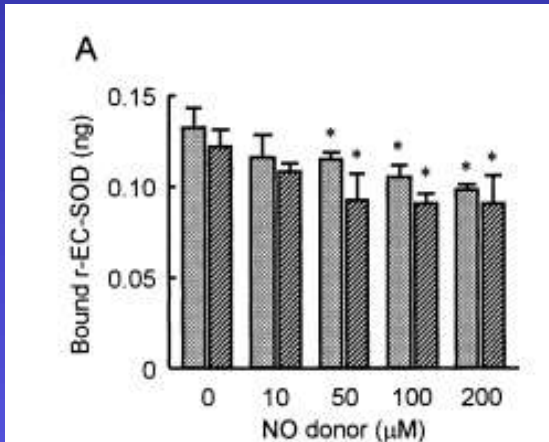
GK fonksiyon: Antioksidan maddeleri taşır.



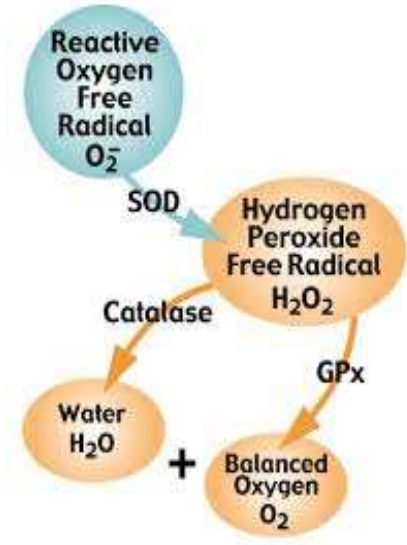
- Superoksit dismutaz
- Sialik asit



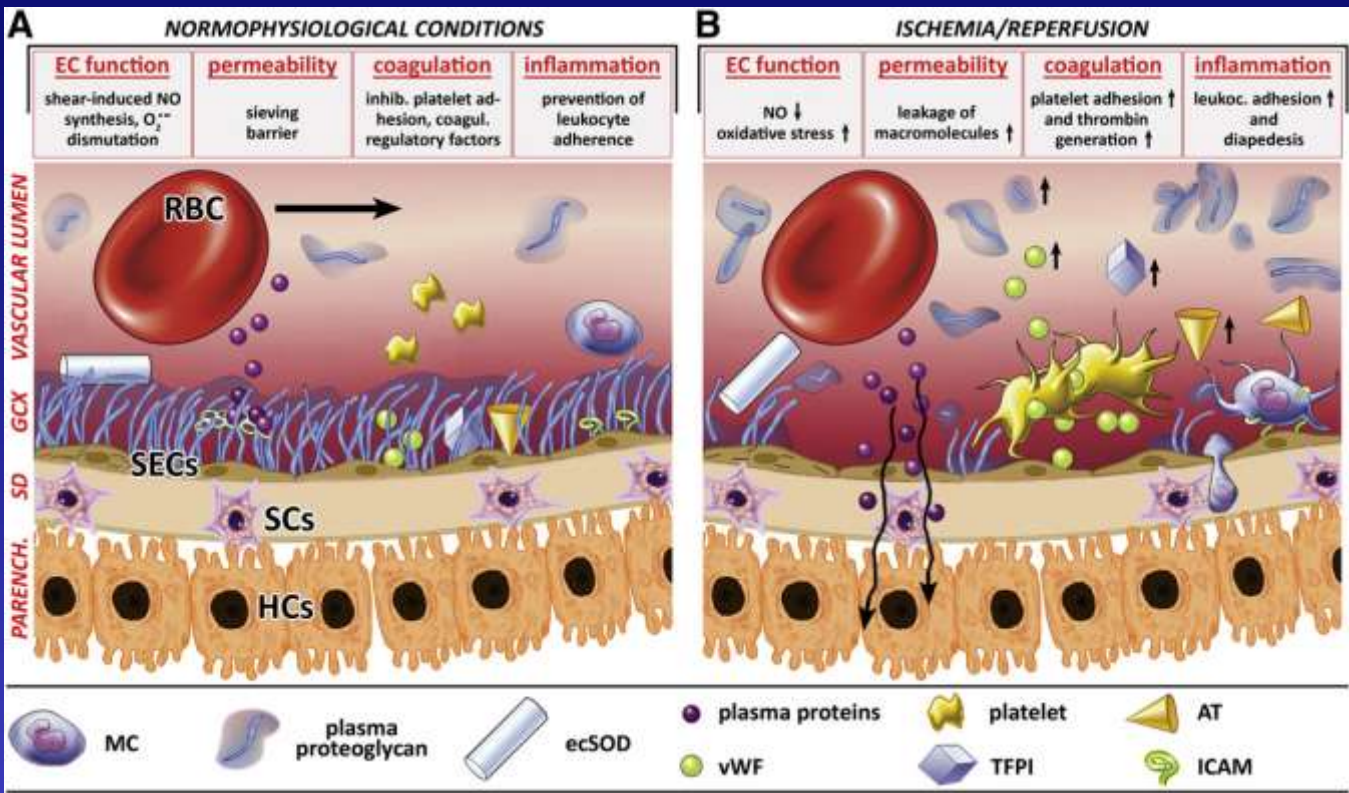
NO, glikokaliks-SOD bağıını azaltabilir.



Heparan sülfat SOD'ü bağlar



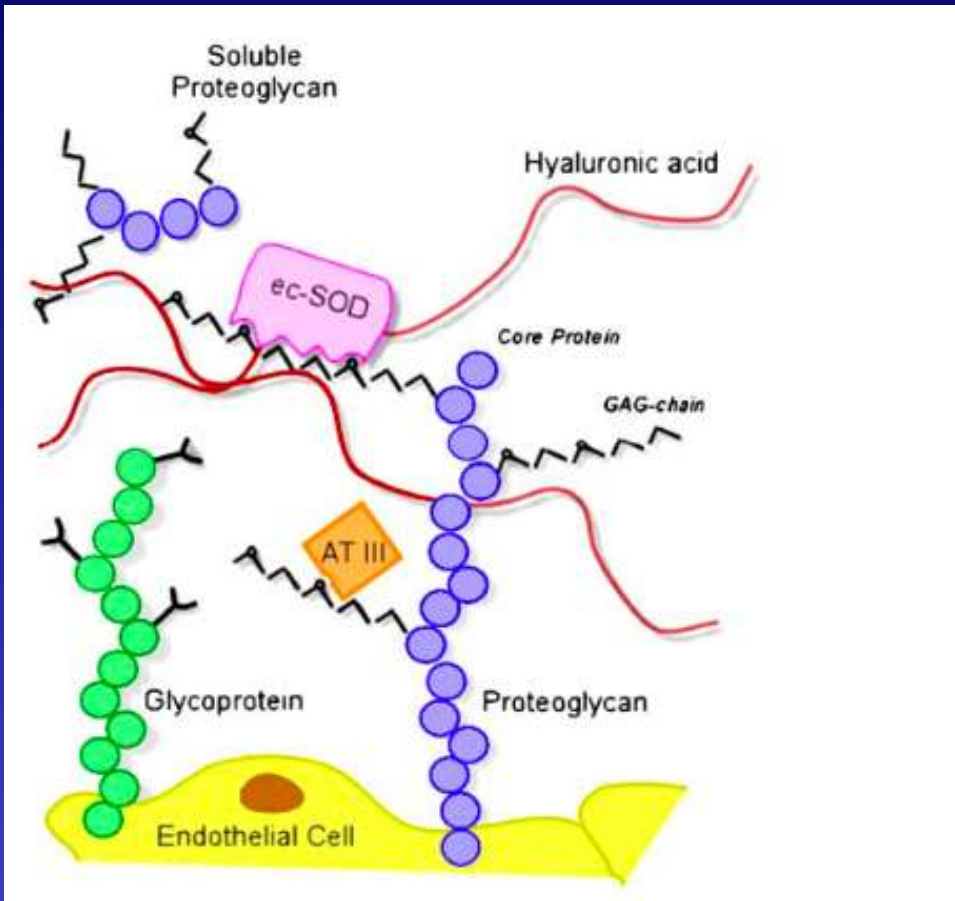
GK fonksiyon: Lökosit endotel ilişkisinin düzenlenmesi



Selektinler sialik asite bağlanabilir.

Curr Opin Cell Biol. 1992 Apr;4(2):257-66.

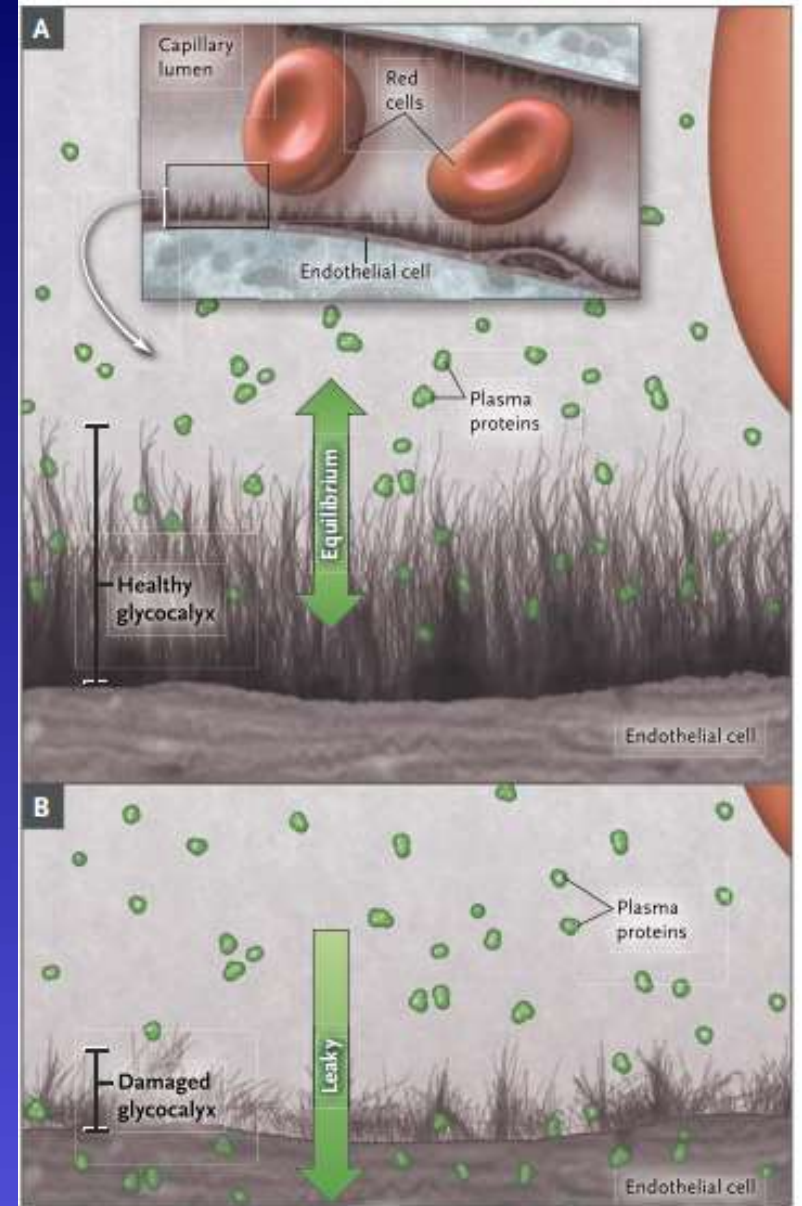
GK fonksiyon: Pıhtılaşmanın düzenlenmesi



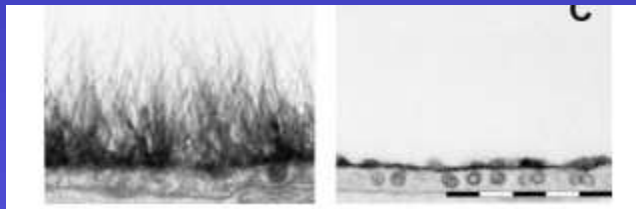
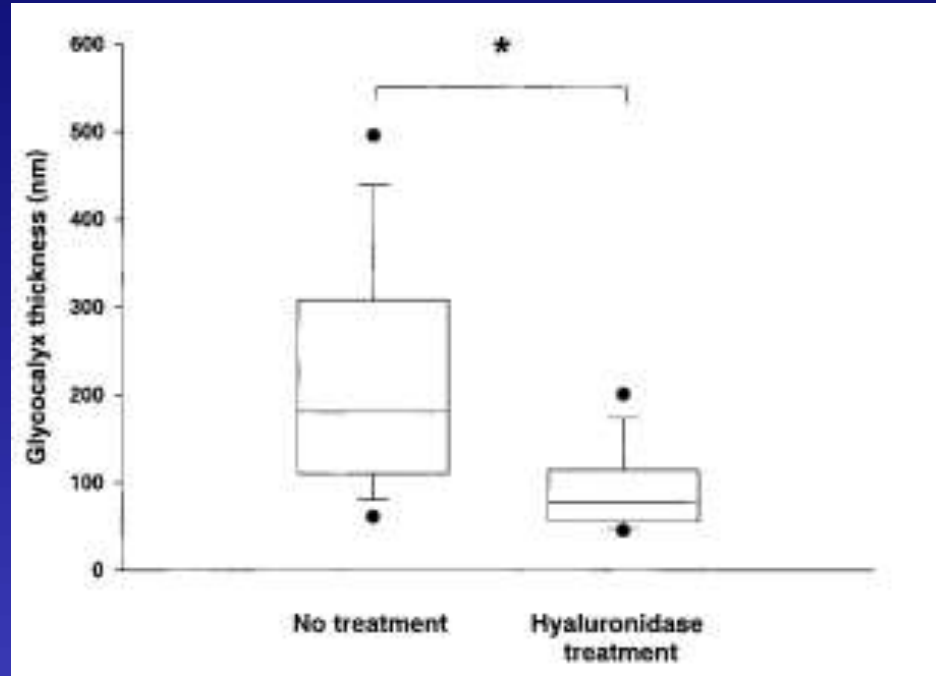
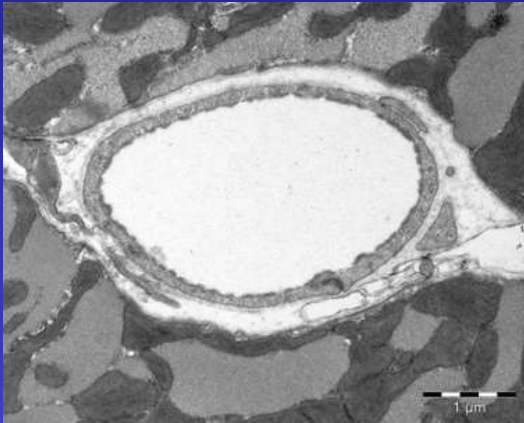
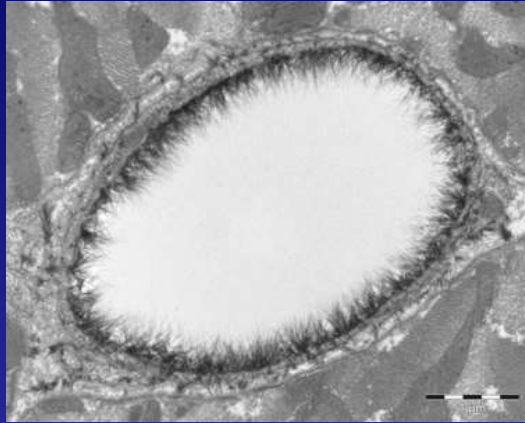
- Antithrombin III,
- Heparin cofactor II,
- Thrombomodulin,
- Tissue factor pathway inhibitor

GK fonksiyon: Kapiler duvar permeabilitesinin düzenlenmesi

- Proteinler
- Sialik asit
- Sialik asitce zengin oligosakkaridler hücre yüzünde su tutma özelliği sağlar.
- Su polar ve kısmen pozitif yüklüdür. Dolayısıyla hücre tarafından çekilir ve sıvı alımı bu yolla kontrol edilmiş olur.



Glikokaliks ödeme karşı korur

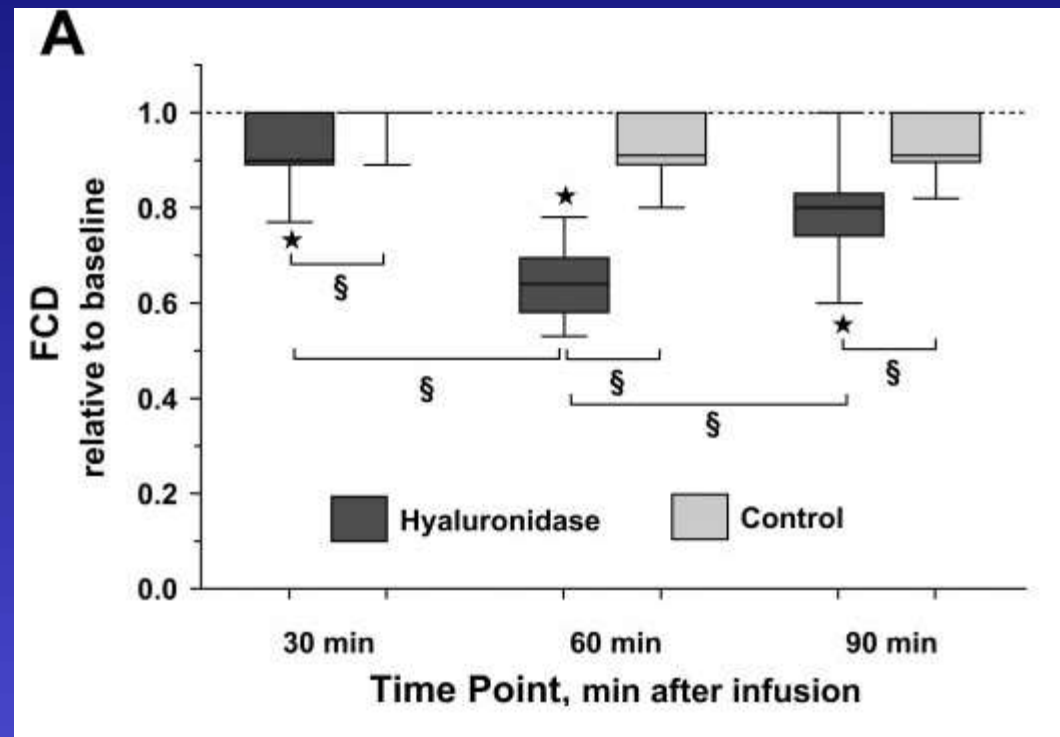
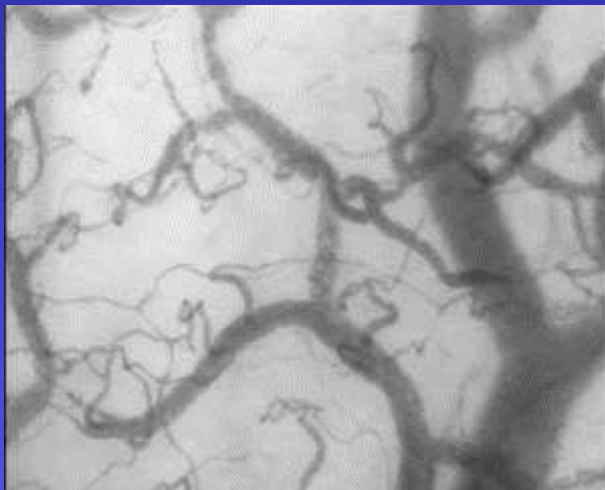


Rat left ventricle myocardial capillary

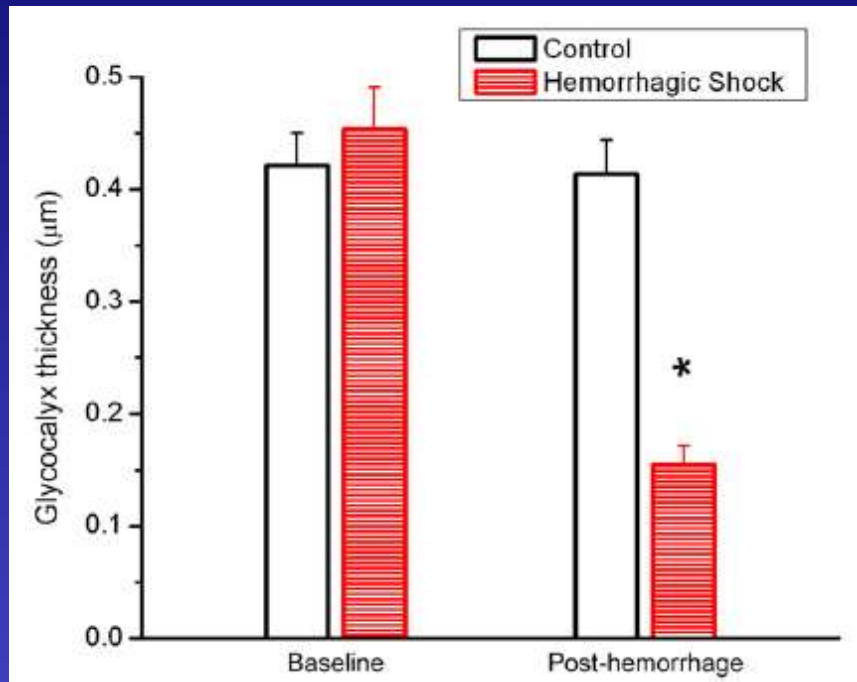
Microvascular and capillary perfusion following glycoalyx degradation.

Effect of hyaluronidase on the microcirculation.

Fonksiyonel kapiller yoğunluk (FCD) =görünür alandaki perfüze olan damar sayısı



Hemorajik şokta glikokaliks



Balanced vs unbalanced crystalloid resuscitation in a near-fatal model of hemorrhagic shock and the effects on renal oxygenation, oxidative stress, and inflammation[☆]

Plasma lactate (mmol/l)	
Control	2.8 ± 0.2
HS	11.2 ± 1.8 ^C
HS + NaCl	3.3 ± 0.7 ^H
HS + Lyte	3.6 ± 0.5 ^H
Plasma TNF-α (pg/ml)	
Control	68 ± 13
HS	291 ± 16.26 ^C
HS + NaCl	368 ± 47.99 ^C
HS + Lyte	247 ± 48.7 ^C
Plasma IL-6 (pg/ml)	
Control	170 ± 25
HS	14132 ± 4347 ^C
HS + NaCl	21258 ± 5312 ^C
HS + Lyte	12808 ± 6146 ^C
Tissue MDA/protein content (μmol/g)	
Control	1.7 ± 0.2
HS	3.4 ± 0.6 ^C
HS + NaCl	3.5 ± 0.6 ^C
HS + Lyte	3.1 ± 0.3 ^C
Plasma hyaluronan (ng/ml)	
Control	7.9 ± 2.7
HS	158.1 ± 20.8 ^C
HS + NaCl	97.1 ± 13.4 ^C
HS + Lyte	152.7 ± 56.9 ^C

^C $p < 0.05$ vs control.

^H $p < 0.05$ vs HS.

Dengeli ve dengeli olmayan kristaloid replasmanı

Şok: 40 mmHg

Hedef: 80 mmHg

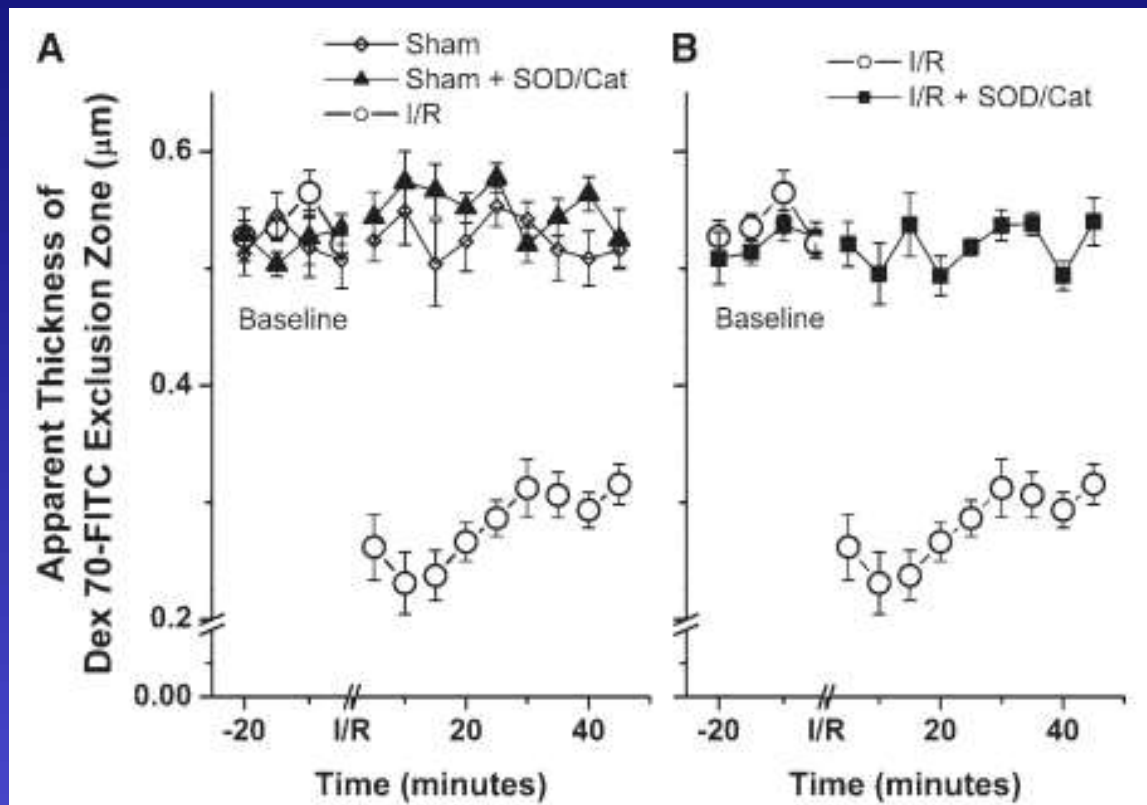
Sıvılar:

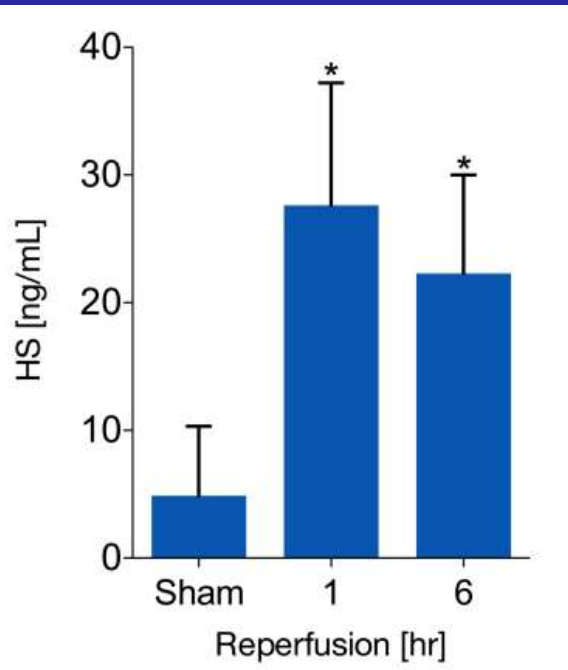
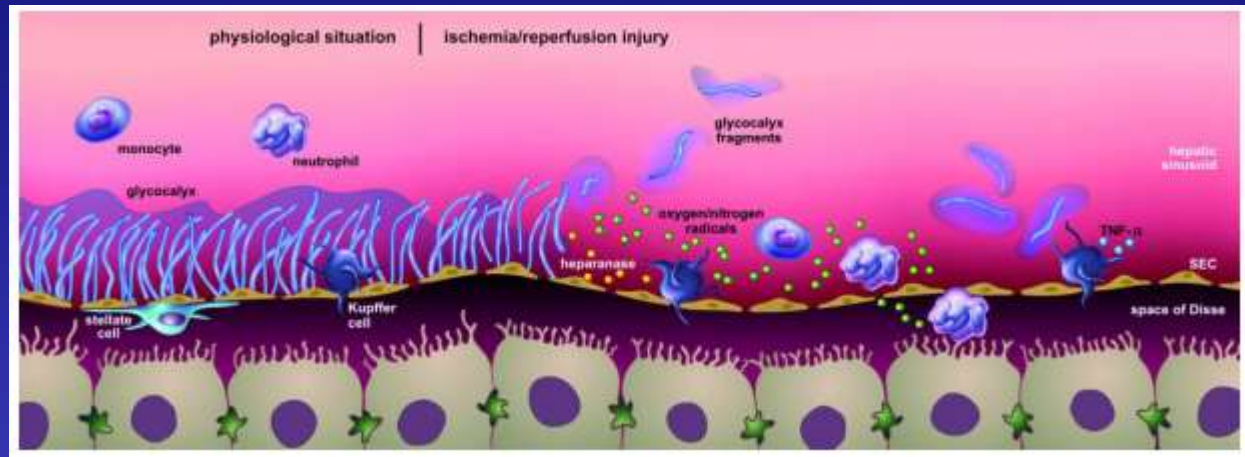
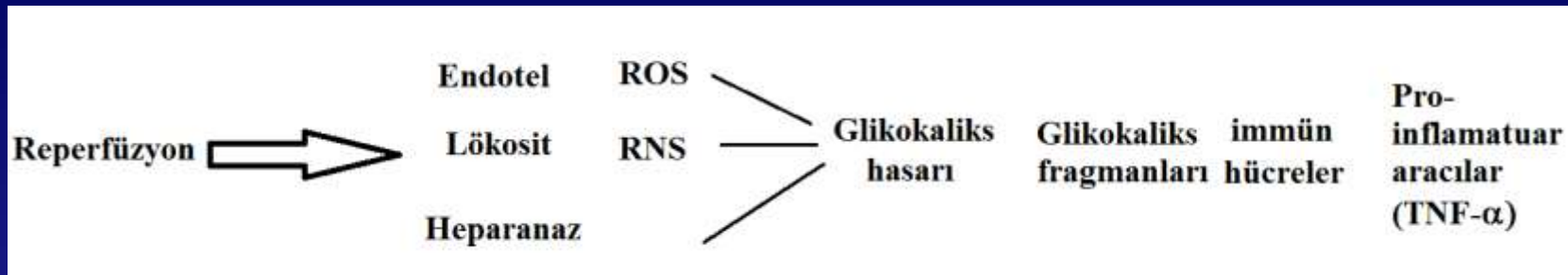
- % 0.9 NaCl
- Plasma Lyte

Hasarı yapan nedir



Reactive oxygen species mediate modification of glycocalyx during ischemia-reperfusion injury





Loss of Endothelial Glycocalyx During Acute Hyperglycemia Coincides With Endothelial Dysfunction and Coagulation Activation In Vivo

Max Nieuwdorp,¹ Timon W. van Haften,² Mirella C.L.G. Gouverneur,³ Hans L. Mooij,¹ Miriam H.P. van Lieshout,¹ Marcel Levi,⁴ Joost C.M. Meijers,¹ Frits Holleman,⁴ Joost B.L. Hoekstra,⁴ Hans Vink,³ John J.P. Kastelein,¹ and Erik S.G. Stroes¹

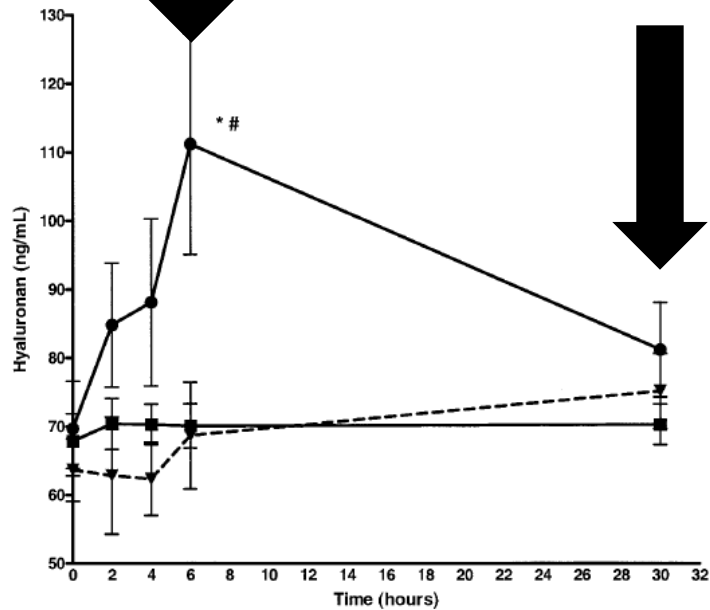
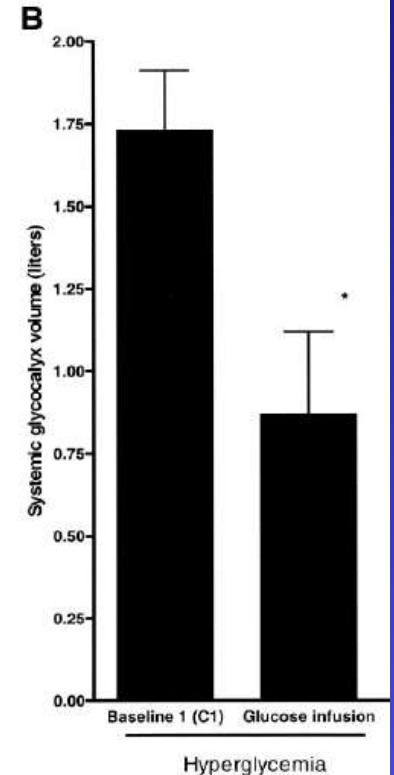


FIG. 3. Shedding of endothelial glycocalyx compounds (as assessed by plasma hyaluronan) in subjects infused with glucose (●), mannitol (■), or glucose-NAC (▲). Data are means \pm SE. * $P < 0.05$ vs. baseline; # $P < 0.05$ among groups.



300 mg/dl for 6 h

Reduced negative surface charge on arterial endothelium explains accelerated atherosclerosis in type 2 diabetic patients.

Nassimizadeh M, Ashrafian H, Drury NE, Howell NJ, Digby J, Pagano D, Frenneaux MP, Born GV.

Diab Vasc Dis Res. 2010 Jul;7(3):213-5. doi: 10.1177/1479164110376207. Epub 2010 Jul 26.

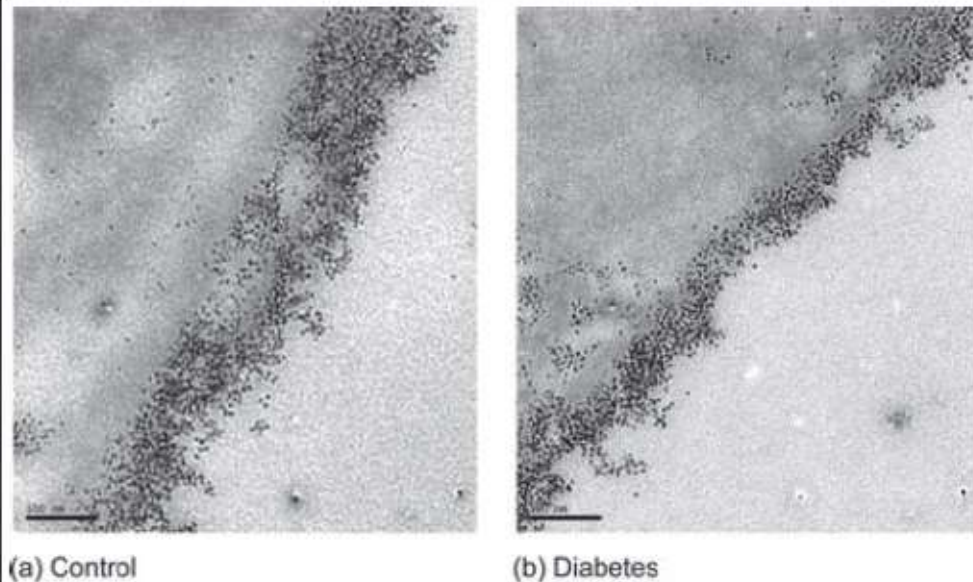


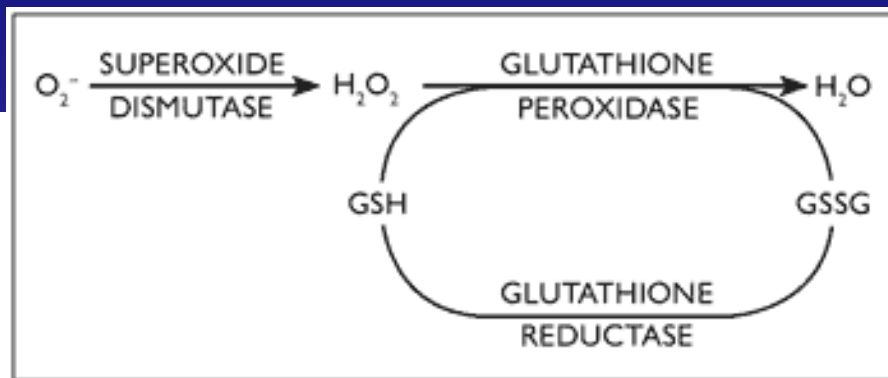
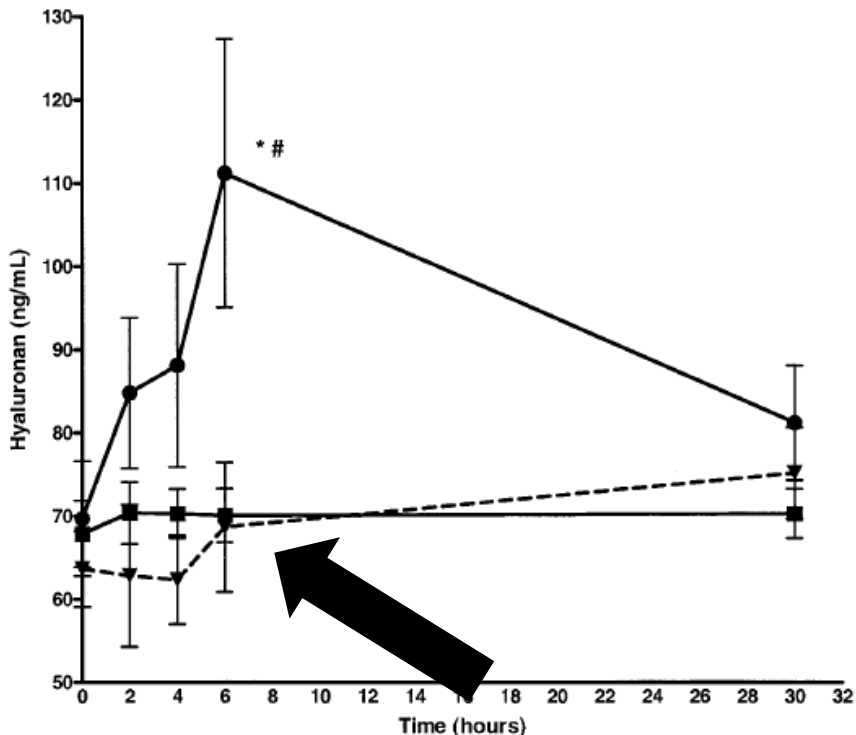
Figure 1. Electron micrographs of ferritin binding in internal mammary arteries from controls and subjects with diabetes. (a) control; (b) diabetic pre-treated (after fixation) with 0.5 mg/ml of cationised ferritin ($\times 30,000$). The lower number of bound ferritin particles is apparent in the subjects with diabetes compared with controls. The thinning of the iron-binding layer is prominent in the presence of diabetes and is likely to correspond to decreased glycocalyx volume.

Nasıl korunur ?

Original Article

Loss of Endothelial Glycocalyx During Acute Hyperglycemia Coincides With Endothelial Dysfunction and Coagulation Activation In Vivo

Max Nieuwdorp,¹ Timon W. van Haften,² Mirella C.L.G. Gouverneur,³ Hans L. Mooij,¹ Miriam H.P. van Lieshout,¹ Marcel Levi,⁴ Joost C.M. Meijers,¹ Frits Holleman,⁴ Joost B.L. Hoekstra,⁴ Hans Vink,³ John J.P. Kastelein,¹ and Erik S.G. Stroes¹



N-asetil sistein= glutatyon prekürsör

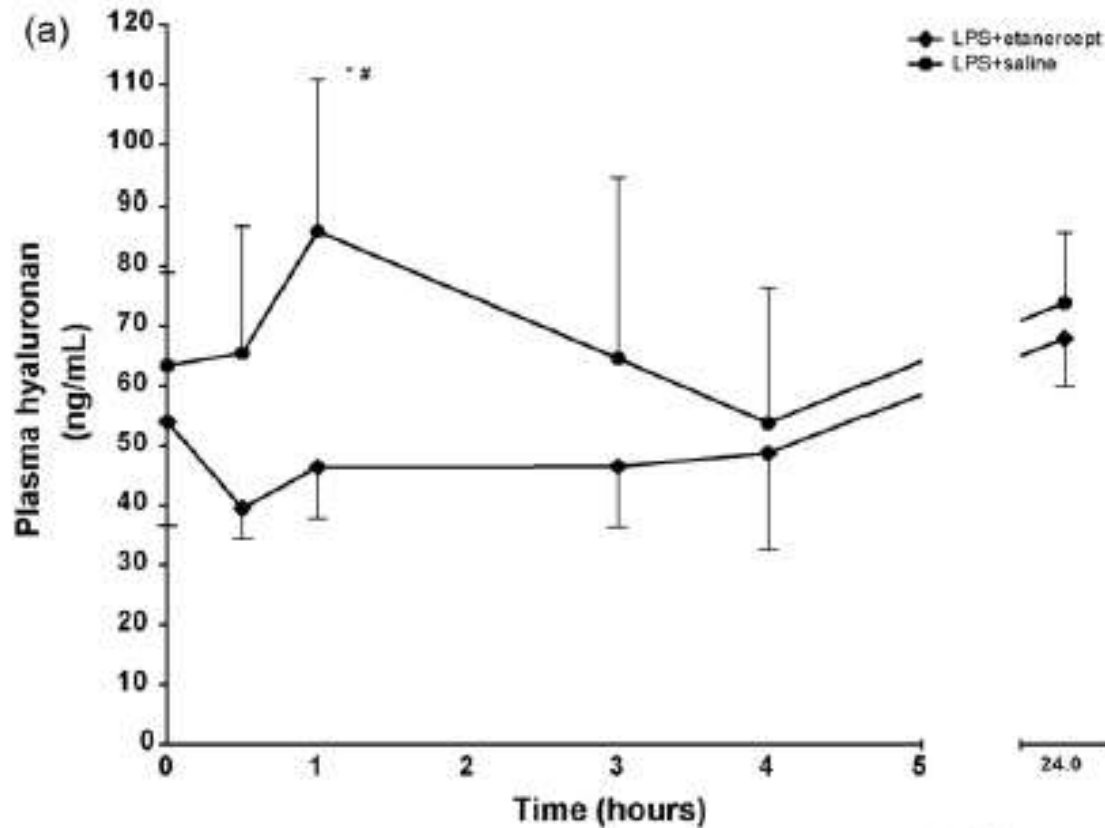
FIG. 3. Shedding of endothelial glycocalyx compounds (as assessed by plasma hyaluronan) in subjects infused with glucose (●), mannitol (■), or glucose-NAC (▲). Data are means ± SE. *P < 0.05 vs. baseline; #P < 0.05 among groups.

Glucose
Glucose + NAC

300 mg/dl for 6 h

Diabetes. 2006 Feb;55(2):480-6.

Tumor necrosis factor- α inhibition protects against endotoxin-induced endothelial glycocalyx perturbation



1 ng/kg endotoksin (LPS)

- LPS
- Etanercept +LPS

Sonuç:

Çok fonksiyonlu glikokaliksin serbest radikaller ve inflamasyondan etkilenmesi öngörülemeyen sonuçlara neden olabilir.



Teşekkürler