DİYABETİK BİREYLERDE PREMATÜR ATEROSKLEROZ BELİRTEÇLERİ

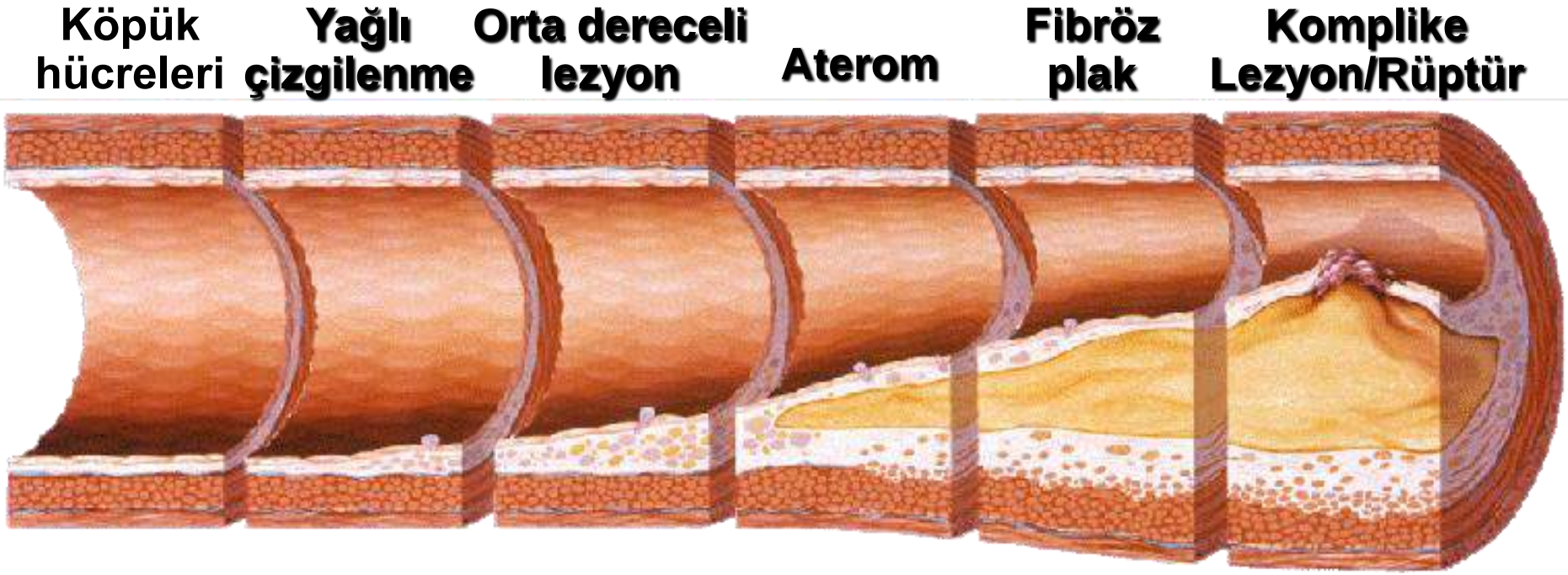
Dr. Mesut Özkaya
Gaziantep Üniversitesi Endokrinoloji Bilim Dalı

26 Nisan 2014 – 50. Diyabet kongresi

Sunum akışı…

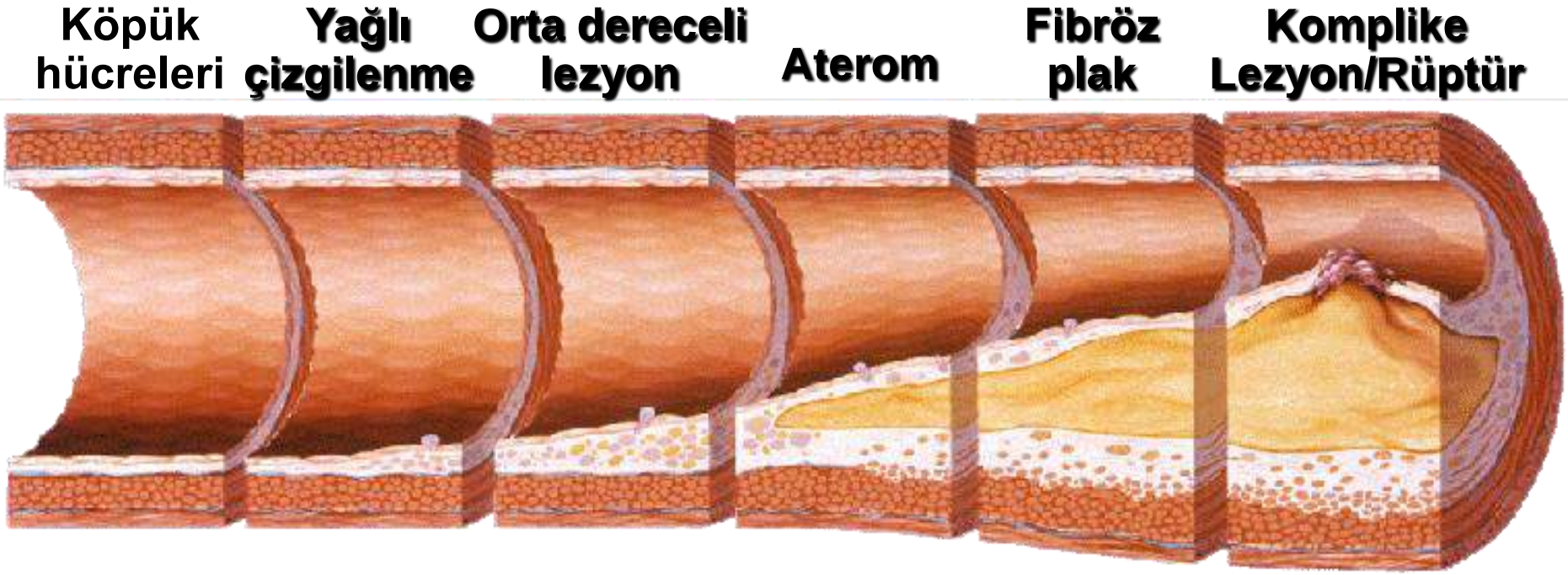
- Genel bilgiler
- Aterosklerozun rol dağılım
- Vasküler düz kas belirteçleri
- Endotel hücresi belirteçleri
- Trombosit ve bağlantılı belirteçler
- Güncel belirteçler
- Genel değerlendirme ve sonuç

Aterosklerozun doğal seyri…



Circulation 1995;92:1355-1374

Aterosklerozun doğal seyri…

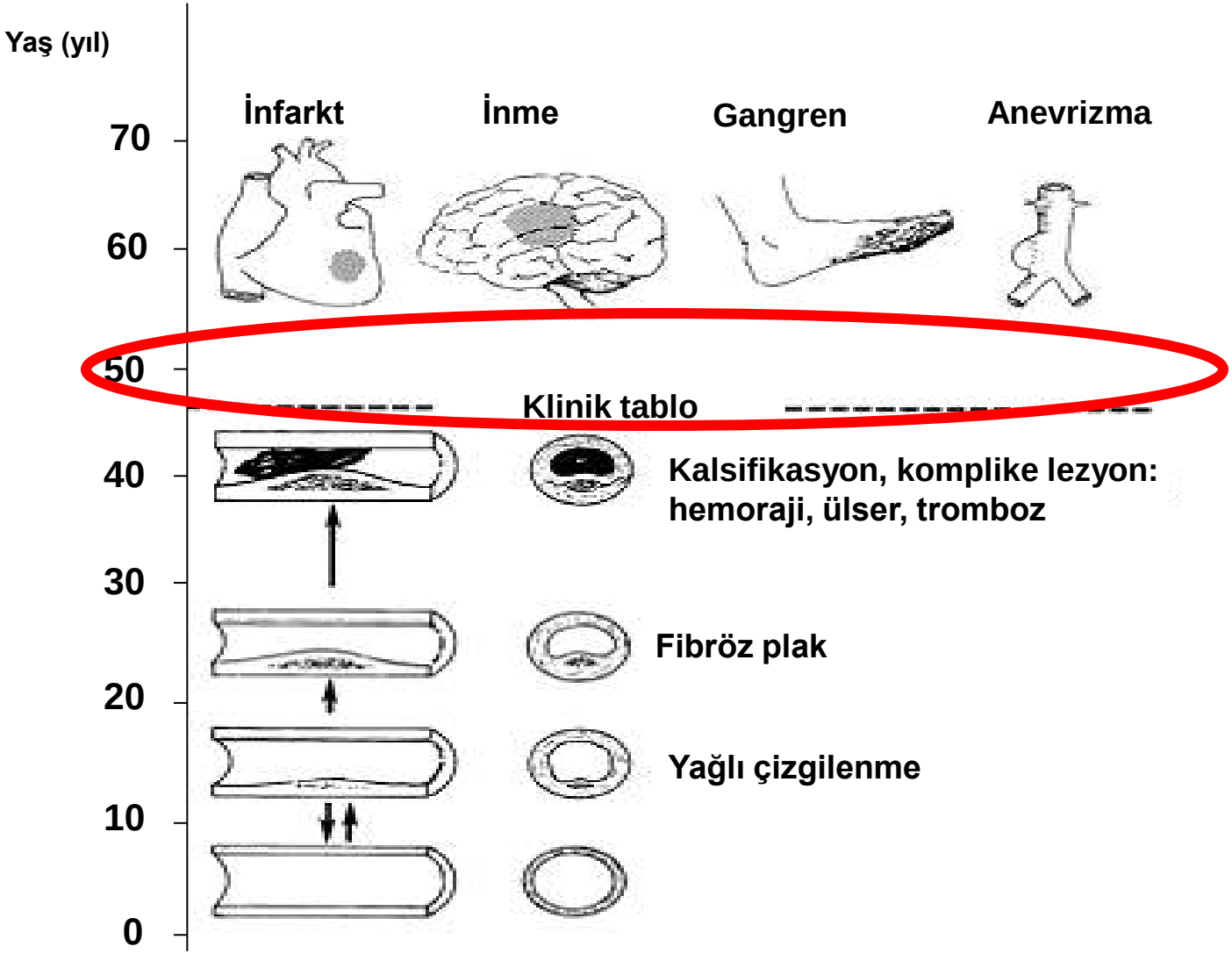


1. dekaddan itibaren | 3. dekaddan itibaren | 4. dekaddan itibaren

Circulation 1995;92:1355-1374

Normal zaman ne ?

Aterosklerozun doğal seyri…



Korean Circ J, 40: 1-9, 2010

Diyabette ateroskleroz farklı mıdır ?

Diyabette ateroskleroz farklı mıdır ?
Evet…

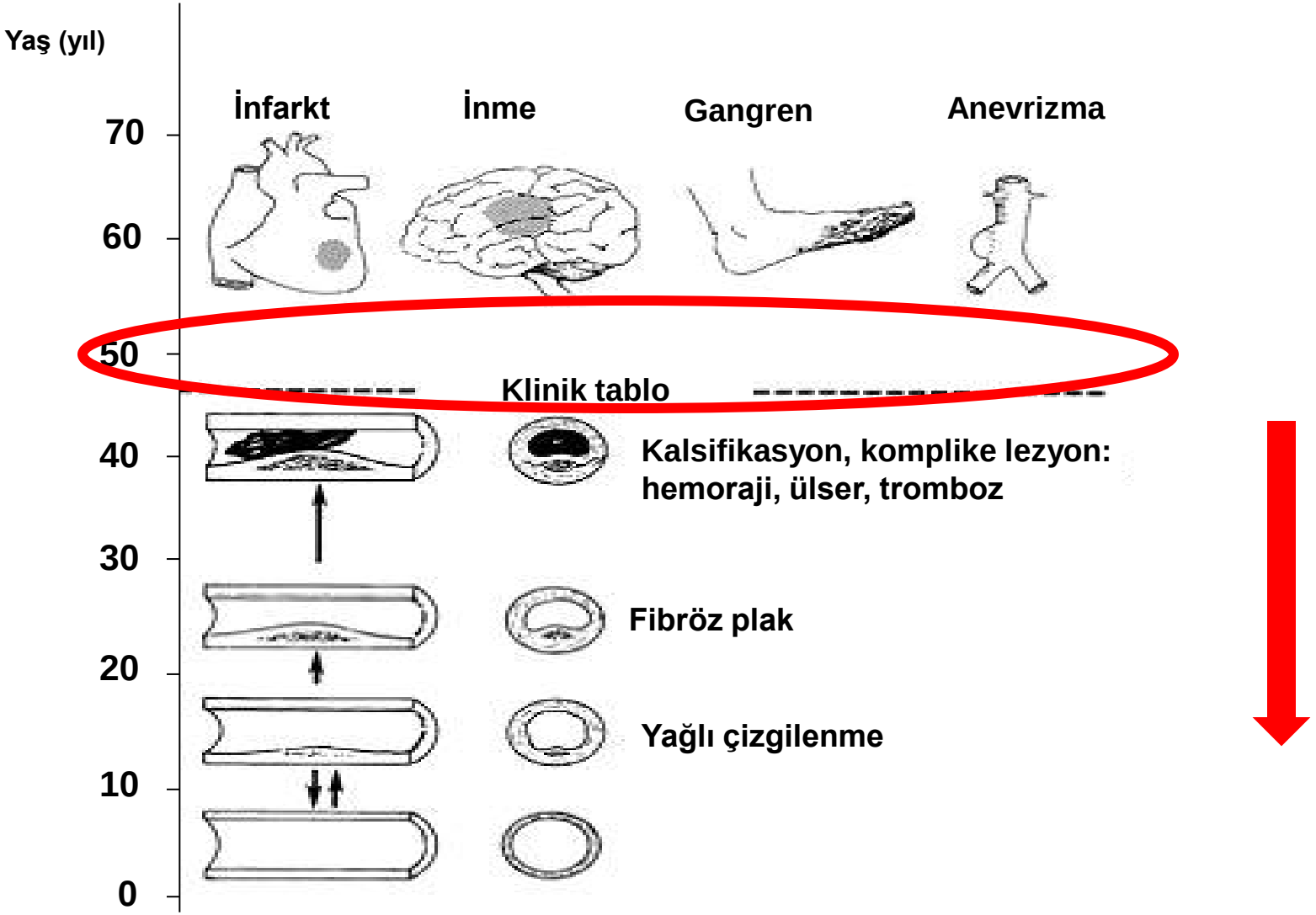
Diyabette ateroskleroz farklıdır. Çünkü…

- Ateroskleroz şiddetli
  - Multi-damar hastalık
  - Distal hastalık – revaskülarizasyon daha zor
- Sessiz iskemi/MI
- İlk klinik prezantasyon majör KV olay olabilir
- Kadın
- Revaskülarizasyona rağmen sonuçlar daha kötü
- Daha genç

Prematür ?

- Vaktinden önce olan veya gelişen
- Erken gerçekleşen

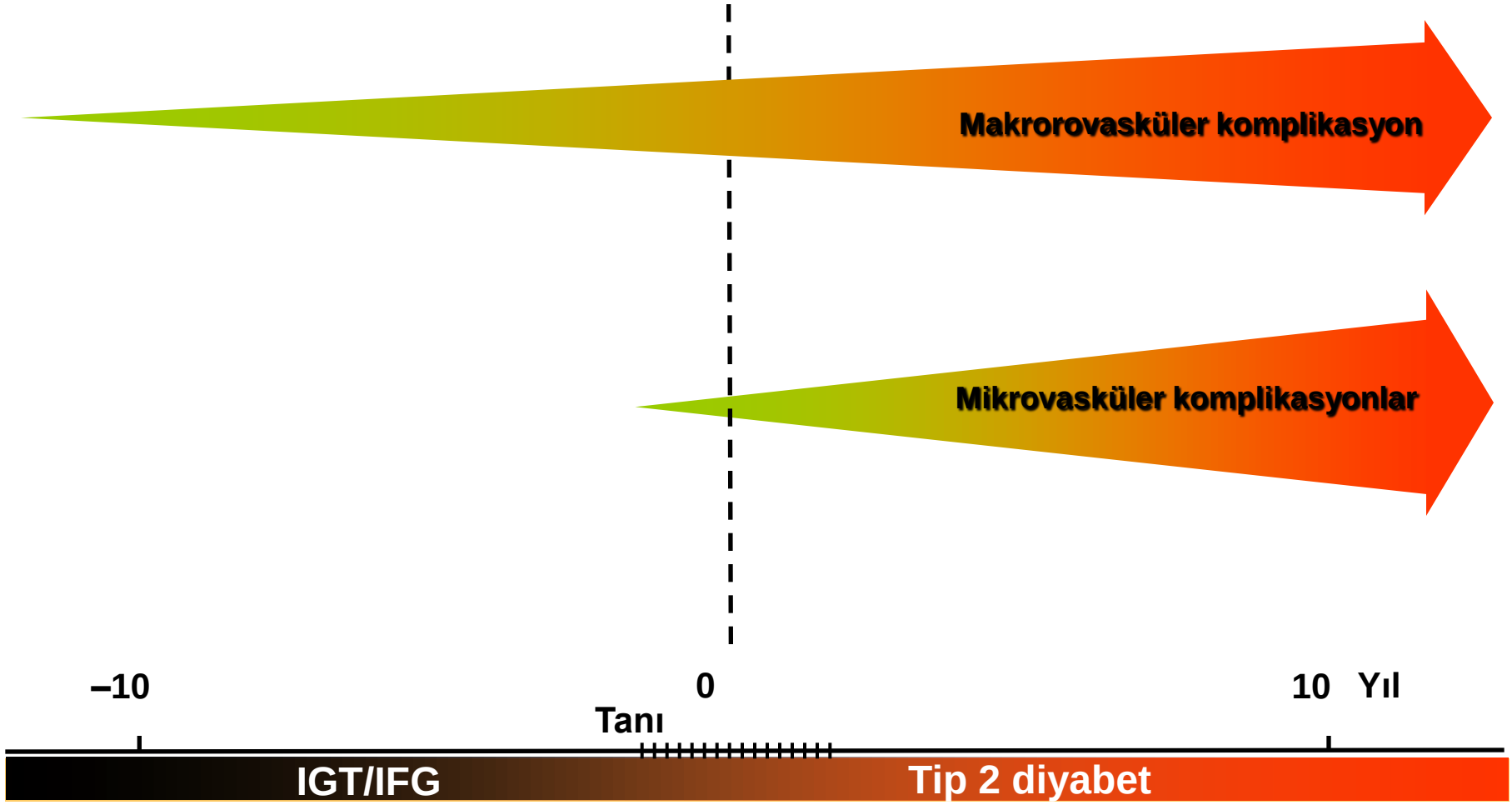
Aterosklerozun doğal seyri…



Korean Circ J, 40: 1-9, 2010

Belki de daha doğrusu ?

- Hem prematür hem akselere ateroskleroz



DeFronzo RA. Med Clin North Am 2004; 88:787–835.

Belirteç ?

- Bir olayla ilgili sayısal, ölçülebilir (niceliksel) göstergeler

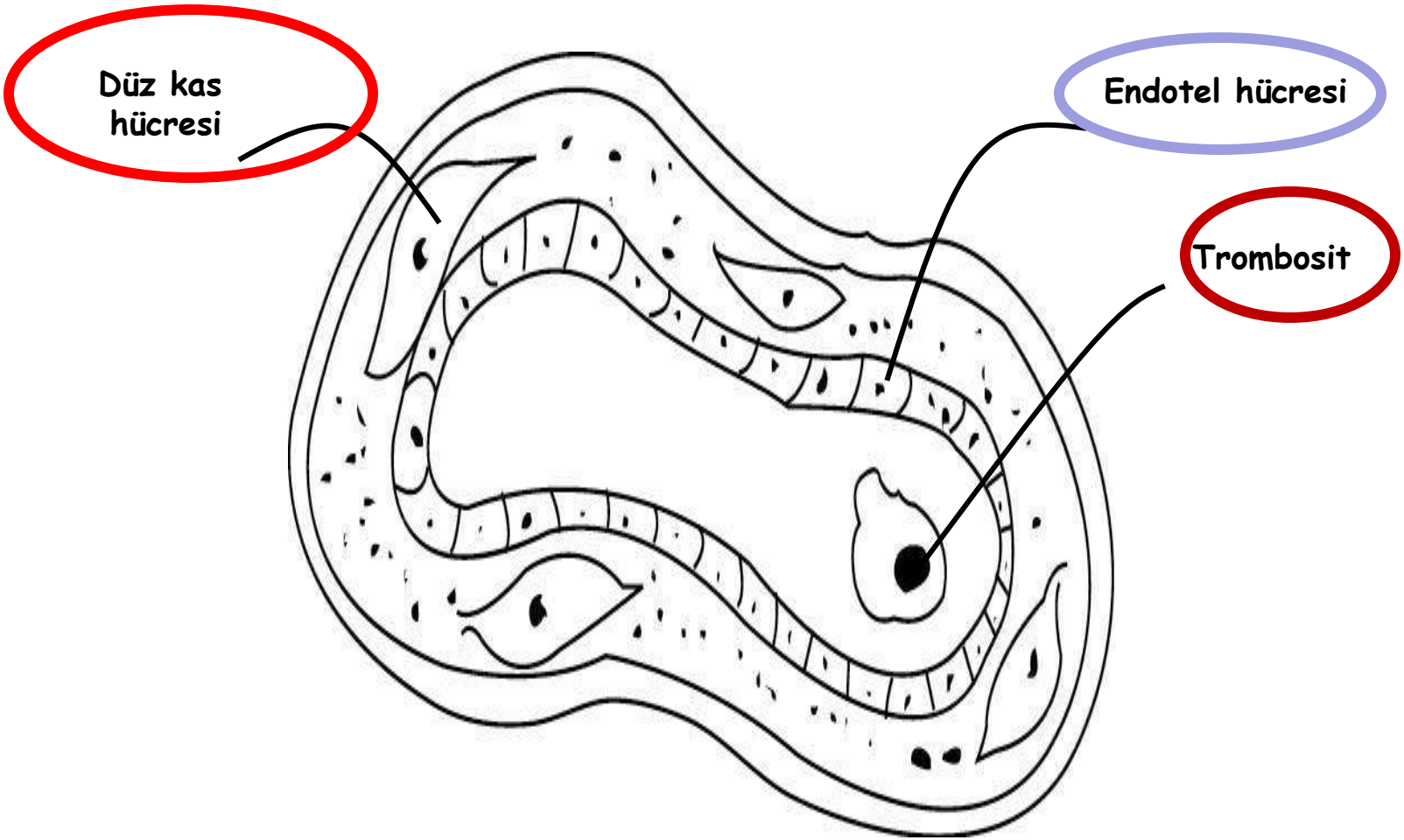
Belirteç ?

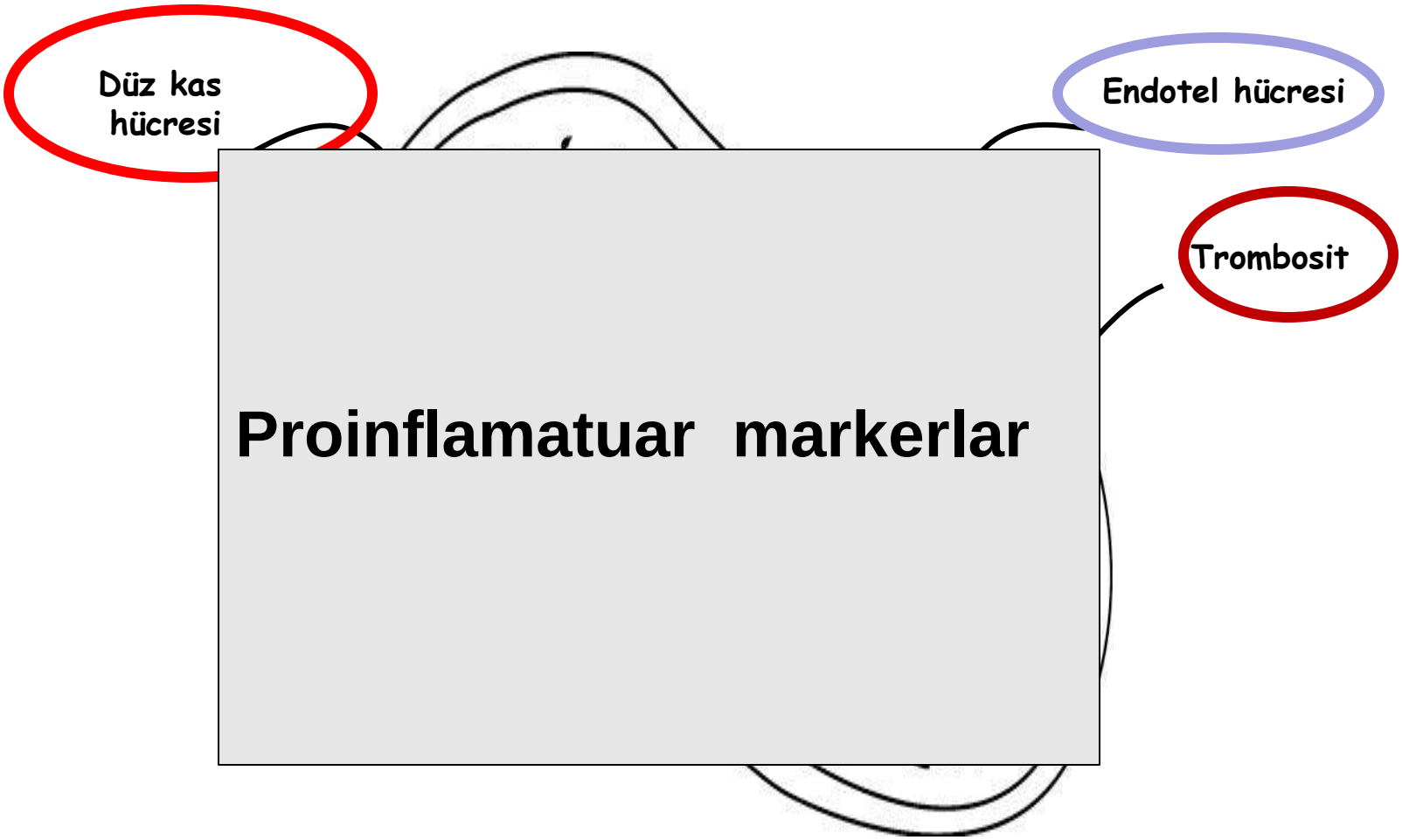
- Bir olayla ilgili sayısal, ölçülebilir (niceliksel) göstergeler

- Neler belirteç olabilir ?

Belirteçlerin sırrı ?

- Etyopatogenezde rol oynayan:
  - Komponentler…..


Düz kas hücresi
Endotel hücresi
Trombosit

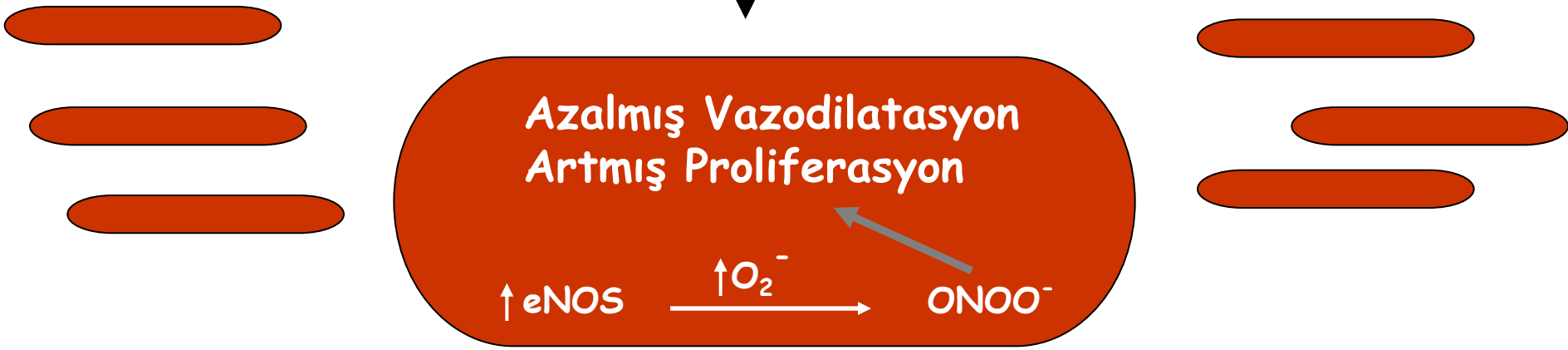

Düz kas hücresi
Endotel hücresi
Trombosit
Proinflamatuar markerlar

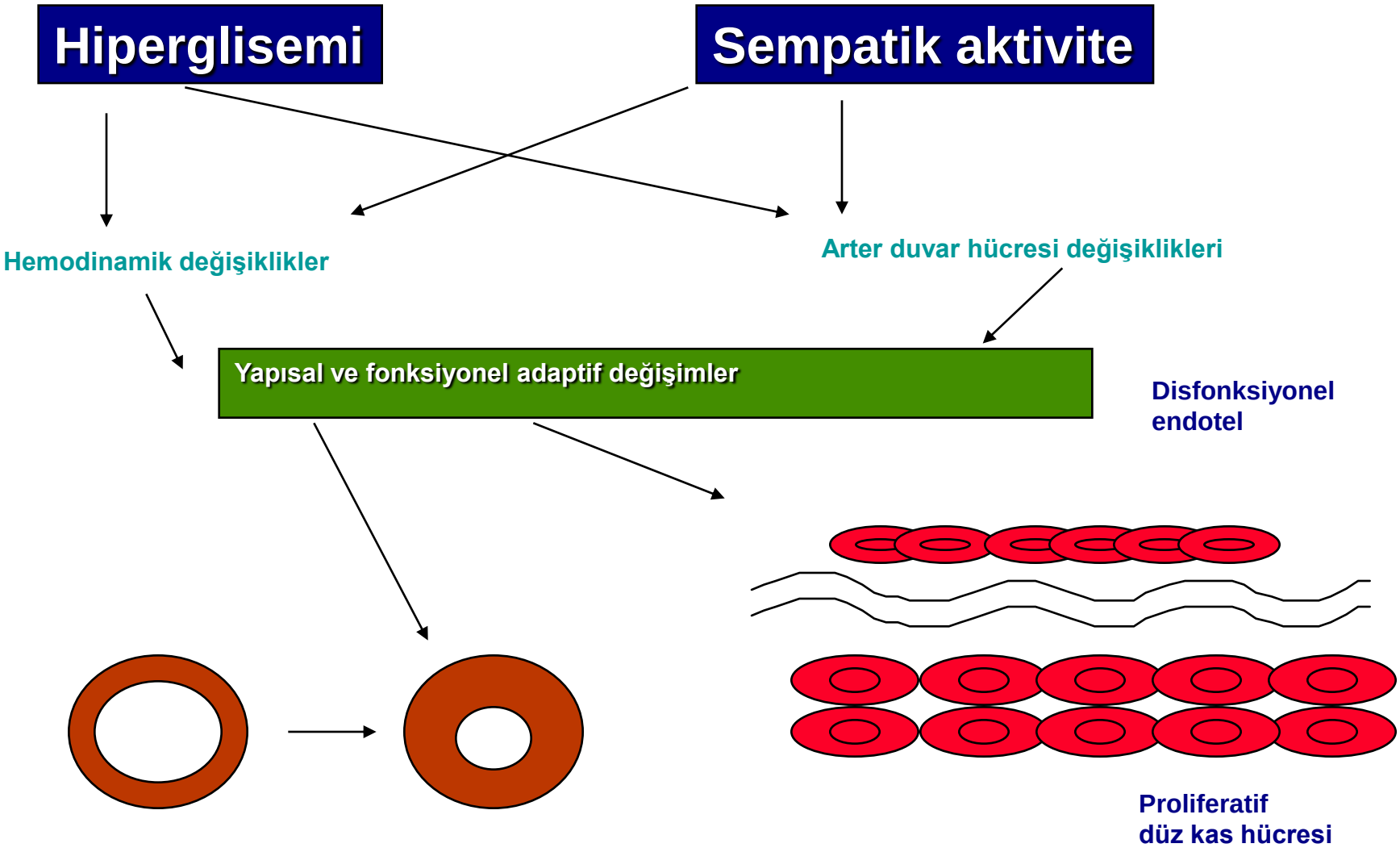
Kronik hiperglisemi

↓

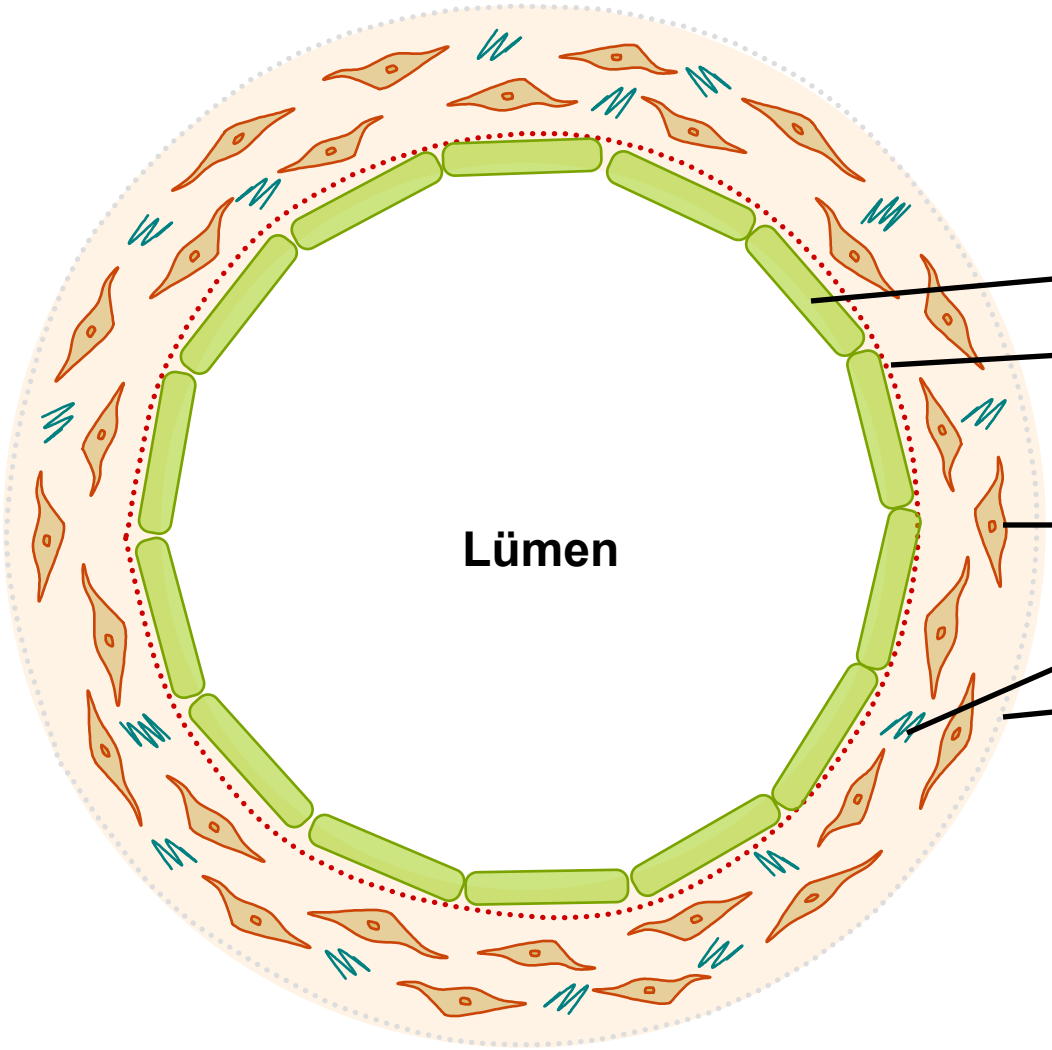
Vasküler Düz Kas Hücre Değişimi

↓




Hiperglisemi
Sempatik aktivite
Hemodinamik değişiklikler
Arter duvar hücresi değişiklikleri
Yapısal ve fonksiyonel adaptif değişimler
Disfonksiyonel endotel
Proliferatif düz kas hücresi

Normal Arter Duvarı

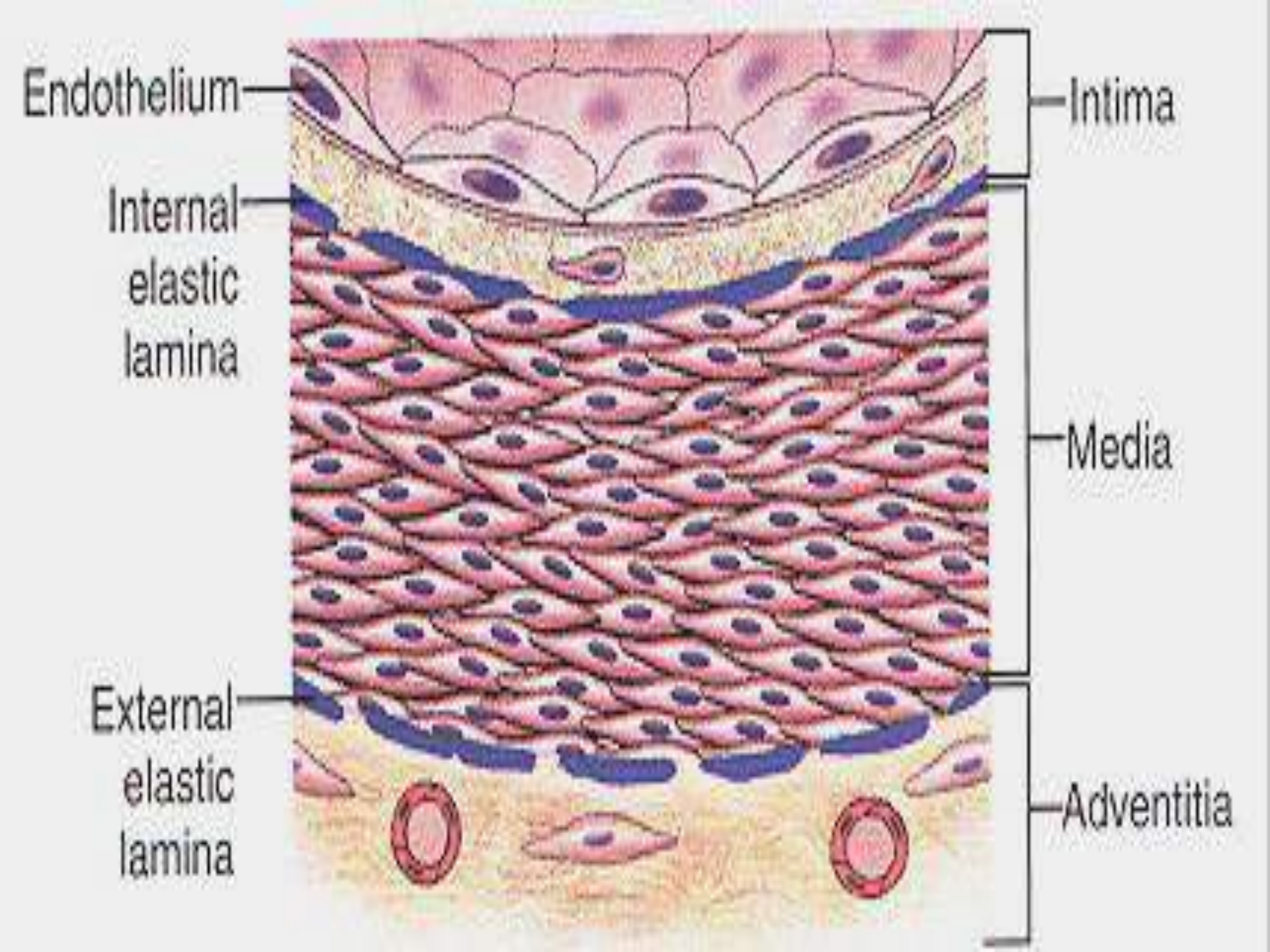


Intima:

- Endotel
- Internal elastik membran

Media:

- Düz kas hücresi
- Matriks proteinleri
- Eksternal elastik membran


Endothelium
Internal elastic lamina
External elastic lamina
Intima
Media
Adventitia

Vasküler düz kas fonksiyon belirteçleri ?

- NMD (nitrate mediated dilation) testi

- Diğer belirteçlerle korele

- FMD (flow-mediated dilation) testinin devamı olarak yapılıyor:
    - 300 micro gram sublingual gliserin trinitrat la

Naka et al. Cardiovascular Diabetology 2012, 11:127
http://www.cardiab.com/content/11/1/127

CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Determinants of vascular function in patients with type 2 diabetes

Katerina K Naka[1,2], Katerina Papathanassiou[3], Aris Bechlioulis[1,2], Nikolaos Kazakos[1,2], Konstantinos Pappas[1,2], Stelios Tigas[3], Dimitrios Makriyiannis[4], Agathocles Tsatsoulis[3] and Lampros K Michalis[1,2,5*]

Abstract

Background: Type 2 diabetes mellitus (T2DM) is independently associated with an increased risk for cardiovascular diseases that is primarily due to the early development of advanced atherosclerotic vascular changes. The aim of our study was to investigate the predictors of vascular dysfunction in T2DM patients.

Methods: We studied 165 T2DM patients without known macrovascular or microvascular disease. Standard demographic (age, gender, cardiovascular risk factors, medications), clinical (body mass index, blood pressure) and laboratory (glucose, glycated hemoglobin, lipids, renal function) parameters were included in analyses. Brachial artery flow-mediated dilation (FMD), nitrate mediated dilation (NMD) and Carotid-Femoral Pulse Wave Velocity (PWV) were measured.

Table 4 Determinants of vascular measurements (FMD, NMD and PWV) in multivariate analysis

		Multivariate analysis	
		B (95% CI)	P
FMD, %	Time since diagnosis of diabetes, years*	−0.40 (−0.66, -0.14)	0.003
NMD, %	Age, years*	−5.66 (−9.49, -1.82)	0.004
	Hypertension	−1.80 (−3.25, -0.35)	0.015
	Fasting glucose, μmol/l	0.26 (−0.51, −0.01)	0.005
PWV, m/sec	Age, years*	6.22 (3.81, 8.63)	<0.001
	Systolic blood pressure, mmHg	0.03 (0.00, 0.05)	0.032

*Natural logarithm transformed variables. *FMD*, flow-mediated dilation of the brachial artery; *NMD*, nitrate-mediated dilation of the brachial artery; *PWV*, carotid-femoral pulse wave velocity.

Endotel

- Yarı geçirgen bir zar özelliği taşıyan tek katlı bir epitel tabaka

- 70 kg ağırlığındaki bir bireyde **700 m²** alan kaplar, **1-1.8 kg** ağırlığındadır ve **1 trilyon** endotel hücre

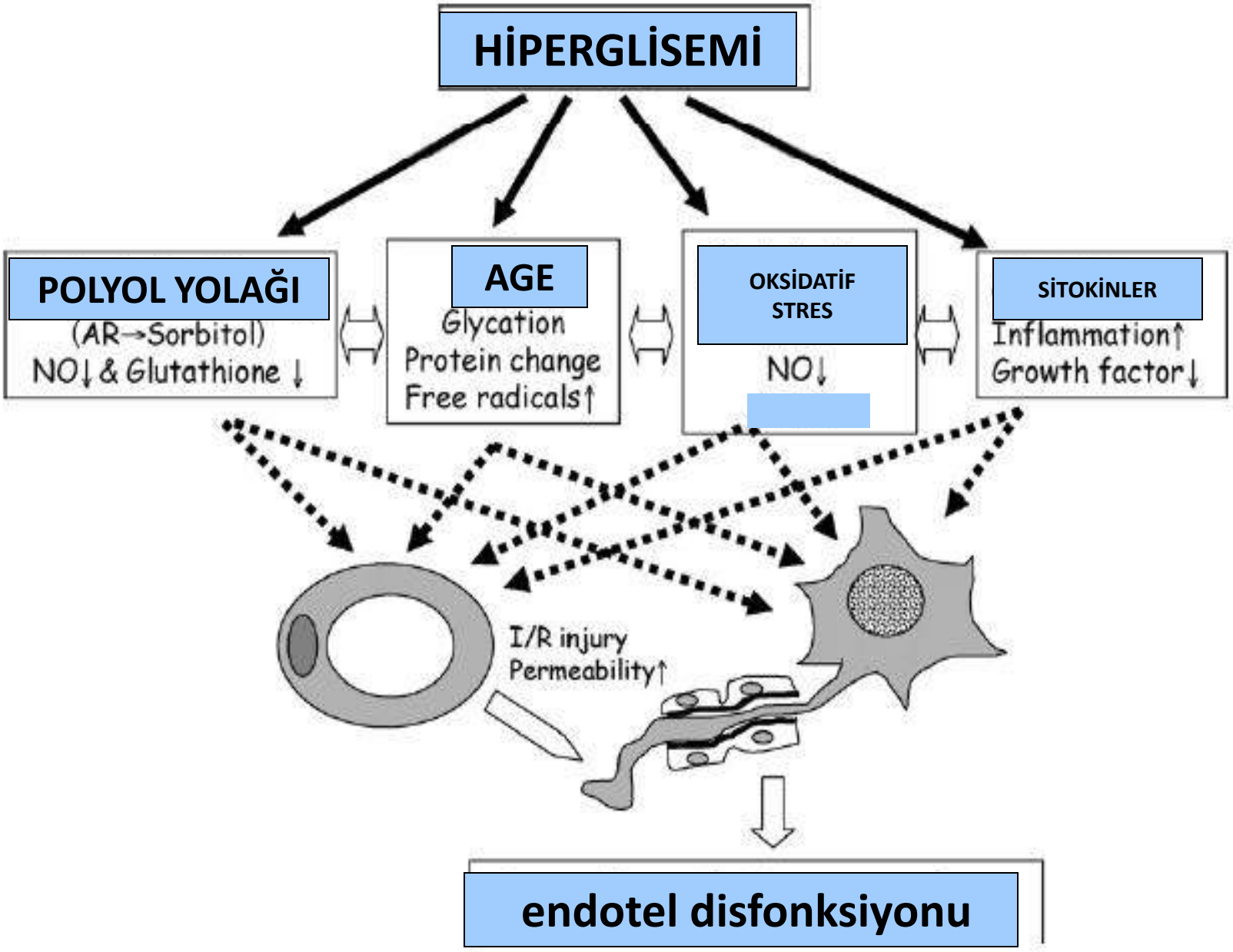
- Endokrin, parakrin ve otokrin fonksiyonları ile vücudun en aktif ve en yaygın dokularından biri

Endotel fonksiyonları

	Hücresel ve fizyolojik spesifik etkiler	
Tonus	Vazokonstriksiyon Endotelin Anjiyotensin-II ET-1 Tromboksan A2 PGH2	Vazodilatasyon NO Bradikinin EDHF
Büyüme	Stimülasyon PGDF FGF IGF-1 Endotelin Anjiyotensin-II	İnhibisyon NO Prostasiklin TGF
İnflamasyon	Proinflamatuvar ELAM, ICAM, VCAM	Antiinflamatuvar
Hemostaz	Protrombotik PAI-1	Antitrombotik Prostasiklin t-PA

Diyabette Endoteldeki Değişiklikler

- ↓eNOS aktivitesi
- ↑Endotelin-I düzeyleri
- ↓Prostasiklin serbestleşmesi
- ↑Adezyon molekül ekspresyonu
- ↑Trombosit ve monosit adezyonu
- ↑Prokoagülan aktivitesi
- ↑İleri glikozilasyon ürünleri
- Fibrinolitik aktivitede bozulma
- Glikozillenmiş fibrinin zayıf degradasyonu



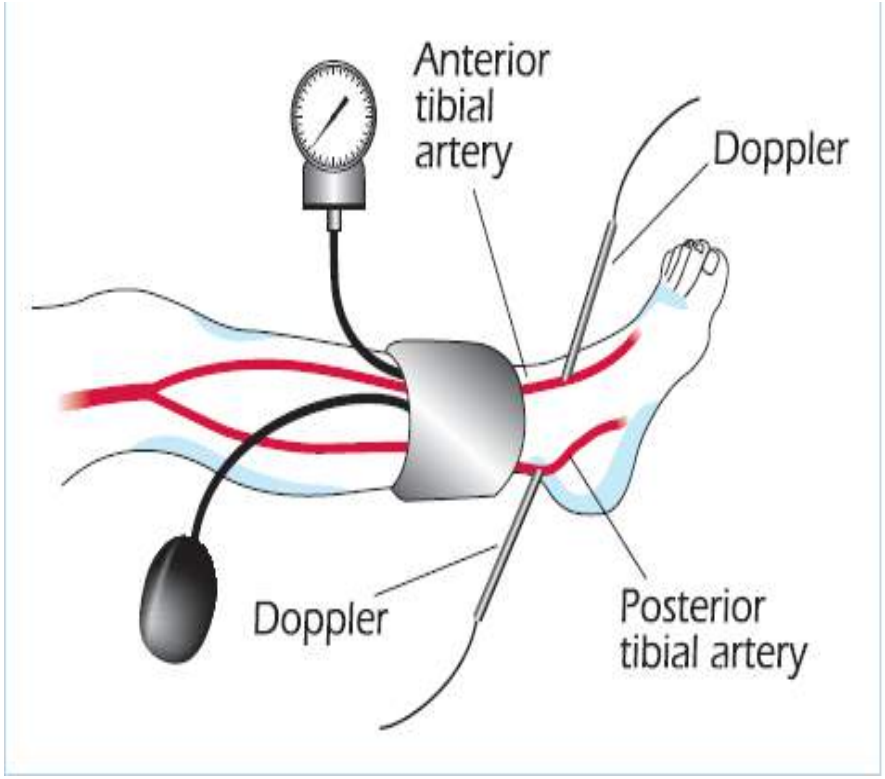
Adapted from Yasigashi et al. Diab Res Clin Pract 2007

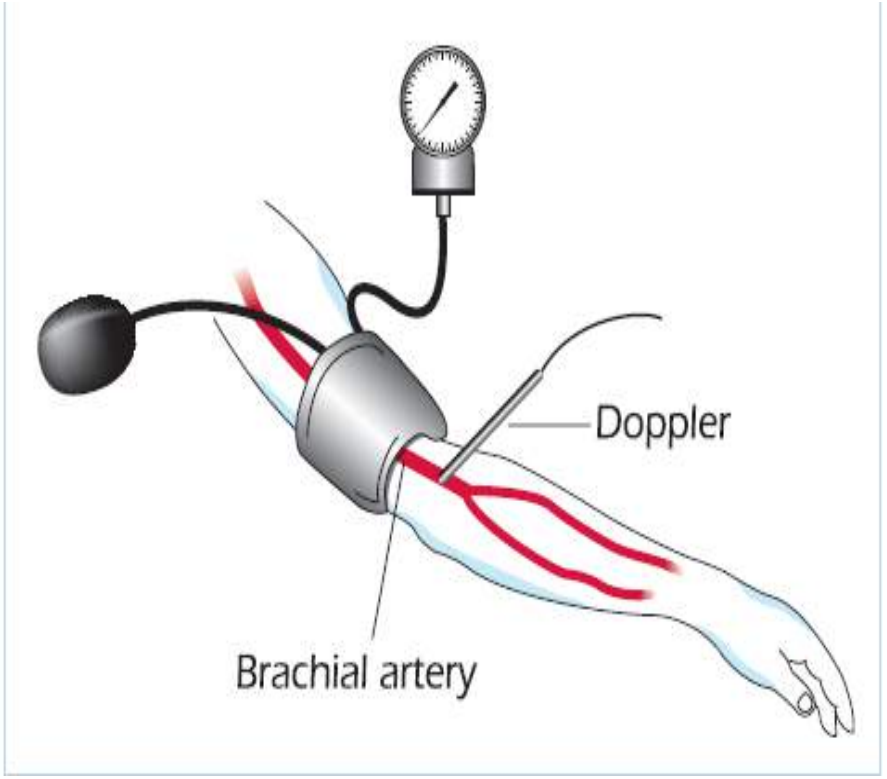
Endotel hücresi fonksiyon belirteçleri ?

- FMD (brachial artery flow-mediated dilation) testi

- PWV (aortic pulse wave velocity) testi

Ayak bileği-brakial indeks ölçümü





AYAK BİLEĞİ SKB / BRAKİAL SKB > 1 OLMALIDIR

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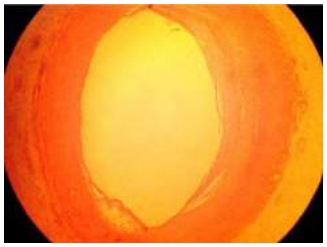
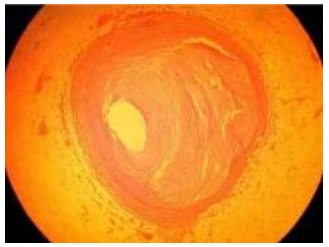
Endotel hücresi inflamatuar belirteçleri ?

AZALMIŞ
ANTİİNFLAMUTUVAR AKTİVİTE



ARTMIŞ
İNFLAMUTUVAR AKTİVİTE



Endotel Fonksiyon Belirteçleri

- FMD yöntemi ile yüzde değişim (NO Aracılı Endotel Fonksiyonu)

- Proinflamatuvar belirteçler
  - **IL-6**
  - **MCP-1**
  - **sICAM-1**
- Endotel fonksiyonu ile ilişkili belirteçler
  - **VCAM-1**
  - **E-selektin**
- Koagülasyon durumu ile ilgili belirteçler
  - **P-selektin**
  - **PAI-1**
  - **tPA**

Kan hücreleri inflamatuar belirteçleri ?

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ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.09.009

STATE-OF-THE-ART PAPER

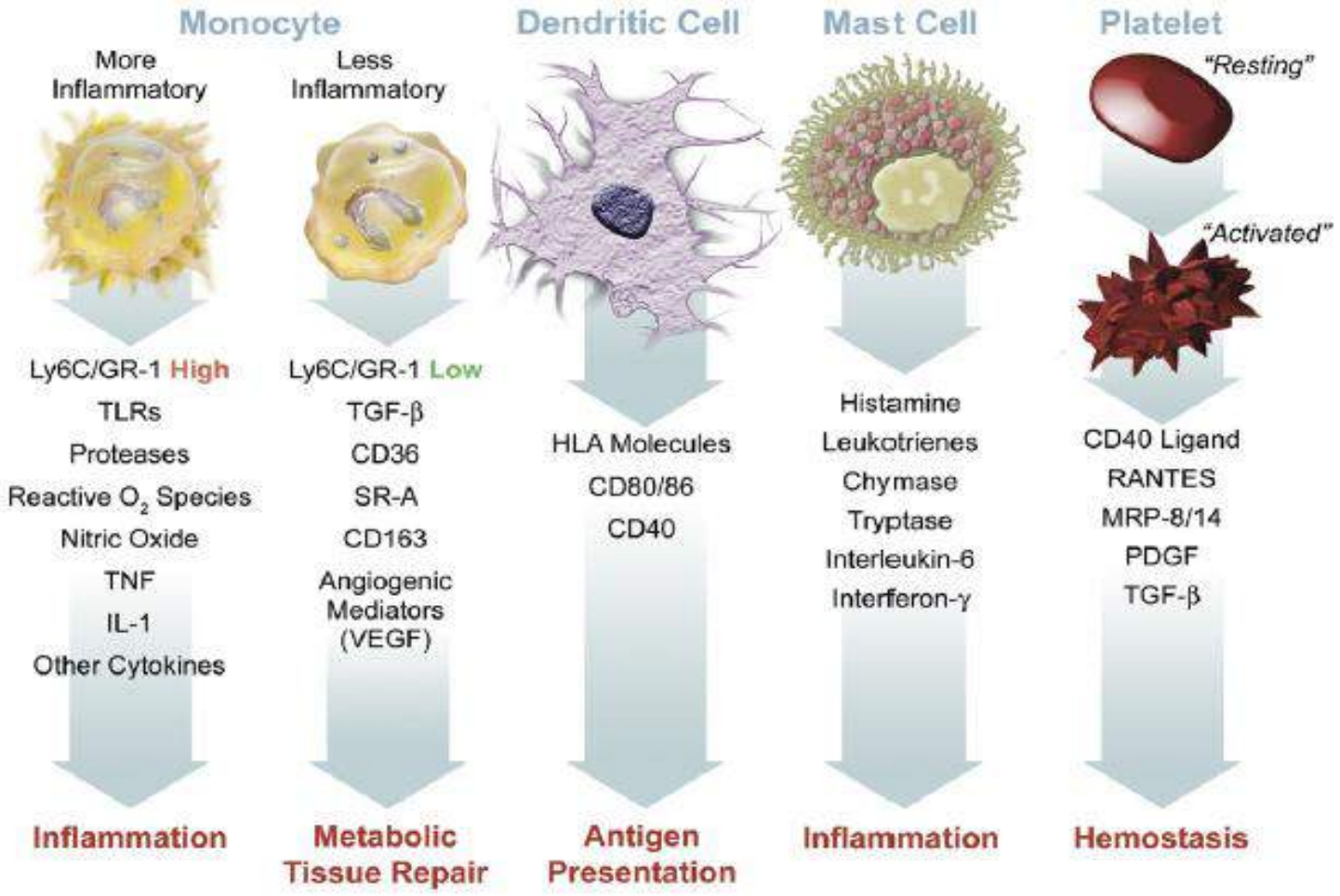
Inflammation in Atherosclerosis

From Pathophysiology to Practice

Peter Libby, MD,* Paul M Ridker, MD, MPH,*† Göran K. Hansson, MD, PHD,‡
for the Leducq Transatlantic Network on Atherothrombosis

Boston, Massachusetts; and Stockholm, Sweden

Until recently, most envisaged atherosclerosis as a bland arterial collection of cholesterol, complicated by smooth muscle cell accumulation. According to that concept, endothelial denuding injury led to platelet aggregation and release of platelet factors which would trigger the proliferation of smooth muscle cells in the arterial intima. These cells would then elaborate an extracellular matrix that would entrap lipoproteins, forming the nidus of the atherosclerotic plaque. Beyond the vascular smooth muscle cells long recognized in atherosclerotic lesions, subsequent investigations identified immune cells and mediators at work in atheromata, implicating inflammation in this disease. Multiple independent pathways of evidence now pinpoint inflammation as a key regulatory process that links multiple risk factors for atherosclerosis and its complications with altered arterial biology. Knowledge has burgeoned regarding the


Monocyte
Dendritic Cell
Mast Cell
Platelet
More Inflammatory
Less Inflammatory
"Resting"
"Activated"
Ly6C/GR-1 High
TLRs
Proteases
Reactive O_2 Species
Nitric Oxide
TNF
IL-1
Other Cytokines
Ly6C/GR-1 Low
TGF-β
CD36
SR-A
CD163
Angiogenic Mediators (VEGF)
HLA Molecules
CD80/86
CD40
Histamine
Leukotrienes
Chymase
Tryptase
Interleukin-6
Interferon-γ
CD40 Ligand
RANTES
MRP-8/14
PDGF
TGF-β
Inflammation
Metabolic Tissue Repair
Antigen Presentation
Inflammation
Hemostasis

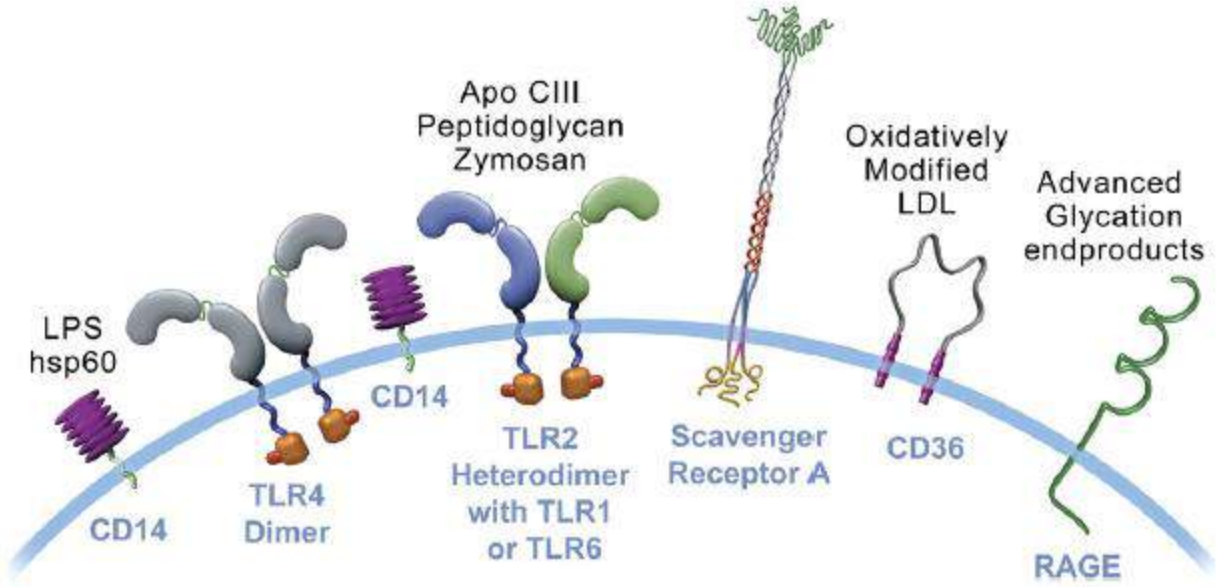


Figure 2 **Cells Involved in Atherosclerosis Express Pattern-Recognition Receptors Involved in Innate Immunity**

With the cooperation of CD14, Toll-like receptor (TLR) 4 binds bacterial lipopolysaccharides (LPS) and a variety of other potential instigators of inflammation and atherosclerosis including heat shock proteins (hsp). TLR2 usually exists as a heterodimer with TLR1 or TLR6. TLR2 complexes can bind microbial products as shown and, in addition, apolipoprotein CIII (Apo CIII). Scavenger receptor A binds modified low-density lipoproteins (LDL). CD36 binds oxidatively modified LDL. The receptor for advanced glycation endproducts (RAGE) also decorates many cells involved in atherosclerosis and may function in inflammatory signaling.

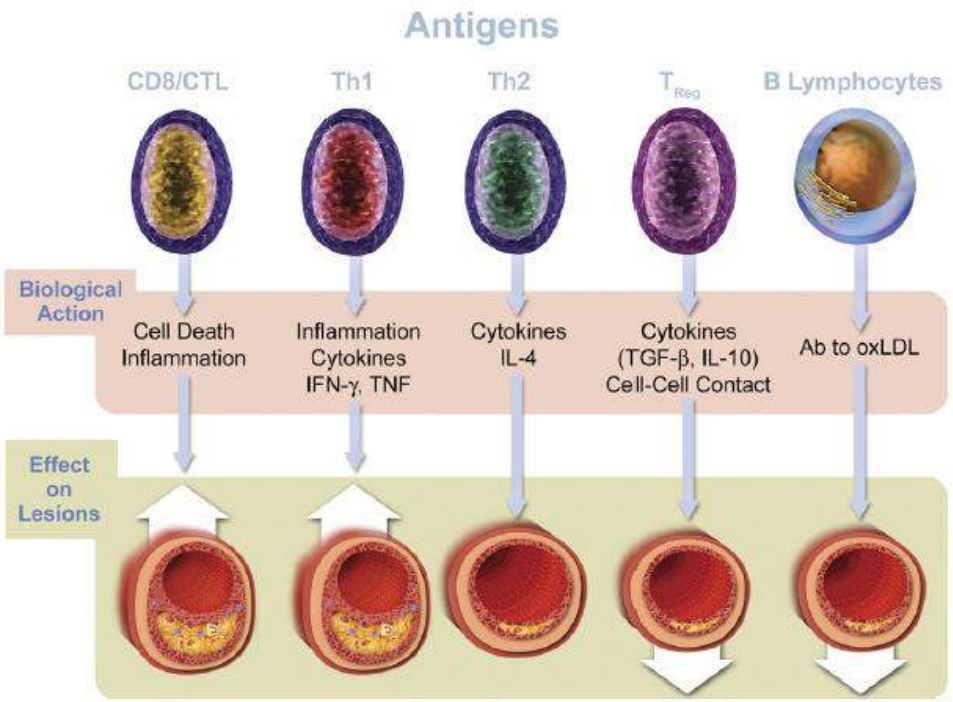
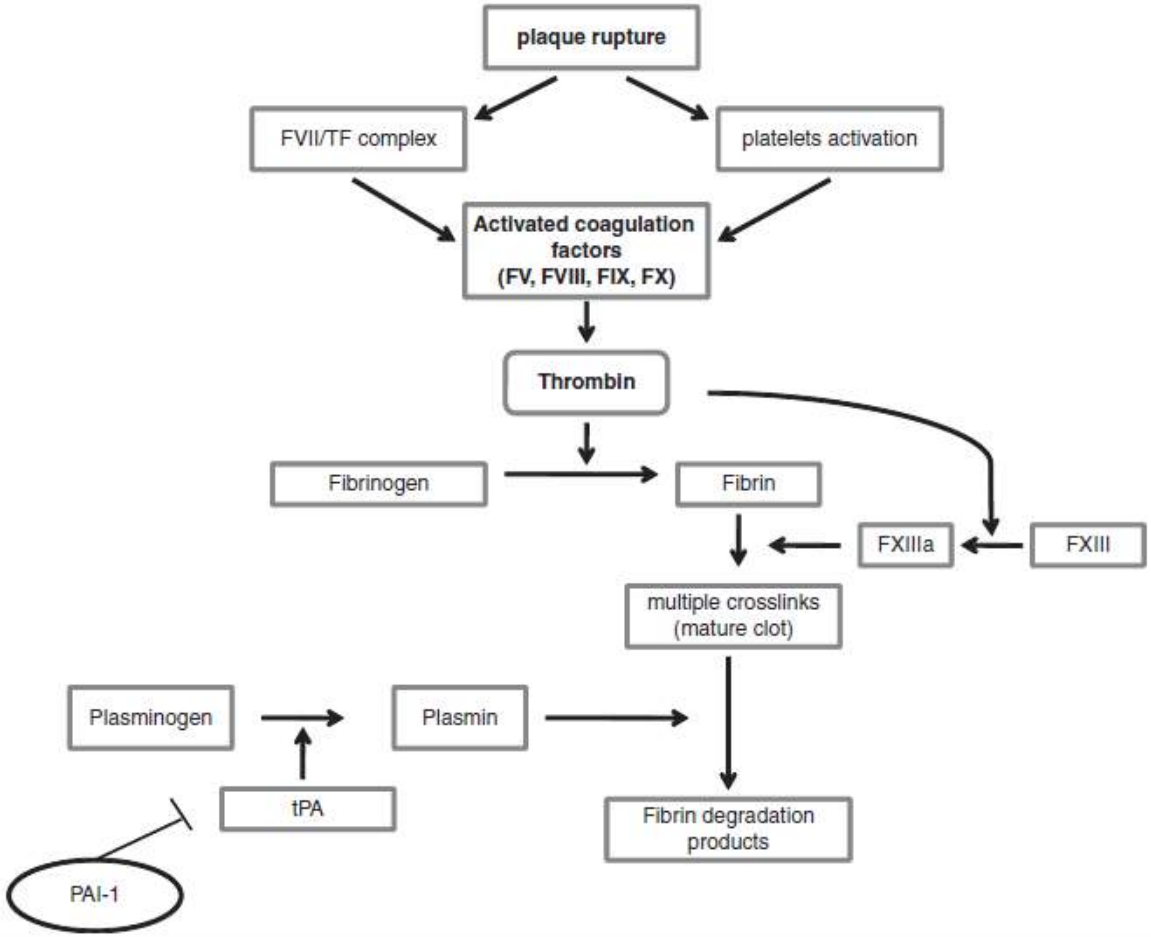
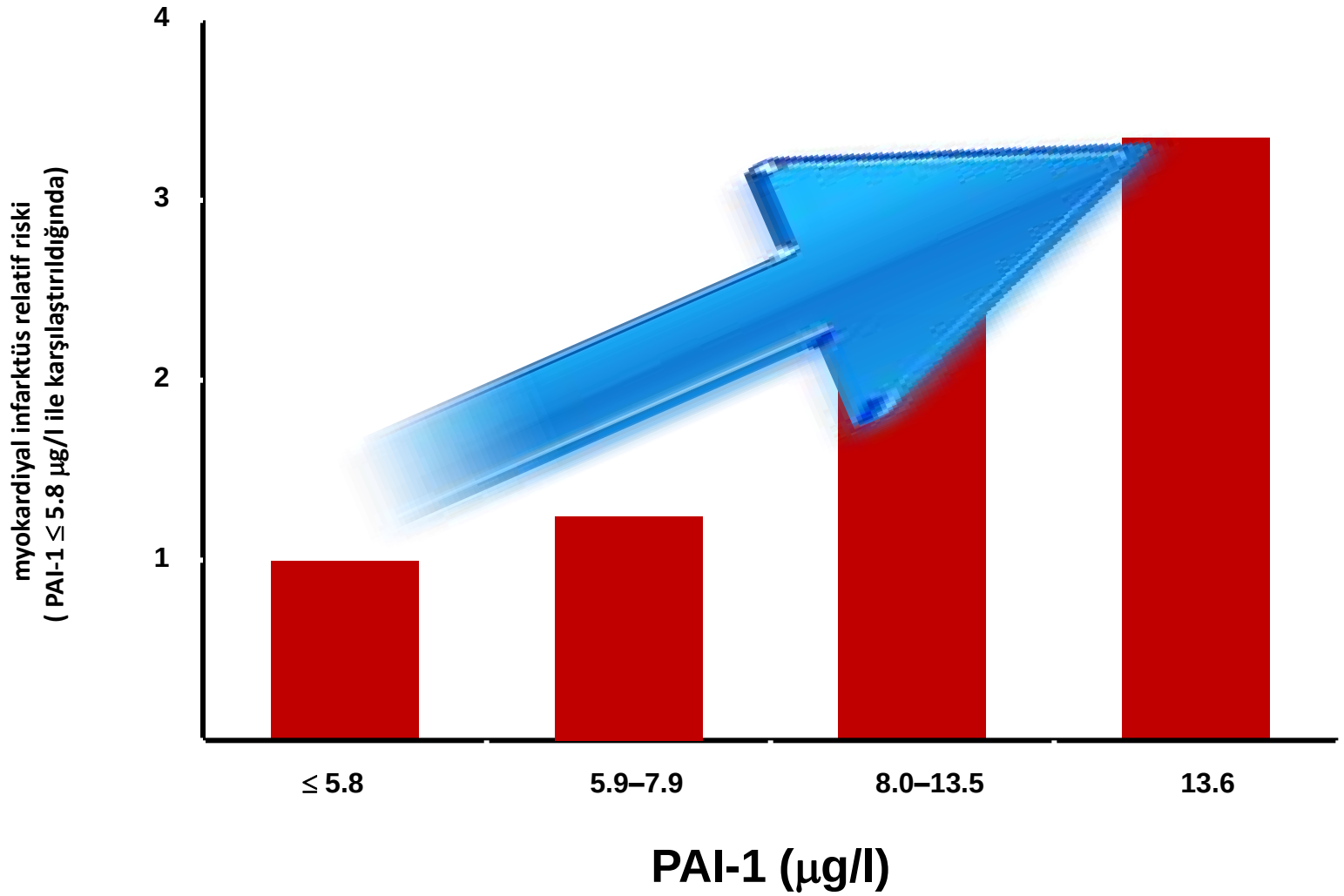


Figure 3 **Cells Involved in Adaptive Immunity**

The text describes the functional roles of the 5 classes of lymphocytes depicted in atherosclerosis. B cells elaborate antibodies (Ab). A specialized subset of B cells (B1 cells) elaborate primarily immunoglobulin M antibodies, including natural antibodies that recognize constituents of oxidized low-density lipoprotein (oxLDL). The **bottom panel** of this figure portrays diagrammatically the effect of the various cell types on lesions, based mostly on experiments in mice. **Up arrows** indicate aggravation of lesion formation. **Down arrows** indicate reduction in lesion formation. This diagram summarizes the "net" effect attributed to the cell type on atherosclerosis primarily on the basis of experiments in mice. In some cases, this figure necessarily oversimplifies the complexity of the data. For example, not all TH_2 cell functions and not all antibodies elaborated by B cells may mitigate atherogenesis. CTL = cytolytic T lymphocytes; IFN = interferon; hsp = heat shock protein; Th = T helper cells; T_{Reg} = regulatory T cells; other abbreviations as in Figure 1.


plaque rupture
FVII/TF complex
platelets activation
Activated coagulation factors (FV, FVIII, FIX, FX)
Thrombin
Fibrinogen
Fibrin
FXIIIa
FXIII
multiple crosslinks (mature clot)
Plasminogen
Plasmin
tPA
Fibrin degradation products
PAI-1

Kardiyovasküler Hastalık Göstergesi Olarak PAI-1



n = 234
P = 0.002

Circulation 1998; 98:2241–2247.

Table 1. Changes in coagulation factors in diabetes and potential mechanisms.

Coagulation factor	Production	Function	Level/activity in DM	Possible mechanisms	Reference
TF	Stimulated EC VSMC	Initiation of clot formation	↑	↑ insulin ↑ glucose ↑ AGE ↑ ROS	13, 15, 18
FVII	Liver	Initiation of clot formation	↑	↑ glucose ↑ triglyceride	20-25
(Pro)thrombin	Liver	Fg conversion to fibrin	↑	↑ glucose	18, 29-31
Fibrinogen	Liver	Formation of the fibrin network	↑	↑ liver synthesis due to IR	36, 42, 43
tPA	EC	clot lysis (converts plasminogen to plasmin)	↑, ↓	Probably EC dysfunction	57, 60, 67
PAI-1	EC, VSMC, adipocytes, liver	Inhibition of clot lysis	↑	↑ glucose IR	63, 65

DM: diabetes mellitus, TF: tissue factor, tPA: tissue plasminogen activator, PAI-1: plasminogen activator inhibitor, EC: endothelial cells, VSMC: vascular smooth muscle cells, Fg: fibrinogen, AGE: advanced glycation end products, ROS: reactive oxygen species, IR: insulin resistance.

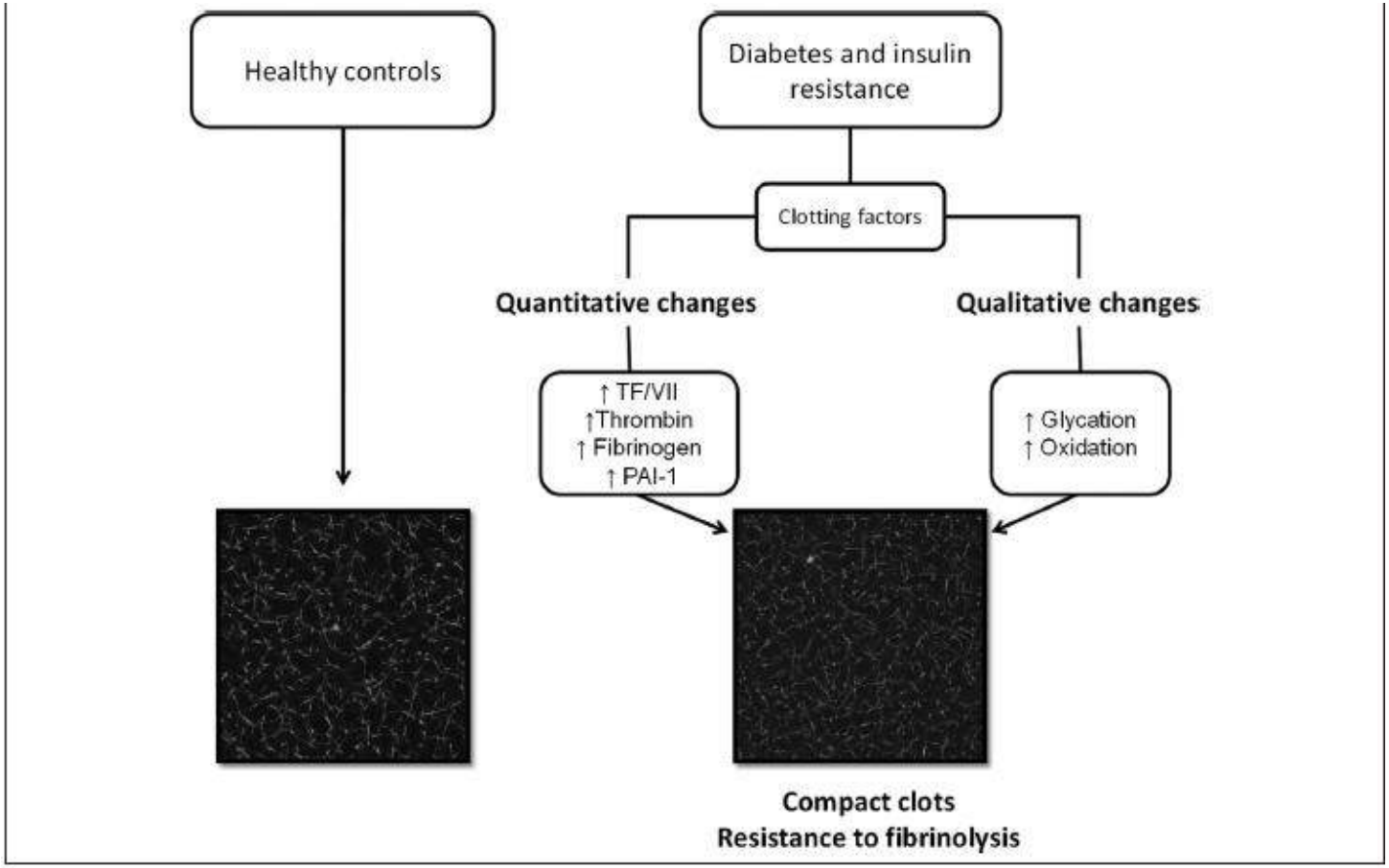


Figure 2. Mechanisms for altered clot structure/fibrinolysis in subjects with diabetes.

Diyabet ve Protrombotik Aktivite

- Trombosit fonksiyonlarında bozulma
- Endotelden:

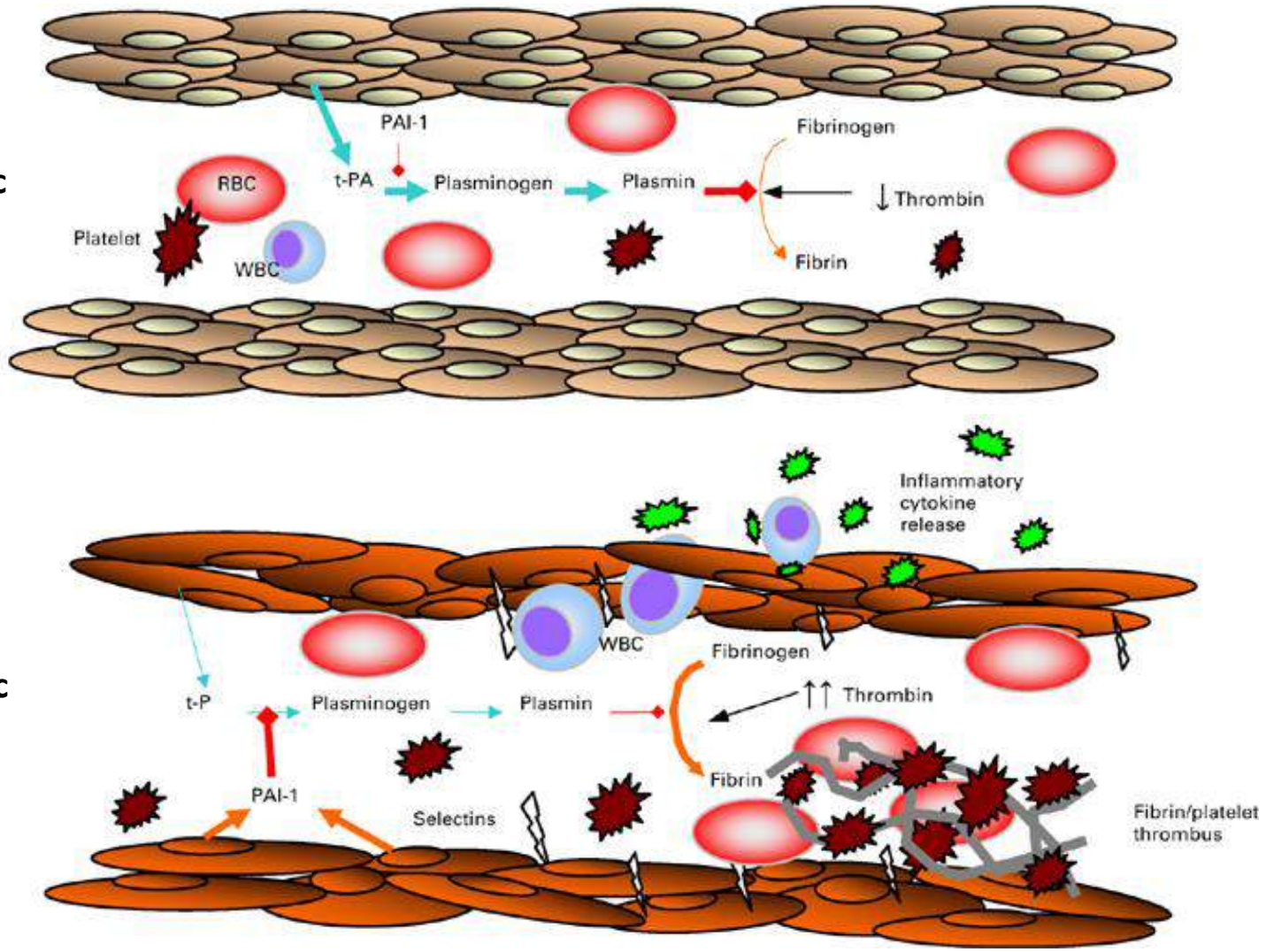
  NO ve prostasiklin salgılanmasında ↓

  trombin ve vWF salgılanmasında ↑ → trombüs oluşumu
- Fibrinojen ve PAI-1 ↑ → Fibrinolitik dengeyi olumsuz yönde etkiler

Protrombotik /Proinflamatuar endotel

Anti-thrombotic endothelium

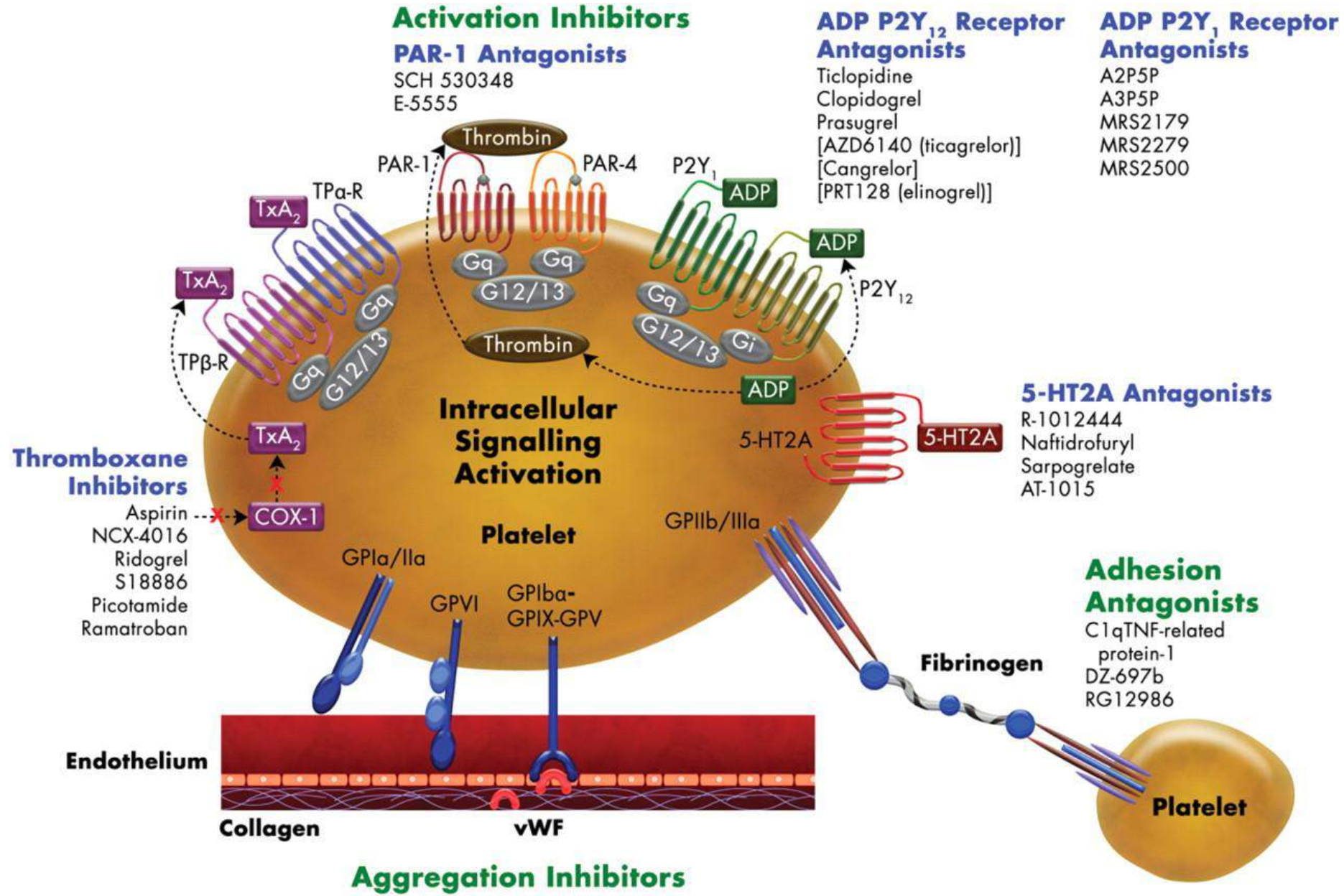
Prothrombotic endothelium



Bone Marrow Transplantation (2008) 41, 677–686

Diyabette Trombosit Değişiklikleri

- Primer Platelet agregasyonu
- Sekonder Platelet agregasyonu
- Platelet aktivasyon artışı
  - Alfa granül içeriğinin salınımı
  - Tromboglobulin salınımı artışı
  - Platelet faktör 4 salınımı artışı
- Fibrinojenin glikoprotein IIb/IIIa kompleksine bağlanmasında artış


Activation Inhibitors
PAR-1 Antagonists
SCH 530348
E-5555
ADP P2Y12 Receptor Antagonists
Ticlopidine
Clopidogrel
Prasugrel
[AZD6140 (ticagrelor)]
[Cangrelor]
[PRT128 (elinogrel)]
ADP P2Y1 Receptor Antagonists
A2P5P
A3P5P
MRS2179
MRS2279
MRS2500
Thrombin
PAR-1
PAR-4
P2Y1
ADP
TPα-R
TxA2
Gq
G12/13
P2Y12
Gi
TPβ-R
Intracellular Signalling Activation
5-HT2A
5-HT2A Antagonists
R-1012444
Naftidrofuryl
Sarpogrelate
AT-1015
Thromboxane Inhibitors
Aspirin
NCX-4016
Ridogrel
S18886
Picotamide
Ramatroban
COX-1
Platelet
GPIIb/IIIa
GPIa/IIa
GPVI
GPIba-GPIX-GPV
Adhesion Antagonists
C1qTNF-related protein-1
DZ-697b
RG12986
Fibrinogen
Endothelium
Collagen
vWF
Platelet
Aggregation Inhibitors
GPIa/IIa Inhibitor
EMS16
GPVI Inhibitors
Monoclonal antibodies
GPIIb/IIIa Inhibitors
Abciximab
Eptifibatide
Tirofiban

Trombositer belirteçler…

- Trombotik faktörler var:
  - Trombositler
  - NO
  - PGI2
  - PAF PLATELET AKTİVATÖR FAKTÖR
  - vWF

- Fibrinolitik faktörler var:
  - Tpa, PAI-1

aterosklerotik belirteç olarak CRP?

- Subklinik ateroskleroz için ön gösterge
- Endotel disfonksiyonu için ön gösterge
- Rekürren iskemi için ön gösterge
- Dayanıksız plak için ön gösterge

AHA / CDC Scientific Statement
Markers of Inflammation and Cardiovascular Disease:
Applications to Clinical and Public Health Practice

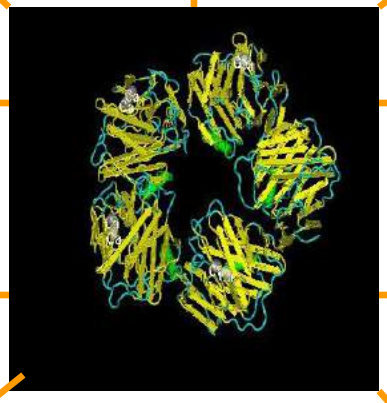
Circulation January 28, 2003

“hs-CRP bağımsız bir risk faktörüdür ve daha önce KVH olduğu bilinmeyen erişkinlerde koroner arter hastalığı risk tahminin bir parçası olarak kullanılabilir.**”**

Monositlerin arter duvarına geçişi CRP bağımlıdır

CRP LDL kolesterolün oksidasyonunu tetikler

CRP aterosklerotik intimada (normalde değil) lokalize olur



CRP endotelin vazoreaktivitesini azaltır

CRP kompleman aktivasyonunu indükler

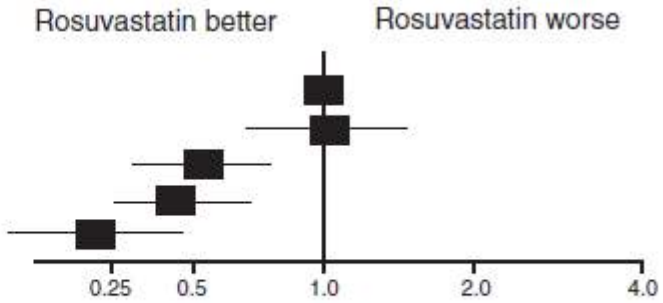
CRP, NO üretimini azaltır

CRP monositlerde doku faktörünün üretimini indükler

CRP, VCAM-1, E-Selectin, MCP-1, MMP-1, MMP-9 üretimini indükler

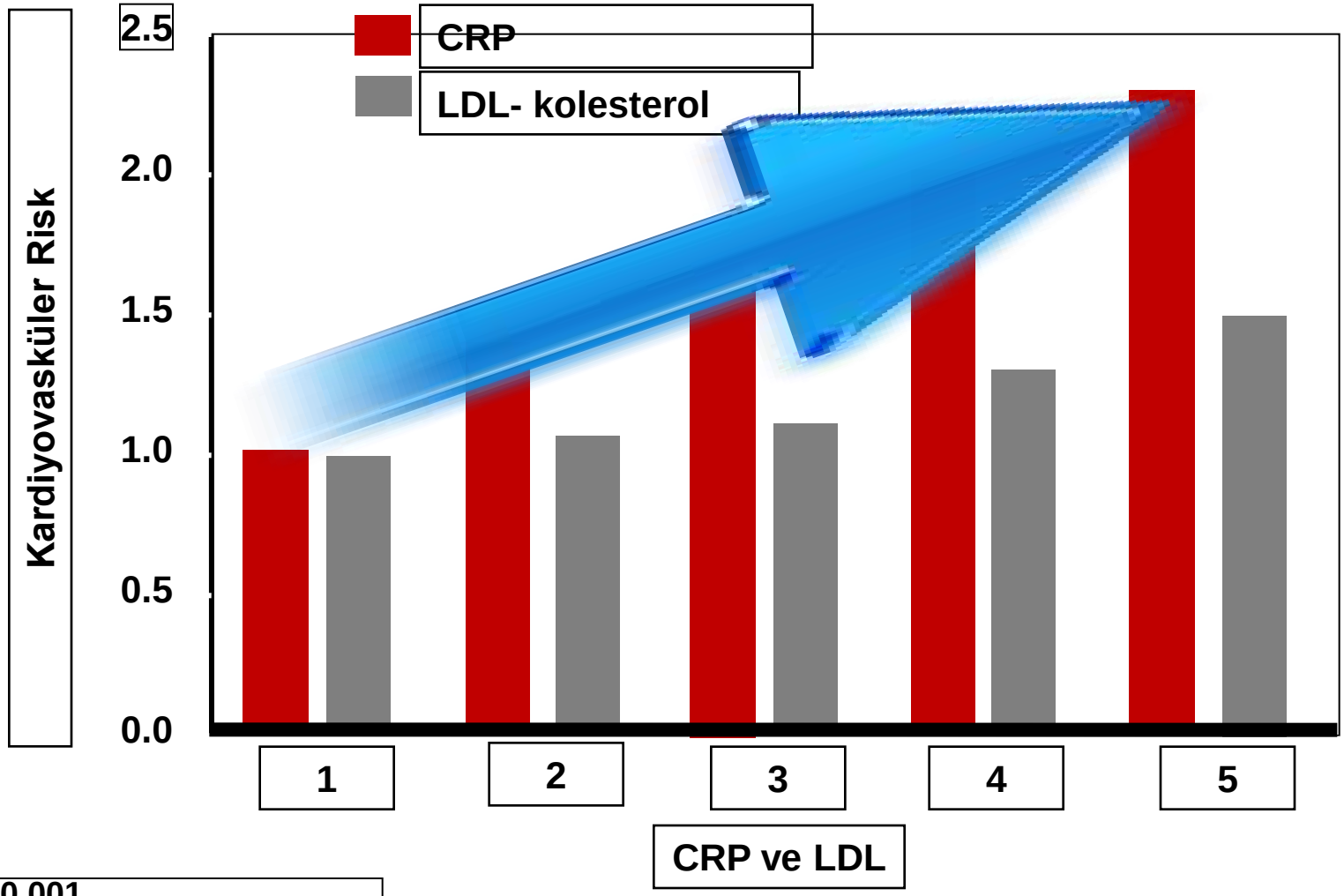
CRP, PAI-1 ekspresyonunu indükler

	N	Rate
Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥2 mg/L	1384	1.11
LDL<70mg/dL,hsCRP≥2 mg/L	2921	0.62
LDL≥70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38



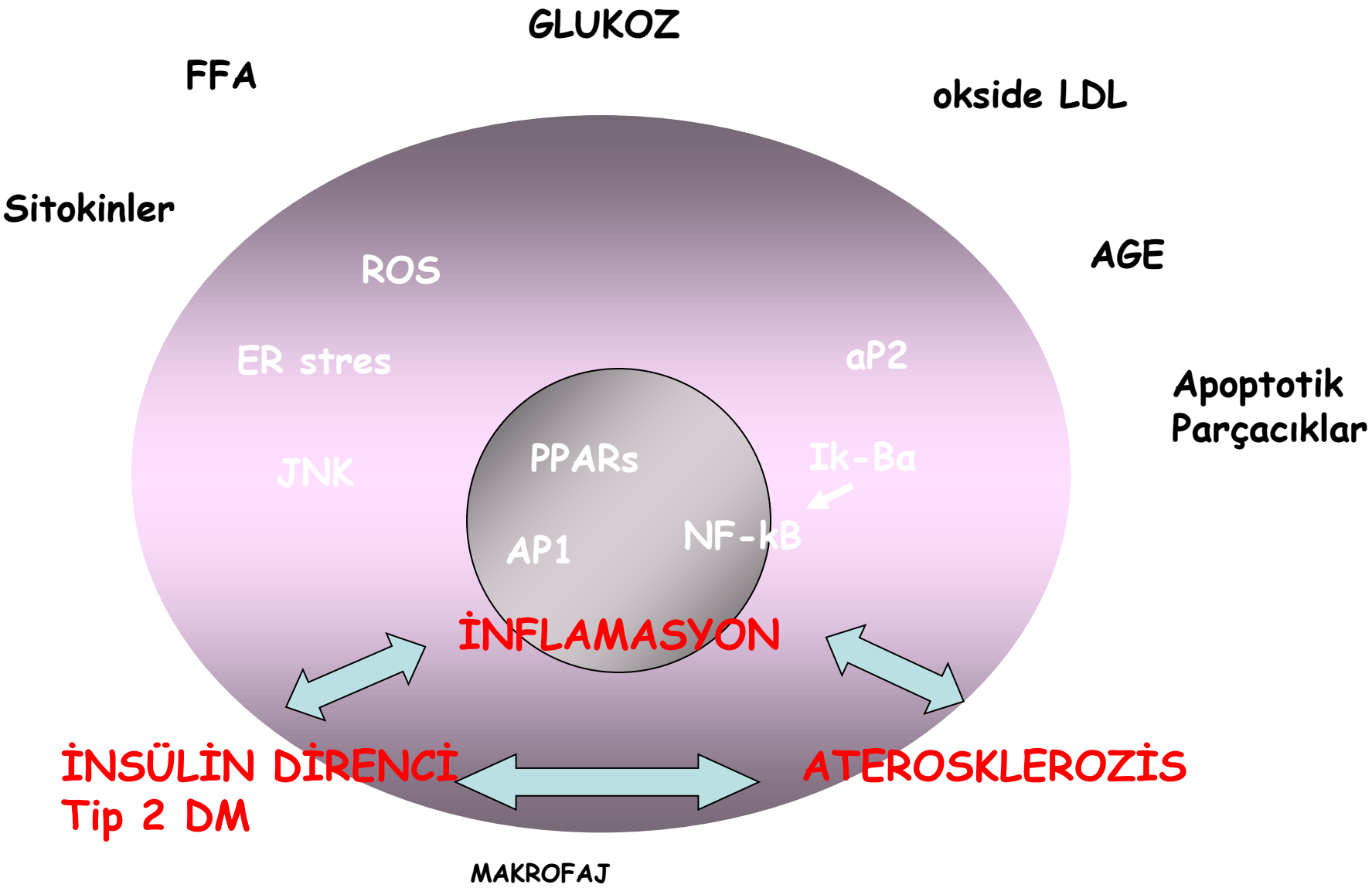
6 **Hazard Ratios for Incident Cardiovascular Events in the JUPITER Trial According to Achieved Concentrations of LDL Cholesterol and hsCRP After Initiation of Rosuvastatin Therapy**

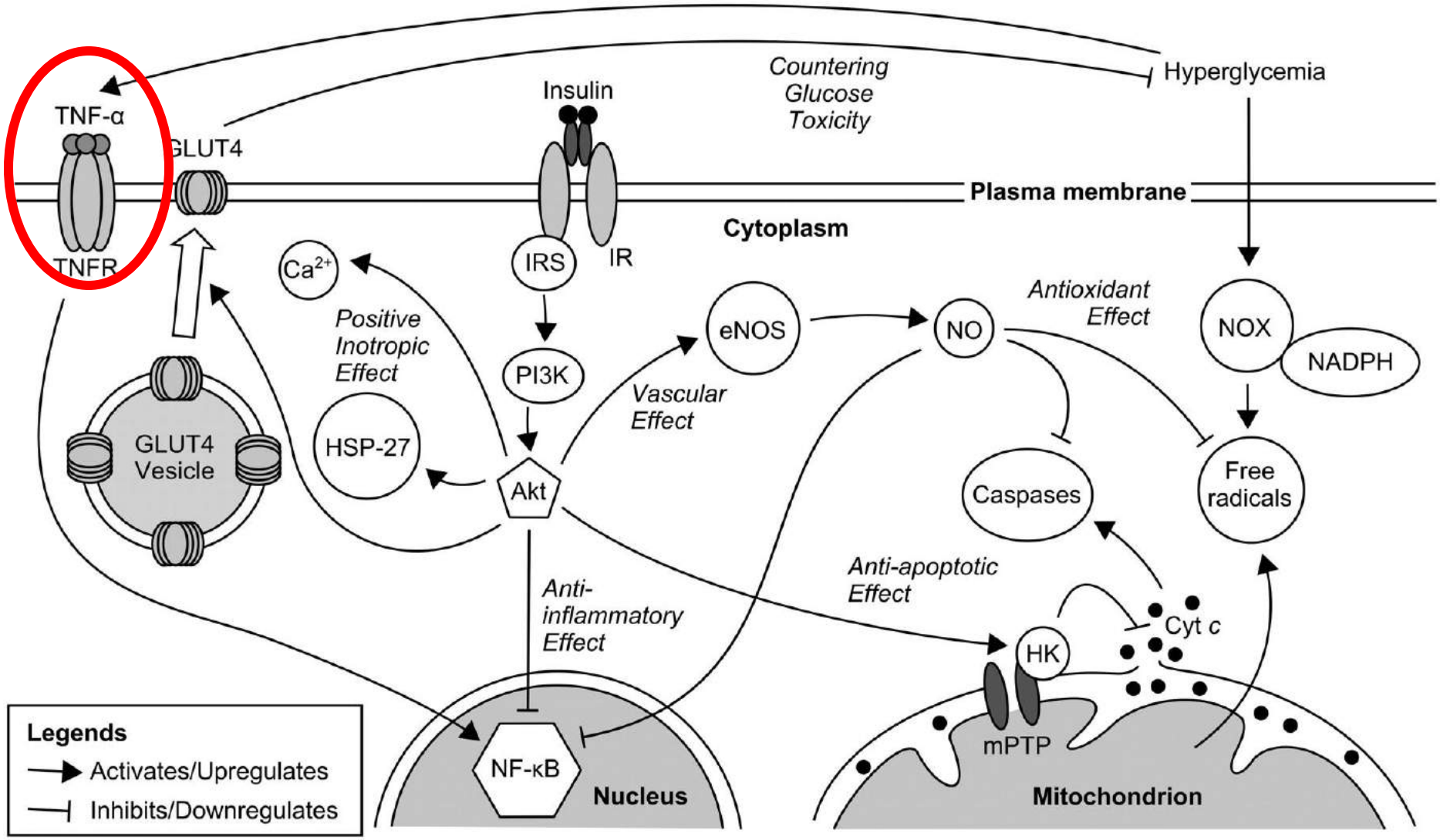
CRP ve Kardiyovasküler Risk



P < 0.001

Ridker PM, et al. N Eng J Med 2002; 347:1557–1565


GLUKOZ
FFA
okside LDL
Sitokinler
AGE
ROS
ER stres
aP2
Apoptotik
Parçacıklar
JNK
PPARs
Ik-Ba
AP1
NF-KB
İNFLAMASYON
İNSÜLİN DİRENCİ
Tip 2 DM
ATEROSKLEROZİS
MAKROFAJ


TNF-α
TNFR
GLUT4
Insulin
IR
IRS
Countering
Glucose
Toxicity
Hyperglycemia
Plasma membrane
Cytoplasm
Ca2+
Positive
Inotropic
Effect
PI3K
eNOS
NO
Antioxidant
Effect
NOX
NADPH
Vascular
Effect
GLUT4
Vesicle
HSP-27
Akt
Caspases
Free
radicals
Anti-
inflammatory
Effect
Anti-apoptotic
Effect
Cyt c
HK
mPTP
NF-κB
Nucleus
Mitochondrion
Legends
Activates/Upregulates
Inhibits/Downregulates

TNF-α

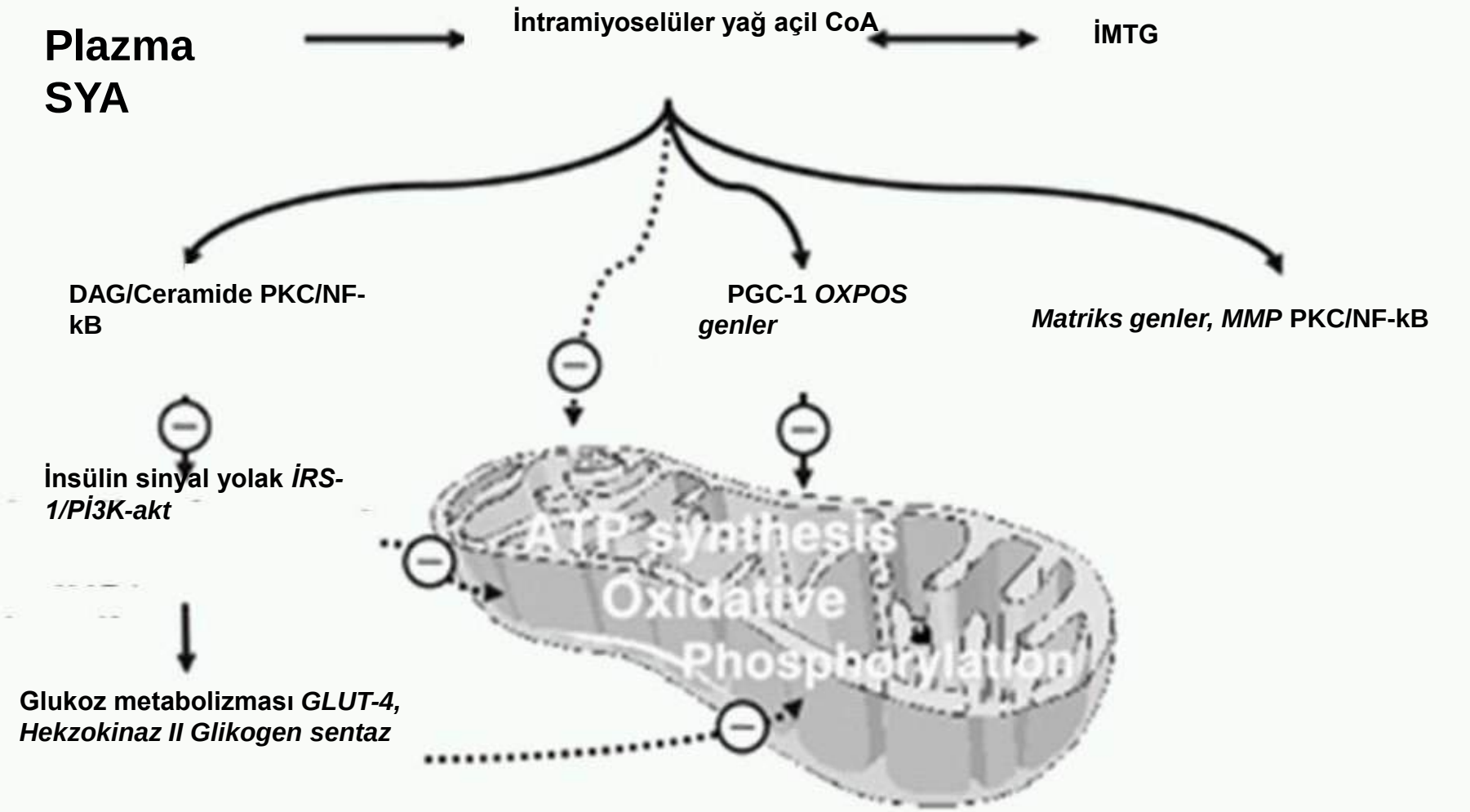
- ROS oluşumu ile NF-κB aktive olur
- Güçlü adiponektin inhibitörüdür
- İL-6, İL-1 gibi sitokinleri ↑
- Endotelde NO biyoyararlılığı↓,endotele bağımlı vazodilatasyonu baskılar.
- VCAM-1, ICAM-1, MCP-1 ve E-selektin aktive olur

Hotamışlıgil et al. Intern Med 1999

Oksidatif stres

- İntraselüler ROS yapımı ile atılımı arasındaki dengesizliktir
- DNA ve protein bütünlüğü bozulur
- Lipid peroksidasyonuna neden olur (malondyaldehyde ve OxLDL)

Victor MV et al. *Current Pharmaceutical Design,* 2009*, 15,* 2988-3002



Roden M. Obesity 2005

Okside LDL

- NO salınımı azalır
- NO sentez kompotetif endogen inhibitörü asimetrik dimetilarginine (ADMA) artar

Victor MV et al. *Current Pharmaceutical Design,* 2009*, 15,* 2988-3002

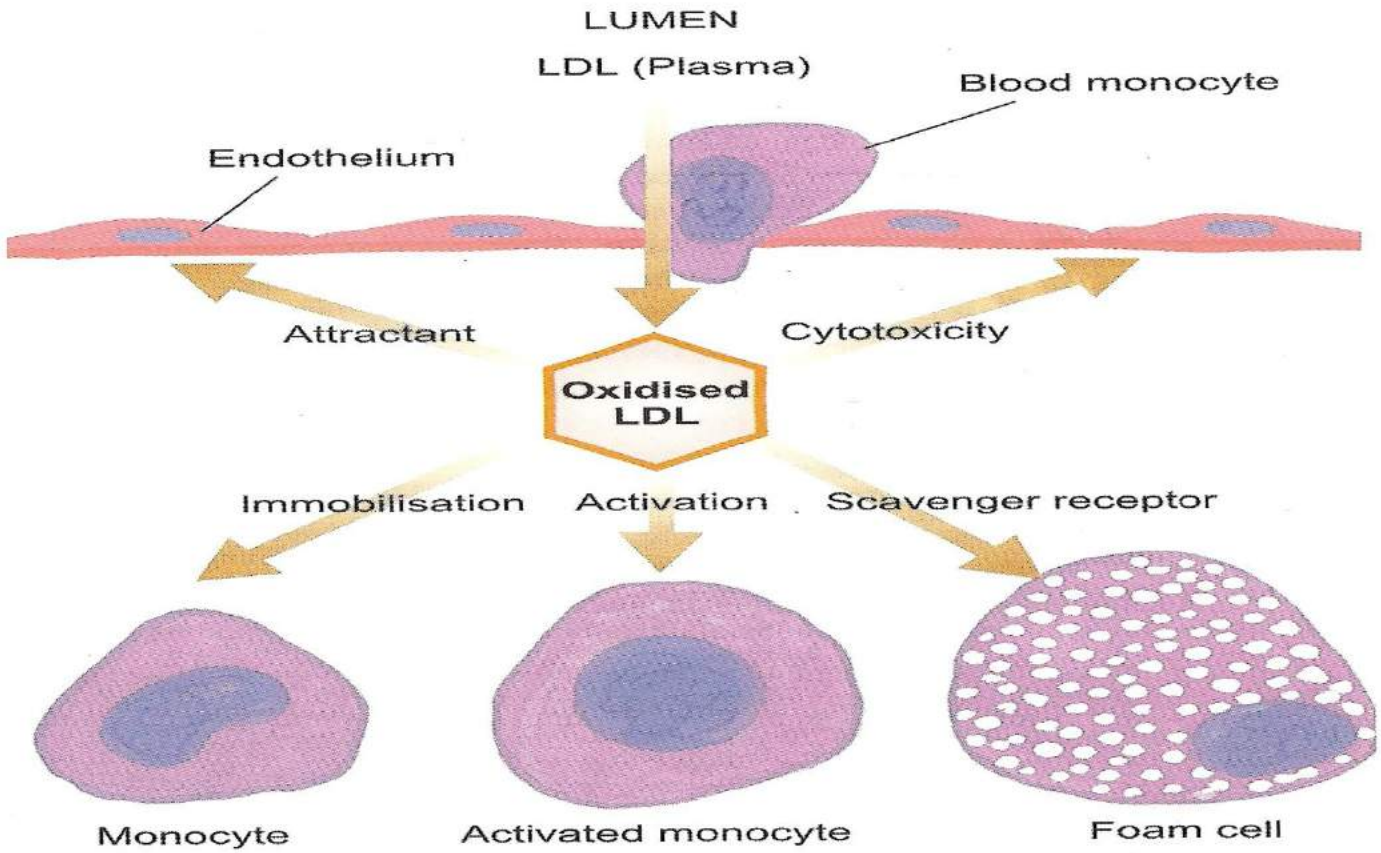


FIGURE 11.5

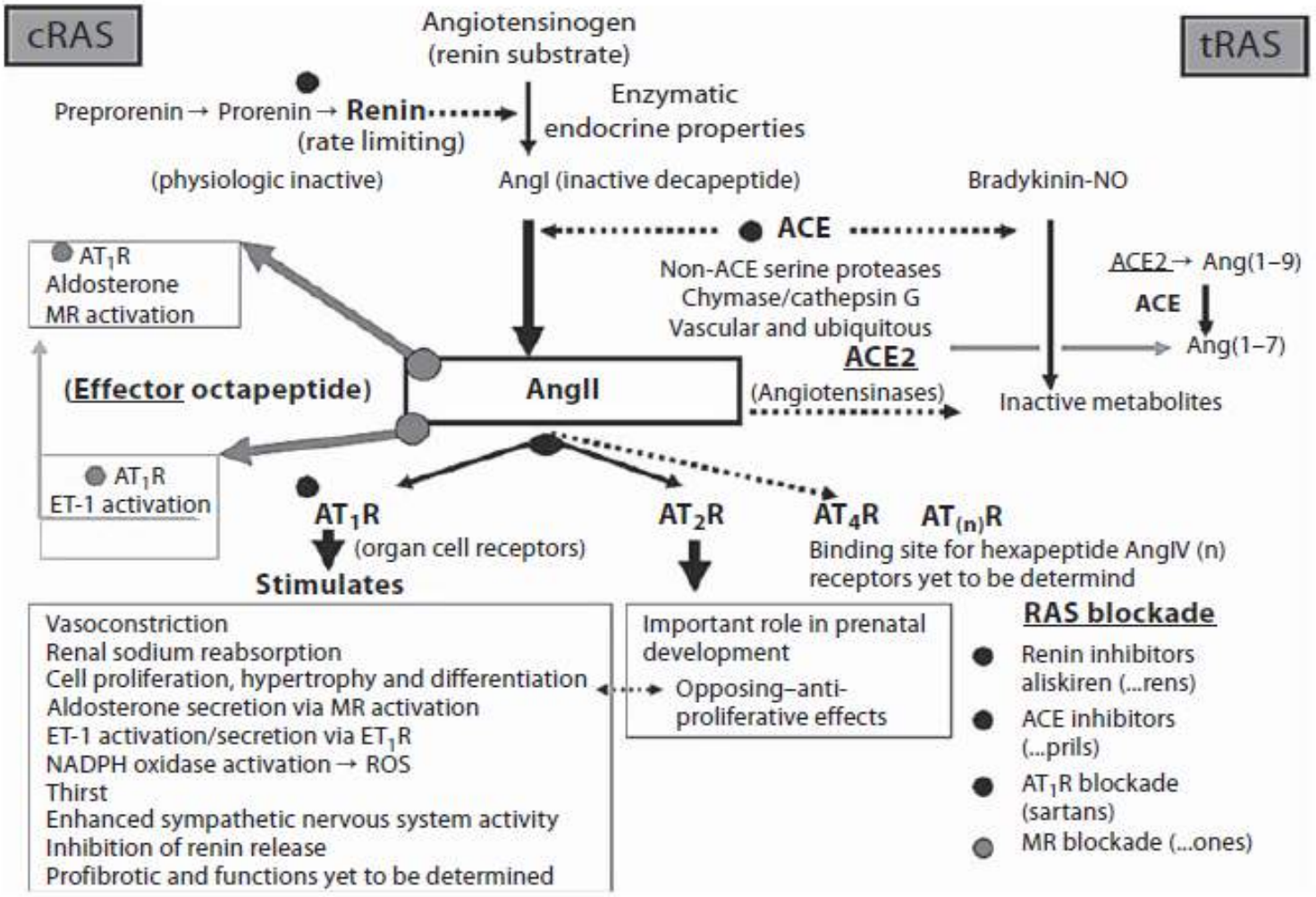
Mechanism of foam cell formation.

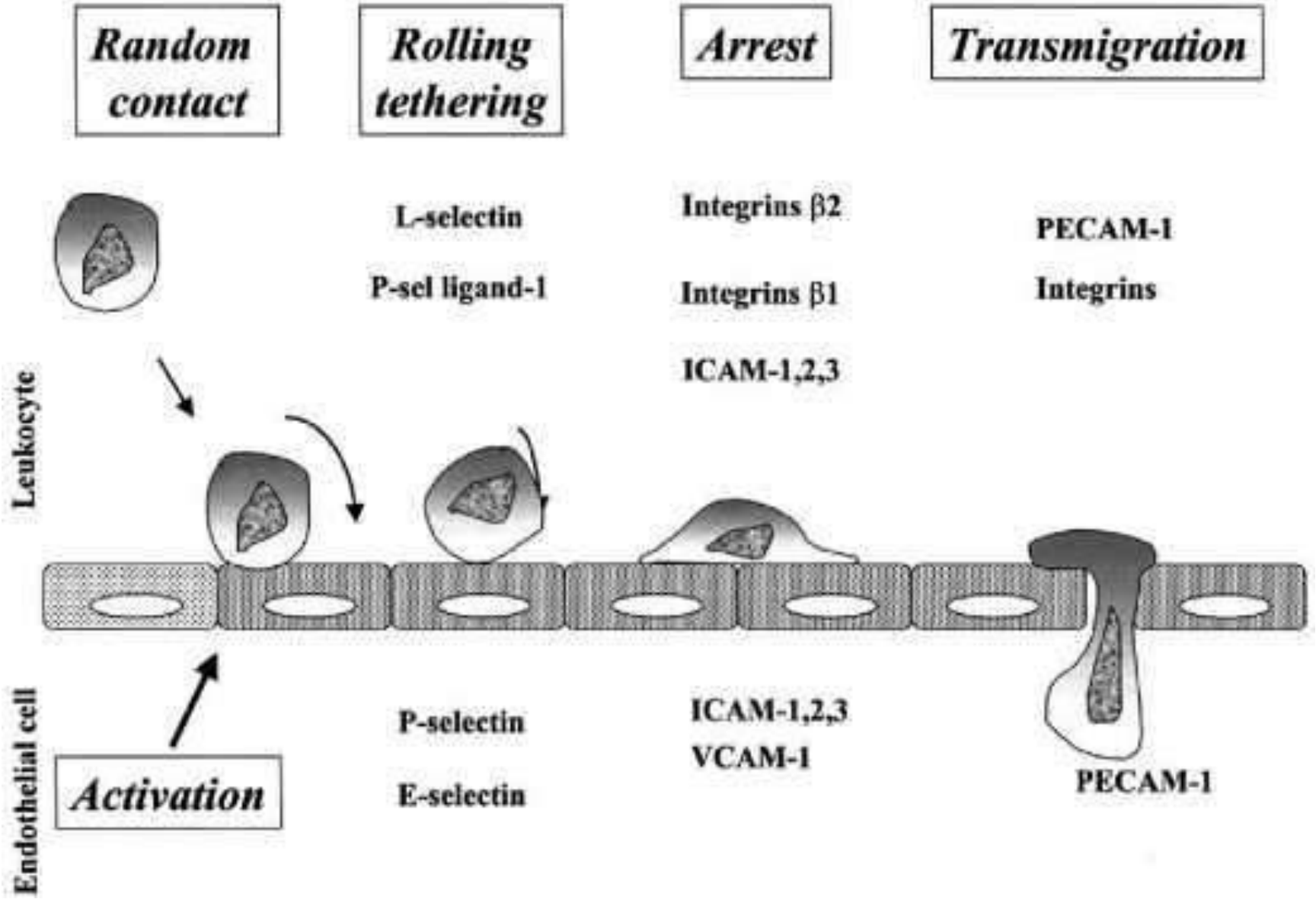
ADMA

- Endotel disfonksiyon
- Ateroskleroz nedenidir
- NO azalması trombosit agregasyonu artar
- Direk koroner iskemi gelişir
- AS ve ED'da eksojen NO kaynağı nitrogliserine endotelyal yanıt azalır

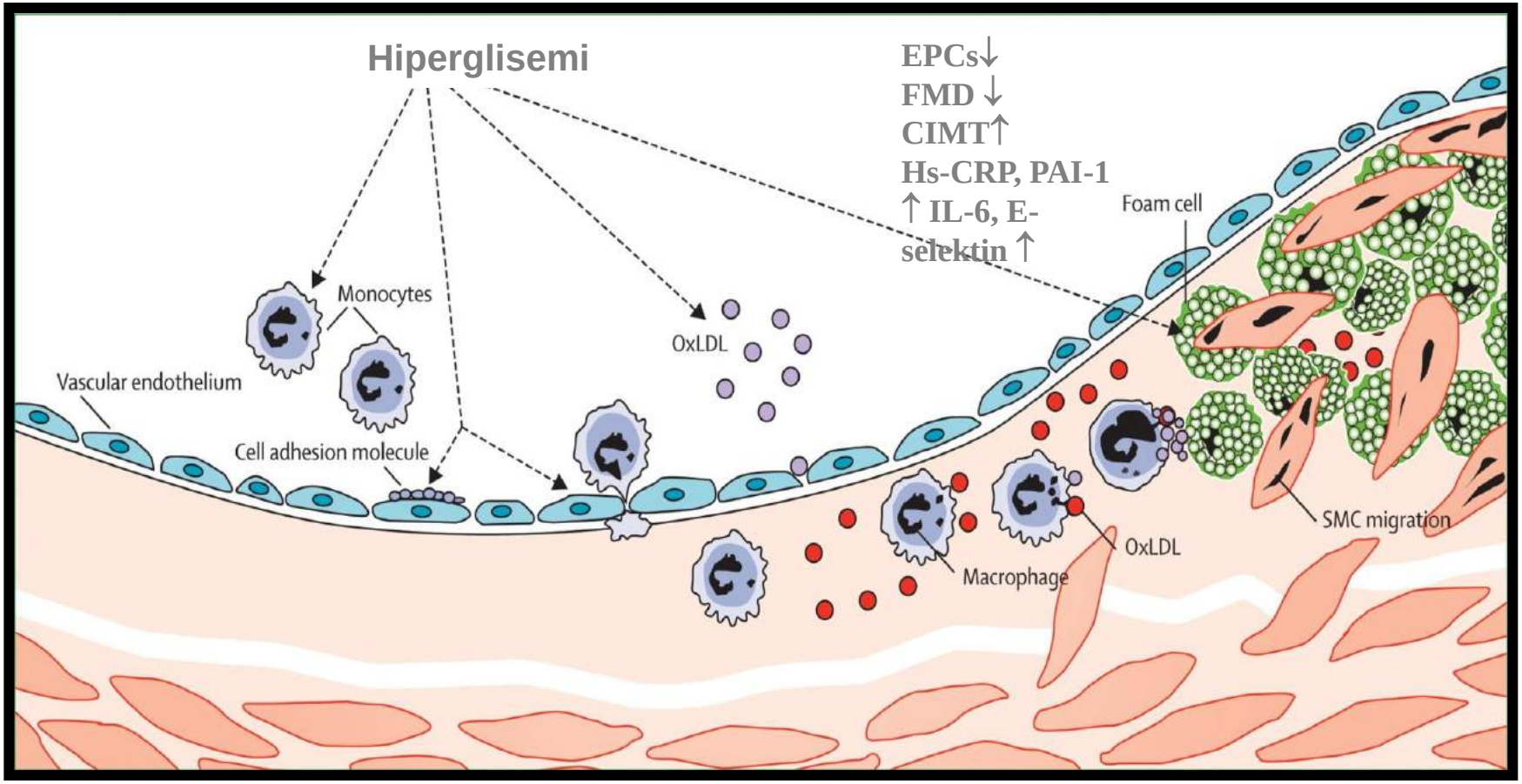
Victor MV et al. *Current Pharmaceutical Design,* 2009*, 15,* 2988-3002

Anjiotensinojen-Anj 2



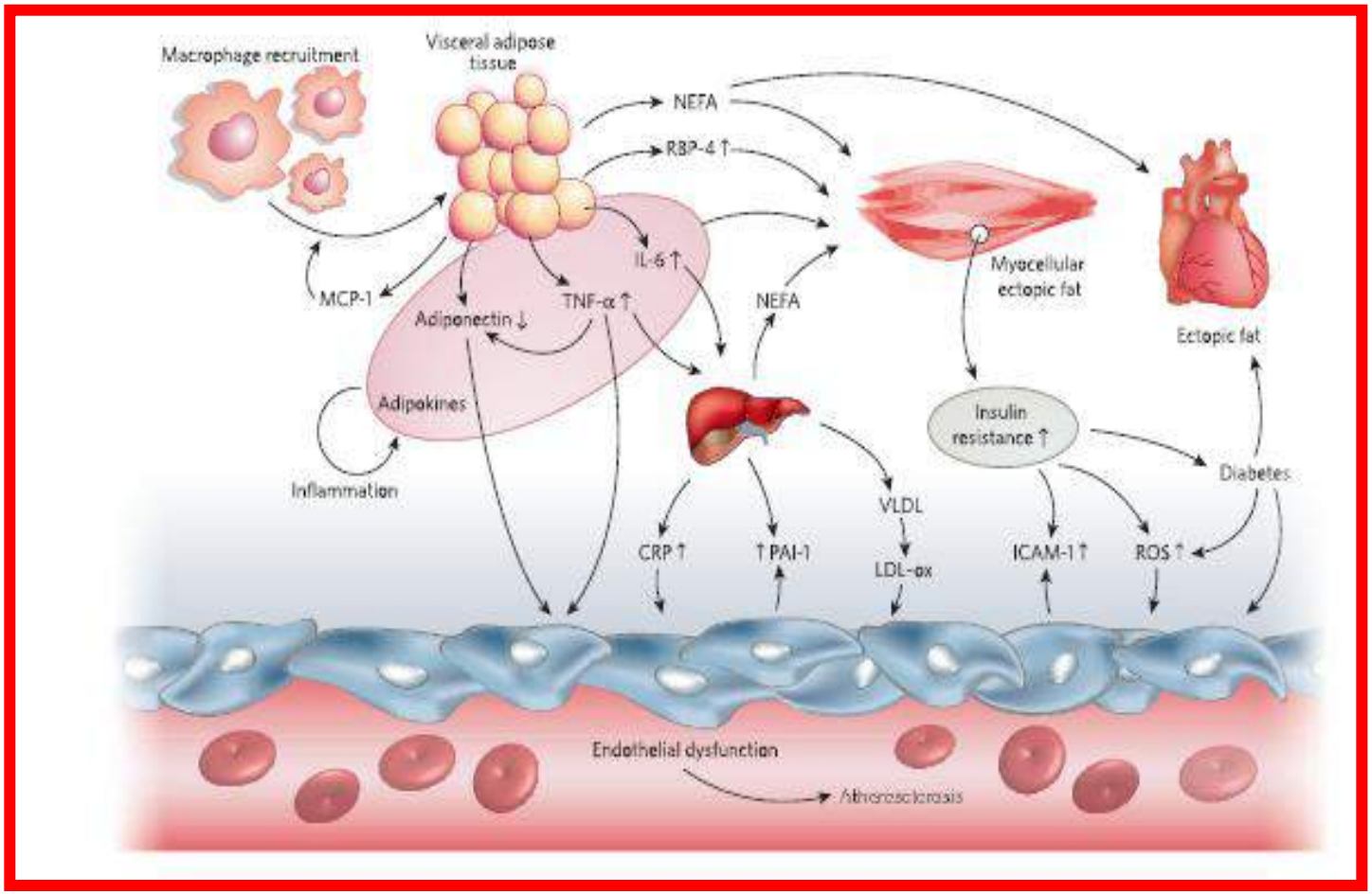


Endothelial Dysfunction, Cellular Adhesion Molecules and the metabolic syndrome



EPC: endotel progenitör hücre
FMD: akım-aracılı dilatasyon
CIMT: carotis intima-media kalınlığı

Retnakaran R, *Lancet,* 2008; 371: 1790-99.
Sibal L, *Diabetologia,* 2009; 52: 1464-73.


Macrophage recruitment
Visceral adipose tissue
NEFA
RBP-4 ↑
IL-6 ↑
MCP-1
Adiponectin ↓
TNF-α ↑
NEFA
Myocellular ectopic fat
Ectopic fat
Adipokines
Inflammation
Insulin resistance ↑
Diabetes
VLDL
CRP ↑
↑ PAI-1
LDL-ox
ICAM-1 ↑
ROS ↑
Endothelial dysfunction
Atherosclerosis

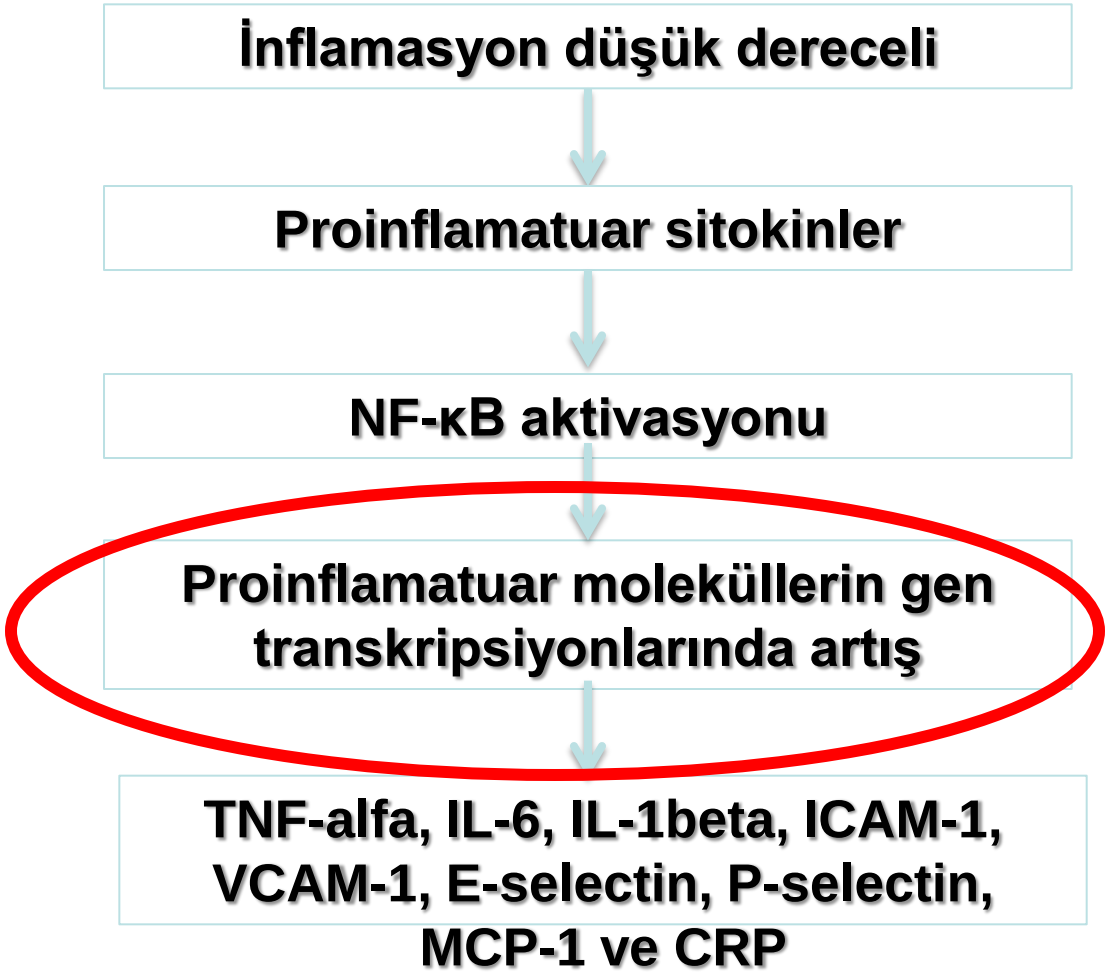
Deneysel pek çok belirteç

- Lokal hormonlar :
  - TNF-alfa, IL-6
  - NO, PGI2
  - Endotel derive hiperpolarize faktör
  - Endotelin-1
  - Trbx A2
  - Endoperoksidaz
- Trans membran proteinleri:
  - P-selektin, E-selektin , L-selektin
  - ICAM-1, VCAM-1

Atersklerozun direkt görüntü belirteçleri ?

- CIMT
- CACS (Computed tomography coronary calcium skore)
- KORONER ANJİOGRAFİ
- SPECT

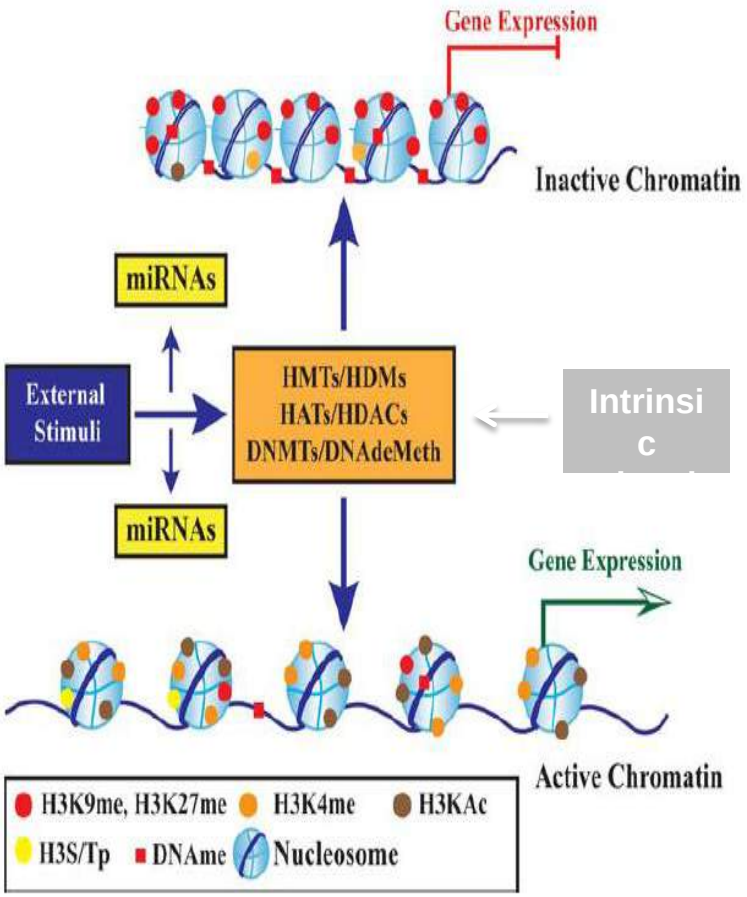
……..



Diabetologia. 2002;45(6):924-30.

Epigenetik belirteçler

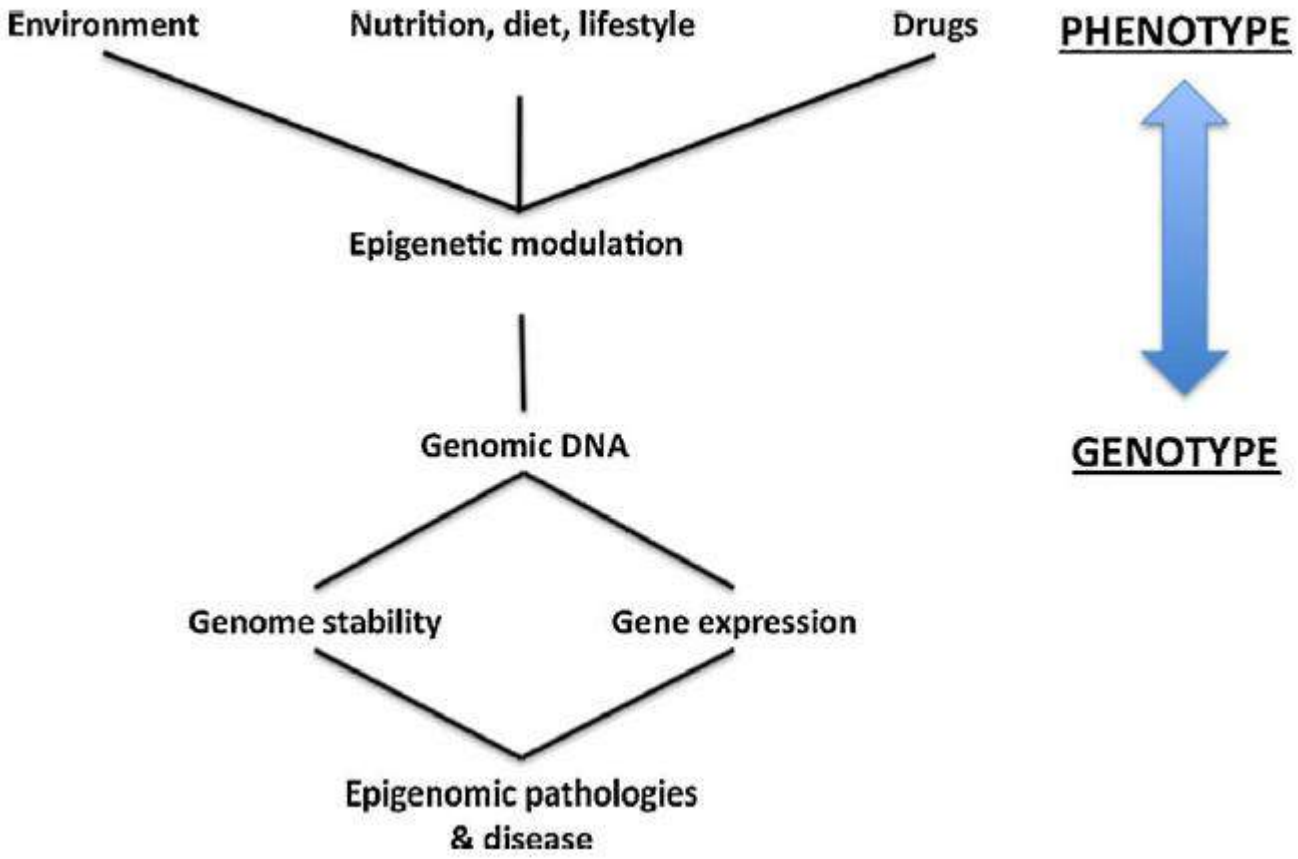
Epigenetik: **DNA dizi değişiminden bağımsız, gen aktivitesi ve ekspresyonunda değişime neden olan kalıtımsal özellikler.**



- Genomik DNA histon proteinleri
- Protein/DNA kompleks = kromatin
- Inaktif/Aktif Kromatin yapısı
- Histon modifikasyonları
- DNA dizi (CG zengini)
  - Metilasyon
- Kromatin aktif:
  - DNA transkripsiyona açık = gen ekspresyonu

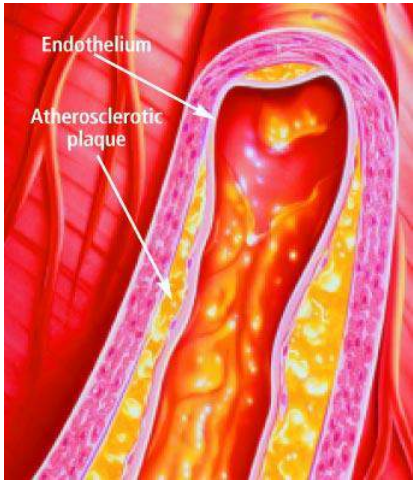
Cardiovascular Research, 2011.

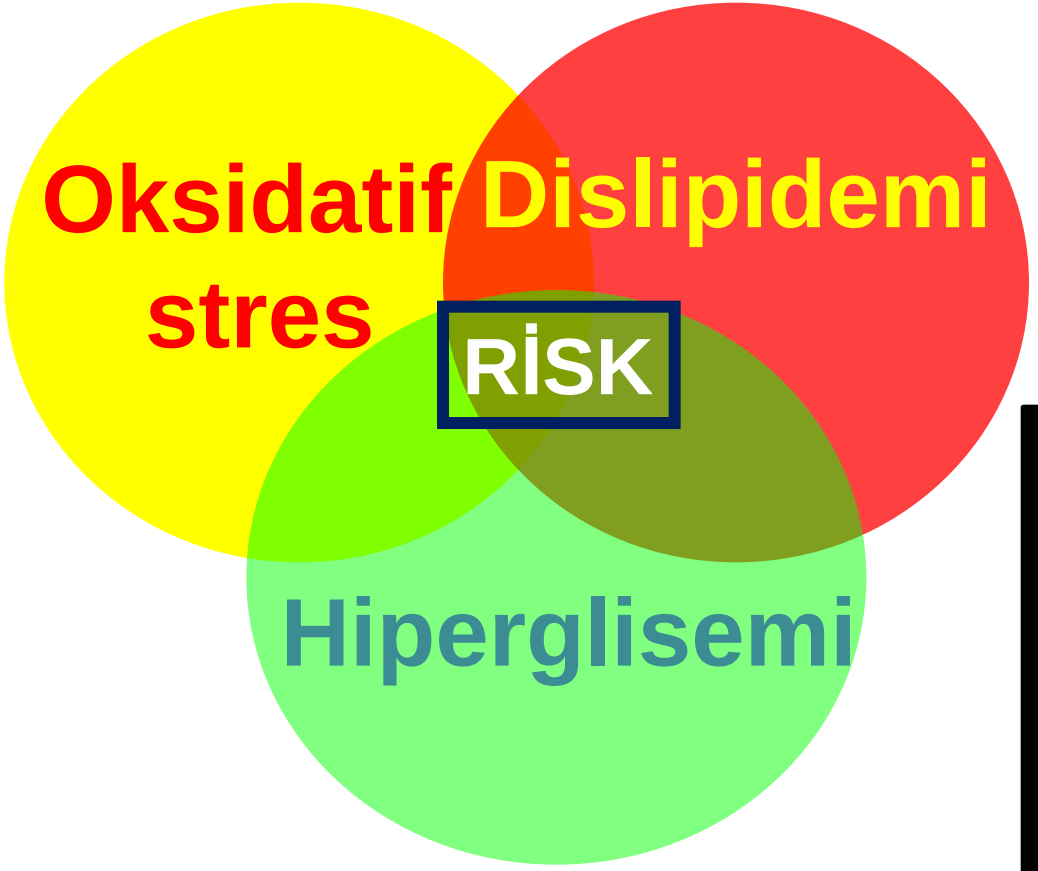
Epigenetik Mekanizmalar



Cardiovascular Research, 2011.

Epigenetik belirteçler





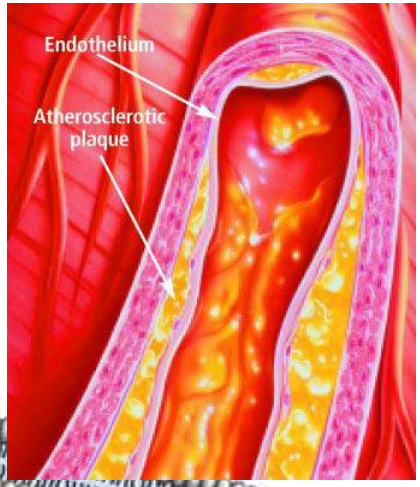
Vasküler diyabet komplikasyon gelişimi

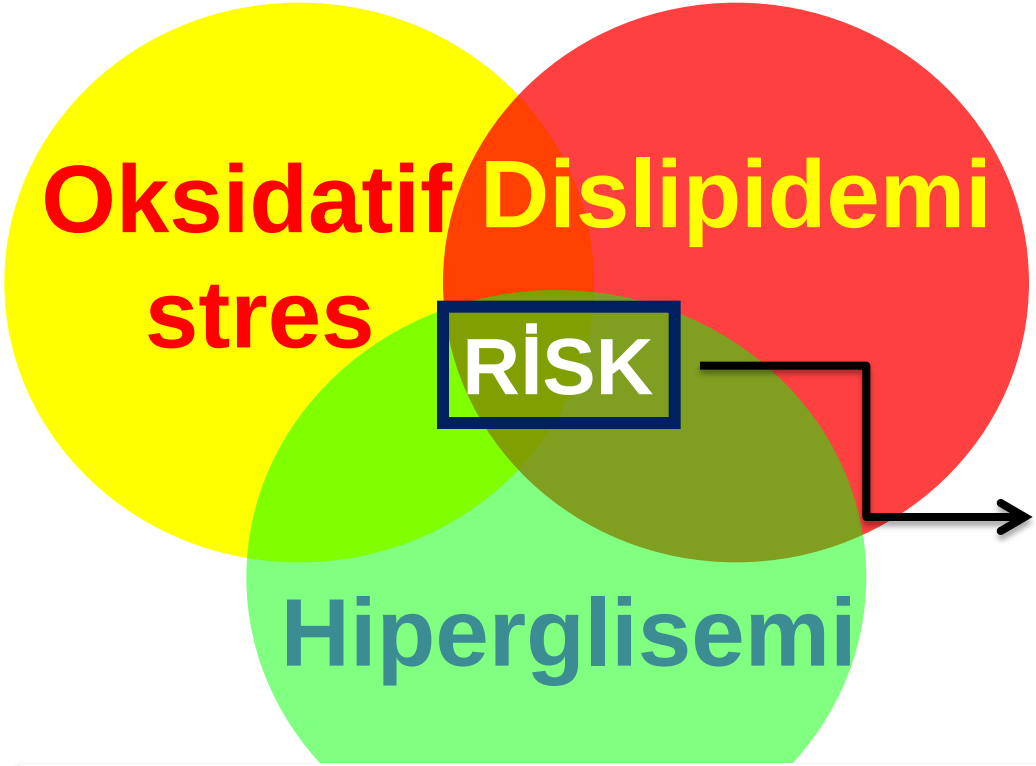
Inflamasyon gen ekspresyonu artar

Monositler endotel ve vasküler düz kas hücrelere bağlanır

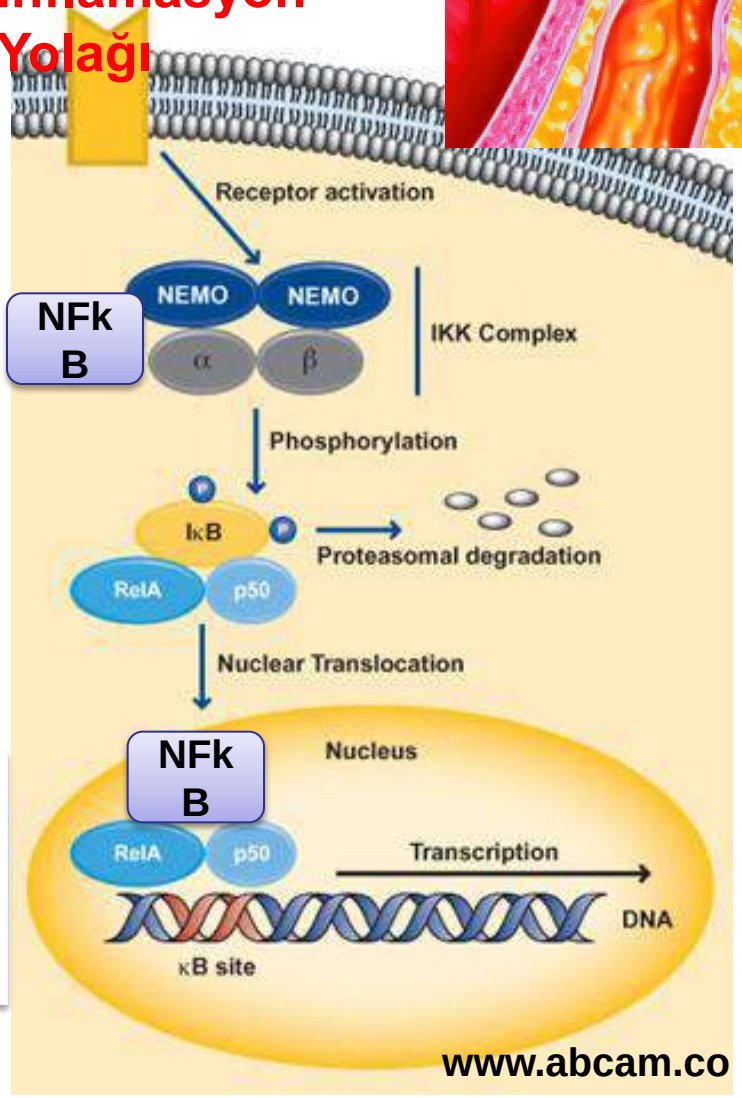
Monosit → makrofaj diferansiyasyon: ATEROSKLERİK PLAK

Epigenetik belirteçler

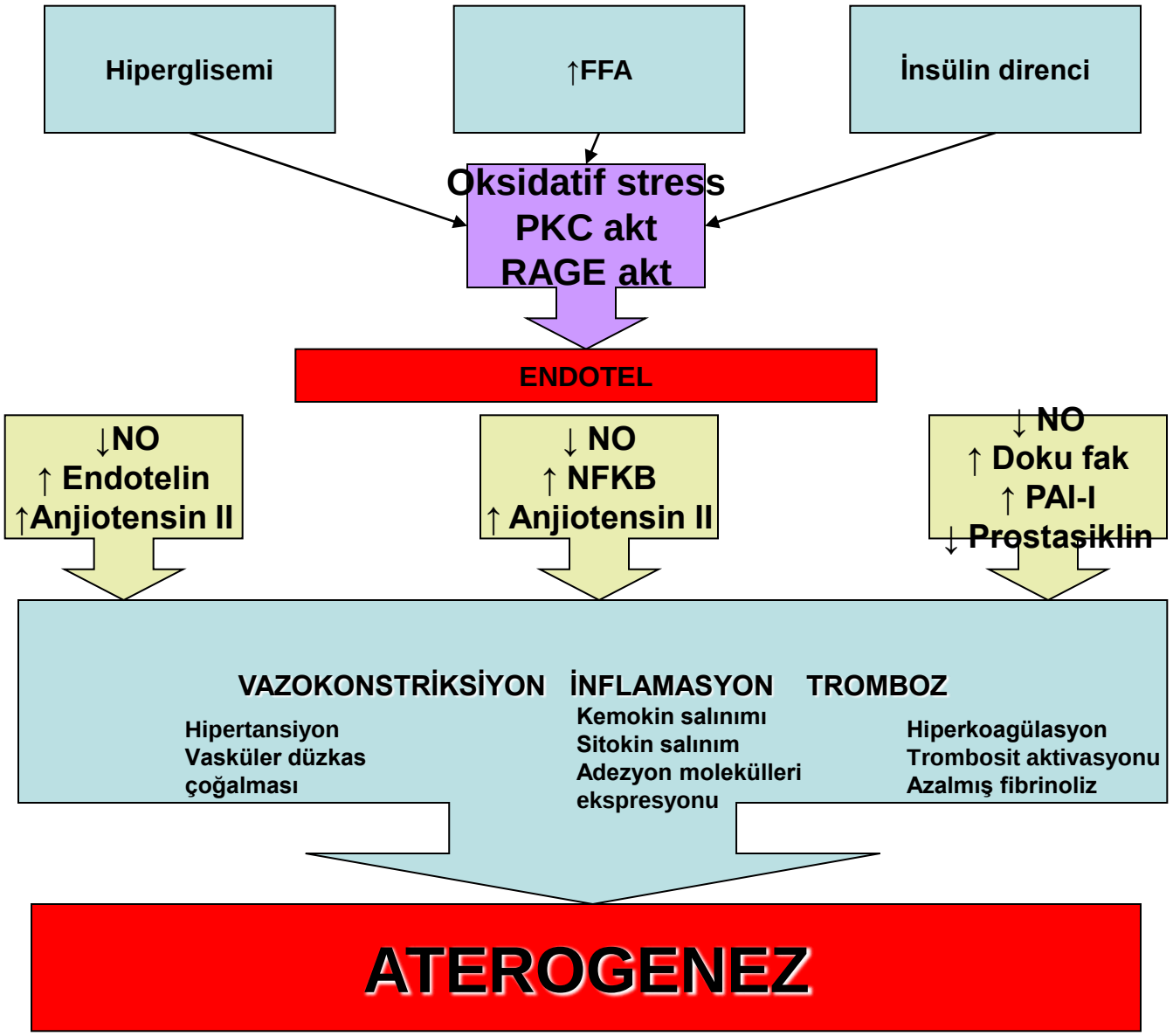




İnflamasyon Yolağı



NFkB aktivasyonu & Epigenetik Mekanizmalar
<u>Endotel & Vasküler Düz Kas Hücrelerinde</u>
Histon lizin asetilasyonunda artış
Histon deasetilasyon mekanizması inhibisyonu


Hiperglisemi
↑FFA
İnsülin direnci
Oksidatif stress
PKC akt
RAGE akt
ENDOTEL
↓NO
↑ Endotelin
↑Anjiotensin II
↓ NO
↑ NFKB
↑ Anjiotensin II
↓ NO
↑ Doku fak
↑ PAI-I
↓ Prostasiklin
VAZOKONSTRİKSİYON
Hipertansiyon
Vasküler düzkas çoğalması
İNFLAMASYON
Kemokin salınımı
Sitokin salınım
Adezyon molekülleri ekspresyonu
TROMBOZ
Hiperkoagülasyon
Trombosit aktivasyonu
Azalmış fibrinoliz
ATEROGENEZ

Bernal-Lopez MR *et al. Cardiovascular Diabetology* 2012, **11**:86
http://www.cardiab.com/content/11/1/86

CARDIO VASCULAR DIABETOLOGY

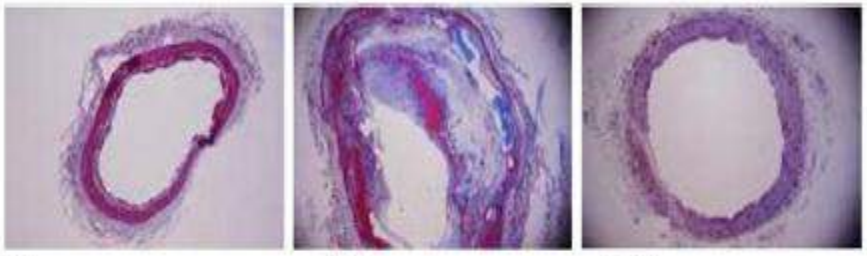
ORIGINAL INVESTIGATION **Open Access**

Alterations of specific biomarkers of metabolic pathways in vascular tree from patients with Type 2 diabetes

Bernal-Lopez M Rosa[1,5*], Llorente-Cortes Vicenta[2], Gomez-Carrillo Victor[3], Lopez-Carmona Dolores[3], Calleja Fernando[4], Gomez-Huelgas Ricardo[3,5], Badimon Lina[2,5*] and Tinahones Francisco J[1,5]

Abstract

The aims of this study were to check whether different biomarkers of inflammatory, apoptotic, immunological or lipid pathways had altered their expression in the occluded popliteal artery (OPA) compared with the internal mammary artery (IMA) and femoral vein (FV) and to examine whether glycemic control influenced the expression of these genes. The study included 20 patients with advanced atherosclerosis and type 2 diabetes mellitus, 15 of whom had peripheral arterial occlusive disease (PAOD), from whom samples of OPA and FV were collected. PAOD patients were classified based on their HbA1c as well (HbA1c ≤ 6.5) or poorly (HbA1c > 6.5) controlled patients. Controls for arteries without atherosclerosis comprised 5 IMA from patients with ischemic cardiomyopathy (ICM). mRNA, protein expression and histological studies were analyzed in IMA, OPA and FV. After analyzing 46 genes, OPA showed higher expression levels than IMA or FV for genes involved in thrombosis (F3), apoptosis (MMP2, MMP9, TIMP1 and TIM3), lipid metabolism (LRP1 and NDUFA), immune response (TLR2) and monocytes adhesion (CD83). Remarkably, MMP-9 expression was lower in OPA from well-controlled patients. In FV from diabetic patients with HbA1c ≤6.5, gene expression levels of BCL2, CDKN1A, COX2, NDUFA and SREBP2 were higher than in FV from those with HbA1c >6.5.



igure 1 Histological sections of arteries, internal mammary (A) and popliteal artery (where the atheroma plaque is located) (B) and emoral vein (C). The sections were stained with Masson's trichrome and photographed by routine light microscopy (4x).

tF3: inflamatuar gen

LRP-1: lipid ilişkili gen

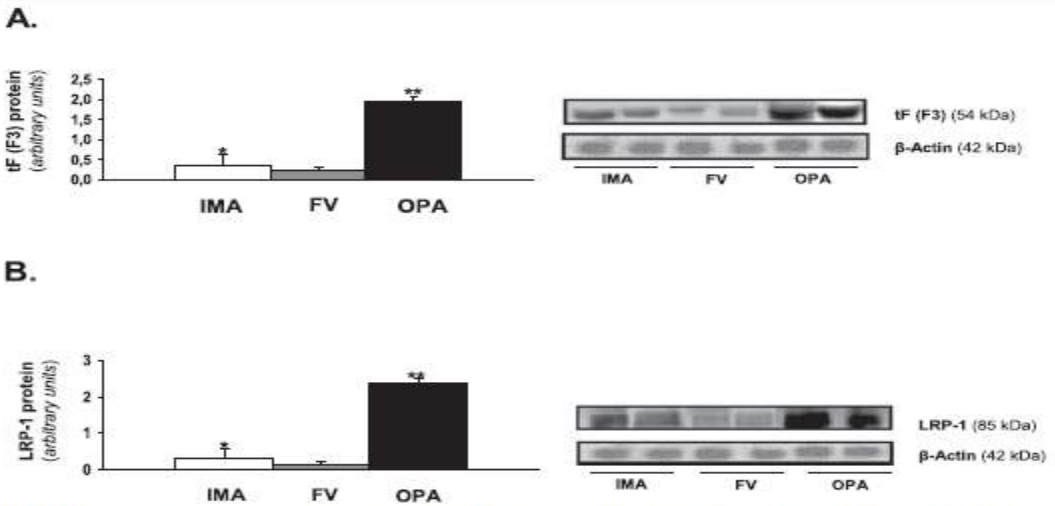


Figure 3 tF (F3) and LRP-1 expression levels in human vessels from atherosclerotic patients with ICM or PAOD. A.- Bar graphs showing the densitometric analysis of showing tF bands (results are expressed as mean ± SD. * $p<0.04$ vs FV or OPA, ** $p<0.04$ vs control (IMA) and FV) and autoradiography showing tF (54 KDa) and β-actine (42 KDa) protein levels in internal mammary artery (IMA), femoral vein (FV) and occluded popliteal artery (OPA) from two subjects from each vessel **B.-** Bar graphs showing the densitometric analysis of showing tF bands (results are expressed as mean ± SD. * $p<0.05$ vs FV or OPA, ** $p<0.05$ vs control (IMA) and FV) and autoradiography showing LRP-1 (85 KDa) and β-actine (42 KDa) protein levels in internal mammary artery (IMA), femoral vein (FV) and occluded popliteal artery (OPA) from two subjects from each vessel.

MMP 2, MMP9

Free Radical Biology and Medicine 64 (2013) 85–94

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

MicroRNAs: potential mediators and biomarkers of diabetic complications

Mitsuo Kato, Nancy E. Castro, Rama Natarajan*

Department of Diabetes, Beckman Research Institute, City of Hope, Duarte, CA 91010, USA

ARTICLE INFO

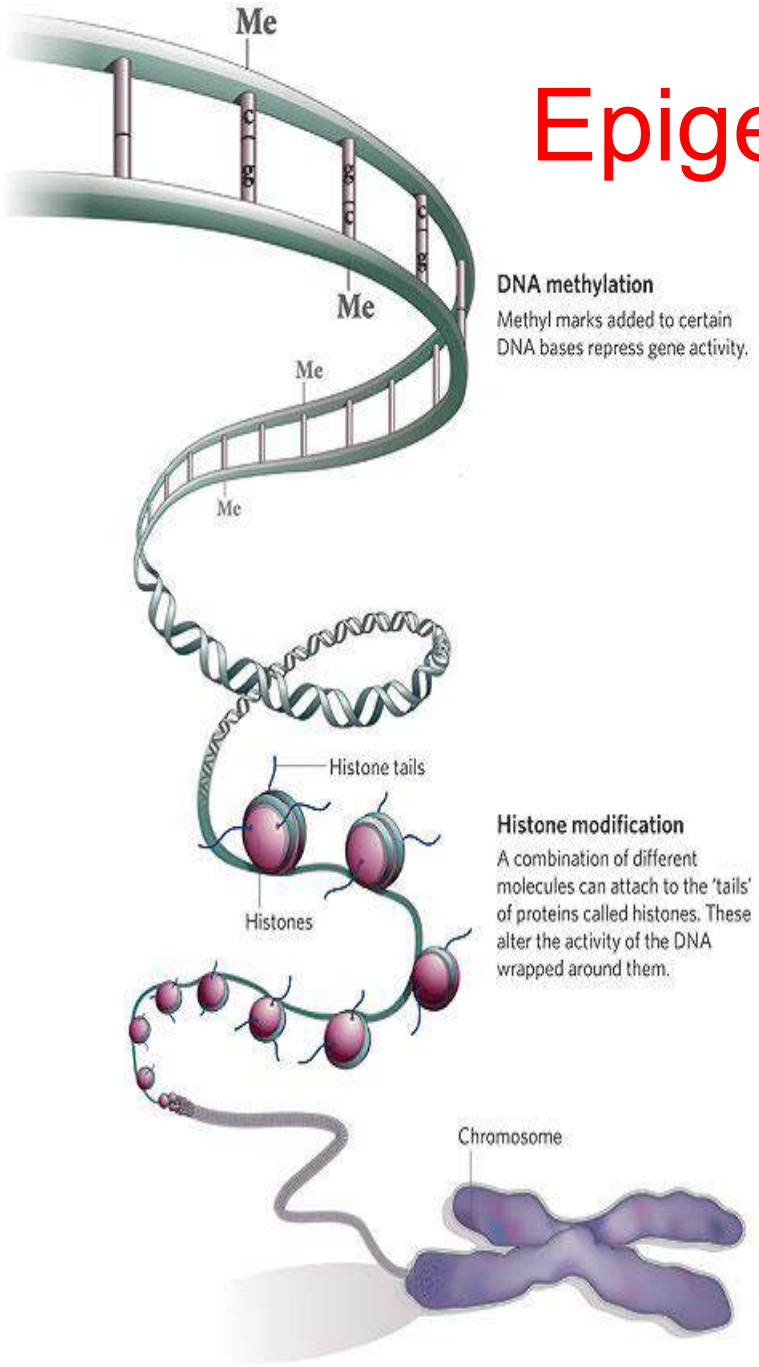
Available online 12 June 2013

Keywords:
MicroRNA
Diabetic complications
Free radicals

ABSTRACT

The incidence of diabetes is escalating worldwide and, consequently, this has become a major health care problem. Moreover, both type 1 and type 2 diabetes are associated with significantly accelerated rates of microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as atherosclerotic cardiovascular and hypertensive diseases. Key factors have been implicated in leading to these complications, including hyperglycemia, insulin resistance, dyslipidemia, advanced glycation end products, growth factors, inflammatory cytokines/chemokines, and related increases in cellular oxidant stress (including mitochondrial) and endoplasmic reticulum stress. However, the molecular mechanisms underlying the high incidence of diabetic complications, which often progress despite glycemic control, are still not fully understood. MicroRNAs (miRNAs) are short noncoding RNAs that have elicited immense interest in recent years. They repress target gene expression via posttranscriptional mechanisms and have diverse cellular and biological functions. Herein, we discuss the role of miRNAs in the pathobiology of various diabetic complications, their involvement in oxidant stress, and also the potential use of differentially expressed miRNAs as novel diagnostic biomarkers and therapeutic targets.

Epigenetik belirteçler



- Aday gen çalışması;

DNA metilasyon patern farklılığı

(vasküler düz kas ve endotel hücreler)

- Hipoksi-inducible faktör-1a
- c-fos
- p53
- Östrojen reseptörü
- Büyüme faktörleri
- Araşidonik asit metabolize enzimleri
- Matriks metalloproteinleri

Yeni populer belirteçler

Yeni populer belirteçler

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 7 (2013) 108–111

Contents lists available at SciVerse ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original article

Paraoxonase 1: A better atherosclerotic risk predictor than HDL in type 2 diabetes mellitus

Surajeet Kumar Patra*, Kamna Singh, Ritu Singh

Department of Clinical Biochemistry, Lady Hardinge Medical College, New Delhi, India

ARTICLE INFO

Keywords:
Paraoxonase 1(PON 1)
Atherogenic index of plasma (AIP)
Atherogenic coefficient (AC)
Castelli's risk index I (CRII)
Castelli's risk index II (CRI II)

ABSTRACT

Introduction: Type 2 diabetes mellitus is a state of glycative stress and oxidative stress. Lower level of serum PON 1 has been correlated to higher morbidity and mortality related to cardiovascular complications in type 2 diabetes mellitus.
Objectives: To estimate and compare the serum PON 1 levels in type 2 diabetes mellitus and controls and to predict which one is the better atherosclerotic risk predictor among HDL and PON 1 in T2DM patients.
Materials and methods: An observational analytical case-control study was conducted with a sample size of 30 in two groups like group I (30 cases of type 2 diabetes mellitus diagnosed by ADA 2010 criteria) and group II (30 age and sex matched controls). Human serum paroxonase 1 levels were measured by ELISA.

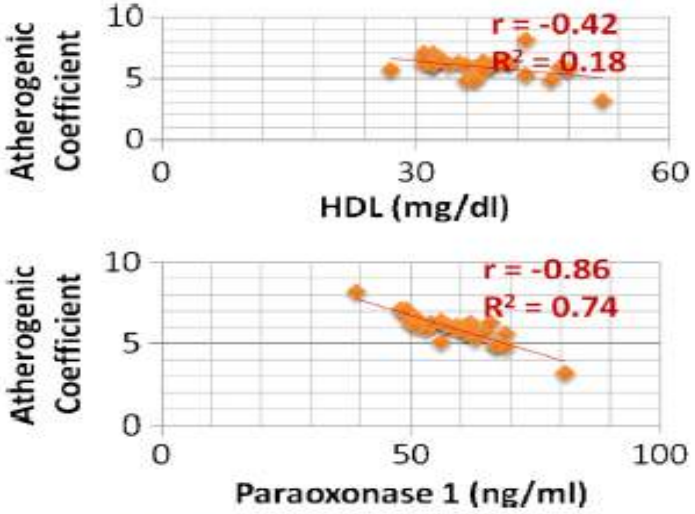


Fig. 2. Correlation of AC with HDL and PON 1.

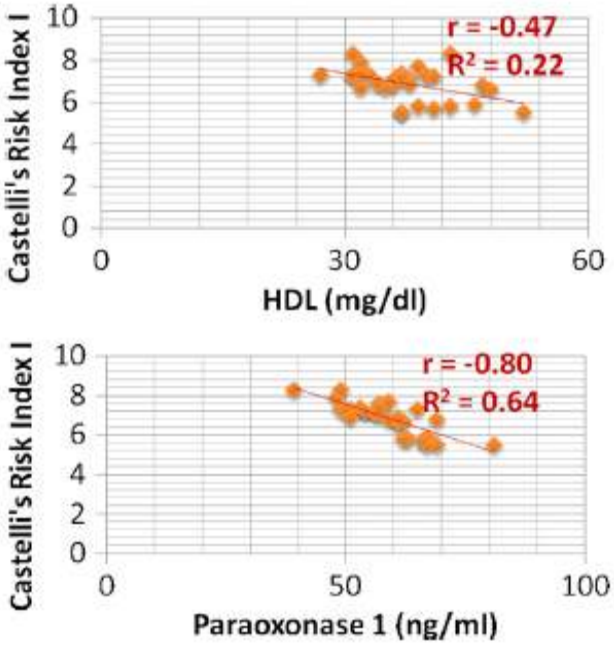


Fig. 3. Correlation of CRI I with HDL and PON 1.

Atherosclerosis 228 (2013) 270–276

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Serum monomeric α_2-macroglobulin as a clinical biomarker in diabetes

Tesshu Takada [a], Yoshio Kodera [b], Madoka Matsubara [a], Yusuke Kawashima [b], Tadakazu Maeda [b], Yoshikuni Fujita [a], Masayoshi Shichiri [a,*]

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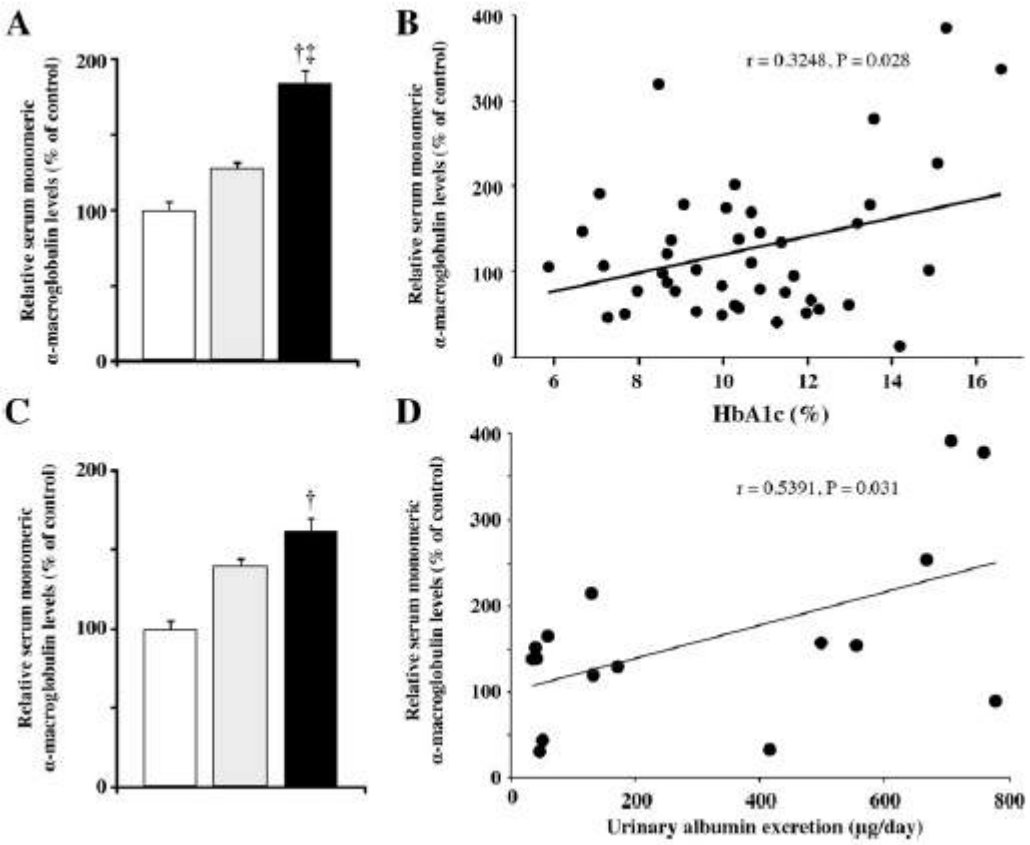
ABSTRACT

Objective: Despite the number of potential biomarker proteins for diabetes, very few of them have proven useful as clinically beneficial indicators, because of the technical difficulties associated with their identification among highly abundant serum proteins. We attempted to identify a protein with distinguishable expression in human diabetes.
Methods: We applied a highly efficient strategy for the purification of endogenous low abundance proteins from diabetic and non-diabetic serum samples. Extracted sera were fractionated by SDS-PAGE and protein bands were isolated and analyzed by mass spectrometry using an ion-trap mass spectrometer. The identities of the proteins were confirmed by western blotting and the serum levels evaluated.
Results: A significantly upregulated protein in diabetic patients was identified as monomeric α_2-macroglobulin. Its tetramer, another dominant circulating molecular form, was only marginally increased in diabetes.
Conclusion: Serum monomeric α_2-macroglobulin is highly expressed in many diabetic subjects. It is identical to the human 'cardiac isoform of α_2-macroglobulin' described in the literature, a well-known acute phase serum biomarker protein mechanistically involved in cardiac and atherosclerotic diseases.


A
Relative serum monomeric α-macroglobulin levels (% of control)
200
100
0
†‡
B
Relative serum monomeric α-macroglobulin levels (% of control)
400
300
200
100
0
r = 0.3248, P = 0.028
6
8
10
12
14
16
HbA1c (%)
C
Relative serum monomeric α-macroglobulin levels (% of control)
200
100
0
†
D
Relative serum monomeric α-macroglobulin levels (% of control)
400
300
200
100
0
r = 0.5391, P = 0.031
0
200
400
600
800
Urinary albumin excretion (μg/day)

Pratikde…

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- PREMATÜRE aterosklerozis belirteçlerini derinlerde aramaya gerek yok
- Zaten çok yakınımızda ve kolay belirleyebileceğimiz durumlarla kendini belirli ediyor

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Aslında…

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- Fizik muayenede: TA, dislipidemi , ağırlık,
- Lab da: glukoz, hba1c, insülin, idrarda mikro albumin varlığı, homosistein

Göz ardı edilen bir belirteç..

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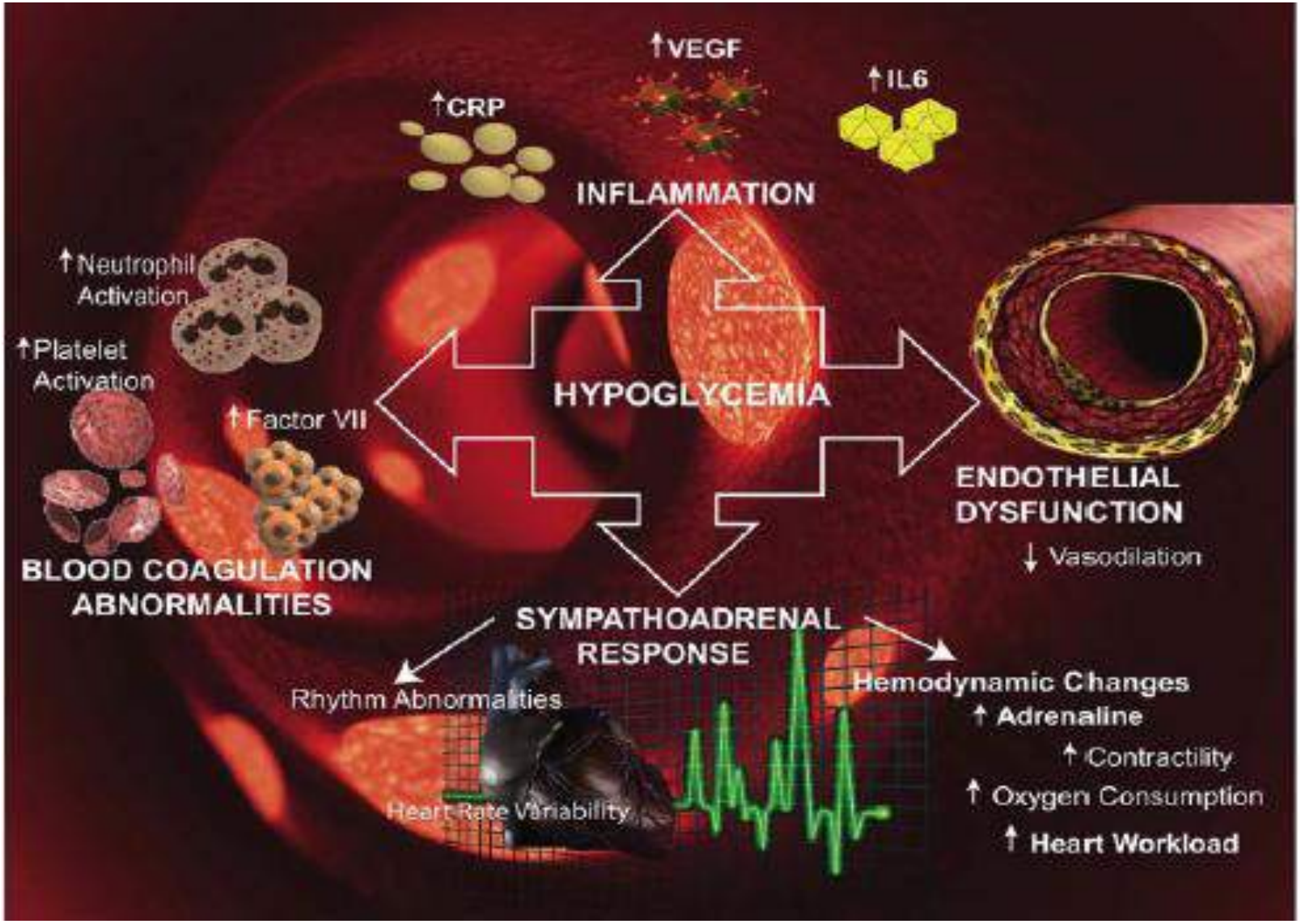
- Hipoglisemi….



Desouza CV, Diabetes Care, 6 ,2010

Teşekkürler…