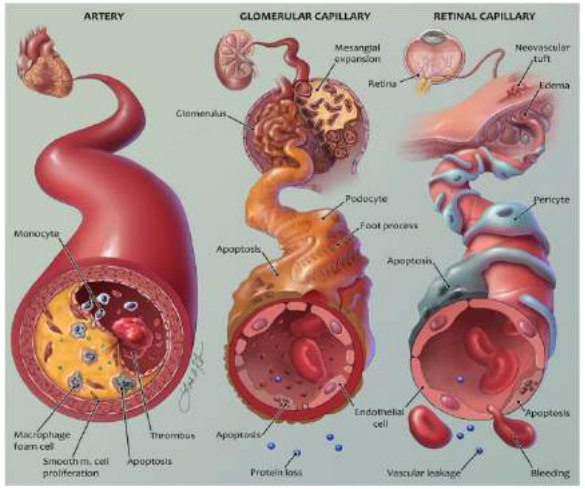

# Diyabette vasküler komplikasyonların patogenezinde yeni görüşler




Prof. Dr. Sevim Güllü

Ankara Üniversitesi Tıp Fakültesi
Endokrinoloji ve Metabolizma
Hastalıkları Bilim Dalı

# Sunum Planı

- Klasik yolaklar
- Genetik
- Epigenetik
- Glukoz değişkenliği

# Diabetes Mellitus

- Diyabet dünya çapında sık görülen ve hızla artan bir hastalık
- Mikro ve makrovasküler komplikasyonlar morbidite ve mortaliteden sorumlu

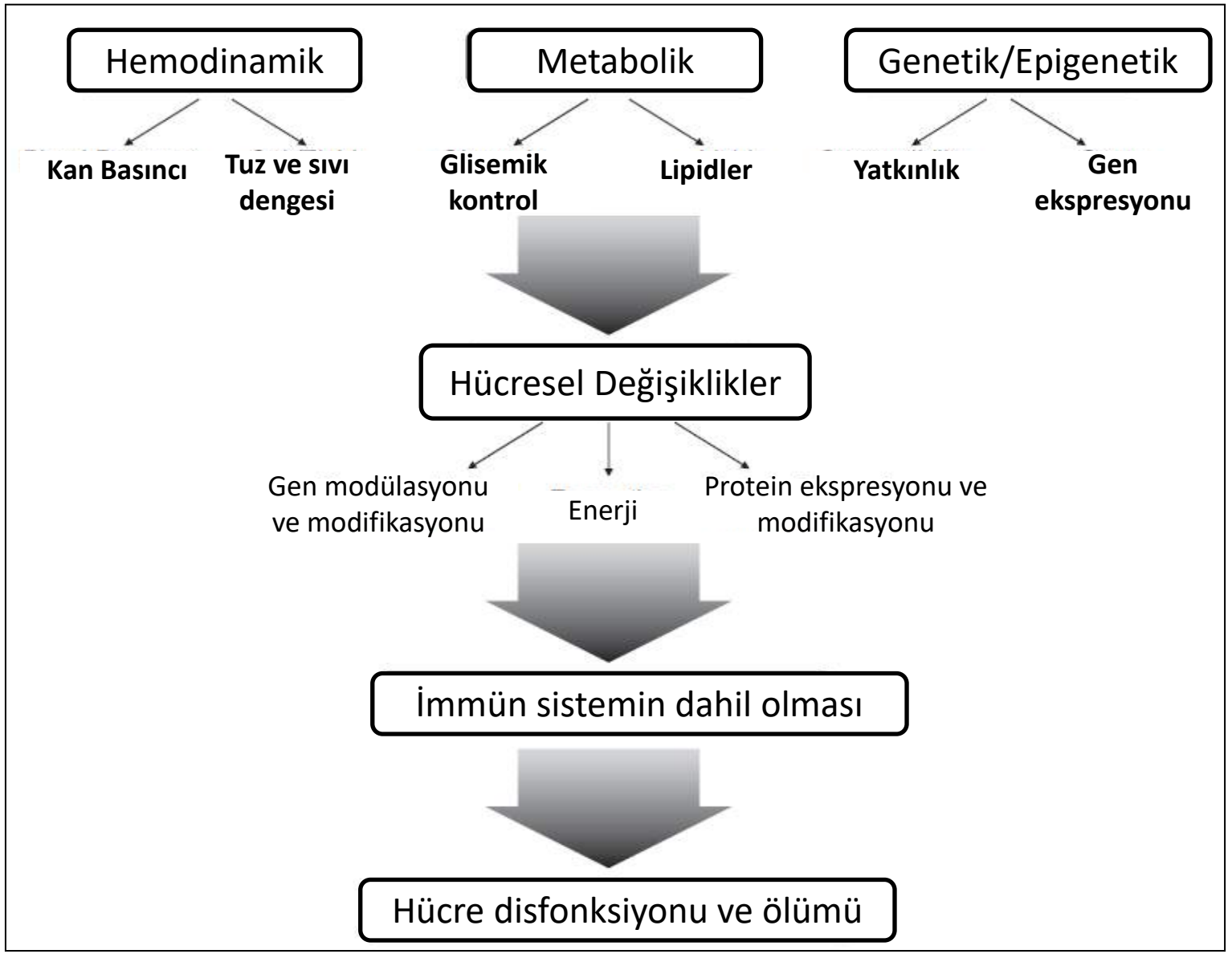
# Diyabetin vasküler komplikasyonları

- Diyabetin vasküler komplikasyonları hastalığın en ciddi sorunlarıdır.
- Diyabetik hastalarda yaşam süresi beklentisinin kısalmasının en önemli nedeni aterosklerozdur.
  - 65 yaş üstü diyabetik bireylerin yaklaşık % 80'i kalp hastalığına, % 16'sı ise inmeye bağlı kaybedilir
- Diyabetik nefropati SDBH'nın , diyabetik retinopati körlüğün, diyabetik nöropati ekstremite amputasyonlarının en sık nedenleridir.



Cell Metab. 2013 January 8; 17(1): 20–33.

# Diyabetik Komplikasyonlara Etki Eden Faktörler






*Physiol Rev 93: 137–188, 2013*

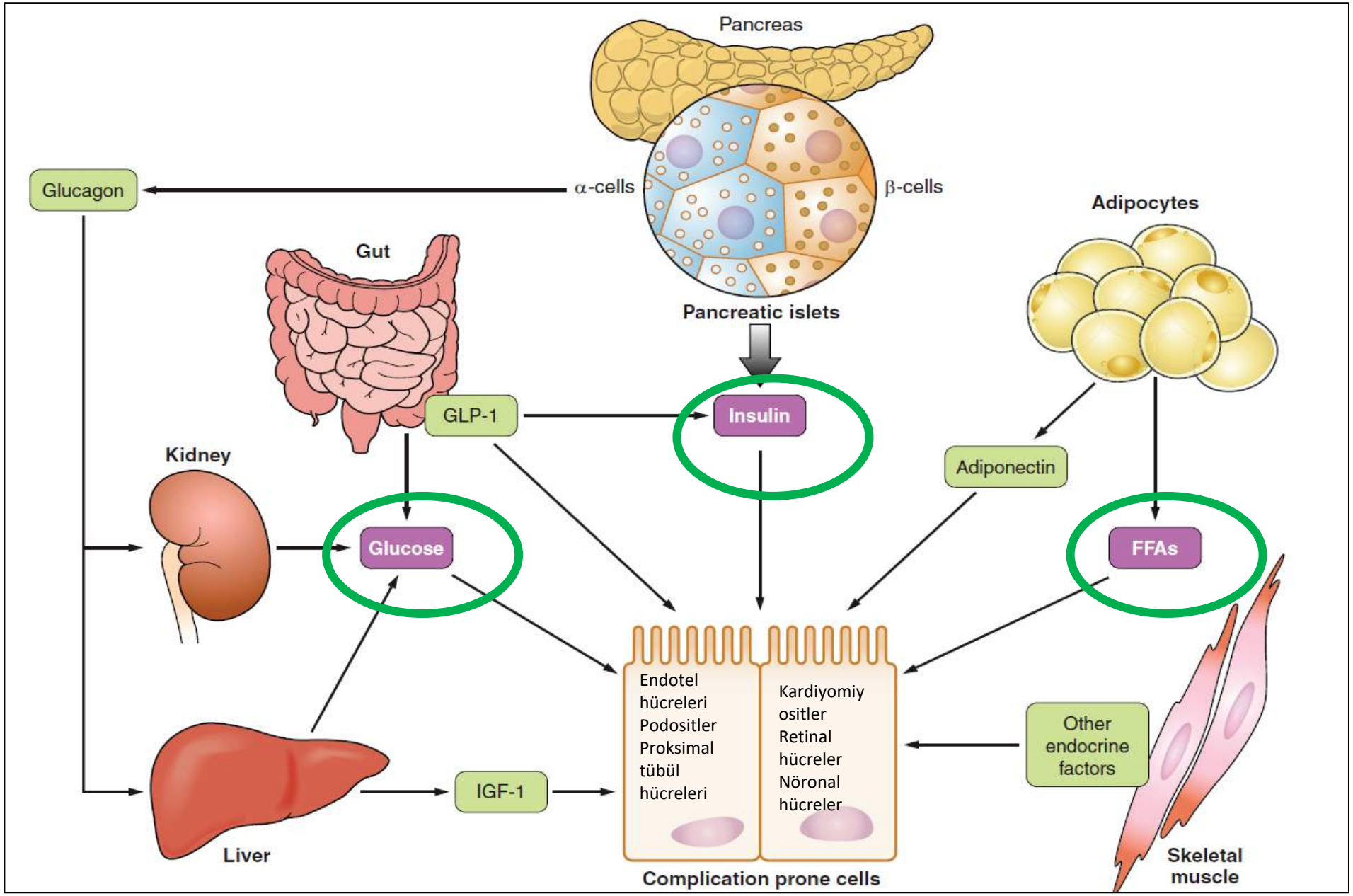
# Diyabetin vasküler komplikasyonları

- Plazma glukozunu düşürmek nefropati ve retinopati başlamasını geciktirir.
- Kardiyovasküler hastalık ise glisemik kontrol ile birebir ilişkili değildir ve glukoz düşürücü tedaviden daha az yarar görür.
- Diyabetik vasküler komplikasyonların patogenezi hasarın moleküler mekanizmaları ve endojen koruyucu faktörler arasında bir denge ile belirlenmektedir.



Cell Metab. 2013 January 8; 17(1): 20–33.

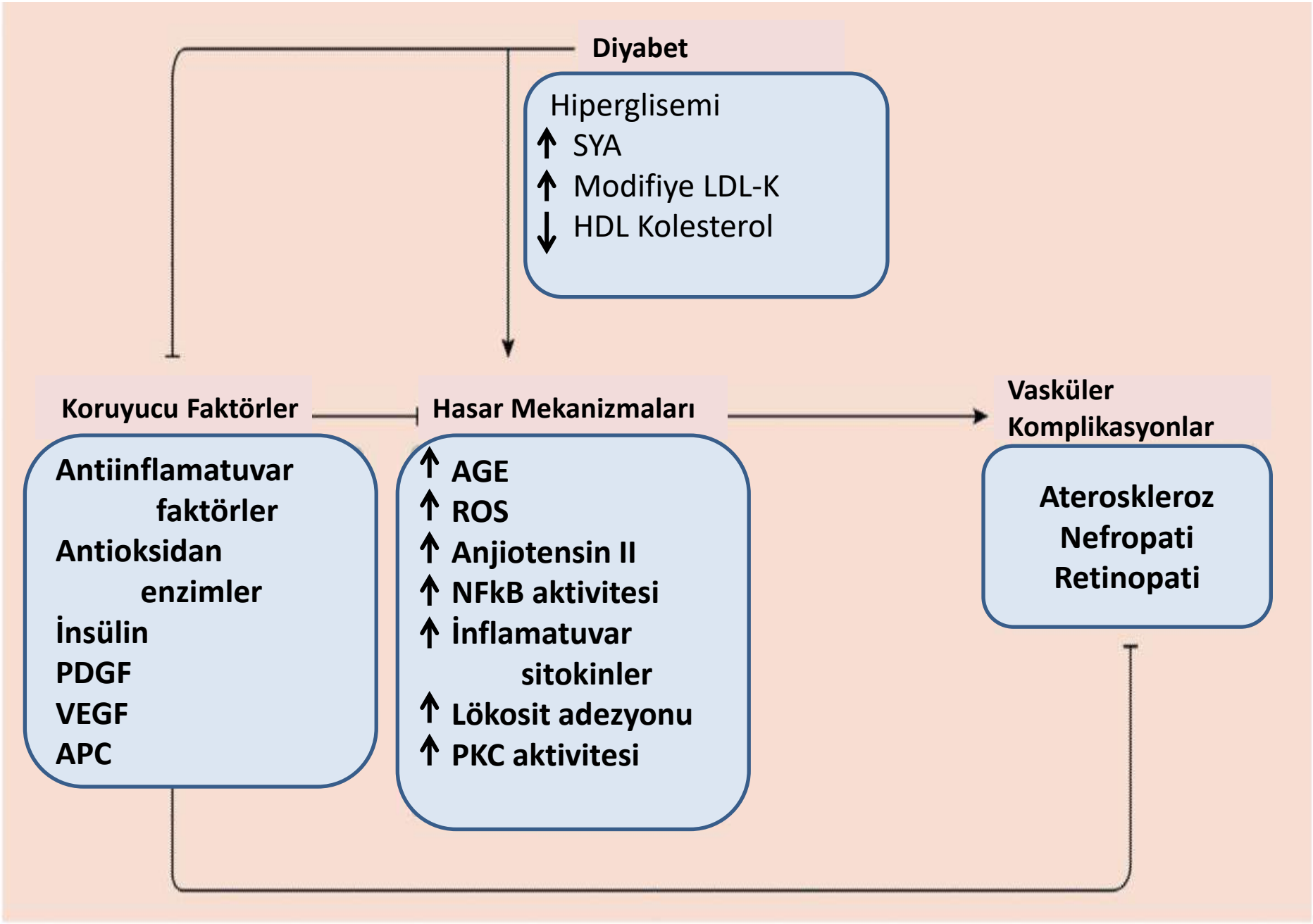
# Glukoz Homeostatik Yolakları






*Physiol Rev 93: 137–188, 2013*

# Diyabetin vasküler komplikasyonları: Koruyucu ve Tetikleyici Faktörler




Cell Metab. 2013 January 8; 17(1): 20–33.

# Diabetes Mellitus

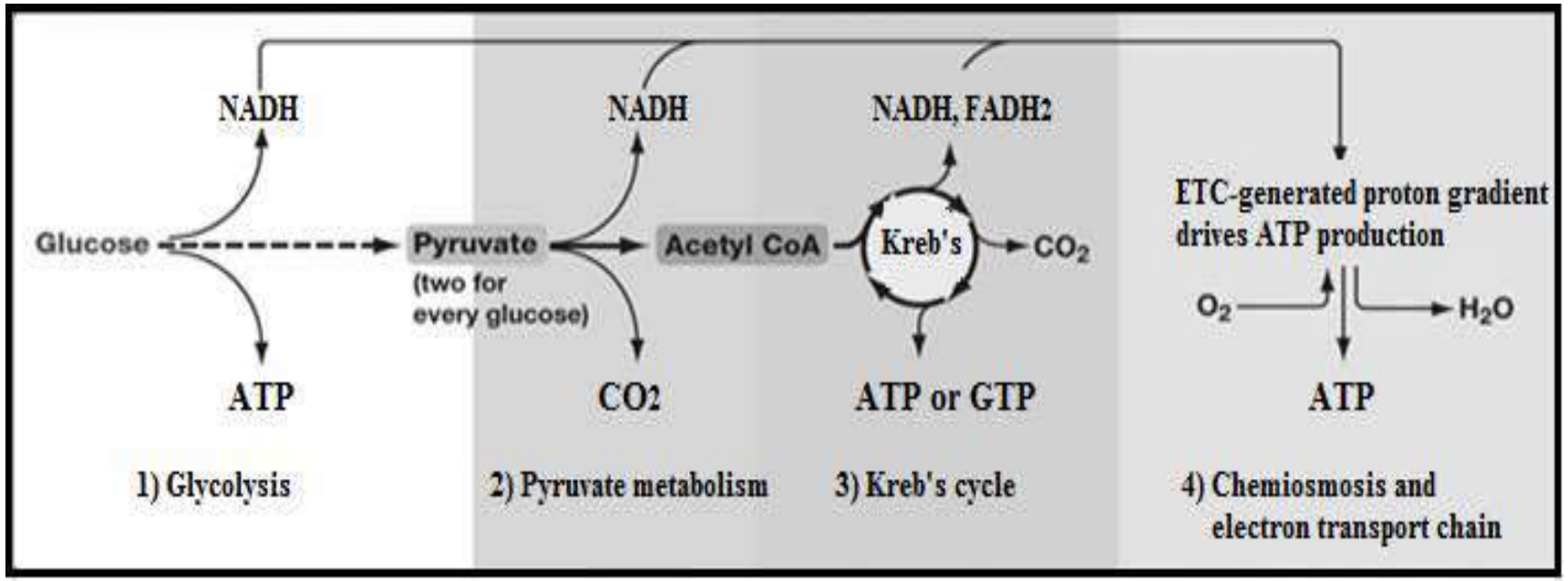
- Hiperglisemi ilişkili vasküler hasarın mekanizmaları hem kompleks hem de tam bilinmemektedir.

- Yüksek seviyelerdeki intraselüler glukoz reaktif oksijen türleri üretimini artırmakta ve önemli yolaklarda değişikliklere yol açmaktadır.

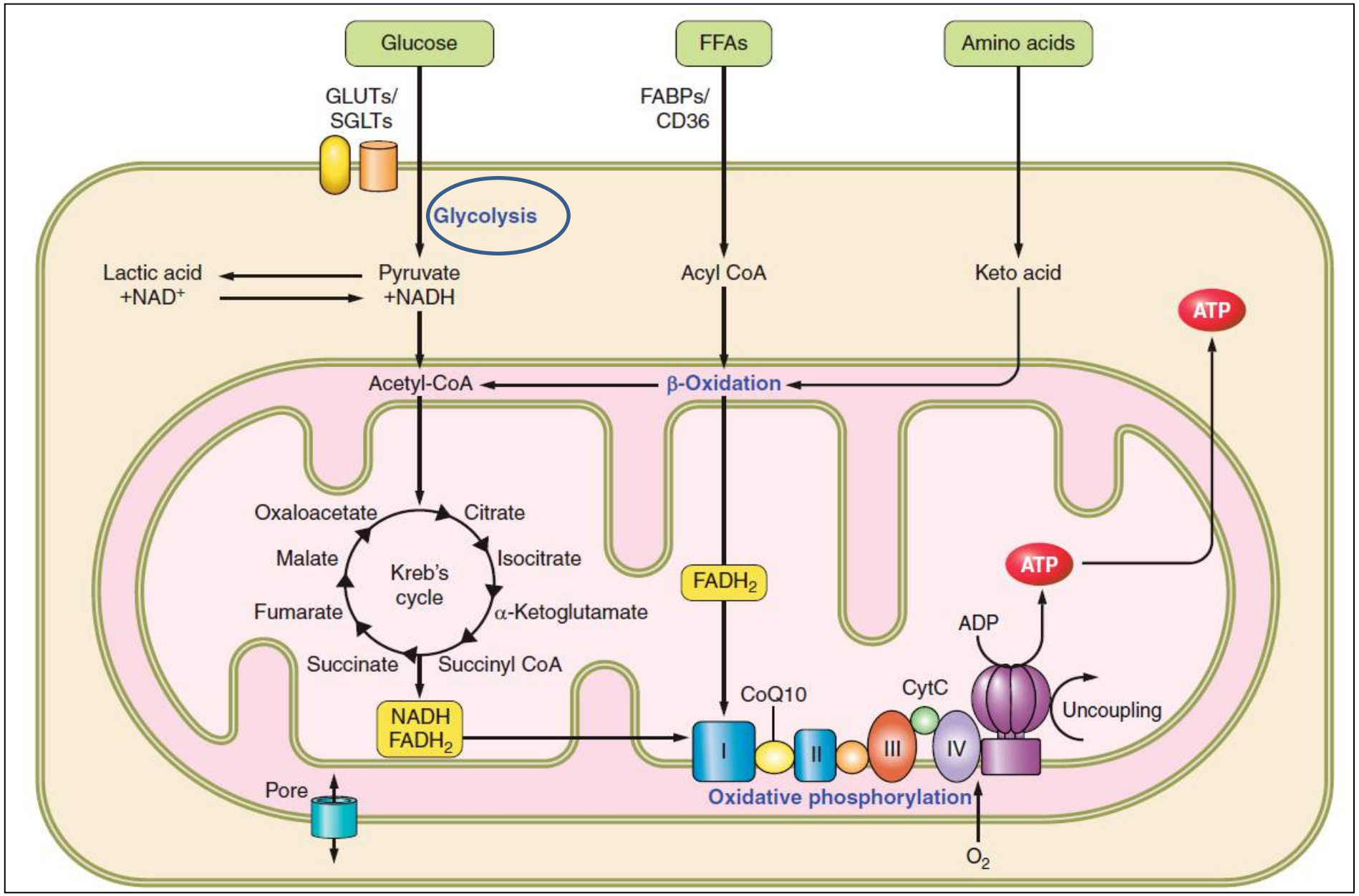


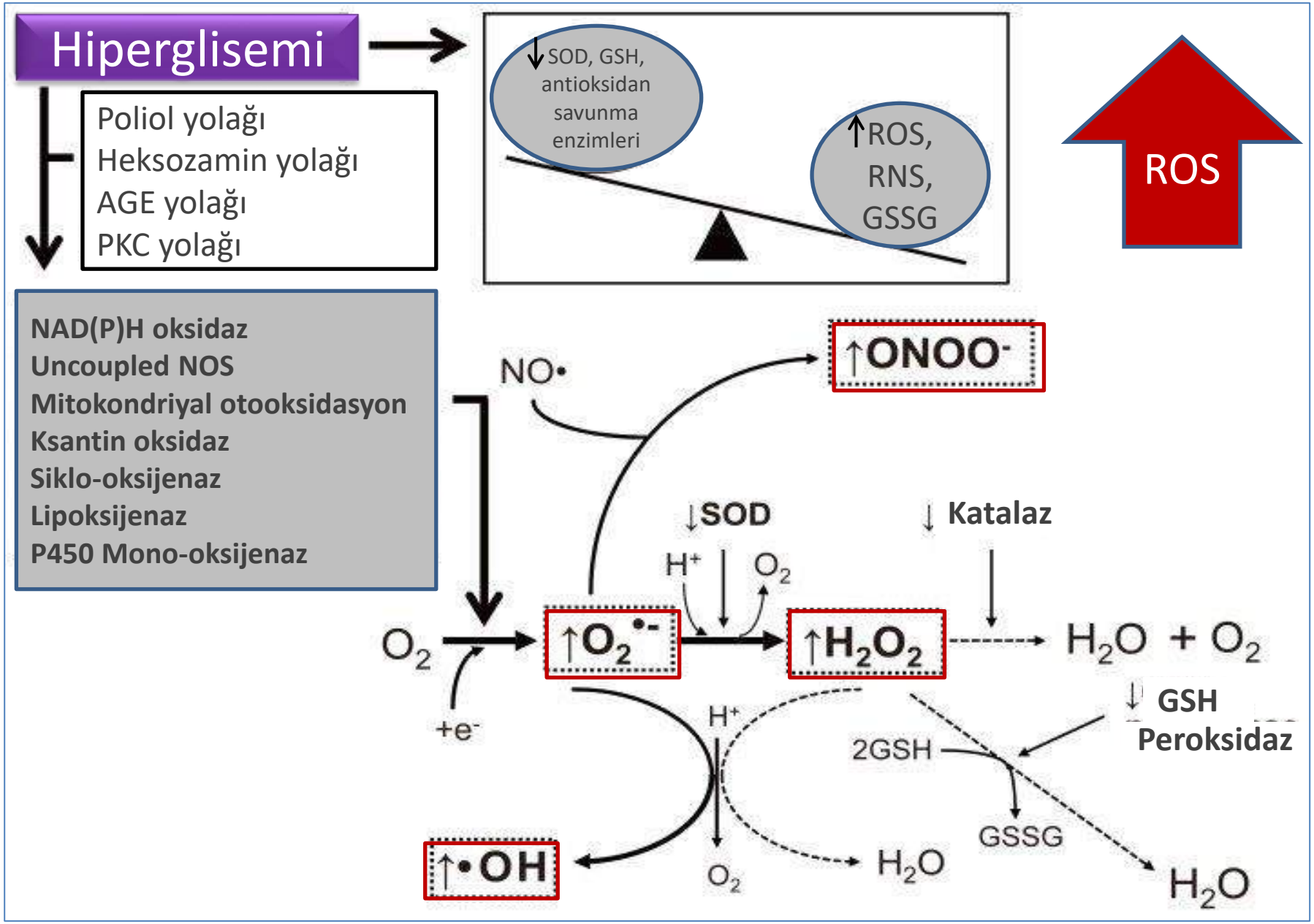
Nature 2001 Dec 13;414(6865):813-20.

# Glukoz Metabolizması



# Mitokondride Enerji Üretimi

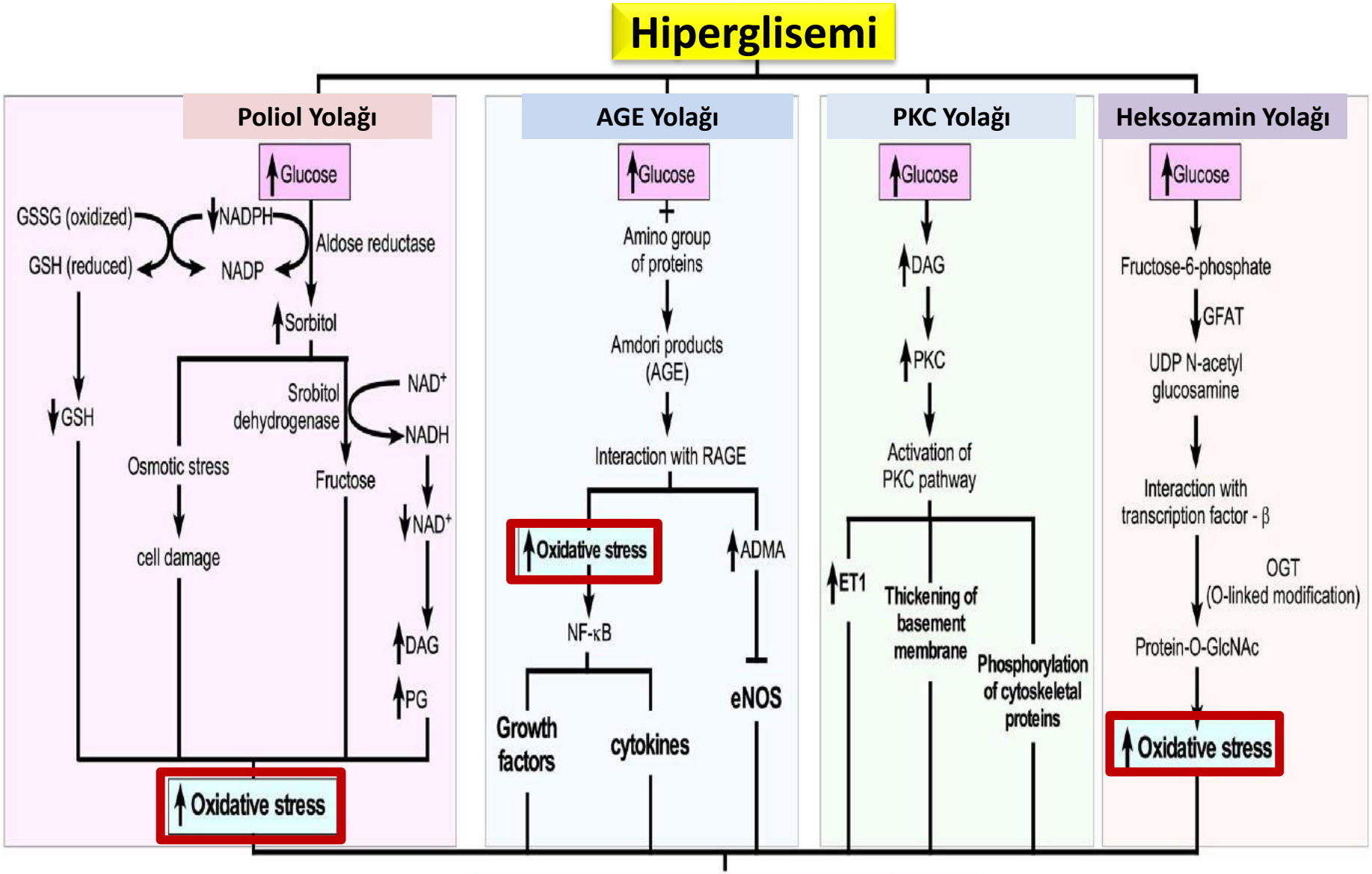







Diabetes Metab J 2012;36:190-198

# Diyabetik Komplikasyonların Patogenezi






S. Paul et al. / Journal of Diabetes and Its Complications 34 (2020) 107613

# Ekzojen AGEler

- Endojen oluşan AGEler dışında çeşitli gıdalar, ticari içecekler ve tütünde de AGEler mevcuttur
- Diyetteki AGEler endojen AGE havuzuna katkıda bulunur:
  - Oksidatif stres,
  - İnsülin direnci,
  - Aberan immün yanıt,
  - Kronik inflamasyon
- Gen ekspresyonunu modüle ederler :
  - Direkt hücresel protein glikasyonu,
  - Pro-oksidan, pro-inflamatuvar ve diğer sinyal  yolaklarının indüksiyonu,
  - ER stresi
  - Epigenetik modifikasyonlar

*Current Nutrition Reports* **volume 6**, pages 1–8 (2017)

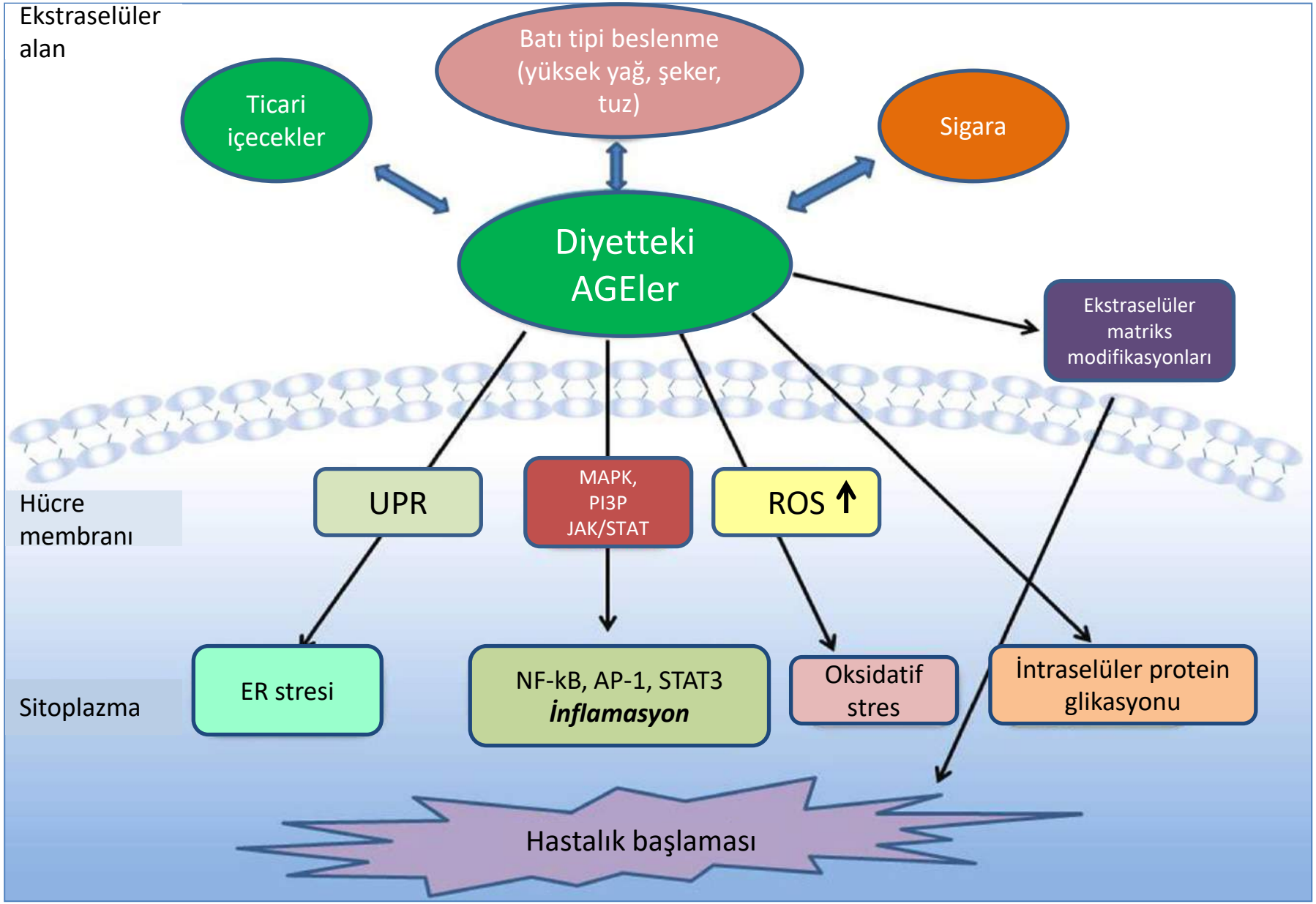
# Ekzojen AGEler

- AGEler gıdanın işlenmesinin yan ürünleridir
- AGE oluşum oranını belirleyen parametreler;  besinlerin içeriği, ısı, nem ve ısıl işlemin süresi
- cipsler,
- krakerler,
- kurabiyeler,
- kahvaltılık gevrekler,
- et-et ürünleri…



*European Journal of Nutrition* **volume 59**, pages 2893–2904 (2020)

# Ekzojen AGEler





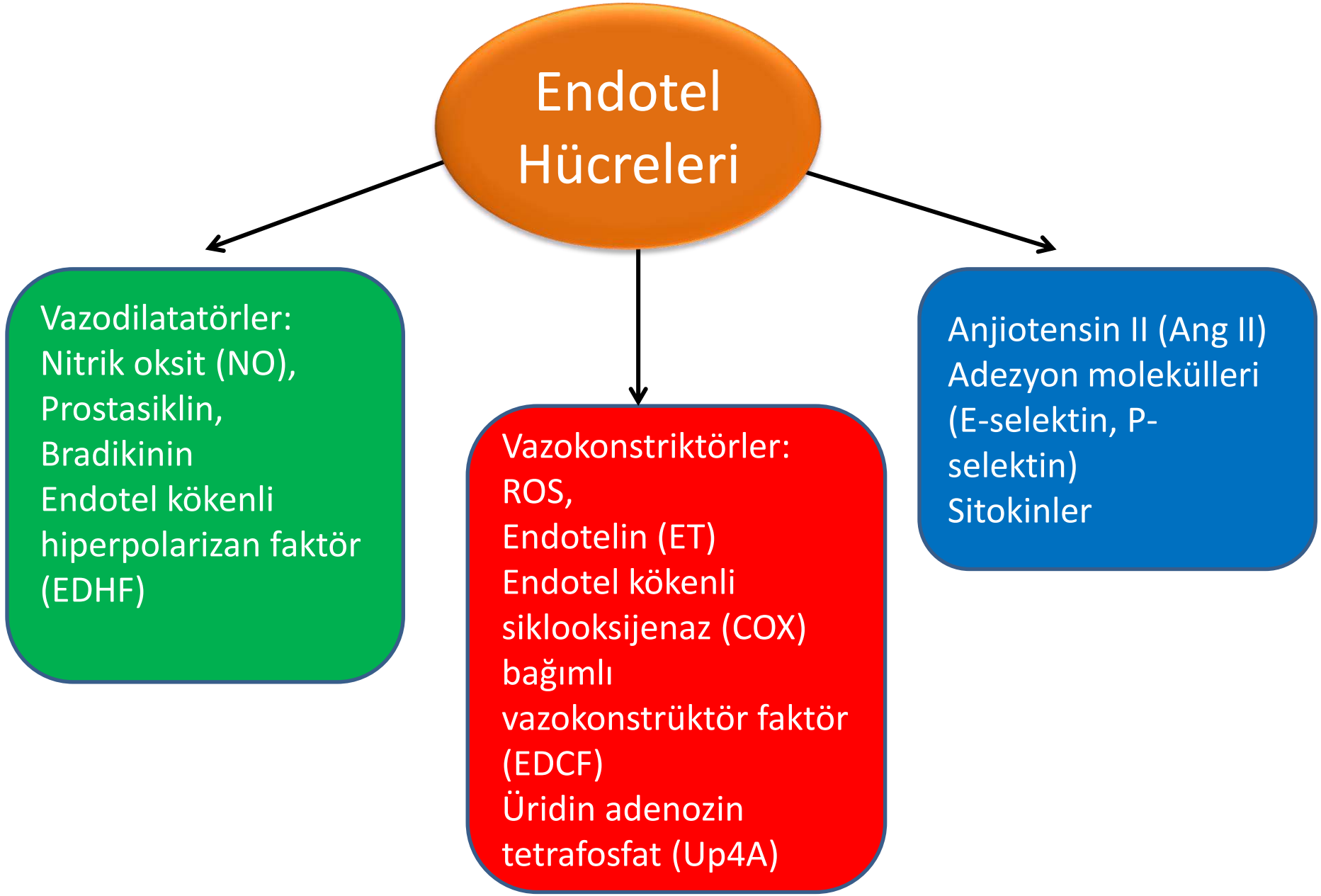

Curr Nutr Rep (2017) 6:1–8

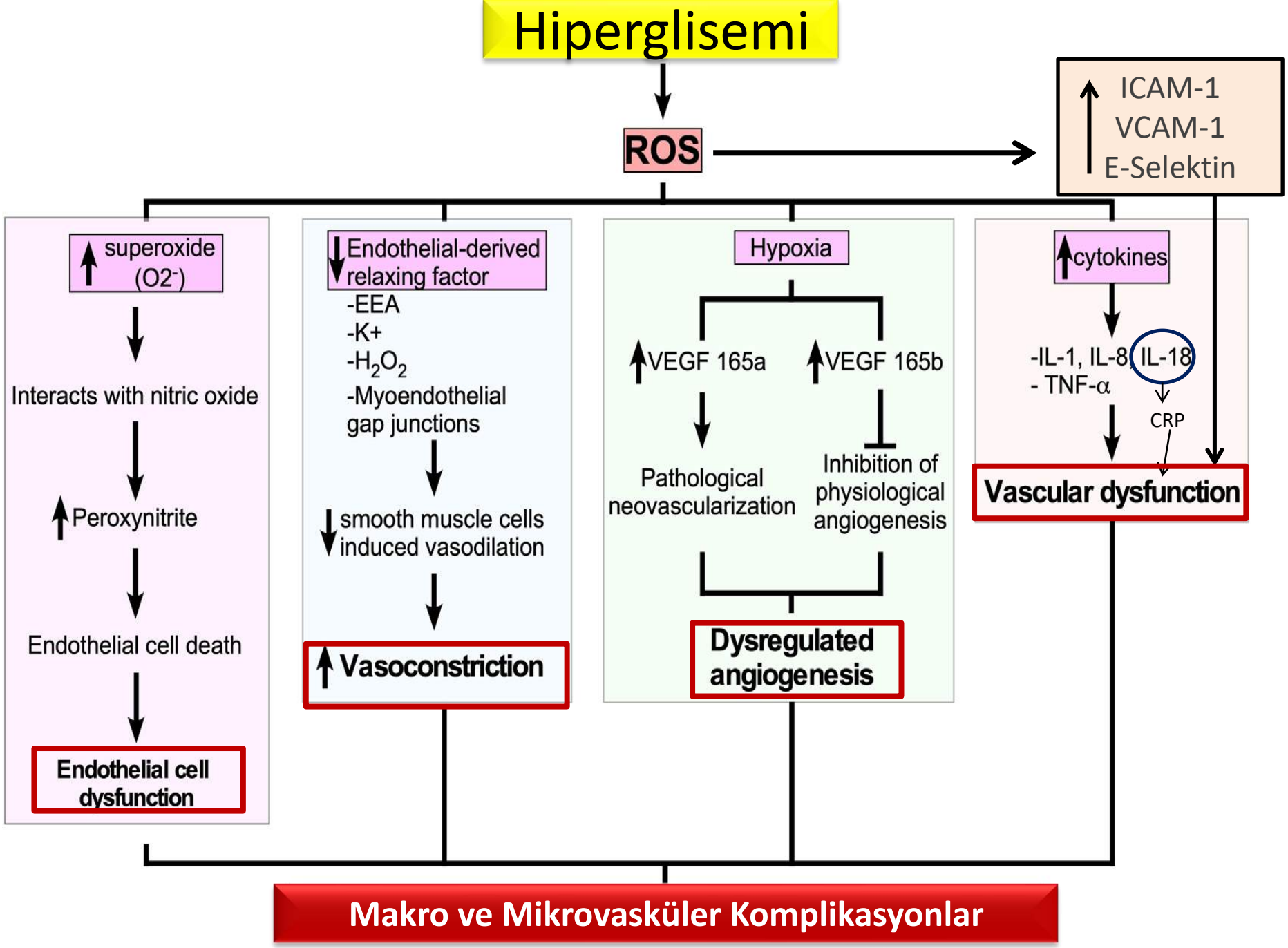
# Büyüme faktörleri ve sitokinler

- Vasküler endotelyal hücreler fizyolojik ve patolojik koşullarda çeşitli gevşetici ve kontrakte edici faktörler salgılayarak bazal vasküler tonu ve vasküler reaktiviteyi regüle etmede önemli rol oynar



S. Paul et al. / Journal of Diabetes and Its Complications 34 (2020) 107613


Endotel Hücreleri
Vazodilatatörler: Nitrik oksit (NO), Prostasiklin, Bradikinin Endotel kökenli hiperpolarizan faktör (EDHF)
Vazokonstriktörler: ROS, Endotelin (ET) Endotel kökenli siklooksijenaz (COX) bağımlı vazokonstrüktör faktör (EDCF) Üridin adenozin tetrafosfat (Up4A)
Anjiotensin II (Ang II) Adezyon molekülleri (E-selektin, P-selektin) Sitokinler






S. Paul et al. / Journal of Diabetes and Its Complications 34 (2020) 107613

# Anjiogenez Bozuklukları

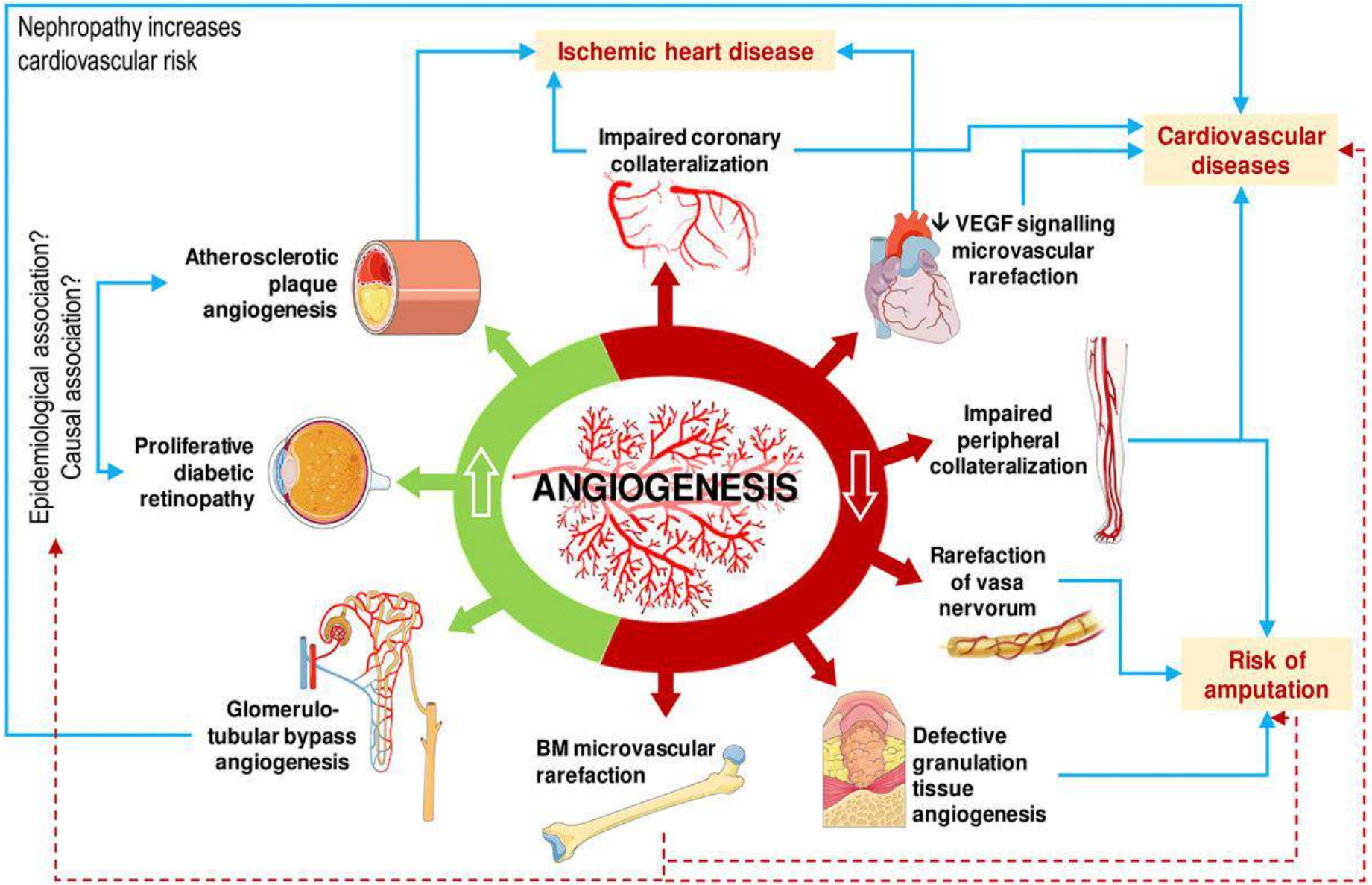
- Diabetes mellitus artmış ya da azalmış anjiogenezle ilişkilidir

- Bu iki durum da kronik diyabetik komplikasyonların gelişiminden sorumlu olmaktadır



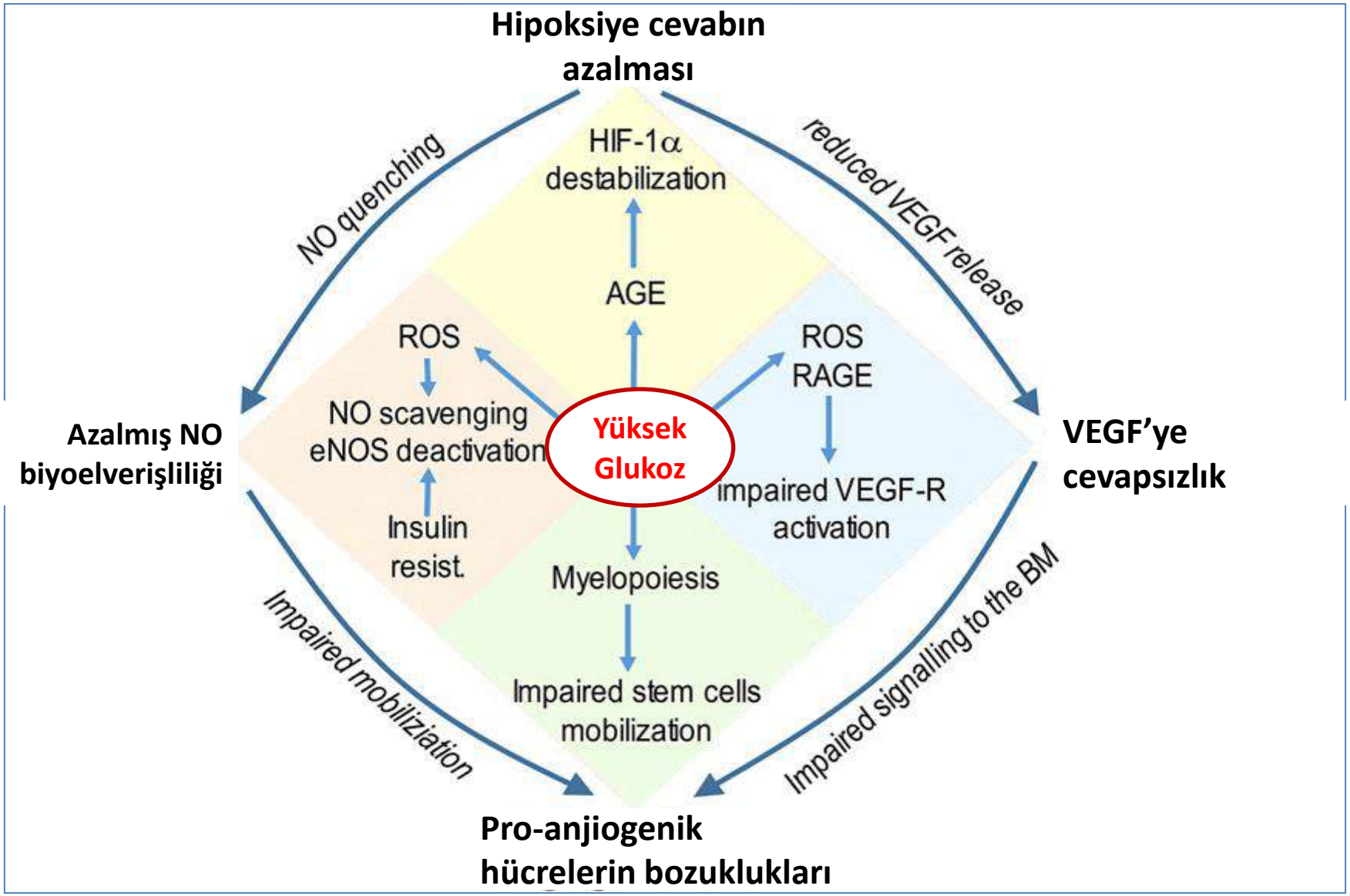
J Clin Endocrinol Metab 104: 5431–5444, 2019

# Anjiogenez Bozuklukları




J Clin Endocrinol Metab 104: 5431–5444, 2019

# Anjiogenez Bozuklukları






J Clin Endocrinol Metab 104: 5431–5444, 2019

# Diyabetik Vasküler Komplikasyonlarda Adipoz doku-İmmün Sistem Etkileşimi

**İnflamasyon İlişkili**

- C-reaktif protein (CRP)
- Pentraksin 3 (PTX3)
- Tümör nekrozis faktör-α
- IL-1, IL-18, IL-6
- Monosit kemoatraktan protein-1 (MCP-1)
- The high mobility group box-1 (HMGB-1)

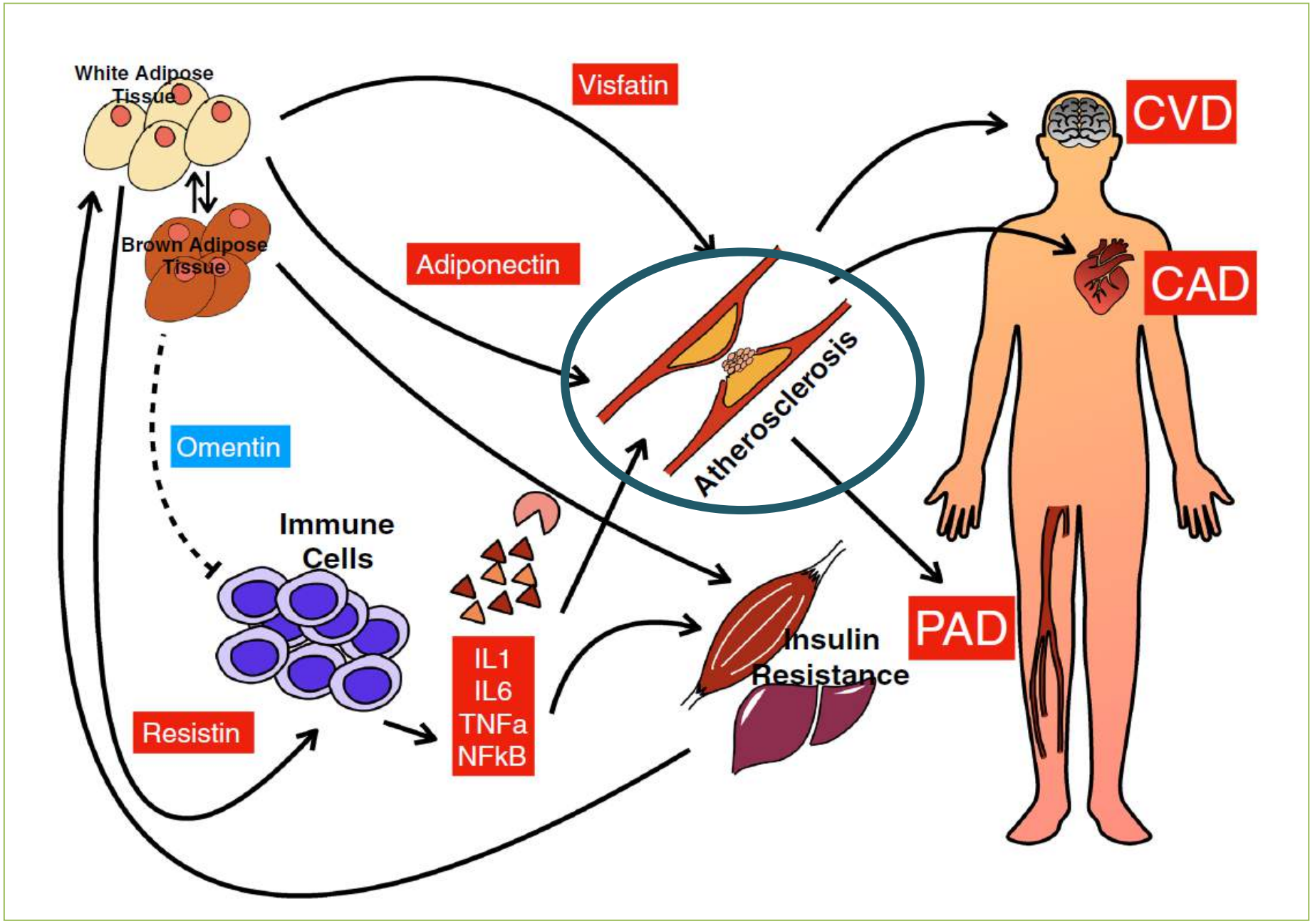
**Adipoz Doku İlişkili**

- Adiponektin
- Omentin
- Resistin
- Visfatin

**Diğer**

- Sortilin
- Osteoprotegerin
- Klotho/FGF23
- Eksozomlar (miRNA)

Internal and Emergency Medicine (2020) 15:381–393




Internal and Emergency Medicine (2020) 15:381–393

# Diabetes Mellitus
# Genetik Farklılıklar

- Tip 2 Diyabet heterojen bir hastalıktır
- Genetik çalışmalarda bu heterojenite daha net gösterilmeye başlanmıştır
- Klinik ve genetik biyobelirteçlerin kullanıldığı kümeleme çalışmalarında T2DM subtipleri belirlenmiştir;
  - Çeşitli insülin direnci kümelerinde artmış renal fonksiyon azalma riski
  - Klinik ciddi insülin eksikliği olan kümelerde artmış diyabetik retinopati riski
  - Azalmış β- hücre fonksiyonu ve lipodistrofi-benzeri yağ dağılımı genetik kümelerinde artmış KAH riski bildirilmiş



PLoS Med. 15, e1002654 (2018), Lancet Diabetes Endocrinol. 6, 361–369 (2018).

# Diabetes Mellitus
# Genetik Farklılıklar

- Diyabet ve komplikasyonları hem major çevresel hem de genetik komponentler ile karmaşık, multifaktöryel durumlardır
- Diyabetik komplikasyonlarda yatkınlık farklılıkları olduğu uzun yıllardır bilinmektedir
- Plazma glukoz düzeylerinde, klinik özelliklerde ve tedavilerde benzerliğe rağmen diyabetik komplikasyon gelişimi farklılıklar göstermektedir
- Aile çalışmalarında komplikasyonu olan diyabetli bireylerle komplikasyonu olmayan diyabetli bireylerde net ve belirgin farklılıklar olduğu gösterilmiştir

Nat Rev Nephrol. 2020 Jul;16(7):377-390

Table 1 | **Genome-wide association studies loci reaching genome-wide significance for diabetes complications**

| SNP | Reported gene | *P* value | Reported phenotype (total *n* or cases vs controls) | Diabetes population | Refs |
|---|---|---|---|---|---|
| NEFROPATİ | | | | | |
| rs7583877 | *AFF3* | $1.2 \times 10^{-8}$ | ESKD (1,399 vs 5,253) | T1D | 66 |
| rs12437854 | 15q26 intergenic — *RGMA, MCTP2* | $2.0 \times 10^{-9}$ | ESKD (1,399 vs 5,253) | T1D | 66 |
| rs4972593[a] | 2q31 intergenic — *SP3, CDCA7* | $3.9 \times 10^{-8}$ | ESKD (688 vs 2,009) | T1D | 67 |
| rs1564939[b] | *GLRA3* | $4.3 \times 10^{-10}$ | 24h urinary albumin excretion rate (3,612) | T1D | 54,74 |
| rs12523822[c] | 6q25 intergenic — *SCAF8, CNKSR3* | $1.3 \times 10^{-8}$ | DKD (5,226 vs 8,510) | T1D + T2D (not all controls had diabetes) | 75 |
| rs13329952[d] | *UMOD* | $2.5 \times 10^{-8}$ | eGFR (16,477) | T1D + T2D | 83 |
| rs56094641[e] | *FTO* | $7.7 \times 10^{-10}$ | Diabetic nephropathy (4,022 vs 6,890) | T2D | 71 |
| rs9942471 | *GABRR1* | $4.5 \times 10^{-8}$ | Microalbuminuria (1,989 vs 2,238) | T2D | 55 |
| rs72858591[f] | *RND3/RBM43* | $4.5 \times 10^{-8}$ | ESKD (3,432 vs 6,977) | T2D cases vs non-diabetic controls | 76 |
| rs58627064[f] | *SLITRK3* | $6.8 \times 10^{-10}$ | ESKD (3,432 vs 6,977) | T2D cases vs non-diabetic controls | 76 |
| rs142563193[f] | *ENPP7* | $1.2 \times 10^{-8}$ | ESKD (3,432 vs 6,977) | T2D cases vs non-diabetic controls | 76 |
| rs142671759[f] | *ENPP7* | $5.5 \times 10^{-9}$ | ESKD (3,432 vs 6,977) | T2D cases vs non-diabetic controls | 76 |
| rs4807299[f] | *GNG7* | $3.2 \times 10^{-8}$ | ESKD (3,432 vs 6,977) | T2D cases vs non-diabetic controls | 76 |
| rs9622363[f] | *APOL1* | $1.4 \times 10^{-10}$ | ESKD (3,432 vs 6,977) | T2D cases vs non-diabetic controls | 76 |
| rs55703767 | *COL4A3* | $5.3 \times 10^{-12}$ | Diabetic nephropathy (4,948 vs 12,076), all vs. control (7,247/12,053), CKD + diabetic nephropathy (2,897/11,766), macroalbuminuria (2,751/12,124) | T1D | 68 |



Nat Rev Nephrol. 2020 Jul;16(7):377-390

Table 1 | **Genome-wide association studies loci reaching genome-wide significance for diabetes complications**

NEFROPATİ

| SNP | Reported gene | *P* value | Reported phenotype (total *n* or cases vs controls) | Diabetes population | Refs |
|---|---|---|---|---|---|
| rs12615970 | *COLEC11* | $9.4\times10^{-9}$ | CKD (4,266 vs 14,838) | T1D | 68 |
| rs142823282 | *TAMM41* | $1.1\times10^{-11}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs145681168 | *HAND2-AS1* | $5.4\times10^{-9}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs118124843 | *DDR1* | $3.4\times10^{-8}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs77273076 | *MBLAC1* | $1.0\times10^{-8}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs551191707 | *PRNCR1* | $4.4\times10^{-8}$ | ESKD vs macroalbuminuria (2,187 vs 2,725) | T1D | 68 |
| rs144434404 | *BMP7* | $4.7\times10^{-9}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs115061173 | *LINC01266* | $4.1\times10^{-8}$ | ESKD vs control (2,187 vs 12,101) | T1D | 68 |
| rs116216059 | *STAC* | $1.4\times10^{-8}$ | ESKD vs non-ESKD (2,18 vs 17,219) | T1D | 68 |
| rs191449639 | *MUC7* | $1.3\times10^{-8}$ | Diabetic neuropathy (4,948 vs 12,076) | T1D | 68 |
| rs149641852 | *SNCAIP* | $1.4\times10^{-8}$ | CKD extreme (2,235 vs 14,993) | T1D | 68 |
| rs183937294 | *PLEKHA7* | $1.7\times10^{-8}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs61983410 | 14q12 intergenic — *STXBP6, NOVA1* | $3.1\times10^{-8}$ | Microalbuminuria (2,447 vs 12,113) | T1D | 68 |
| rs113554206 | *PAPLN* | $8.5\times10^{-9}$ | Macroalbuminuria (2,751 vs 12,124) | T1D | 68 |
| rs185299109 | chr18p11intergenic — *LINC00470, METTL4* | $1.3\times10^{-8}$ | CKD (4,266 vs 14,838) | T1D | 68 |
| rs149131600[g] | *HPN* | $P_{diabetes}=3.5\times10^{-8}$ | UACR (554,659 general population, 46,939 individuals with diabetes) | Unspecified | 88 |
| rs6688849[g] | 1p33 intergenic — *FOXD2, TRABD2B* | $P_{diabetes}=4.1\times10^{-9}$ | UACR (564,135 general population, 51,215 individuals with diabetes) | Unspecified | 88 |
| rs74375025[g] | *CUBN* | $P_{diabetes}=1.1\times10^{-24}$ | UACR (558,518 general population, 50,641 individuals with diabetes) | Unspecified | 88 |
| rs790093h | *GCKR* | $P_{diabetes}=1.5\times10^{-13}$ | UACR (563,291 general population, 51,515 individuals with diabetes) | Unspecified | 88 |

Nat Rev Nephrol. 2020 Jul;16(7):377-390

Table 1 (cont.) | **Genome-wide association studies loci reaching genome-wide significance for diabetes complications**

| SNP | Reported gene | *P* value | Reported phenotype (total *n* or cases vs controls) | Diabetes population | Refs |
|---|---|---|---|---|---|
| **NEFROPATİ** | | | | | |
| rs59825600[h] | *KAZN* | $P_{diabetes} = 3.6 \times 10^{-8}$ | UACR (549,562 general population, 40,668 individuals with diabetes) | Unspecified | 88 |
| rs6706313[h] | *MIR4432HG-BCL11A* | $P_{diabetes} = 2.8 \times 10^{-8}$ | UACR (564,068 general population, 51,162 individuals with diabetes) | Unspecified | 88 |
| rs17137004[h] | *FOXP2* | $P_{diabetes} = 2.7 \times 10^{-8}$ | UACR (563,167 general population, 51,294 individuals with diabetes) | Unspecified | 88 |
| rs4258701[h] | *CDH2* | $P_{diabetes} = 1.1 \times 10^{-8}$ | UACR (564,246 general population, 51,328 individuals with diabetes) | Unspecified | 88 |
| **RETİNOPATİ** | | | | | |
| rs9896052[c] | *GRB2* | $4.2 \times 10^{-8}$ | Sight-threatening diabetic retinopathy (1,175 vs 1,319) | T1D + T2D | 105 |
| **NÖROPATİ** | | | | | |
| rs80028505[i] | *MAPK14* | $2.5 \times 10^{-8}$ | Foot ulcers in diabetic neuropathy cases vs no history of foot ulcers in diabetic neuropathy controls (699 vs 2,695) | T1D + T2D | 123 |
| rs13417783 | *SCN2A* | $7.9 \times 10^{-12}$ | Diabetic peripheral neuropathy (5,175 vs 942) | T2D | 126 |
| **KV HASTALIK** | | | | | |
| rs10911021 | *GLUL* | $2.0 \times 10^{-8}$ | CHD (1,517 vs 2,671) | T2D | 148 |
| rs9299870 | *MGMT* | $9.8 \times 10^{-9}$ | Cardiovascular mortality (2,667) | T2D under intensive glycaemic control | 151 |
| rs57922 | 5q13 intergenic – *ARHGEF28, LINC01335* | $2.0 \times 10^{-8}$ | Cardiovascular mortality (2,667) | T2D under intensive glycaemic control | 151 |



Nat Rev Nephrol. 2020 Jul;16(7):377-390

# Diabetes Mellitus
# Genetik Farklılıklar

- Genom-wide analizler ile her geçen yıl diyabet gelişimi ve komplikasyonları ile ilişkili olduğu saptanan gen sayısı giderek artmaktadır
- Ancak gen tespit edilmesi  hastalık riskini net olarak ön gördürememektedir
- Başka faktörler de önemli…

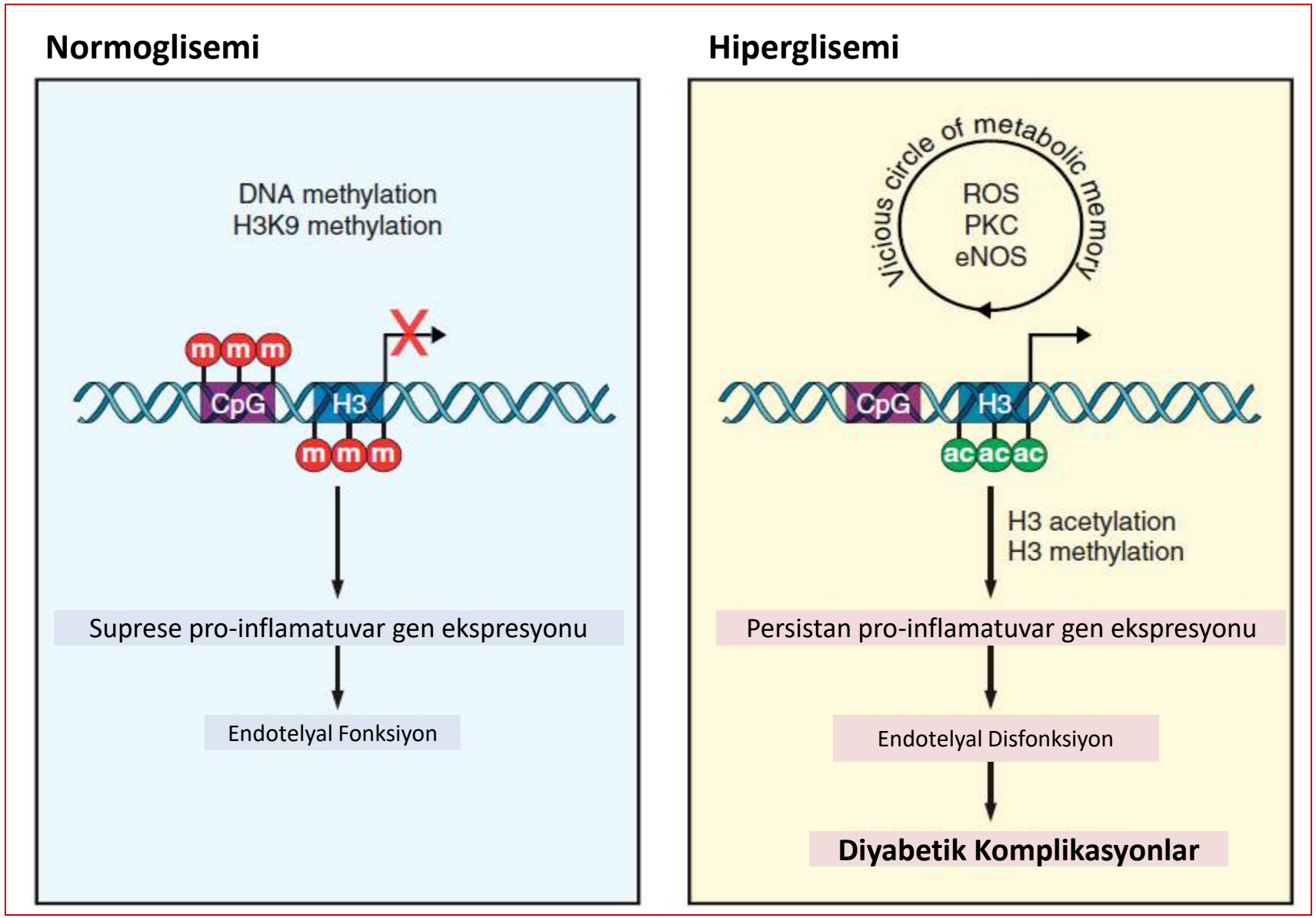
Diabetes Obes Metab 2016;18(9):855–67.

# Epigenetik değişiklikler

- Epigenetik gen yapısı ve içeriğinde değişiklik olmadan gen ekspresyonu ve fenotipinin düzenlenmesidir
  - DNA metilasyonu, histon posttranslasyonel modifikasyonu (metilasyon, asetilasyon)
  - Kodlama yapmayan (non-coding) RNAlar
- Epigenetik değişiklikler yalnızca vücudun çevresel değişikliklere hızlı cevap vermesini sağlayan spesifik genlerin ekspresyonunu düzenlemez aynı zamanda vücudun bu bu koşulları hatırlamasını da (örn. metabolik hafıza) mümkün kılar
- Epigenetik diyabet, ateroskleroz, hipertansiyonda oldukça yoğun bir şekilde çalışılmıştır
- Epigenetik değişikliğin erken engellenmesi veya geriye döndürülmesi diyabete bağlı ölümleri yavaşlatabilecektir

S. Paul et al. / Journal of Diabetes and Its Complications 34 (2020) 107613,
Journal of Molecular Endocrinology (2019) 63, R103–R115 , Heart, Lung and Circulation (2021) 30, 186–196

# Yüksek Glukoz Düzeyleri ile Etkilenen Epigenetik Yolaklar



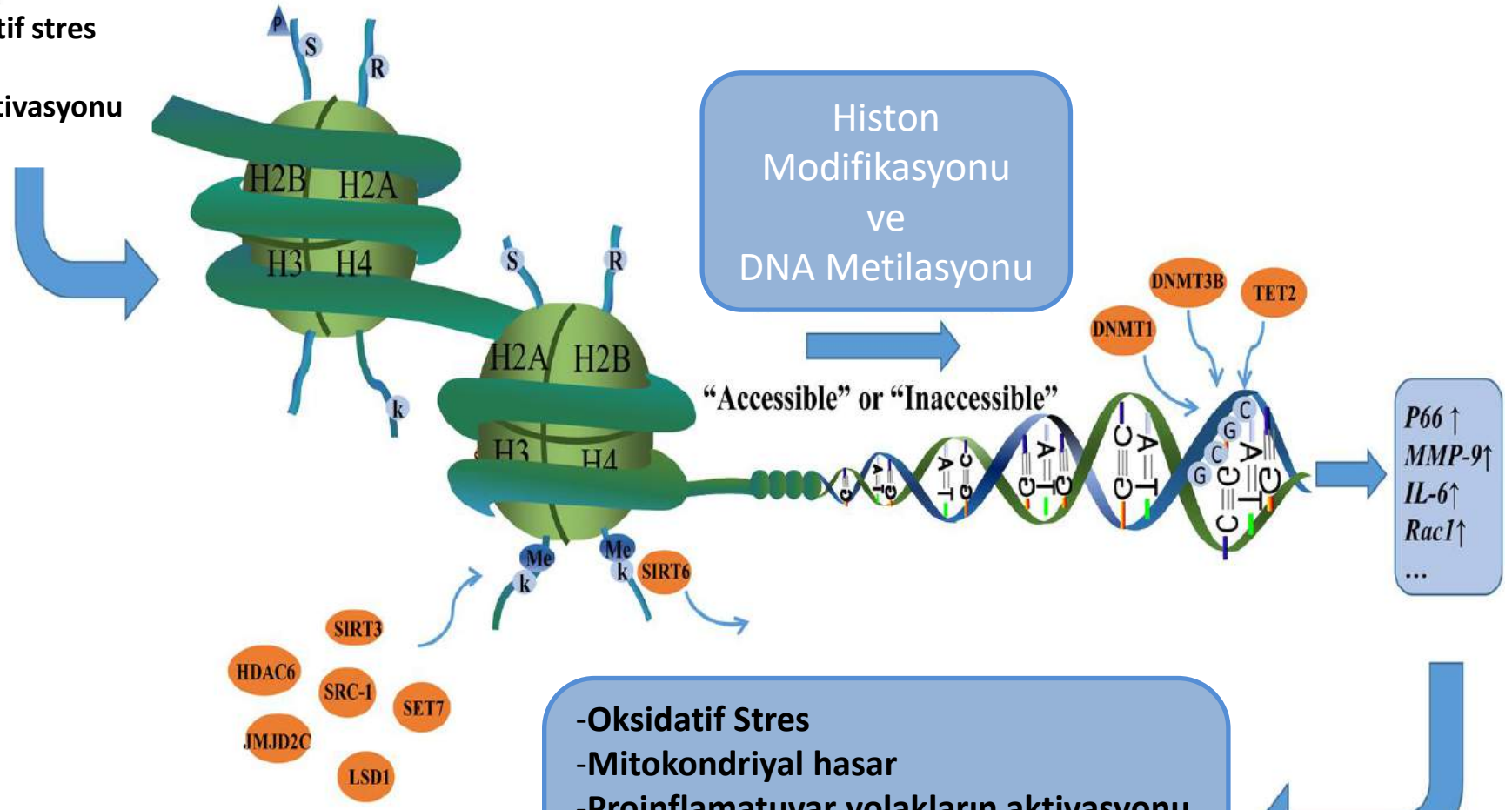



*Physiol Rev 93: 137–188, 2013*

Uyarıcı

Yüksek Glukoz

**Oksidatif stres**
**AGEler**
**PKC aktivasyonu**
**vb**

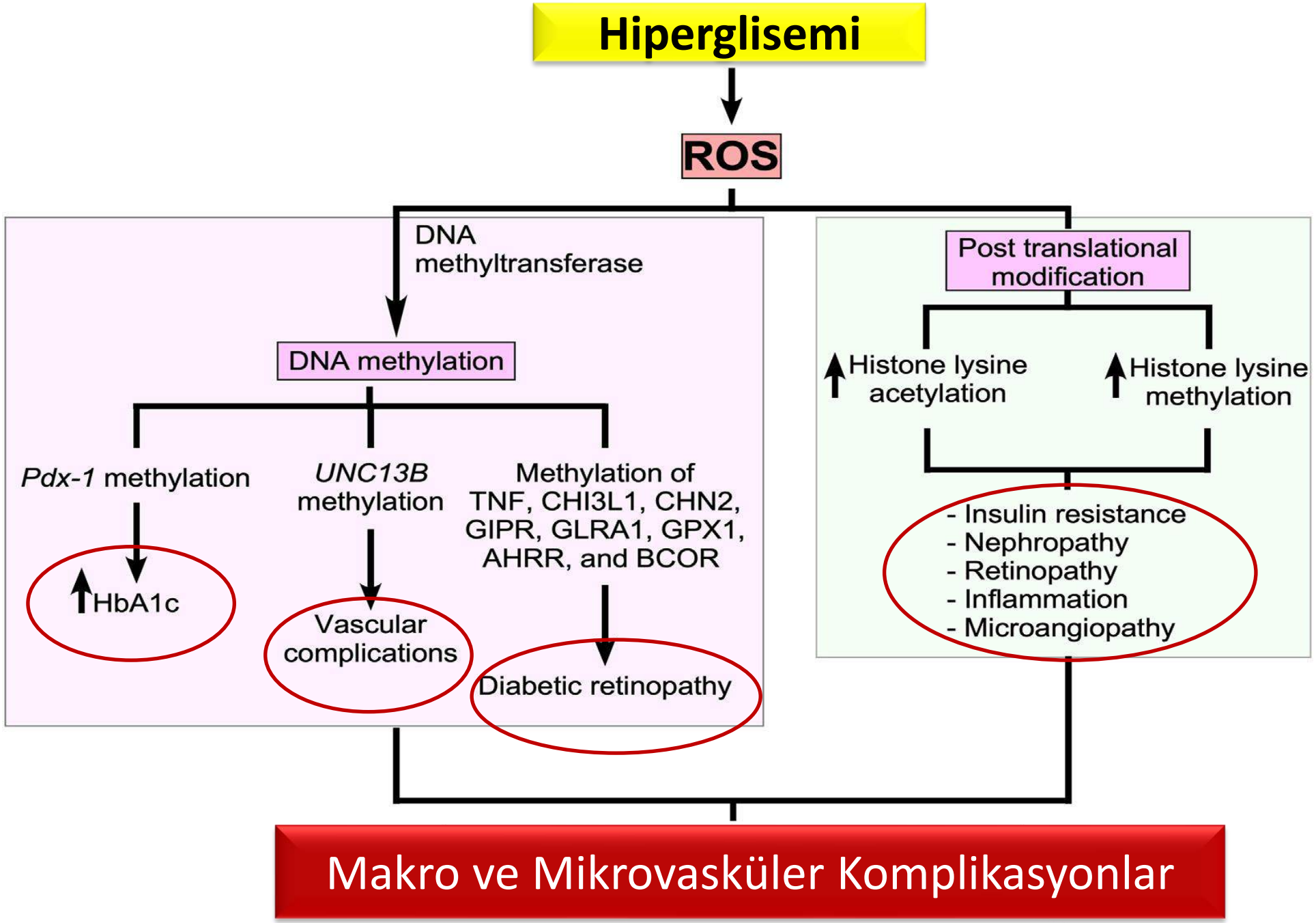



Histon Modifikasyonu ve DNA Metilasyonu

-**Oksidatif Stres**
-**Mitokondriyal hasar**
-**Proinflamatuvar yolakların aktivasyonu**
-**Hücre apopitozu**
-**"Metabolik hafıza"**
-**.....**



*Journal of* Molecular *Endocrinology (2019)* ***63, R103–R115***






S. Paul et al. / Journal of Diabetes and Its Complications 34 (2020) 107613

# Aterokleroz-DNA metilasyonu-Histon modifikasyonu

**Table 1** The role of DNA methylation and histone modification in the pathogenesis of atherosclerosis.

| Epigenetics | Target | Status | Effect |
|---|---|---|---|
| DNA methylation | SOD2 | hypermethylation | SMC proliferation↑, HIF-1a↑ |
| | FGF2 | hypermethylation | cytotoxic effect↑ |
| | ABCA1 | hypermethylation | foam cells↑ |
| | VPO1 | hypomethylation | SMC calcification↑, endothelial cell necrosis↑ |
| | COX-2 | hypomethylation | matrix metalloproteinase↑ |
| | KLF4 | hypermethylation | macrophage M1↑, inflammation↑ |
| | FABP4 | hypomethylation | lipid deposition↑ |
| | ER-α | hypermethylation | oestrogen receptor↓ |
| | SMAD7 | hypermethylation | inflammation↑ |
| Histone modification | | | |
| P300 | OGG1 | acetylation | oxidative DNA repair↑ |
| | STAT1 | acetylation | foam cell↑ |
| HDAC6 | CSEγ | deacetylation | H2S (endogenous vascular function regulator) ↓ |
| HDAC9 | Foxp3 | deacetylation | HMGB1, IL-6, S100A8↑, THBS1↓ inflammation↑ |
| | LRP-1 | deacetylation | inflammation↑ |
| EZH2 | IGFBP5 | methylation | endothelial homeostasis↑, inflammation↓ |
| Kdm6b | TNF/MMP/IL | demethylation | inflammation↑, angiogenesis↓ |



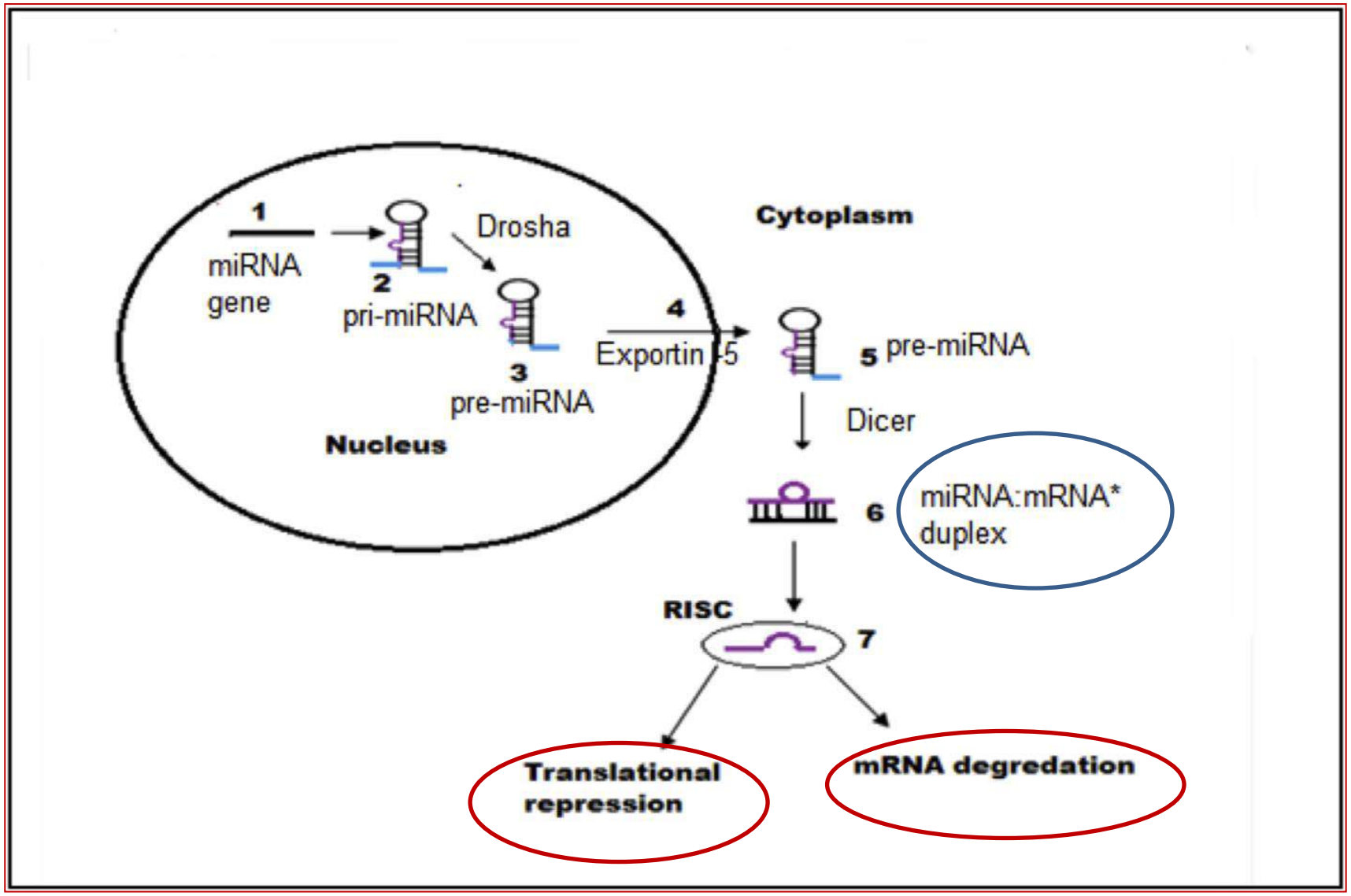
Heart, Lung and Circulation (2021) 30, 186–196

# Kodlama Yapmayan RNAlar'da (ncRNAlar) Anormallik

- Diyabetik vasküler komplikasyonlarda transkripsiyonel düzenleme yaparlar
  - Mikro RNAlar (miRNAlar),
  - Uzun kodlama yapmayan RNAlar (lncRNAlar),
  - Sirküler RNAlar (circ RNAlar)
  - Enhancer RNAs (eRNAlar)
  - tRNA fragmanları (tRFlar).
- ncRNAlar epigenetik komponentler olarak kabul edilmeseler de epigenetik değişikliklerde rol oynarlar

Biochimie 139 (2017) 9e19, Pharmacological Research, (2021) doi:https://doi.org/10.1016/j.phrs.2021.105520

# MiRNA






Biochimie 139 (2017) 9e19

**Table 2**
Circulating miRNAs differentially expressed in patients with and without T2DM complications.

| miRNAs | Sample type | Expression in T2DM vs. CTR | n1 (n2) | T2DM/Complication | Method | Significant findings |
|---|---|---|---|---|---|---|
| miR-146a | PBMCs | Down*** | 20 (20) | T2DM cases without known complications | qPCR | Negative corr. with fasting glucose, $HbA_{1c}$, HOMA-IR, inflammatory signals |
| miR-146a | Plasma | Up* | 90 (90) | New T2DM cases (32% HTN) | qPCR | Positive corr. with HO-1, inverse association with HOMA-β |
| miR-326, let-7a, let-7f | Plasma exosome | miR-326 (Up) let-7a, let-7f (Down) | 18$^{\$}$ (12) | T2DM without complications | qPCR | Negative corr. of miR-326 with ADP, modification of let-7a, let-7f on glucose lowering treatment |
| miR-126 | Plasma | Down** | 30 (30) 30$^{\#}$ | T2DM cases, T2DM susceptible cases | qPCR | No significant difference between patients with medium and high fasting glucose levels |
| miR-126 | Plasma | Down* | 80 (80) | T2DM (88.8% HTN) | Microarray, qPCR | Negative corr. with glucose level |
| miR-126-3p | Plasma | Down** | 193 (136) | T2DM cases (64.2% HTN; 26.4%HC; 17.6% previous AMI) | RT-qPCR | Positive corr. with ApoA1 levels, negative corr. with fasting glucose, $HbA_{1c}$ |
| miR-126-3p, miR-21-5p | Plasma | Down* | 193 (107) | 117 with T2DM complication | RT-qPCR | miR-21: Positive correlation with BMI, fasting glucose, $HbA_{1c}$ miR-126: Negative corr. with fasting glucose, $HbA_{1c}$ |
| miR-126 | Serum | Down*** | 100 (100) 86$^{\#}$ | T2DM without or with complications (macro-vascular and DR) | qPCR | Negative corr. with fasting, pp blood glucose, $HbA_{1c}$. No association with HOMA-IR |
| let-7a-2 | Whole blood | Down | 212 (62) | 104 T2DM; 108 T2DM with DN | qRT-PCR | Association between SNP in let-7a-2 gene with the risk of DN |
| miR-146a, miR-155 | Serum | Down* Down | 56 (40) | T2DM (61% having CVD) | qPCR | Positive corr. of miR-146a to PAI-1 level; Positive corr. of miR-155 to Leptin level |
| miR-103b | Platelet | Down* | 127 (46) | 48 pre-diabetic; 43 T2DM without complication; 36 T2DM with CHD | qPCR | Differential expression of miR-103b and target SFRP4, modification in expression on anti-platelet treatment |
| miR-191, miR-200b | Plasma | Down* Up* (T2DM cases with PAD and chronic wounds) | 61 (20) | 12 T2DM with PAD; 26 T2DM with PAD and chronic wounds; 23 T2DM cases; 20 Healthy controls | qPCR | Positive corr. with C-reactive protein and cytokines |
| miR-192, miR-193b | Serum | Up** (Prediabetics) | 63 (29) | 20 New T2DM cases; 21 prediabetics (IFG); 22 prediabetics (IGT) | qPCR | miR-192 and miR-193b increased in prediabetics and not in T2DM cases, but returned to baseline after chronic exercise |



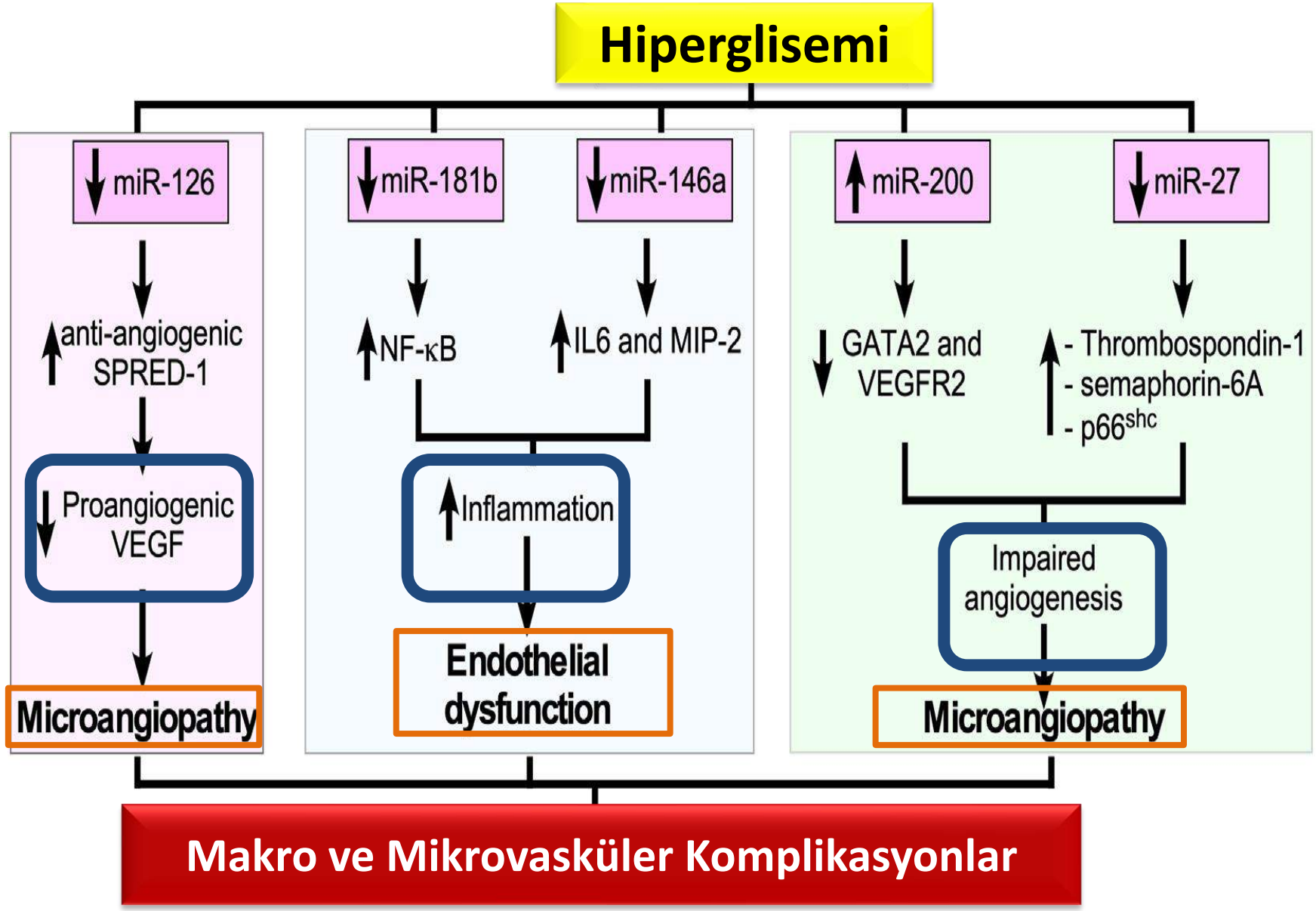
Biochimie 139 (2017) 9e19

**Table 3**
MiRNAs implicated in diabetes-associated complications and their potential mRNA targets in cell lines/animal models/human tissues.

| miRNAs | Level of expression | Model | mRNA target |
|---|---|---|---|
| **Diabetic retinopathy** | | | |
| miR-146a | Down | HUVECs, db/db male mice (retinal tissues) | Fibronectin |
| miR-200b | Down | HUVECs, retina of diabetic rats | VEGF |
| miR-29b | Up | STZ-rat | RAX |
| miR-195 | Up | HRECs | SIRT1 |
| miR-486 | Up | MIO-M1 (Muller cell line), STZ mice | p53 |
| **Diabetic nephropathy** | | | |
| miR-192 | Up | STZ-mice, db/db mice, MCs, Human conditionally immortalized podocytes, NRK-52E | ZEB1/2 |
| miR-377 | Up | Human MCs, Mouse MCs | Pak1, Sod1/2 |
| miR-21 | Up | Human MCs, OVE26 mice | PTEN |
| miR-146a | Up | HRGECs, Type-1 and Type-2 rats, human kidney biopsies | – |
| miR-155 | Up | HRGECs, Type-1 and Type-2 rats, human kidney biopsies | – |
| miR-25 | Down | STZ-rat, MCs | NOX-4 |
| miR-215 | Down | Human conditionally immortalized podocytes, NRK-52E, MCs | ZEB2 |
| miR-216a | Up | STZ mice, db/db mice, MCs | Ybx1 |
| miR-29/a/b/c | Down | Human conditionally immortalized podocytes, NRK-52E | Col1, Col4 |
| miR-135a | Up | Kidney tissues, HMC | TRPC1 |
| miR-93 | Up | STZ mice, db/db mice, ECs, podocytes | VEGF |
| **Diabetic neuropathy** | | | |
| miR-184-5p | – | STZ (DNP) mice | – |
| miR-190a-5p | | | |
| miR-182 | Up | Diabetic mice | NOX-4 |
| miR-146a | Up | Diabetic rats | – |
| miR-29b | Down | STZ-diabetic rats | Smad3 |
| **Diabetic cardiovascular complications** | | | |
| miR-16 | Down | THP-1 monocytes | Cox-2 |
| miR-133 | Down | Cardiac hypertrophy | Rho-A, Cdc42 |
| miR-223 | Up | Cardiomyocytes | GLUT-4 |
| miR-492 | Down | HUVECs, ApoE KO mice (atherosclerosis) | Resistin |
| miR-320 | Up | MMVECs, GK T2DM rats | IGF-1 |
| miR-503 | Up | STZ mice, HUVEC, HMVEC | Ccne1,Cdc25A |
| miR-373 | Down | STZ mice, cardiomyocytes | Mef2C |
| miR-1 | Up | STZ mice, cardiomyocytes | Pim-1 |
| miR-504 | Up | VSMC from db/db mice | Grb10, Egr2 |



Biochimie 139 (2017) 9e19






S. Paul et al. / Journal of Diabetes and Its Complications 34 (2020) 107613

# Ateroskleroz patogenezinde non-coding RNA'lar

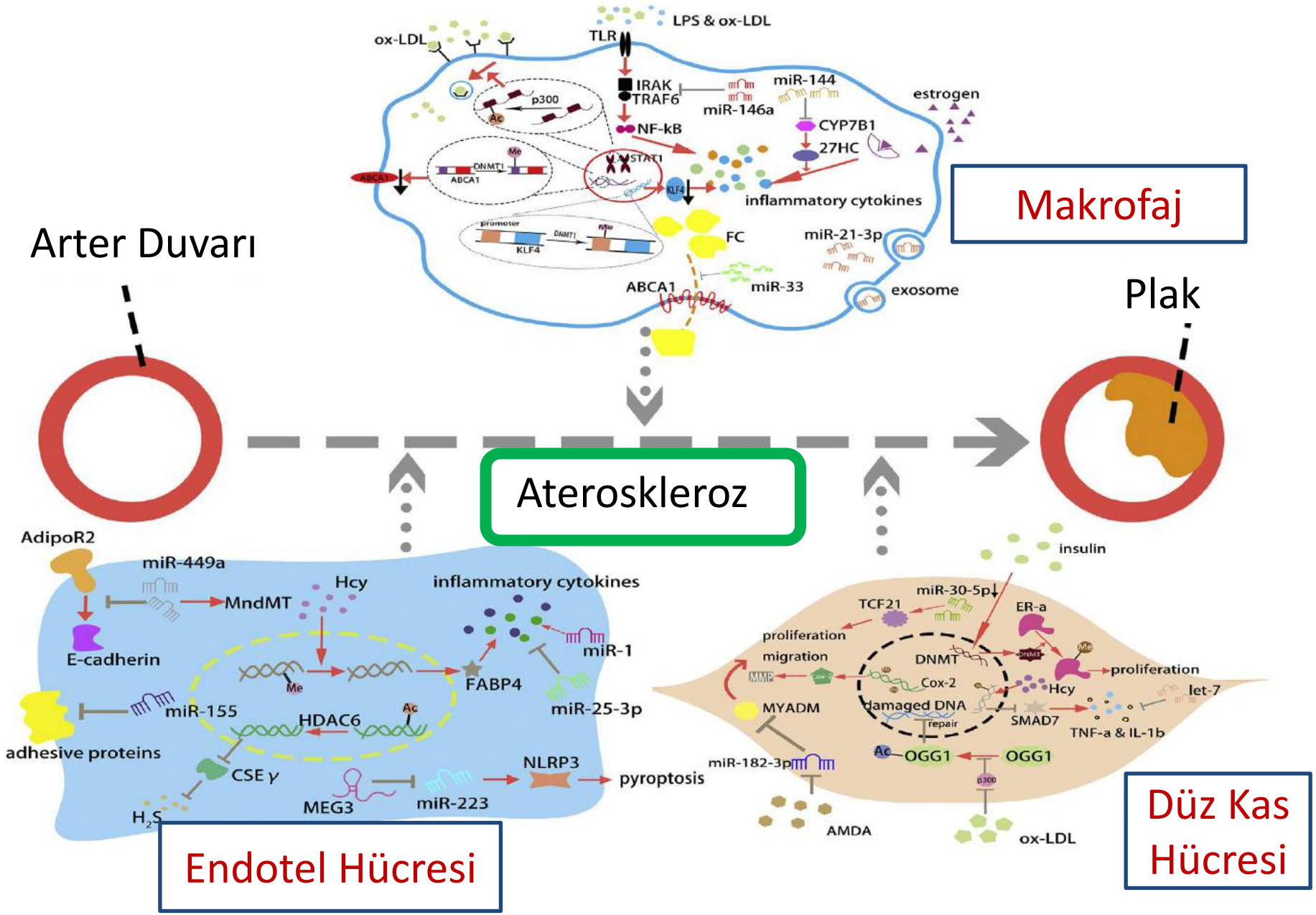
Table 2 The role of non-coding RNA in the pathogenesis of atherosclerosis.

| Epigenetics | Status | Target | Effect |
|---|---|---|---|
| Non-coding RNA | | | |
| miR-144 | up-regulation | CYP7B1 | hyperlipidaemia, inflammation↑ |
| miR-449a | up-regulation | AdipoR2, E-cadherin | AdipoR2↓, E-cadherin↓, endomesenchymal transformation↑ |
| let-7 | down-regulation | IL/TNF | inflammation↑ |
| miR-1 | up-regulation | KLF4, NF-κB | KLF4↓, NF-κB↑, inflammation↑ |
| miR-146a | down-regulation | - | monocyte and macrophage↑, inflammation↑ |
| miR-25-3p | up-regulation | Adam10/IL | inflammation↓, lipid deposition↓ |
| miR-30-5p | down-regulation | TCF21 | TCF21↑, SMC proliferation and migration↑ |
| miR-182-3p | down-regulation | MYADM | SMC proliferation and migration↑ |
| miR-155 | up-regulation | TJ protein, gap junctions | endothelial cell dysfunction |
| miR-223 | down-regulation | NLRP3 | cell pyroptosis↑ |
| miR-33 | up-regulation | - | lipid deposition↑ |
| miR-21-3p | up-regulation | PTEN | SMC proliferation and migration↑ |



Heart, Lung and Circulation (2021) 30, 186–196

# Aterosklerozda epigenetik



# LncRNAlar

- LncRNAlar hücre diferansiyasyonu ve kendi-yenilenmesinde rol alır
- Ayrıca diyabetik retinopati gibi patolojik anjiogenezde de rolleri vardır
- VEGF veya FGF2 ekspresyonunu artırarak anjiogenezi uyarmak için makrofaj-ilişkili yolakları veya miRNAları hedef alırlar
- Bazı lncRNAlar makrofaj infiltrasyonu, diferansiyasyonu ve polarizasyonu ile ilişkilidirler

# LncRNAlar

- Endotel hücreleri, vasküler düz kas hücreleri ve perisitler vasküler hastalıkta rol oynayan LncRNA eksprese ederler
- lncRNAlar endotel hücrelerde apopitozu inhibe ederler, VSMC'de büyümeyi artırıcı etkileri vardır
- Diyabet ilişkili nefropati, retinopati, hipertansiyon ve aterosklerozda rol oynarlar
- Yüksek glukoz şartlarında vasküler hücrelerde lncRNA sayılarının düzenlenmesinde bozukluk olmaktadır

Vascul Pharmacol. 2019 March ; 114: 139–144

# LncRNAs in Diabetic vascular complications

| LncRNA | Biological Function | Mechanism |
|---|---|---|
| *ANRIL* | Atherosclerosis, Hypertension, Diabetes, Retinopathy, Nephropathy | Regulation of *CDKN2A/B* |
| *MIAT* | Retinal microvascular dysfunction | Sponging miR-150-5p |
| *MALAT1* | Inflammation in diabetes | Upregulation of *IL-6* and *TNFα* |
| *MEG3* | Microvascular dysfunction | PI3K/Akt signal activation |
| *Lnc-Ang362* | Ang II induced VSMC proliferation | Expression of miR-221 and miR-222 |
| *E330013P06* | Macrophage inflammation in Diabetes | Upregulation of *IL-6 and Ptgs2* |
| *Lethe* | Regulation of macrophage ROS production | Modulating *Nox2* gene expression |
| *Pvt1* | ECM accumulation & diabetic nephropathy | Regulation of *Fn1* and *Col4a1* expression |
| *Lnc-MGC* | Renal fibrosis and early diabetic nephropathy | Regulation of *EDEM3* expression |
| *Tug1* | Mitochondrial energetics of podocytes in diabetes | Interaction with PGC-1α |

Vascul Pharmacol. 2019 March ; 114: 139–144

# circRNAlar

- Biyolojik fonksiyonları tam bilinmemekle birlikte miRNAların hedef gen ekspresyonunu etkiledikleri gösterilmiştir
- RNA-bağlayan proteinlerle etkileşerek post-transkripsiyonel gen ekspresyonunu da düzenledikleri gösterilmiştir
- Hiperglisemi ile uyarılmış endotel hücre disfonksiyonu ve diyabet ilişkili vasküler komplikasyonlarda rol alırlar

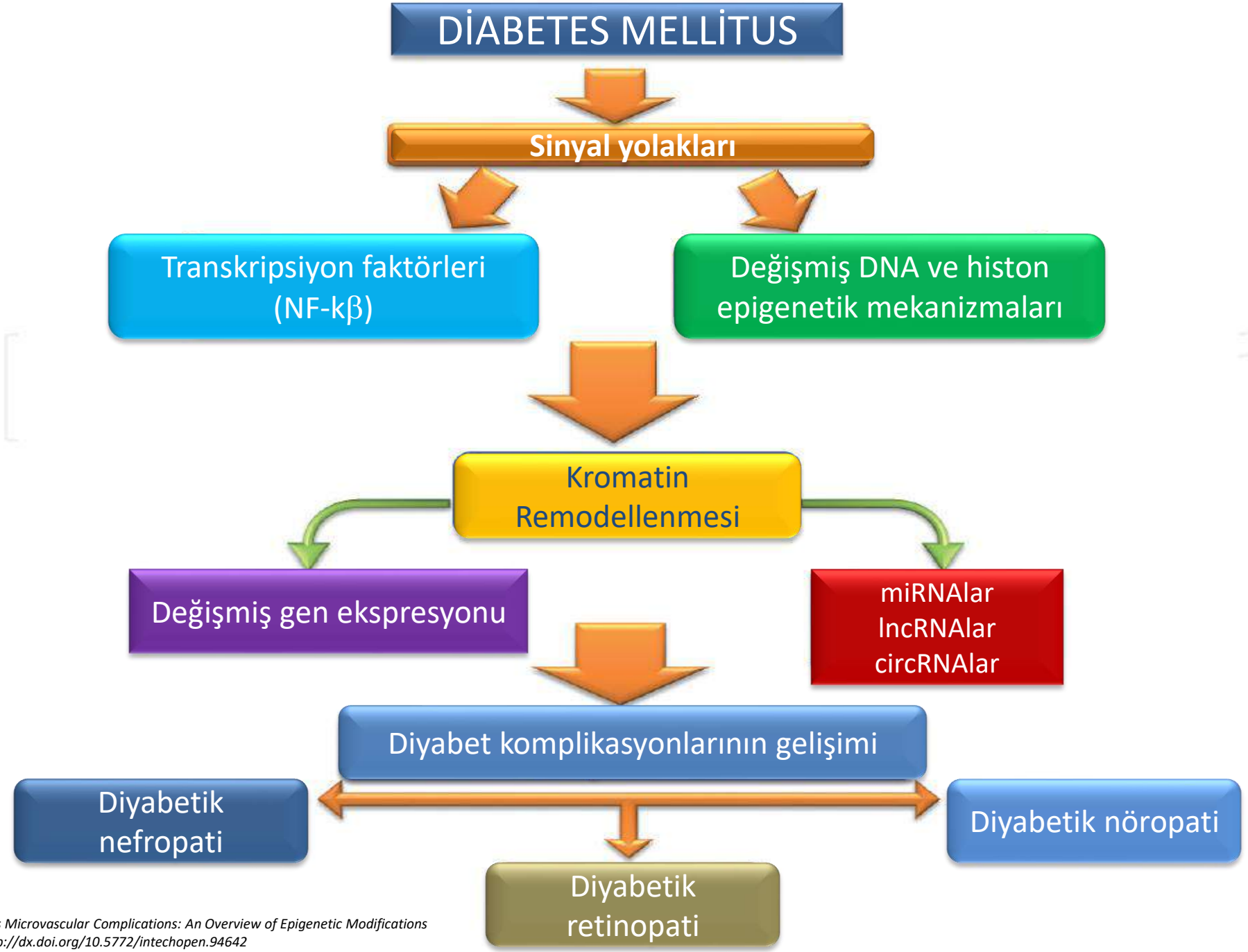
Cells 2020, 9, 659

**Table 2.** Putative functions of relevant circular RNAs in diabetes mellitus and associated vascular complications

| Circular RNA | Expression | Potential Function and Phenotype | R |
|---|---|---|---|
| | | **Diabetes/Glucose Homeostasis/CVD** | |
| CDR1as/cirRS-7 | ↑ | Improves insulin secretion and transcription through inhibiting miR-7 and accelerating Myrip and Pax6 expression | |
| circRNA-HIPK3 | ↑ | Regulates islet cell function by sequestering miR-124–3p and miR-338–3p and elevating Slc2a2, Akt1 and Mtpn | |
| hsa_circ_0054633 | ↑ | Potential diagnostic biomarker of pre-diabetes and T2DM in peripheral blood cells | |
| circRNA-WDR77 | ↑ | Regulates proliferation and migration of high glucose-induced VSMCs by affecting the expression of FGF-2 through miR-124 sponging | |
| circANKRD36 | ↑ | Potential biomarker for screening chronic inflammation in patients with T2DM | |
| | | **Diabetic Cardiomyopathy** | |
| circRNA_000203 | ↑ | Exacerbates myocardial fibrosis in mouse cardiac fibroblasts via inhibiting the interaction of miR-26b-5p with the target genes | |
| circRNA_010567 | ↑ | Promotes the development of diabetic cardiomyopathy through the circRNA_010567/miR-141/TGF-β1 axis | |
| hsa-circ-0076631 (CACR) | ↑ | Mediates pyroptosis of diabetic cardiomyopathy by functioning as miR-214-3p sponge | |
| | | **Diabetic Nephropathy** | |
| cirRNA_15698 | ↑ | circRNA_15698/miR-185/TGF-β1 axis promoted extracellular matrix (ECM)-related protein synthesis in diabetic nephropathy progression | |
| | | **Gestational Diabetes** | |
| circ_5824, circ_3636, circ_0395 | ↓ | Suspected to be involved in the occurrence and pathogenesis of GDM | |
| hsa-circRNA_0054633 | ↑ | Change in its expression in the placental villi of GDM patients may reflect its potential role in the development of GDM | |
| | | **Diabetic Retinopathy** | |
| circRNA-0005015 | ↑ | Involved in diabetes retinopathy by acting as miR-519d-3p sponge to increase the expression of its target genes, MMP-2, XIAP, and STAT3 | |
| circRNA-HIPK3 | ↑ | Promotes retinal vascular disorders by blocking miR-30a-3p members function to reverse the expression of their target genes VEGF, FZD4, and WNT2 | |
| cZNF609 | ↑ | Role in mediating vascular dysfunction by acting as miR-615-5p sponge | |
| circRNA-cPWWP2A | ↑ | Alleviates diabetes mellitus-induced retinal vascular dysfunction by sponging miR-579 | |



Cells 2020, 9, 659

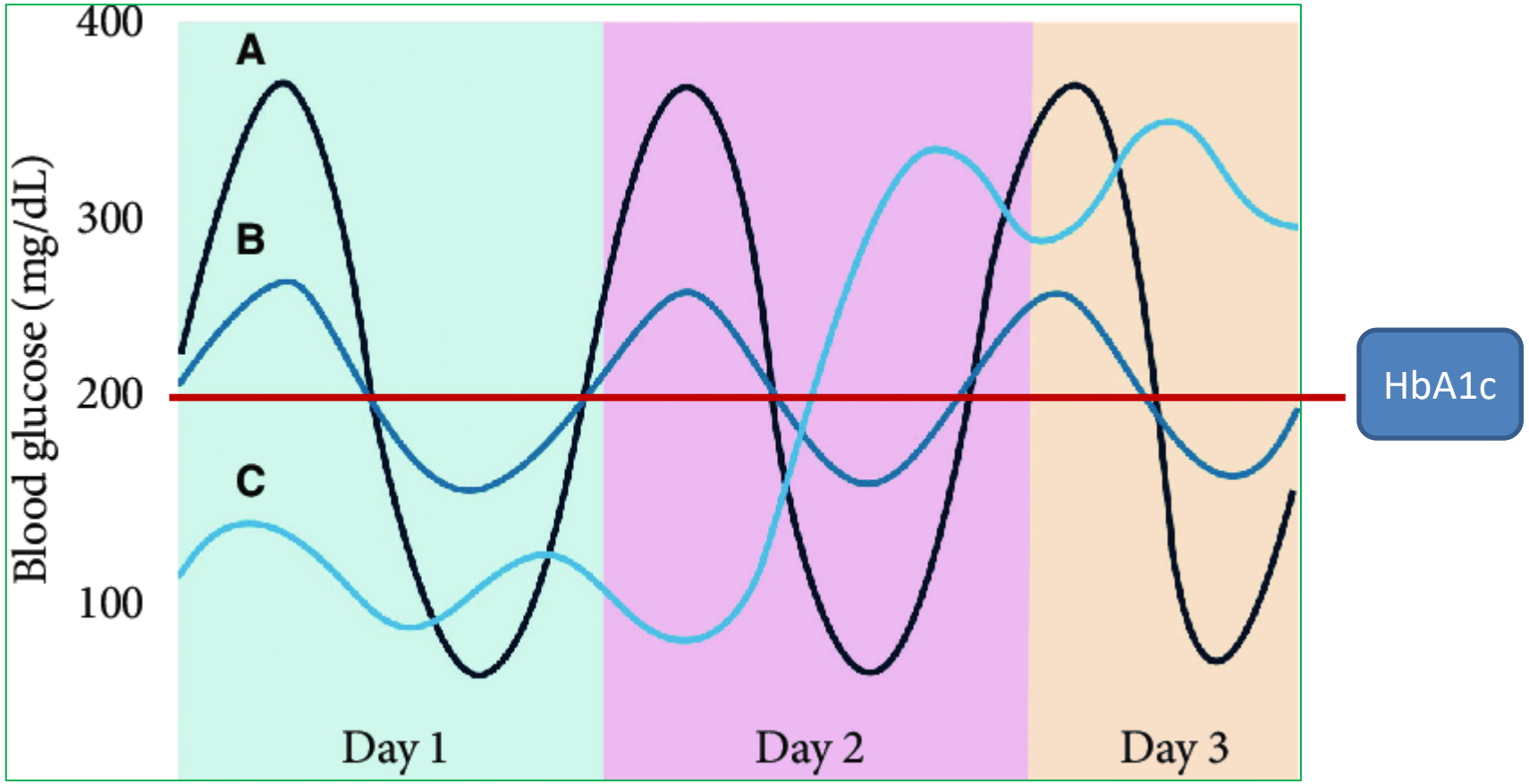



*Diabetes Microvascular Complications: An Overview of Epigenetic Modifications*
*DOI: http://dx.doi.org/10.5772/intechopen.94642*

# Glukoz Değişkenliği

- Diyabetteki disglisemi üç şekilde karşımıza çıkar;
  - Persistan hiperglisemi
  - Glukoz değişkenliği
  - Hipoglisemik olaylar

# Glisemik Değişkenlik

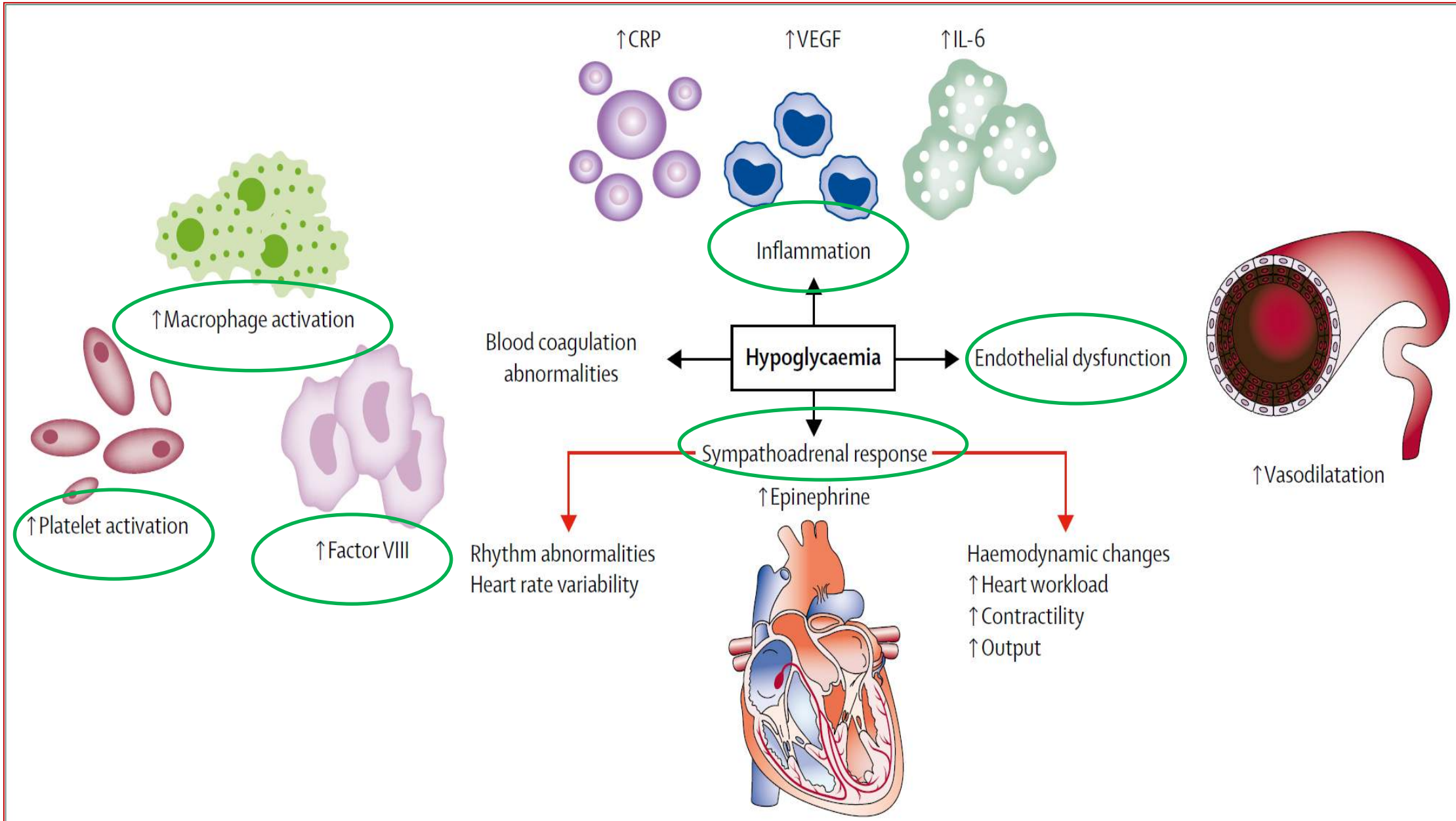


# Glisemik Değişkenlik

- Glisemik değişkenliğin diyabetik mikro ve makrokomplikasyonlarla ilişkisi bir çok çalışmada gösterilmiştir
- Altta yatan mekanizma olarak oksidatif stres gösterilmiştir
- Glisemik değişkenlik sürekli hiperglisemiden daha fazla ROS üretimi ve vasküler hasara yol açmaktadır

Journal of Diabetes Research Volume 2020, Article ID 7489795, 17 pages

# Hipoglisemi





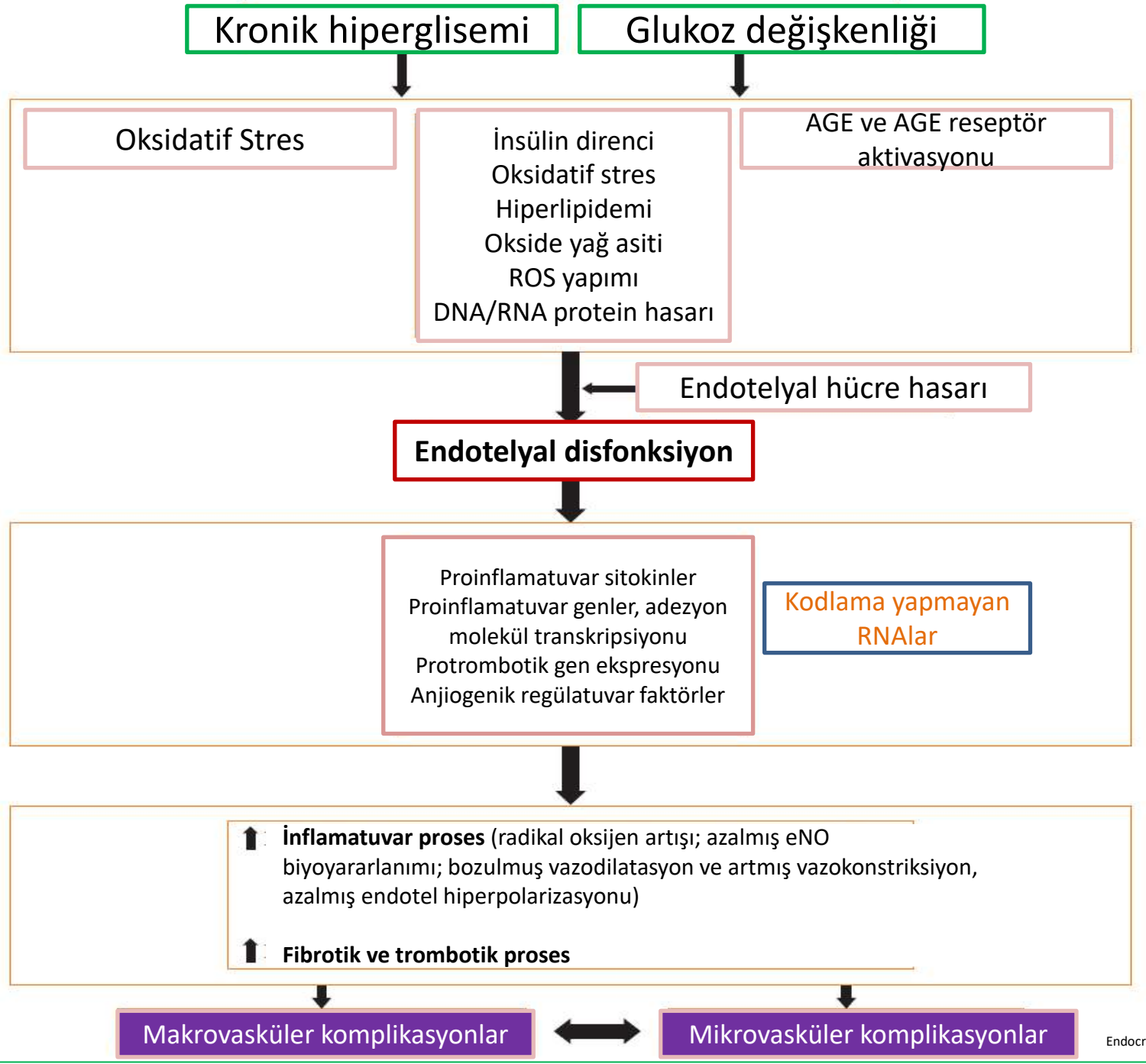

*Lancet Diabetes Endocrinol* 2019; 7: 385–96

# Hipoglisemi

- Renin–anjiotensin sistemi: endotel disfonksiyonu
- Artan kardiyak yük: artmış platelet aktivasyonu, azalmış fibrinolitik denge
- Pro-inflamatuvar cevap artışı: endotel disfonksiyonu, pro-aterojenik şartlar
- Artmış ROS



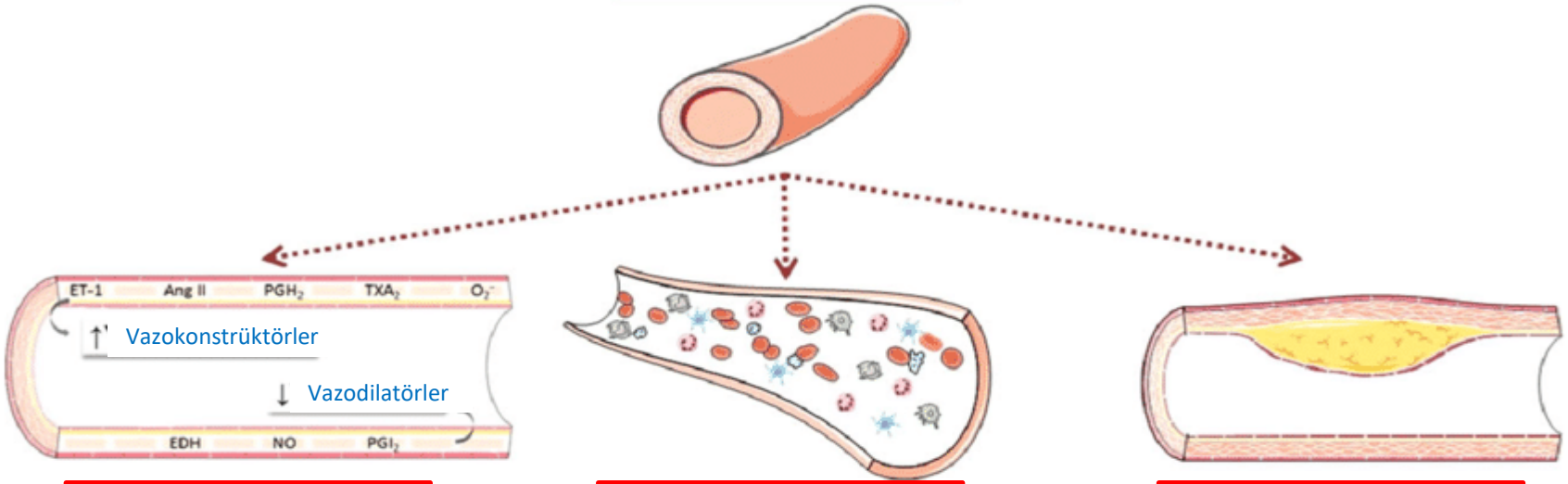
*Lancet Diabetes Endocrinol* 2019; 7: 385–96




Endocrinol Metab 2020;35:260-271

# Makrovasküler Komplikasyonlar

## Diyabet




### Endotel disfonksiyonu

ROS

- ↓NO bioavailability
- ↑$O_2^-$
- ↑$ONOO^-$
- ↓EDH (F) bioavailability

### İnflamasyon

Adezyon molekülleri

- ↑ VCAM-1
- ↑ ICAM-1

Proinflamatuvar faktörler

- ↑ TNFα, NF-kB
- ↑ MCP-1
- ↑ IL-6, IL-1β, IL-18
- ↑ CRP

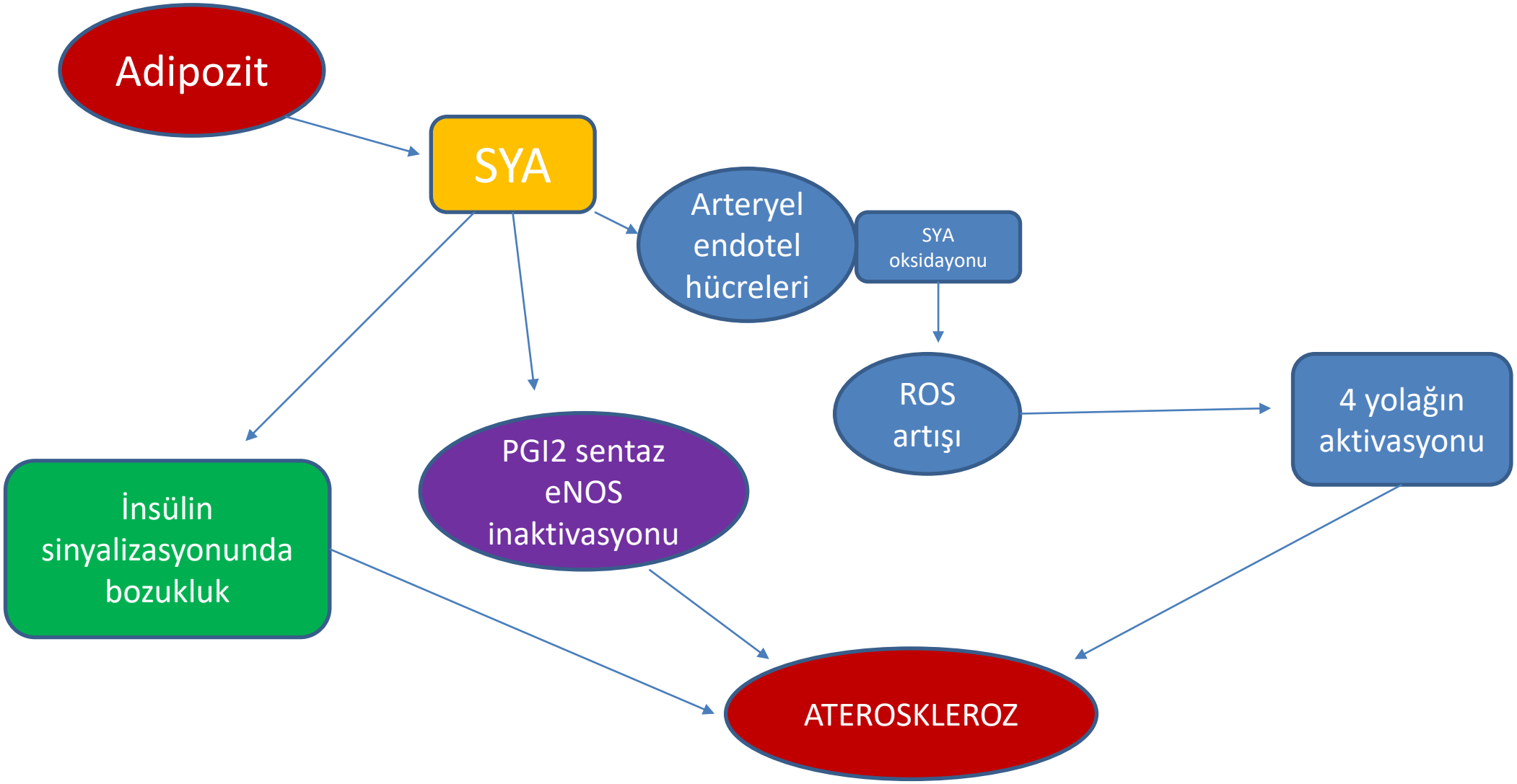
### Fibrozis ve remodelling

Fibrotik faktörler

- ↑ PAI-1
- ↑ MMP-2, MMP-9
- ↑ TF
- ↑ vWF

## Ateroskleroz

# Makrovasküler Komplikasyonlar



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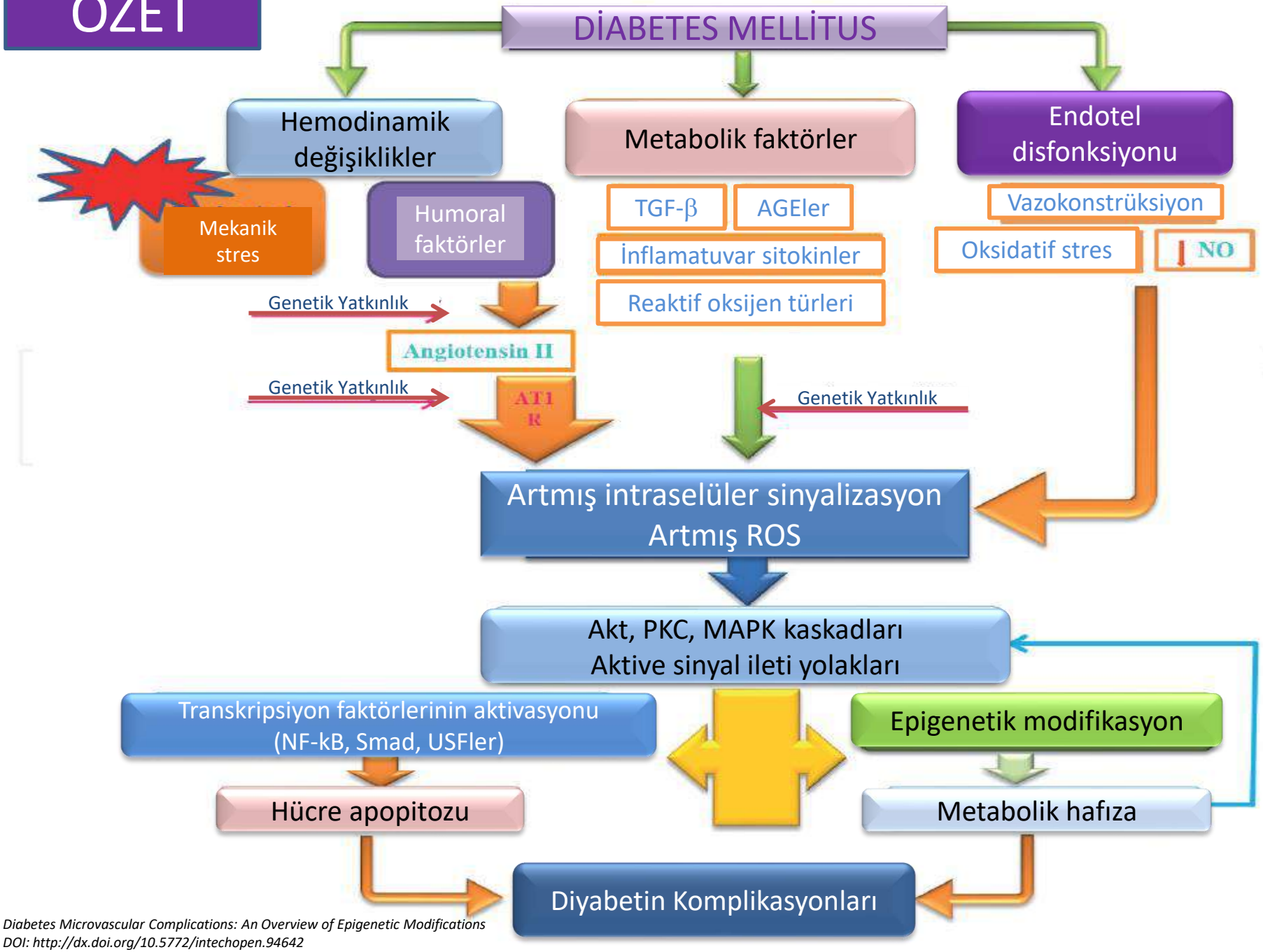
# ÖZET




*Diabetes Microvascular Complications: An Overview of Epigenetic Modifications*
*DOI: http://dx.doi.org/10.5772/intechopen.94642*

# Diğer Mekanizmalar

- Glukagon
- C-peptid
- Ürik asit
- ……..

# TEŞEKKÜR EDERİM