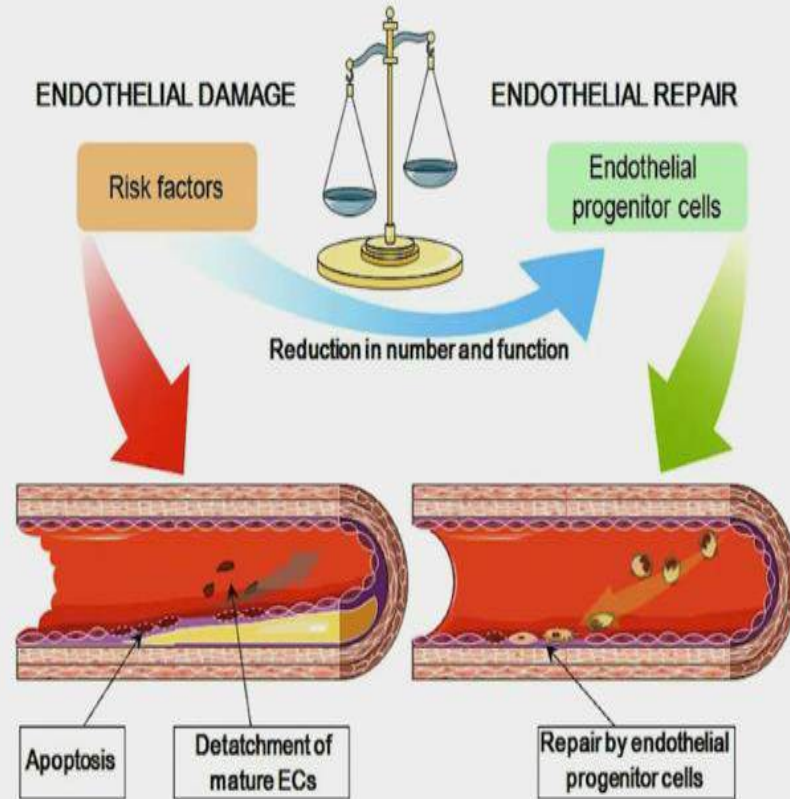


DİYABET VE KÖK HÜCRE MOBİLOPATİSİ: DİYABETTE KEMİK İLİĞİ TRAFİĞİ NASIL ETKİLENİYOR?

Dr. Filiz Ekşi Haydardedeođlu
Bařkent Üniversitesi Tıp Fakóltesi
Endokrinoloji ve Metabolizma Hastalıkları

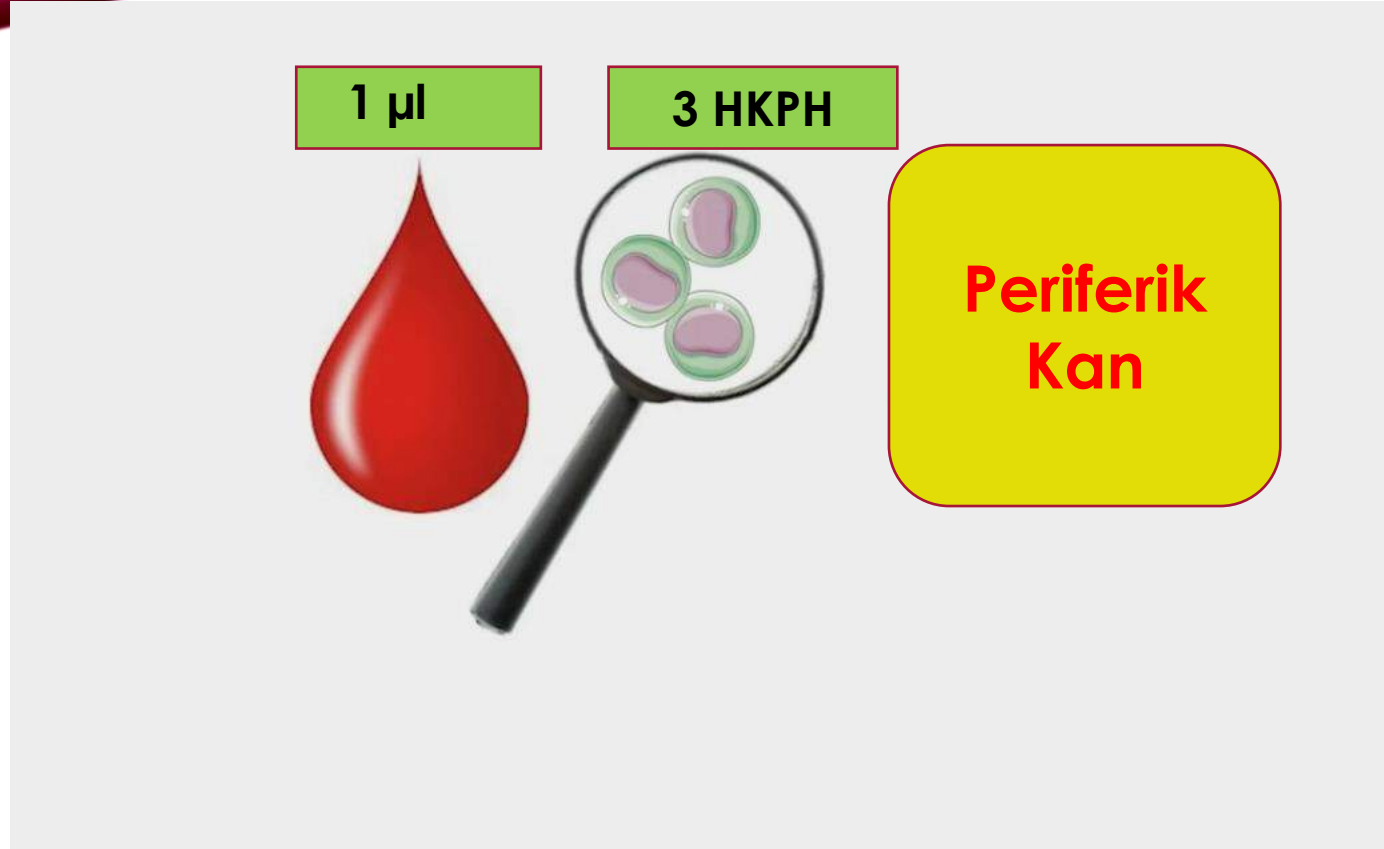


EPH

(Endotelial Progenitor Hücresi)

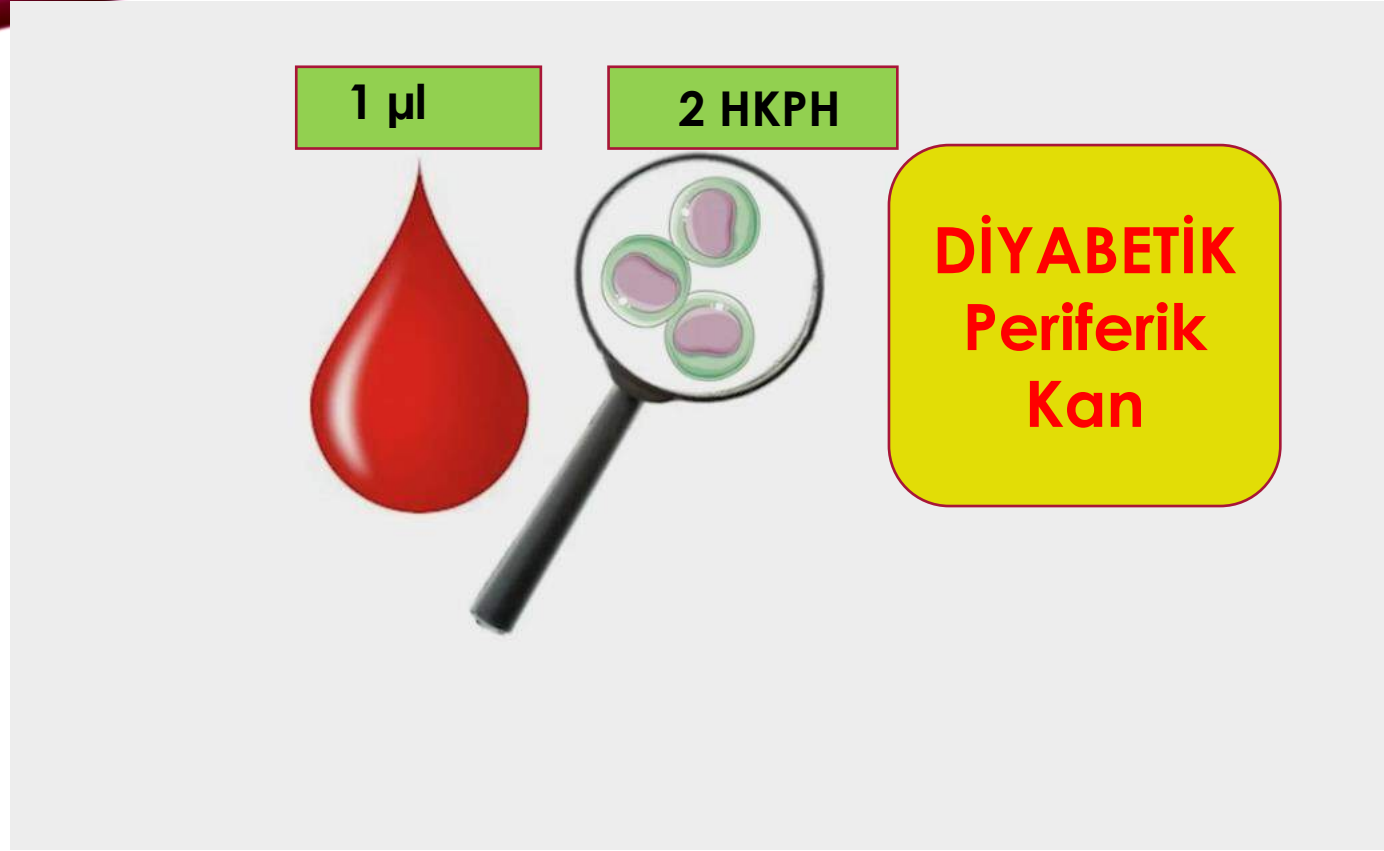
** EPH-Endotelial rejenerasyonu ve anjiyogenez

**Vasküler hasarı onarma potansiyeli



Hematopoietik kök/Progenitor hücre (HKPH)

WBC nin % 0.05 i

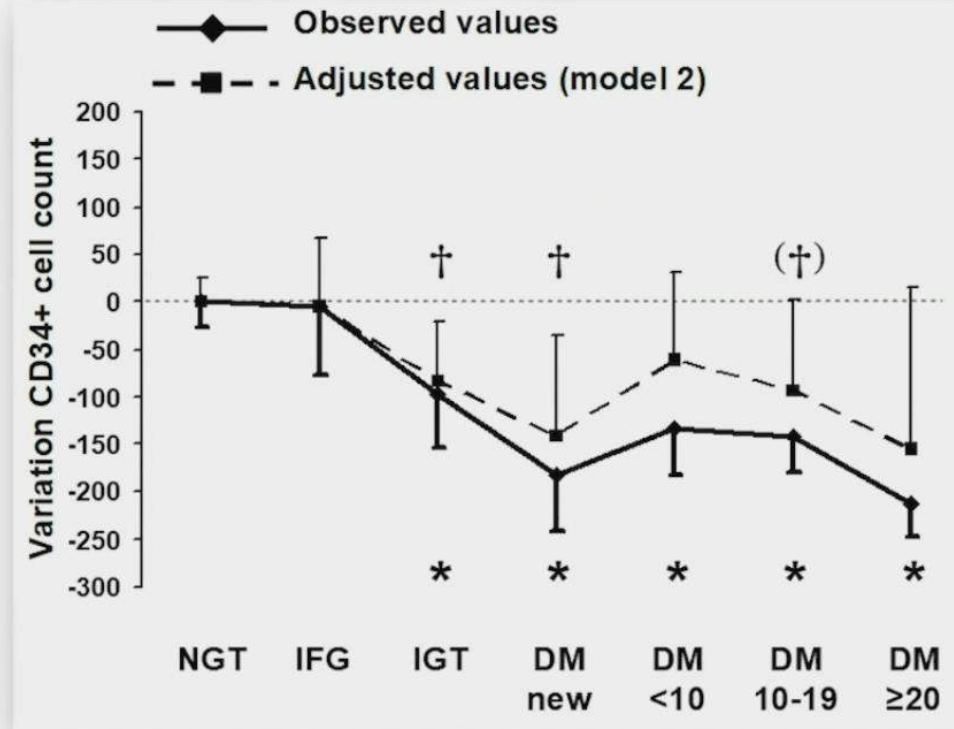
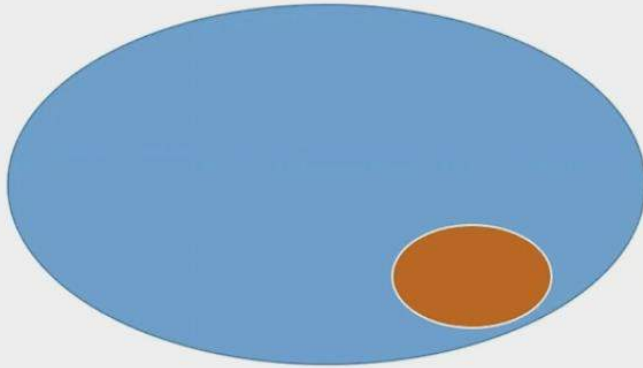


HKPH VE EPH ler diyabetik bireylerde % 30-50

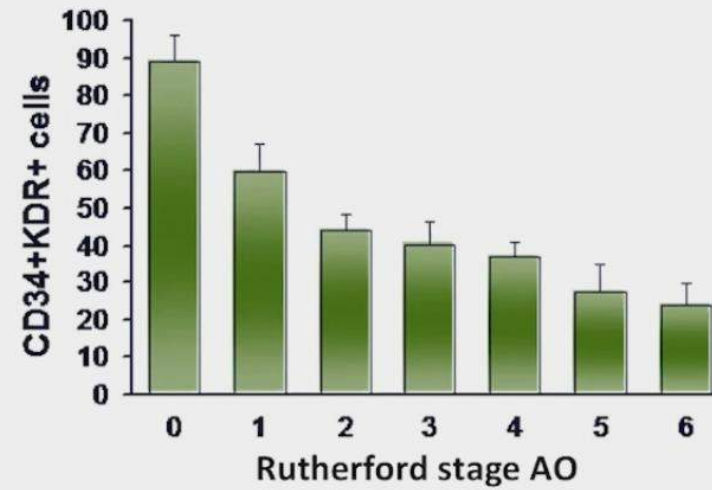
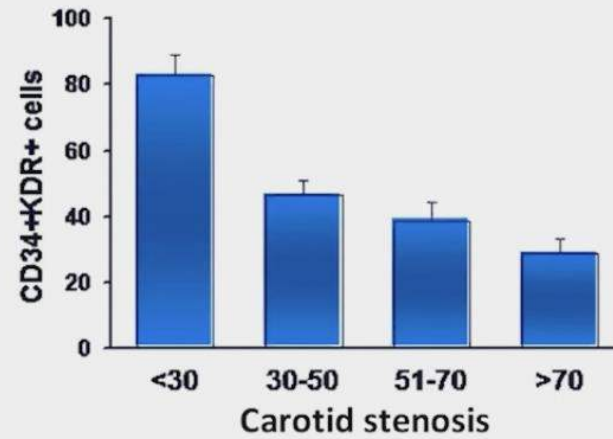
Özellikle vasküler komplikasyon mevcutsa...

Sirkülasyondaki HKPH sayısı erken dönemlerde azalmaya başlar ve bu azalma zaman içinde devam eder

Hematopoietic stem / progenitor cells (HSPCs)
Endothelial progenitor cells (EPCs)



Endothelial progenitor cells in diabetic vascular disease



Fadini et al. JACC 2004
Fadini et al ATVB 2006
Rigato et al. Circ Res 2017



Endothelial progenitor cells in diabetic vascular disease

Circulation Research

Volume 120, Issue 8, 14 April 2017, Pages 1326-1340

<https://doi.org/10.1161/CIRCRESAHA.116.309045>



CLINICAL TRACK

Autologous Cell Therapy for Peripheral Arterial Disease

Systematic Review and Meta-Analysis of Randomized, Nonrandomized, and Noncontrolled Studies

Editorial, see p 1227

In This Issue, see p 1213

Mauro Rigato, Matteo Monami, and Gian Paolo Fadini

Fadini et al. JACC 2004

Fadini et al ATVB 2006

Tip 1 ve Tip 2 Diyabetik bireylerde



Kök hücre/progenitör hücre

****Hiperglisemi** kök hücre trafiği ve seviyesinin en önemli belirteci

Glukoz düzeyi ve HBA1C



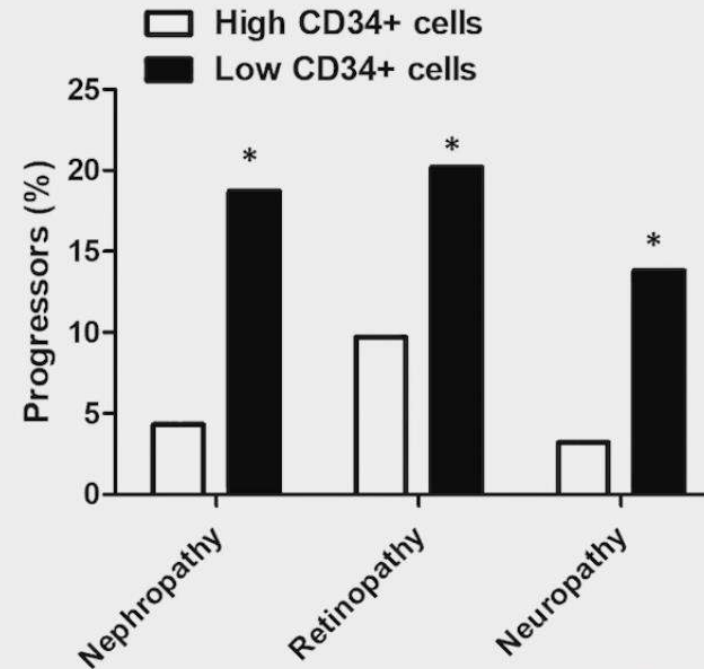
HKPH ve EPH

Circulating Progenitor Cell Count Predicts Microvascular Outcomes in Type 2 Diabetic Patients

Mauro Rigato, Cristina Bittante, Mattia Albiero, Angelo Avogaro, and Gian Paolo Fadini

N=187 type 2 diabetic patients, followed-up for 3.9 years

Baseline measure of CD34⁺ cells and determination of microangiopathy progression



Rigato et al. JCEM 2015





Niche cellular components

- LeptinR + cell
- MSC
- Endothelial Cells
- Osteoblastic Cells
- Nestin cell
- Adipocyte
- Osteoclast

Niche noncellular components

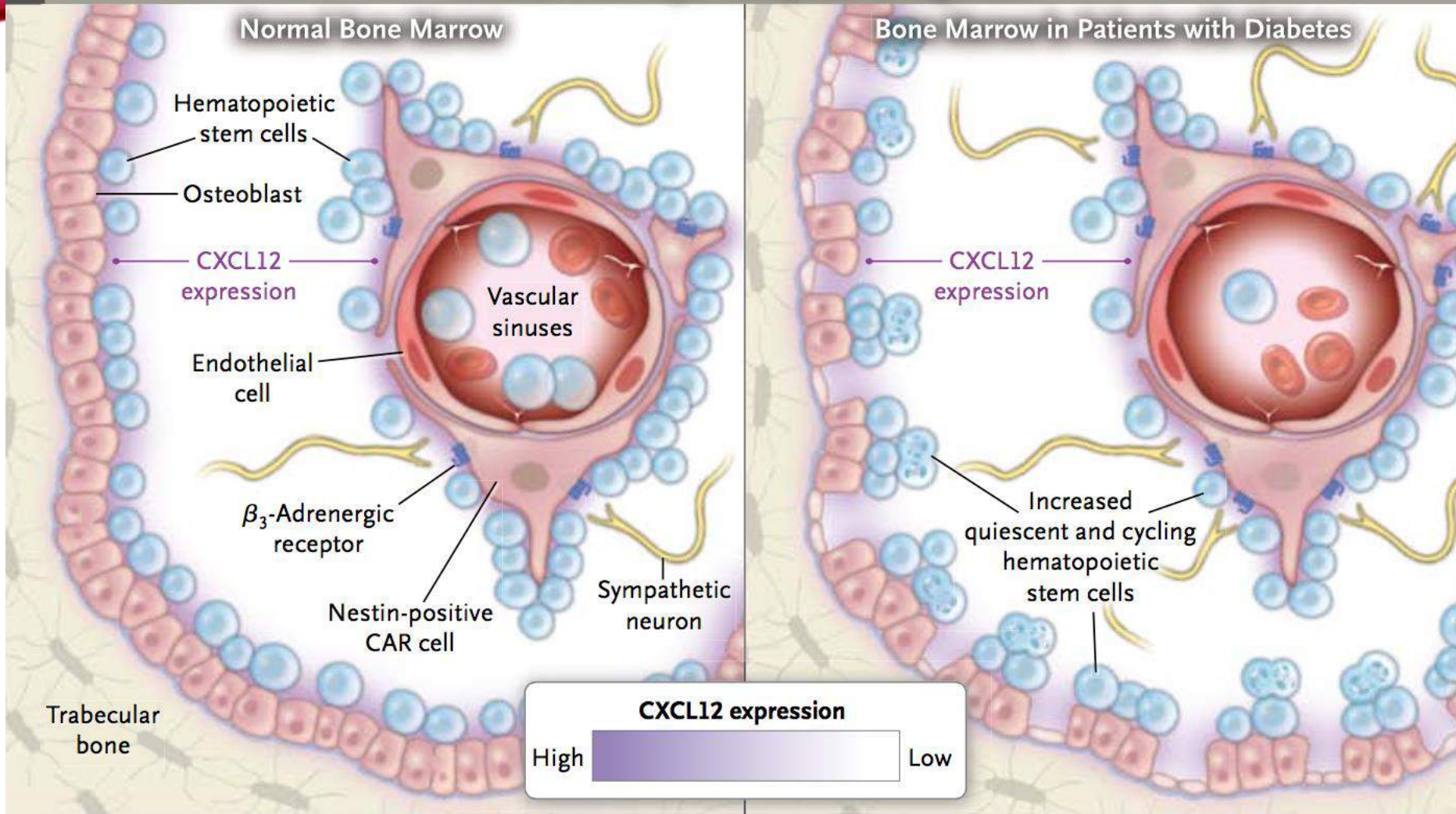
- Nerve terminal and non-myelinating Schwann cell
- Heparan (HSPG)
- Oxygen

Hematopoietic Cells

- HSC
- Hematopoietic progenitor
- Myeloid cells
- Lymphoid cells
- Megakaryocyte
- Erythrocyte
- Macrophage

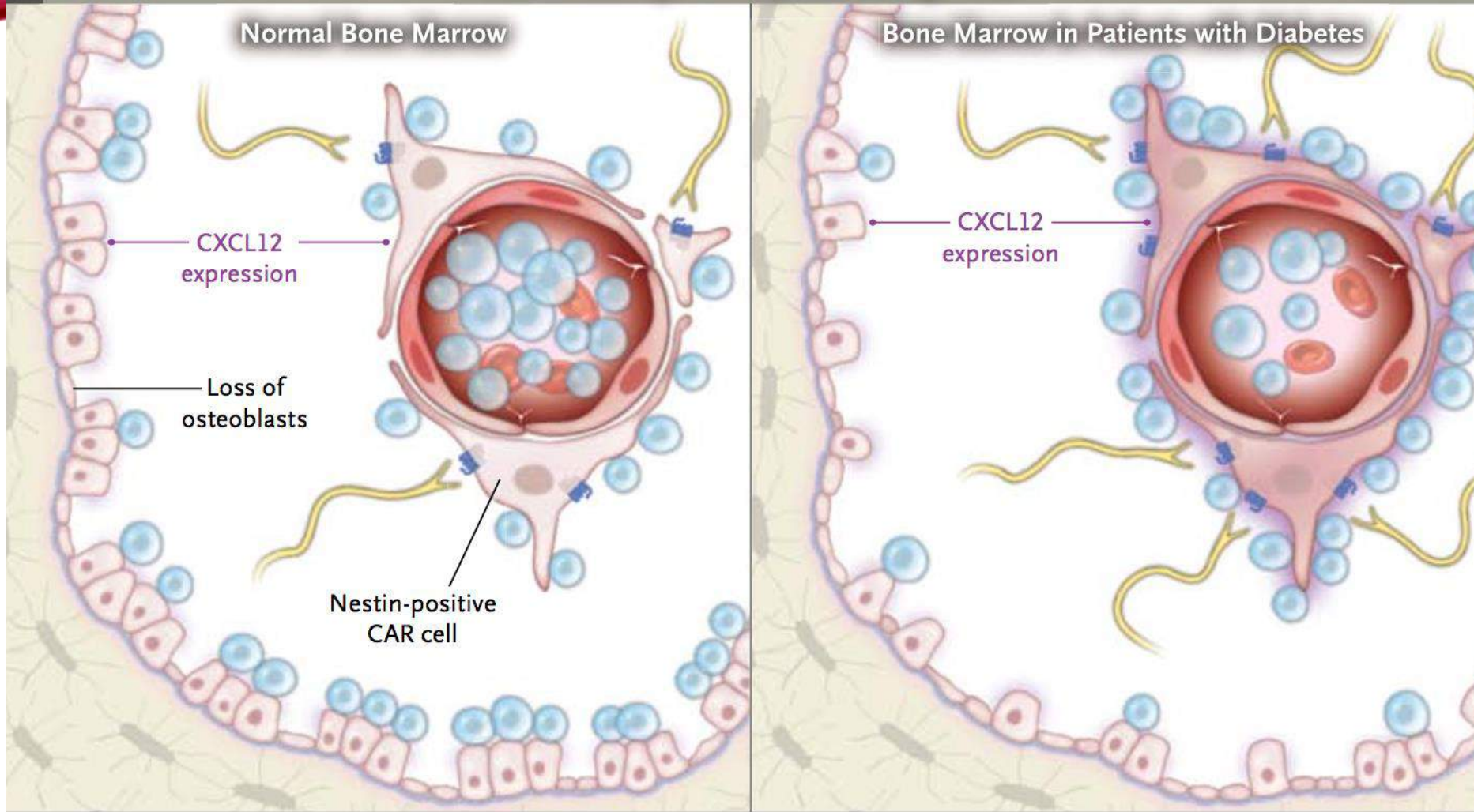
A

Without Granulocyte Colony-Stimulating Factor



B

With Granulocyte Colony-Stimulating Factor



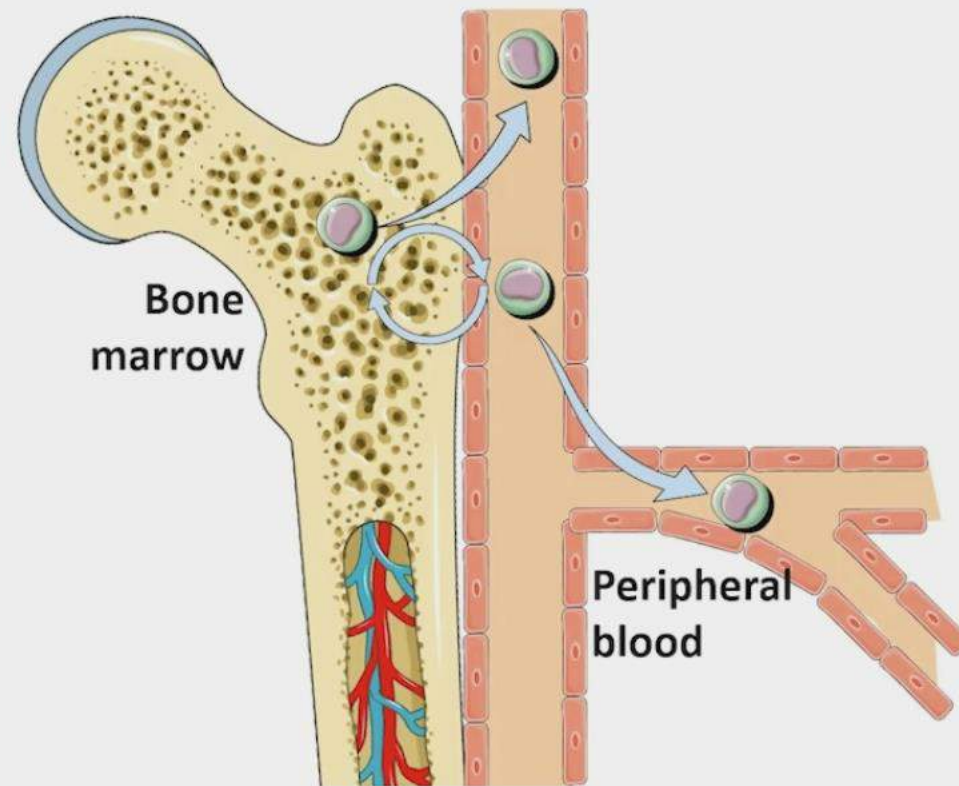
HKPH sayısı

Nişleri oluşturan hücreler, sayıları, yerleşimleri, sinyaller ve yüzey etkileşimleri

OB delesyonu- HKPH MOBİLİZASYONU

***G-CSF OB sayı ve aktivitesini AZALTIR
CXCL12 (SDF-1alpha) AZALTIR

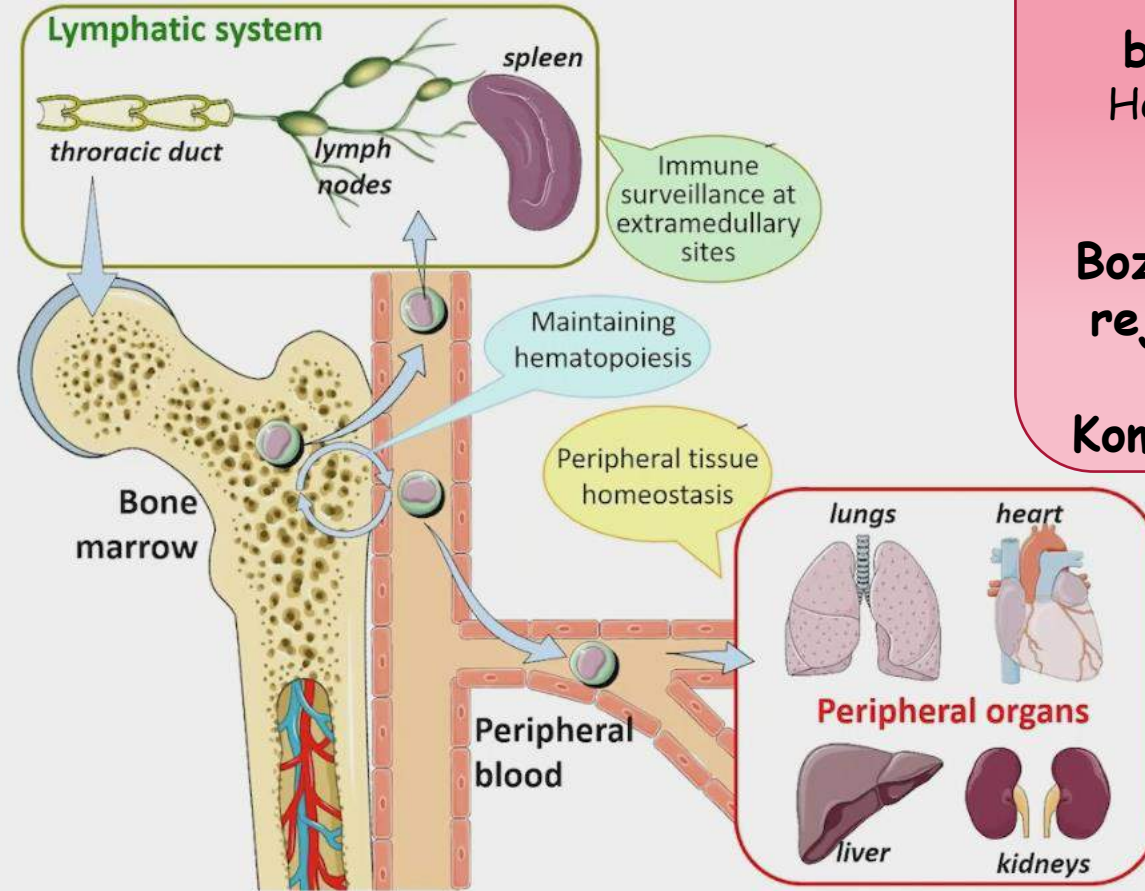
MOBİLİZASYONU SAĞLAR



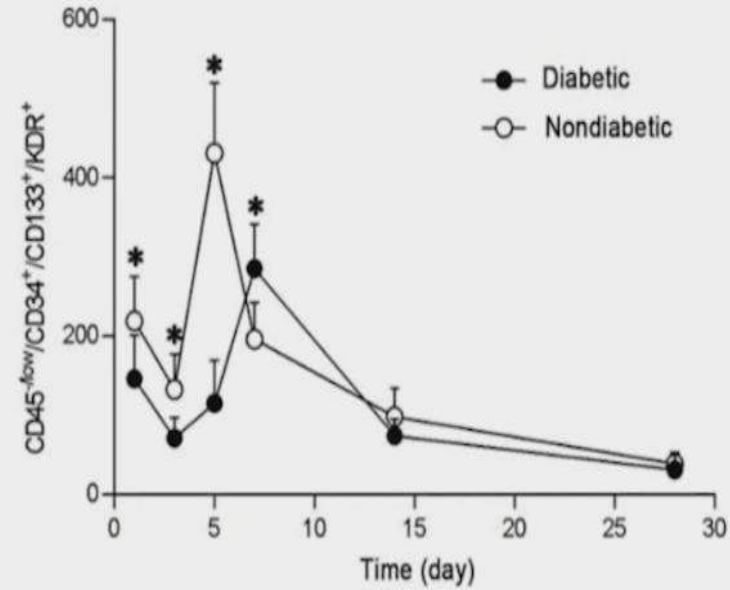
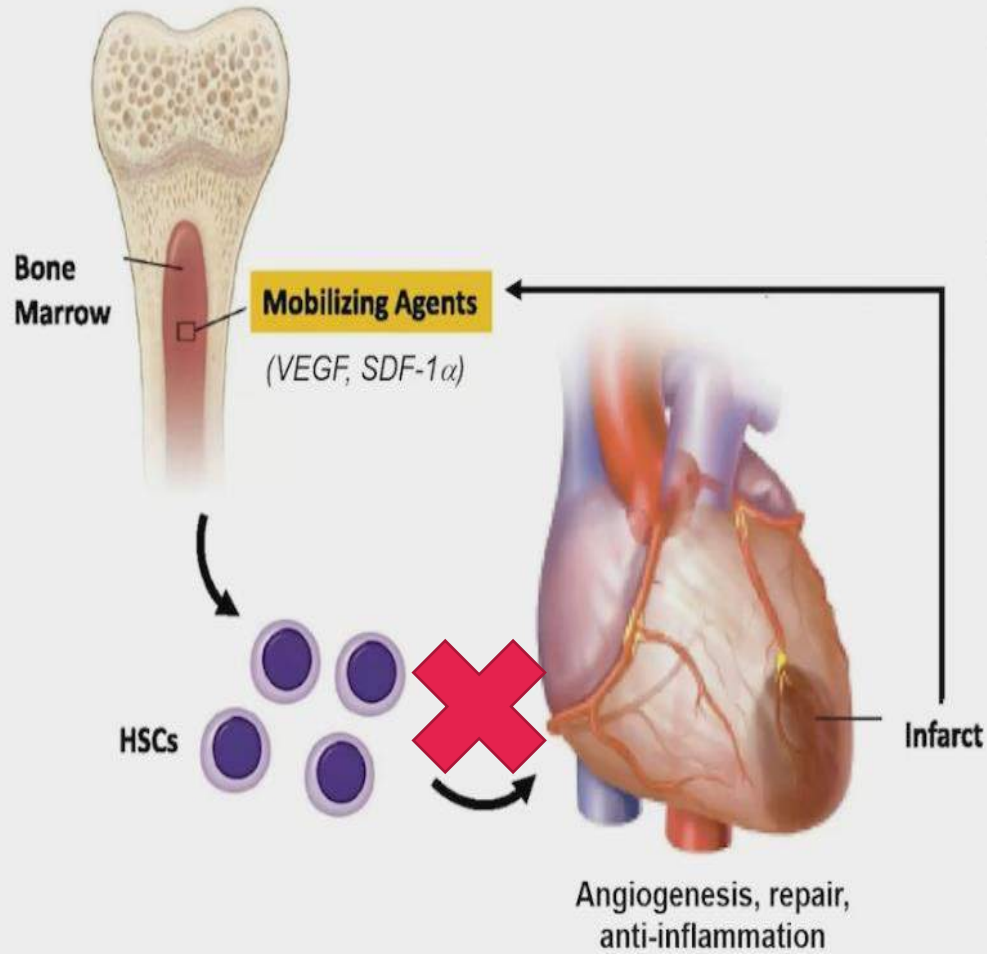
Fadini et al. Stem Cells 2017

DIYABET

**Kronik
inflamasyon
İmmun
bozukluklar
Hematopoyetik
Kök hücre
defektleri
Bozulmuş hasar
rejenerasyonu
Kr.
Komplikasyonlar**



İskemi ile indüklenmiş kök hücre Akışı

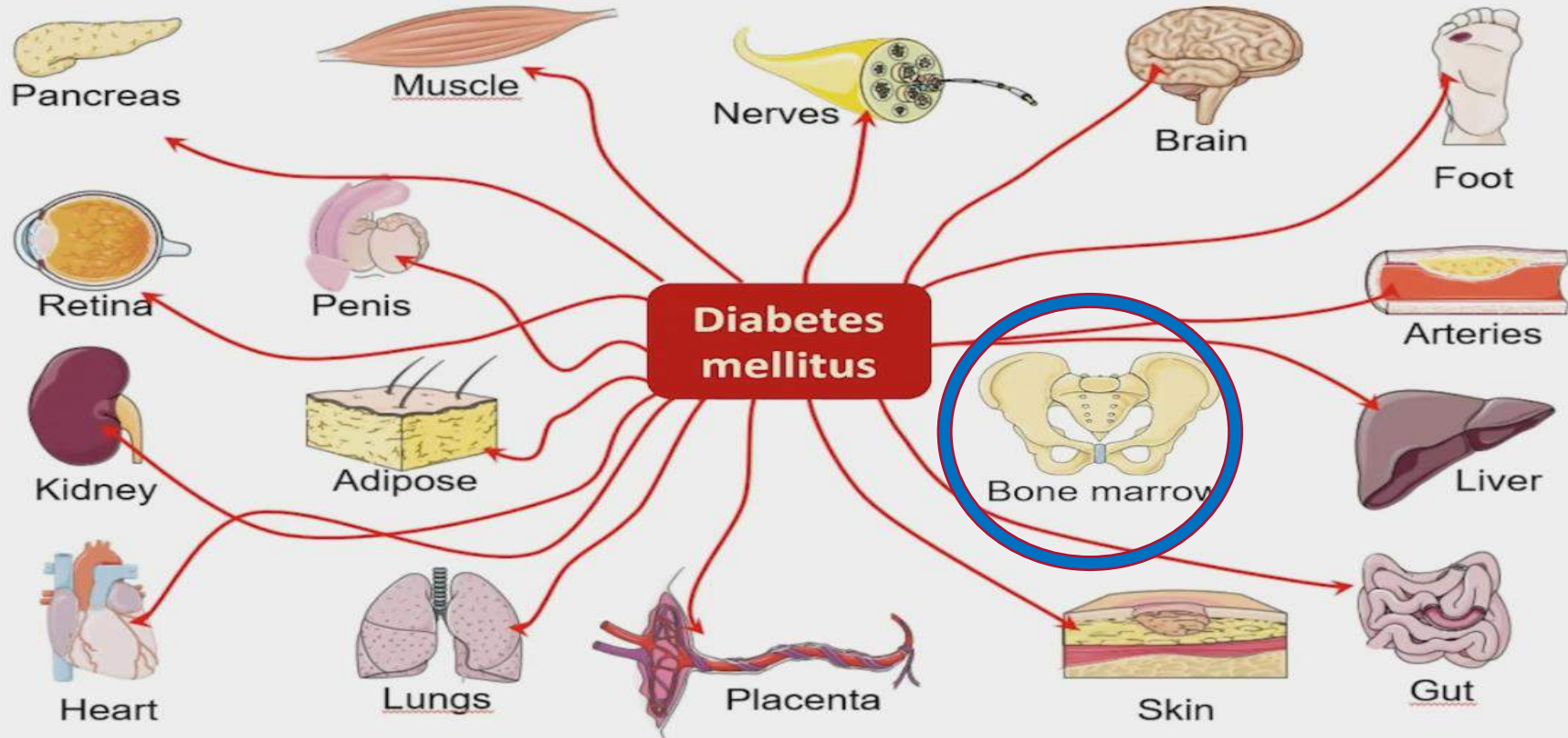


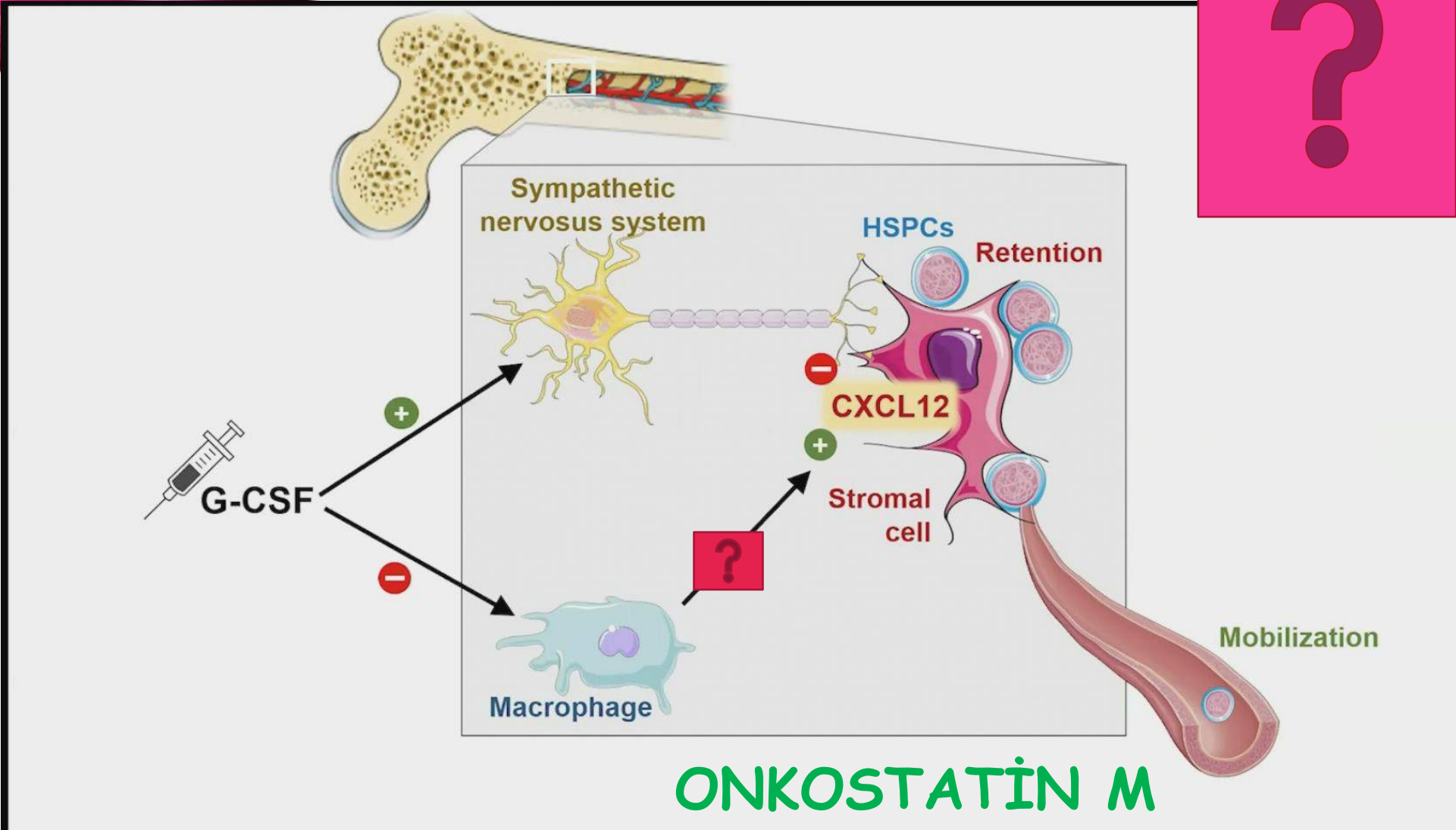
CLINICAL IMPLICATIONS OF BASIC RESEARCH



Diabetic Stem-Cell “Mobilopathy”

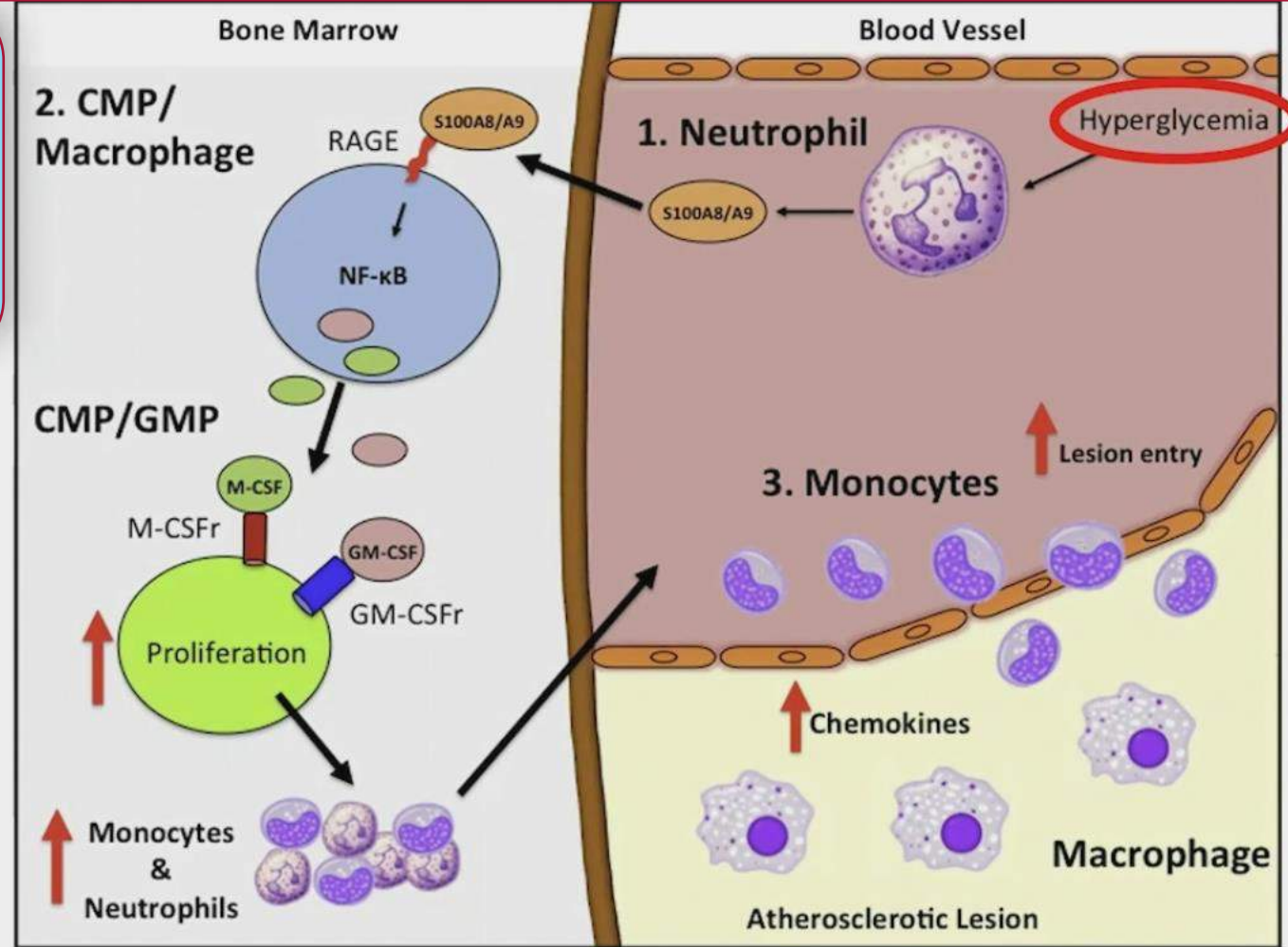
John F. DiPersio, M.D., Ph.D.



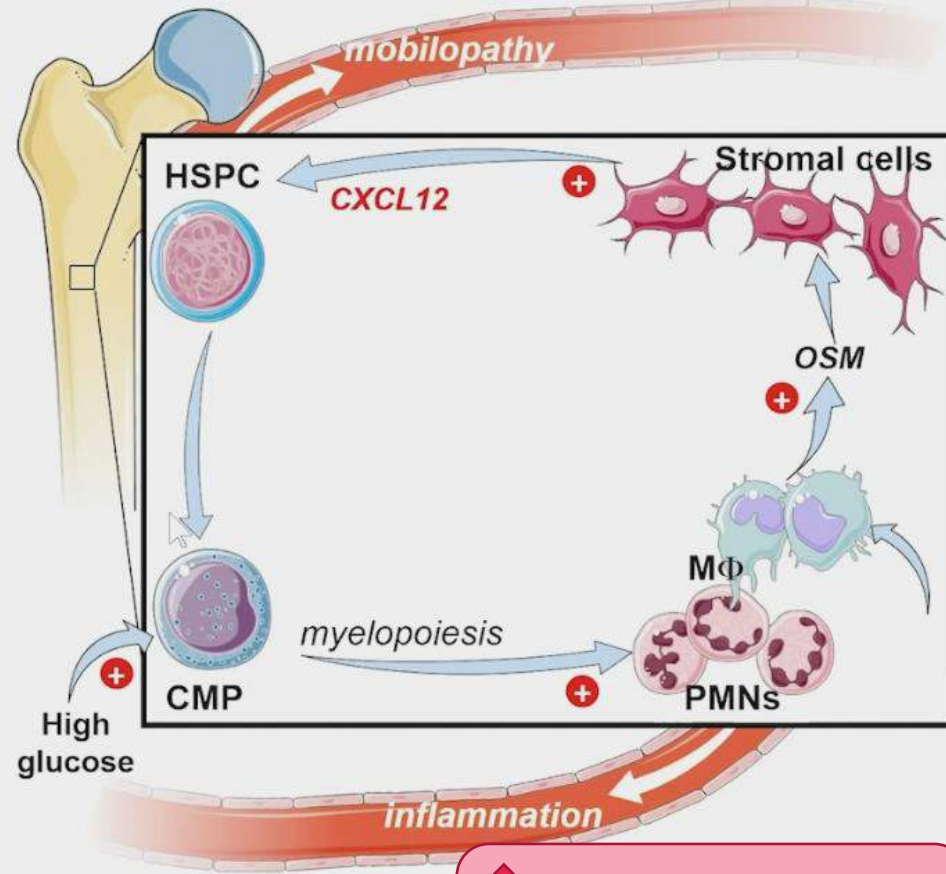


DIYABETİK KEMİK İLİĞİ

İnflamasyon



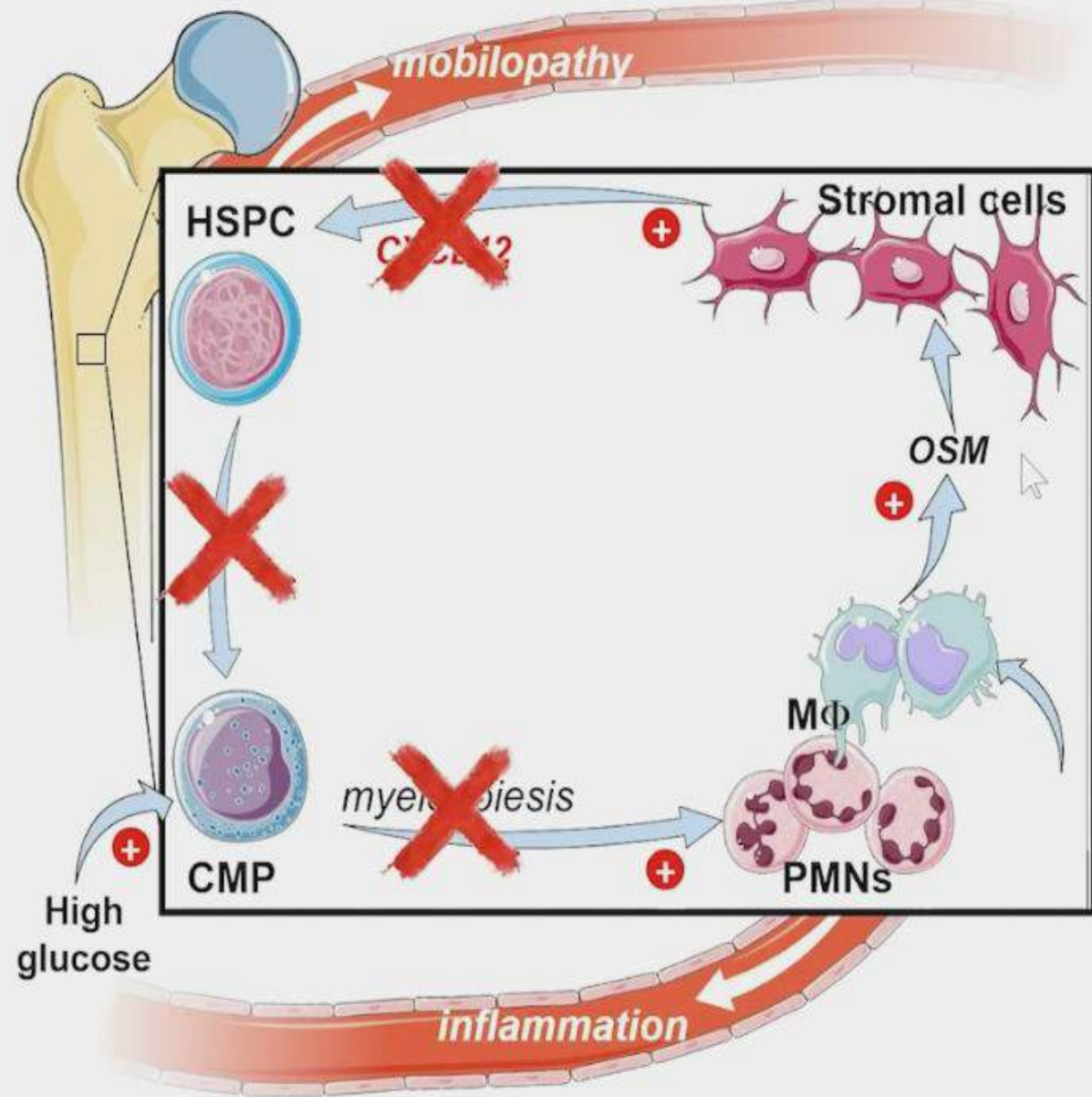
İnflamasyon Vs Mobilopati



Albiero et al. Diabetes 2019

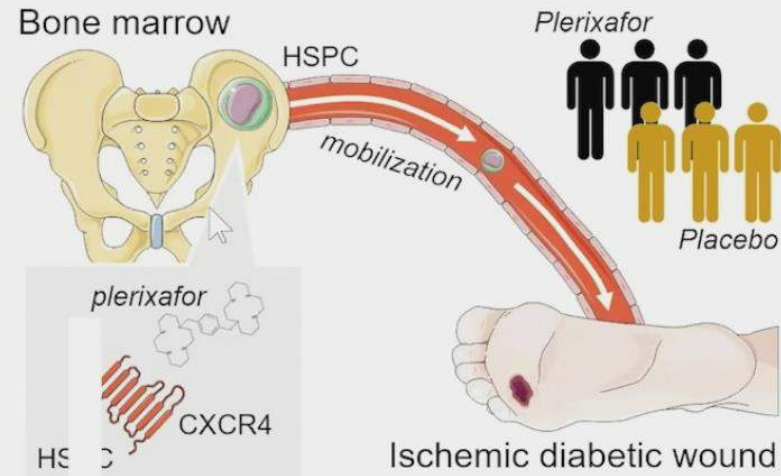
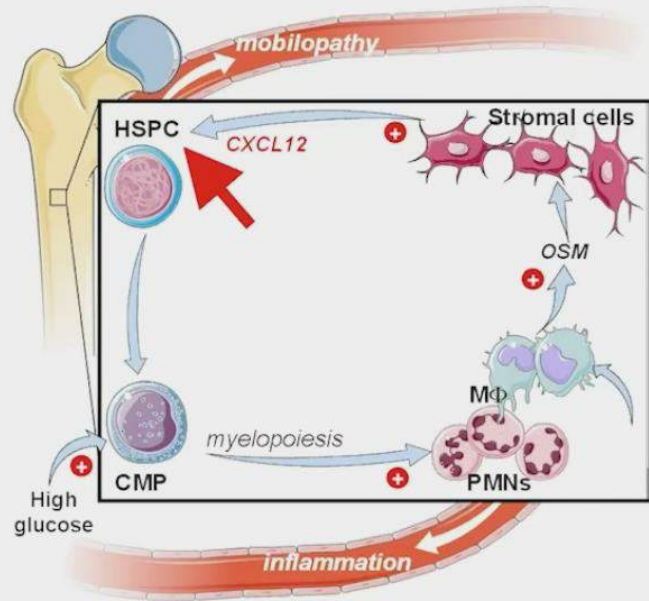
↑ Nötrofil/Lenfosit

Yaşlanma
Kanser
KVH
Diyabetik
komplasyon
lar



PLERİXAFOR (CXCR4 inh)
Diyabetiklerde kök hücre mobilizasyonunu sağlanmıştır

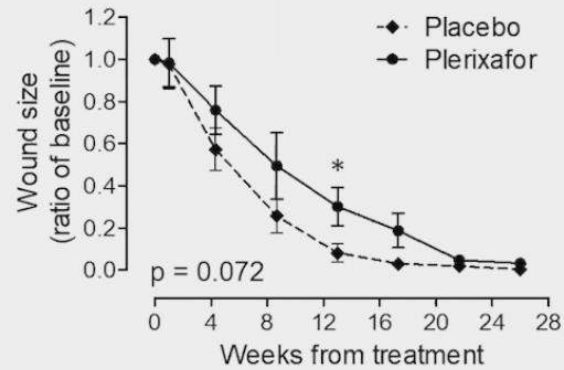
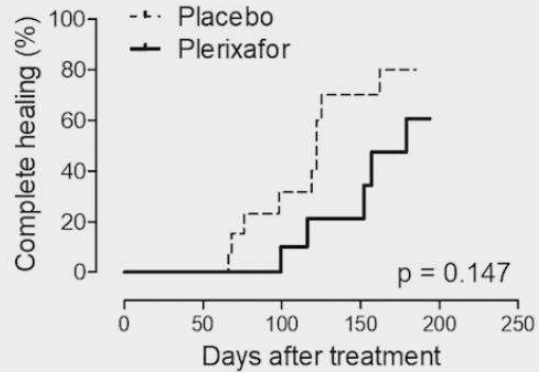
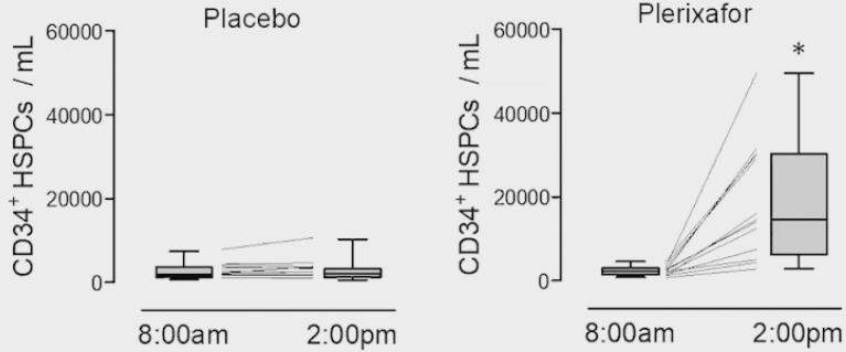
PLERIXAFOR-İskemik Diyabetik Yara



Bonora et al. Stem Cells TM 2020



PLERIXAFOR-İskemik Diyabetik Yara



Etkisi kısa süreli
HKPH sayısı artmış
Yara iyileşmesi kötü
Erken sonlanım


**İNFLAMASYON
KISMINA ETKİSİ
YOK???**

FARMAKOLOJİK AJANLAR

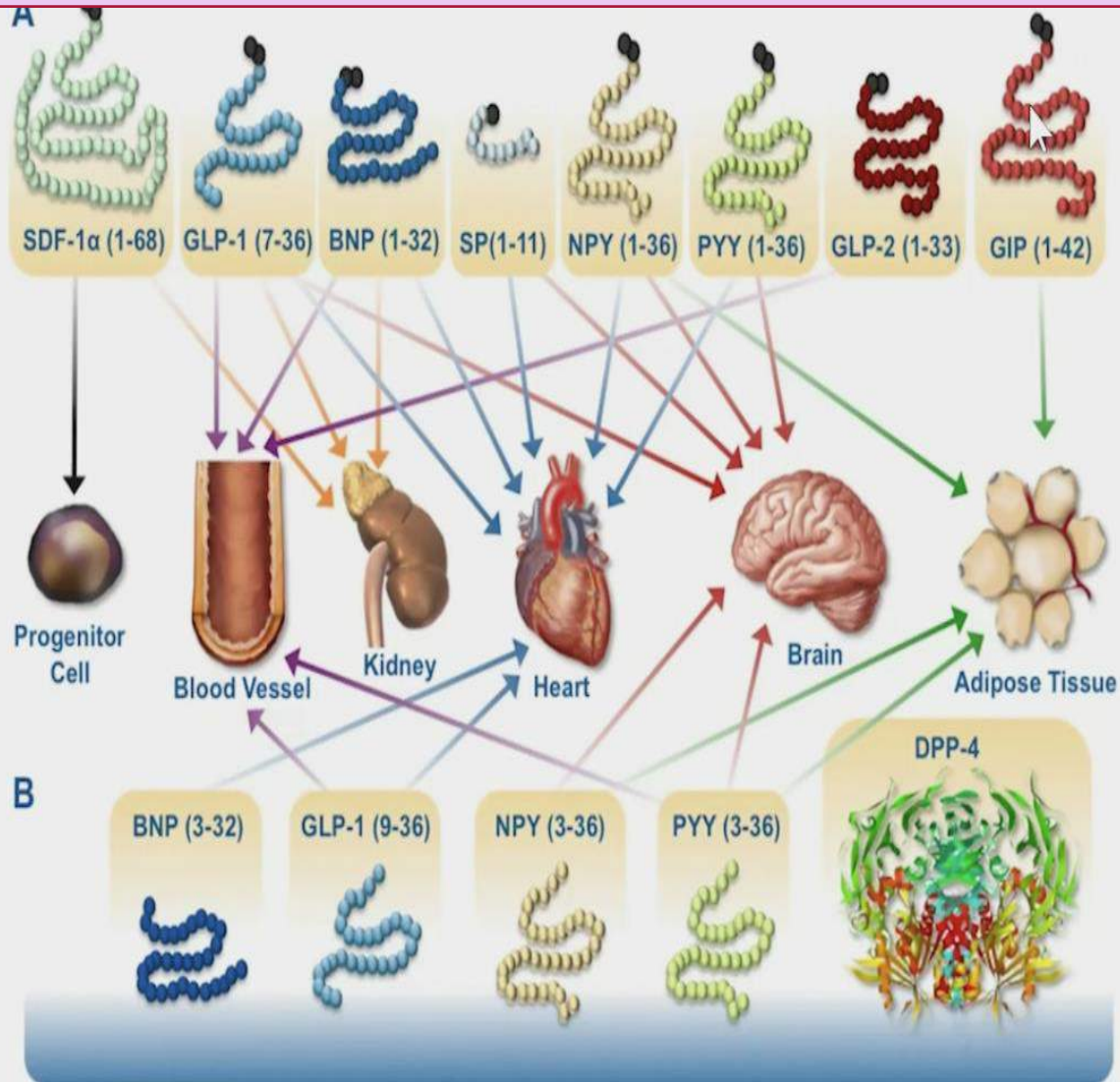


- HHPH 
- Diyabetik komplikasyonlar 

TEDAVİ	HHPH SAYISI	DİYABET SONLANIM
Glisemik Kontrol	✓	!?
DPP-4 İNHİBİTÖRÜ	✓	✗
GLİTAZONLAR	✓	✓
SGLT-2 İNHİBİTÖRLERİ	?	✓

- 
- DPP-4 -birçok peptidi parçalamakta ve inaktive etmekte
 - Bunların bir kısmı immün-inflamasyon ve kök hücre biyolojisini düzenlemektedir

DPP-4



SDF-1 Alfa= CXCL12

DPP4 için substrattır

Fadini et al. Diabetes Care 2010

Fadini et al. Basic Res Cardiol 2013

Poncina et al. Cardiovasc Diabetol 2014

Aso et al. Endocrine 2015

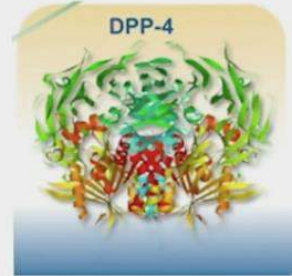
Fadini et al. JCEM 2016

Dei Cas et al. Cardiovasc Diabetol 2017

DPP-4 İNH. DOLAŞIMDAKİ PROGENİTÖR HÜCRE ARTIRIR



Kök hücre
mobilizasyonu



- Fadini et al. Diabetes Care 2010
Fadini et al. Basic Res Cardiol 2013
Poncina et al. Cardiovasc Diabetol 2014
Aso et al. Endocrine 2015
Fadini et al. JCEM 2016
Dei Cas et al. Cardiovasc Diabetol 2017

Sitagliptin > Tedavi almayan, Glimepid

Vildagliptin > Glibenklamid

Etki kısa sürede ortaya çıkmaktadır

CXCL 12 konsantrasyonu ile koreledir

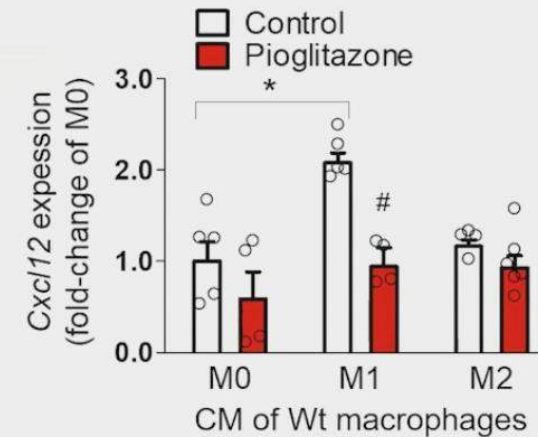
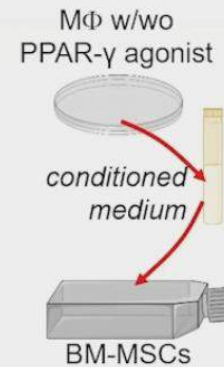
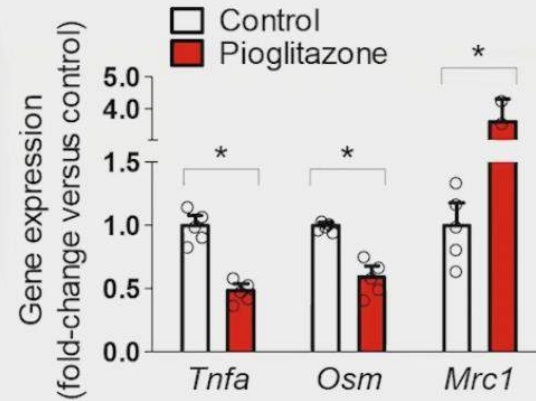
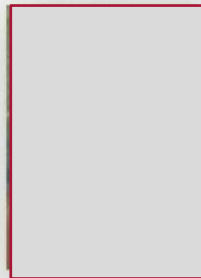
PPAR Gama , OSM ve CXCL12 yolađı

OSM- M1 makrofajlarca üretilir

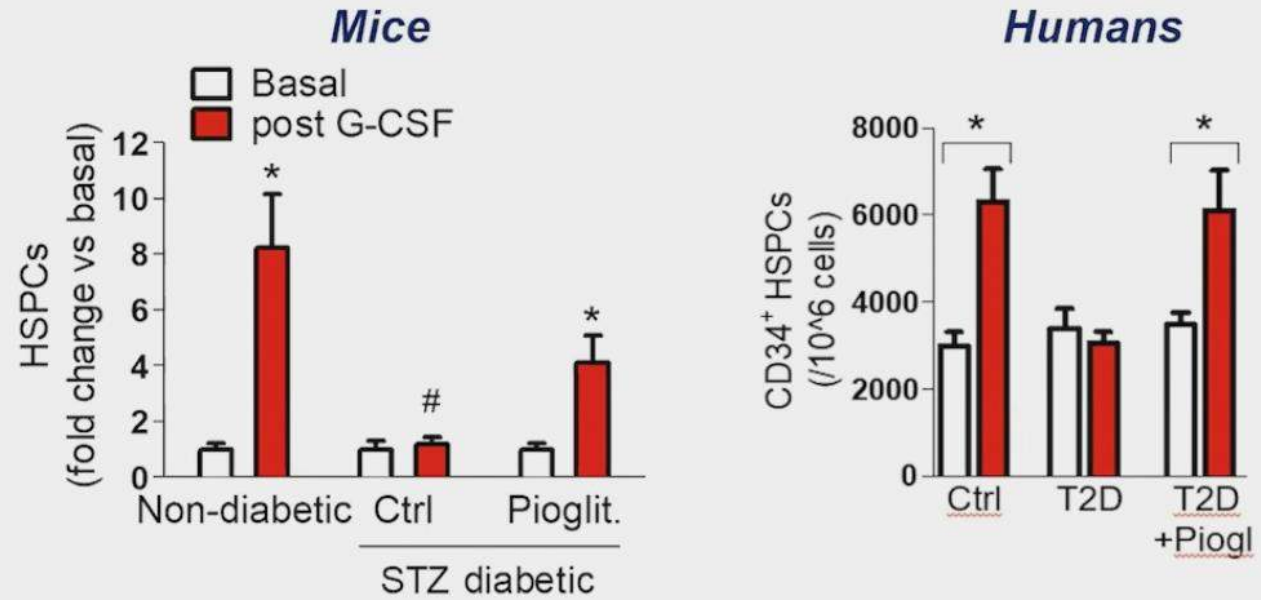
Albiero ve ark, Diabetes 2015

PPAR Gama MaQ2 >MaQ1

Bouhlei ve ark, Cell Metab 2007



Pioglitazon, HHPH sayısını artırır



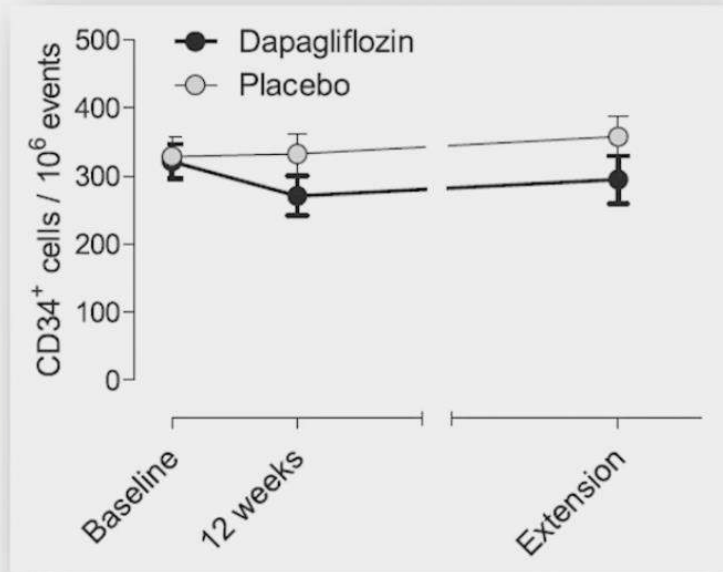
- Pioglitazon > Metformin
- Glisemik kontrolden bağımsız etki
- DPP-4 e göre, daha uzun sürede etki gösterir

Hiperglisemi ---Miyelopoezi aktive eder ve PMNLs birikimi ARTAR

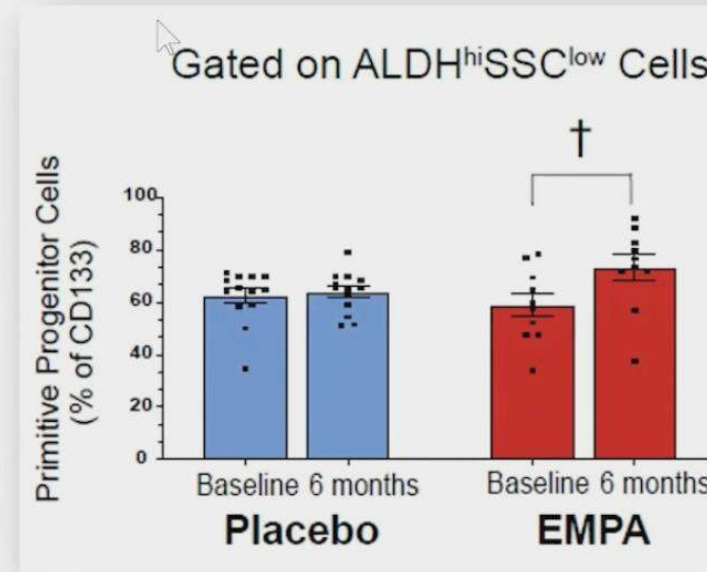
- PPAR-Gamma aktivasyonu kemik iliğinde makrofajları yeniden programlayarak antiinflamatuvar fenotipe Yönlendirir
- CXCL12 konsantrasyonu azalır ve HKPK perifere çıkar

- Esposito K, Diabetes Obes Metab 2011, Wang CH, Am Heart J 2006, Albiero M,Diabetes 2015

SGLT-2 İNHİBİTÖRLERİ VE PROGENİTÖR HÜCRELER

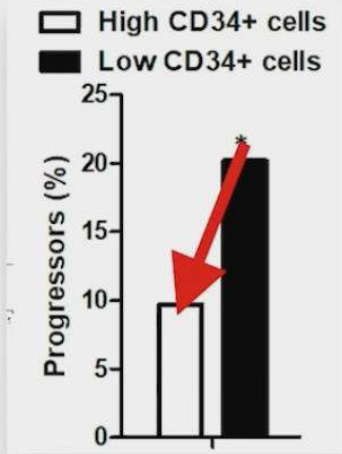


No direct effect of dapa or empa on HSPCs and EPCs in T2D

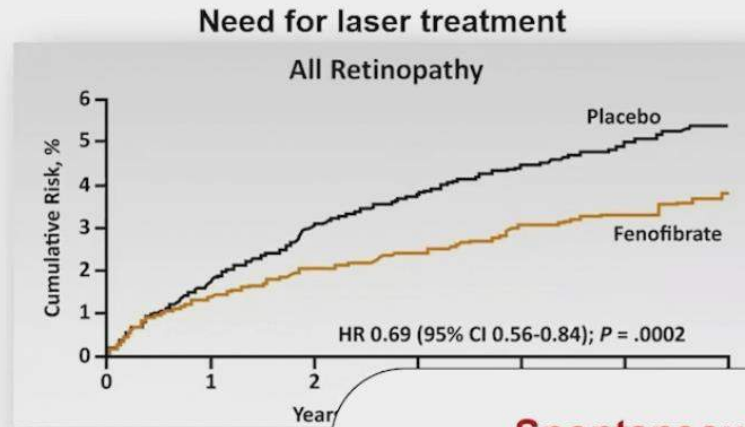


Link between SGLT2 inhibitor and recovery of circulating pro-vascular cells in T2D

PPAR ALFA ? FENOFIBRAT ??



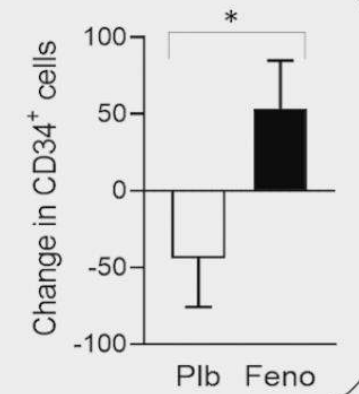
Rigato et al. JCEM 2015



FIELD study, Lancet 2008

Spontaneous trial

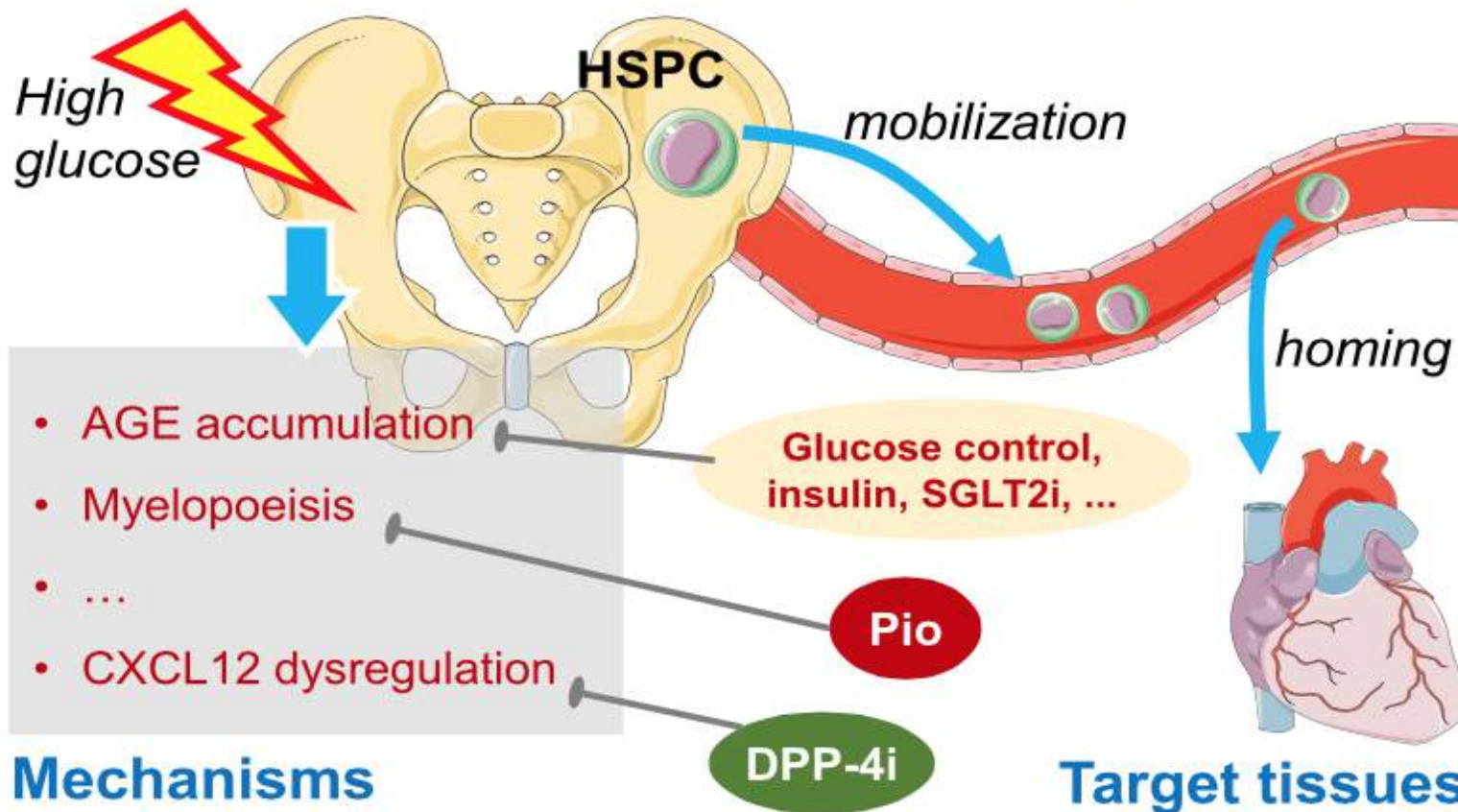
- 41 patients with diabetic retinopathy
- Randomized to Feno or placebo
- HSPCs examined at baseline and 12 wks



unpublished data

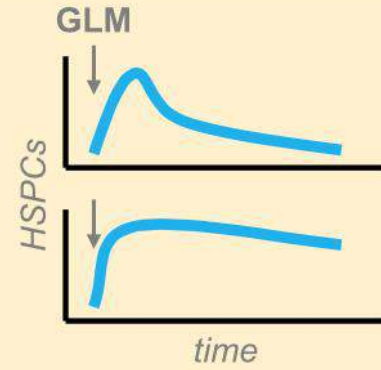
Bone marrow

Peripheral blood



(—● inhibition)

**Etki Kalıcı mı
Geçici mi**

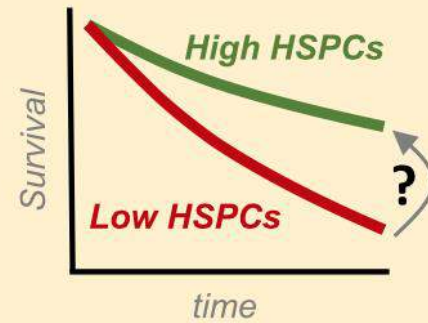


**Diğer
ilaçlar?**



- Statins
- RAS blockers
- G-CSF
- Plerixafor
- ...

**Artan HKPH
Diyabetik
sonlanımı
etkiliyor mu?**



???

SONUÇ OLARAK



- Diyabetik hastada kök hücre mobilopatisi
 - Diyabetik komplikasyon????
- Diyabetik hastada kemik iliği kök hücre trafiği bozulmuş
- HKPH /EPH sayısı azalmış
- Antidiyabetik tedaviler ile hücre sayısı artıyor
- Kardiyovasküler sonlanım??
- GLP-1 ?? SGLT-2 ??



Bildiğim bir şey
varsa, o da hiçbir
şey bilmediğimdir

SOCRATES