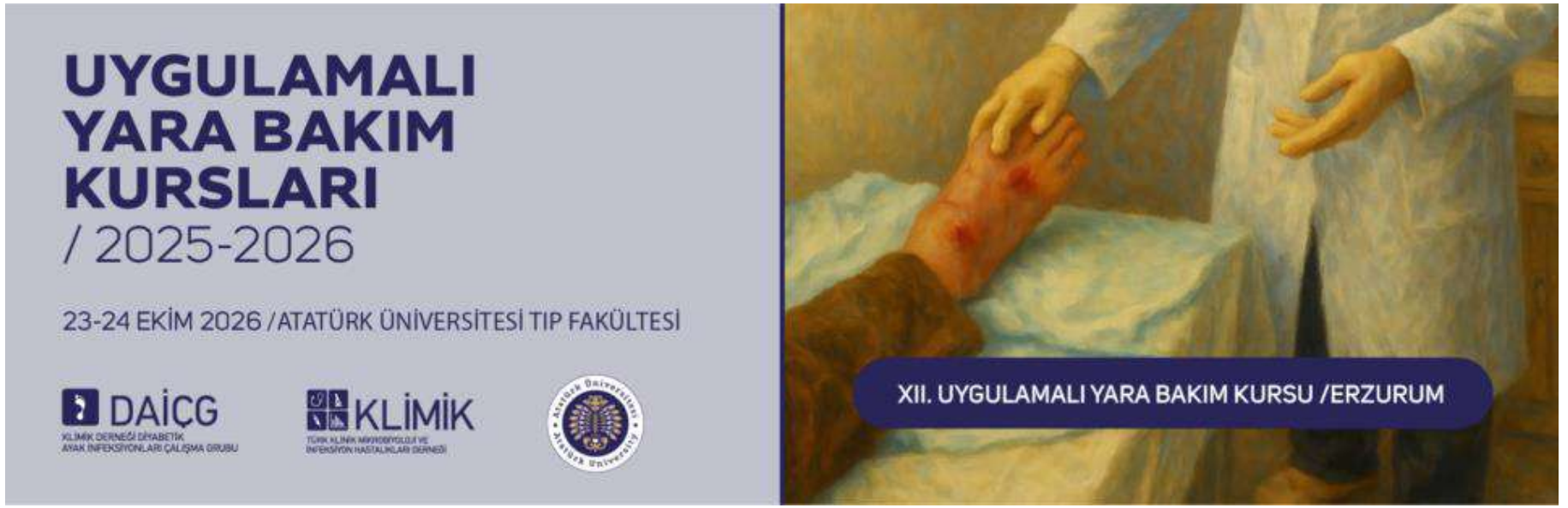
İZMİR KÂTİP ÇELEBİ ÜNİVERSİTESİ



ATATÜRK EĞİTİM VE ARAŞTIRMA HASTANESİ İZMİR

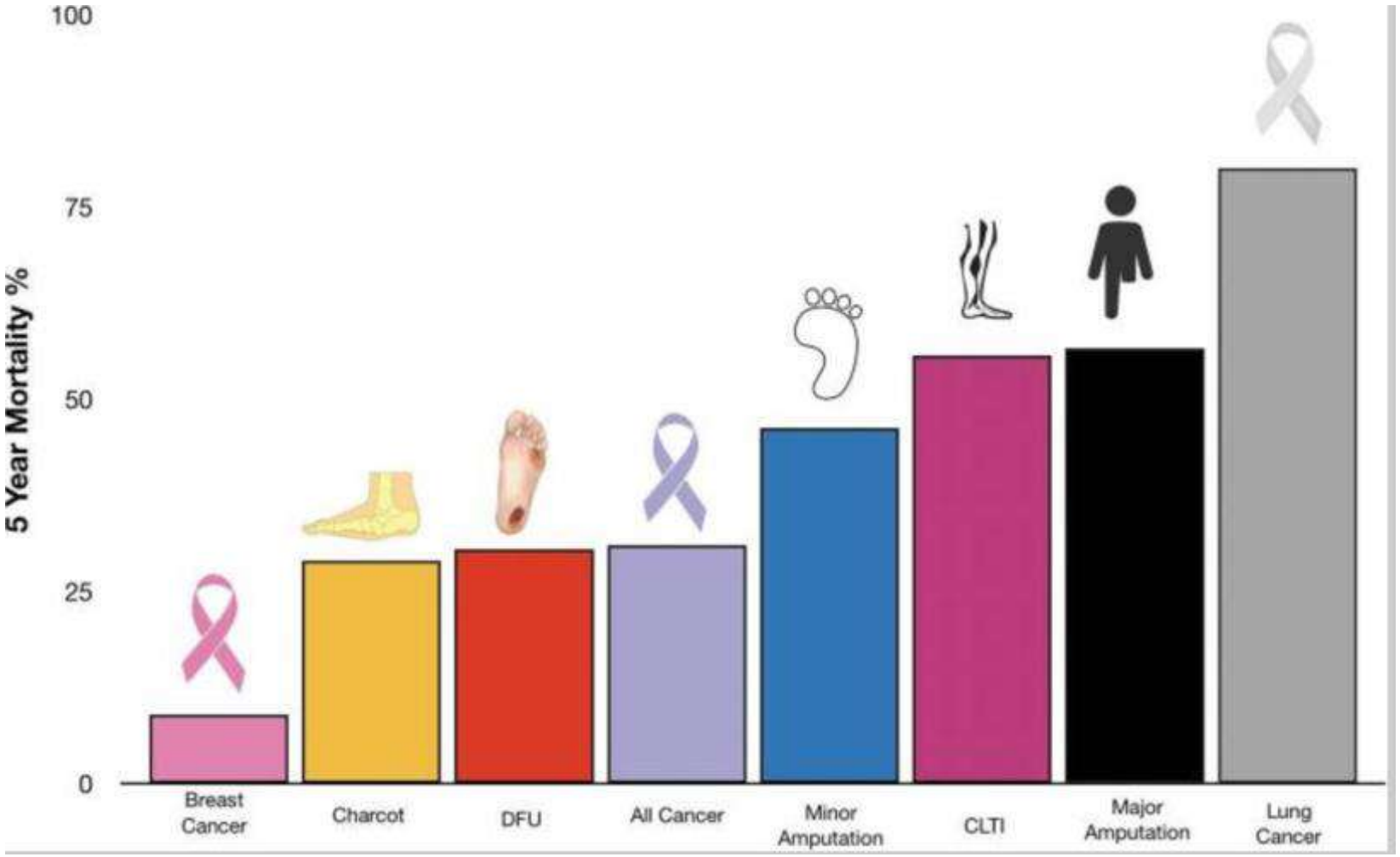
Büyüme Faktörleri
Hücresel Tedaviler
Hiperbarik-Topikal Oksijen
Plasma
GETAT

Alper Şener

Kronik yara neden önemli?

- Kronik yaralar dünya genelinde **%1–2 prevalans**
- Diyabetik ayak ülserleri:
  - amputasyonların **%85'i ülser sonrası**
  - mortalite bazı kanserlerle benzer…

Klinik tablo	**5-yıllık mortalite**
Diabetik ayak ülseri	%~30–35
DFU sonrası majör ampütasyon	%50–70
Diyaliz + DFU	>%70–75 (2-yıllık)
Venözbacak ülseri	%~20–25
Bası yarası/ülser (yaşlılarda)	>% 40



Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res. 2020 Mar 24;13(1):16. doi: 10.1186/s13047-020-00383-2. PMID: 32209136; PMCID: PMC7092527.

Parametre	Diyabetik Ayak Ülseri (DFU)	Kanser
Toplam sağlık harcaması (ABD)	Diyabet: ~237 milyar $, bunun ~%30'u alt ekstremite komplikasyonları (1)…72 milyar $	~80 milyar $ (2015 verisi) (1)
DFU'nun ulusal sağlık bütçesine etkisi	İngiltere'de NHS bütçesinin %0.8–0.9'u (2)	Kanserle karşılaştırılabilir veya bazı ülkelerde daha düşük
Yıllık DFU toplam maliyet (ABD)	9–13 milyar $ (1)	Kanser toplam maliyeti daha yüksek ama DFU spesifik olarak bazı kanserlerle benzer
Kişi başı maliyet	~11.000–23.000 $ / hasta (3)	Kanser türüne göre çok değişken (genelde yüksek ama heterojen)
Amputasyon durumunda maliyet	~49.000 $/hasta (4)	Cerrahi + onkolojik tedavi maliyetleri yüksek
Sağlık sistemi yükü	Diyabet maliyetinin %30'una kadarını oluşturur (1)	Büyük global yük, ancak DFU kadar "önlenebilir" değil
Dolaylı maliyet (iş gücü kaybı)	**Çok yüksek** (uzun bakım, sakatlık, amputasyon) (1,3,)	Yüksek (iş gücü kaybı, erken mortalite)
5 yıllık mortalite	**~%30–56 (amputasyonda daha yüksek)** (1,4) KBY'de >%70	Ortalama ~31% (kanser türüne göre değişir) (1)
Ekonomik karşılaştırma sonucu	DFU maliyet ve mortalite açısından kanserle **karşılaştırılabilir**	Referans hastalık

1. Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res. 2020 Mar 24;13(1):16. doi: 10.1186/s13047-020-00383-2. PMID: 32209136; PMCID: PMC7092527.
2.Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G, Sutton-Smith M, Todd G, Young B, Jeffcoate WJ. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med. 2019 Aug;36(8):995-1002. doi: 10.1111/dme.13973. Epub 2019 Jun 5. PMID: 31004370.
3. Kuşcu, B.; Gürbüz, K. A Cost Analysis of Diabetic Hand Infections: A Study Based on Direct, Indirect, and One-Year Follow-Up Costs. *Healthcare* **2025**, *13*, 1826. https://doi.org/10.3390/healthcare13151826
4. Syed MH, Salata K, Hussain MA, et al. The economic burden of inpatient diabetic foot ulcers in Toronto, Canada. *Vascular*. 2020;28(5):520-529. doi:10.1177/1708538120923420

Diyabetik ayak ülseri varlığı 5 yıllık mortaliteyi 2.5 kat arttırıyor

Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med 2016;33:1493-8.

Diyabetik ayak ülserlerinin >%50 enfekte…

Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54(12): e132-e173. 12.

Orta / Ağır Diyabetik ayak enfeksiyonlarının ortalama %20'si ampütasyon ile sonuçlanıyor…

Ülsere eşlik eden periferik arter hastalığı enfeksiyon ve ampütasyon riskinin arttıran en önemli bağımsız risk faktörü

Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017 Jun 15;376(24):2367-2375. doi: 10.1056/NEJMra1615439. PMID: 28614678.

Basit ülserlerde 5 yıllık mortalite %30, amputasyon sonrası mortalite %70, renal replasman tedavisi alanlarda 2 yıllık mortalite %74…

Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. JAMA. 2023 Jul 3;330(1):62-75. doi: 10.1001/jama.2023.10578. PMID: 37395769; PMCID: PMC10723802.

ABD-diyabetik ayak ülserinin yıllık tedavi maliyeti 9-13 milyar dolar

22.3 milyon DM hastası, 245 milyar dolar ilaç-tedavi gideri…176 milyar dolar sağlık, 69 milyar dolar iş gücü kaybı

Tedavi maliyeti diyabetik ayak ülseri

- İlk tanı anında ortalama 4,595 ile 35,000 dolar
- Ülser varlığı göre ortalama yıllık hasta başına 11,710- 16,883 dolar ek maliyet

Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care. 2014;37(3):651-8. doi: 10.2337/dc13-2176. Epub 2013 Nov 1. Erratum in: Diabetes Care. 2014 Sep;37(9):2660. PMID: 24186882.

YARANIN TAM KAT KAPANMASI



S

SOSYAL FAKTÖRLER

R

REJENERASYON-HÜCRESEL AKTİVİTE

E

EPİTELİZASYONUN UYARILMASI

M

NEM DENGESİNİN SAĞLANMASI

I

ENFEKSİYON -ENFLAMASYONUN KONTROLÜ

T

DOKU YÖNETİMİ-DEBRİDMAN-REVASKÜLERİZASYON

Konvansiyonel ülser tedavisi?

- Medikal…AB, antiagregan, KŞ regülasyonu…
- Cerrahi…debridman, flap, graft…ampütasyon…
- Makrovasküler onarım… girişimsel kapalı, açık cerrahi…
- Mikrovasküler onarım?
- Nöropati…ağrı varsa…medikal, cerrahi
- Nöroprotektif ? Nöropreservatif yöntemler?
- Yükten kurtarma…
- Eğitim…hasta, yakını…
- Pansumanlar ve diğer yöntemler …

İleri düzey yara bakım/tedavisi?

1. **Hücreler**
   -Kök hücre
   -Fİbroblast…
   -Exosomlar (tam olarak hücre değil aslında)**…**göbek kordonu wharton jeli…
   -3D yazıcılar ile hücre-doku…
2. **Sinyal Molekülleri**
   -Büyüme faktörleri…
   -PRP, PRF…
3. **İskelet Yapılar (Scaffolds)**
   -Amniyotik membran,
   -Ekstraselüler matriks (dermal / epidermal) analogları…
4. **Bunların kombinasyonları…**

Diğer İleri düzey yara bakım/tedavisi?

- TWOT
- Plazma
- ESWT…

Önemli uyarı…kulağa küpe olacaklar…

- Bu hastaların metabolik kontrolü ilk basamaktır…
- HbA1c<6.1
- LDL Kolesterol optimum <130
- Kan gitmeyen doku iyileşemez…
- Enfeksiyon kontrol altına alınmayan doku iyileşmez…
- Yükten kurtarma olmadan bu tedaviler başarılı olmaz…plantar yüz…
- TİME yara bakımında ilk tedavi aşamasıdır… **TİMERS**

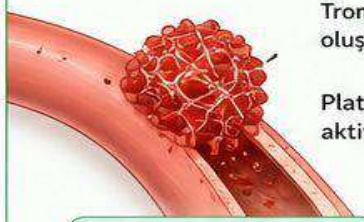
Bir yara neden iyileşmez?

YARA İYİLEŞMESİ: NORMAL vs KRONİK

Kronik Yara: İnflamatuar Fazda Takılma ve Sitokin Dengesizliği

NORMAL YARA İYİLEŞMESİ FAZLARI

1 HEMOSTAZ
(Dakikalar – Saatler)

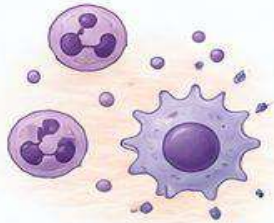


Trombüs oluşumu

Platelet aktivasyonu

PDGF, TGF-β salınımı

2 İNFLAMASYON
(1 – 3 Gün)

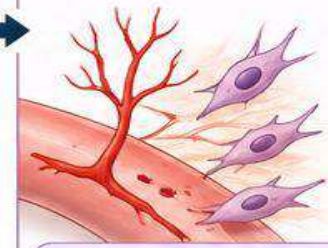


Nötrofiller bakteri ve debris temizliği

Makrofajlar sitokin salınımı

IL-1, TNF-α, IL-6 (proinflamatuar sitokinler)

3 PROLİFERASYON
(3 – 21 Gün)



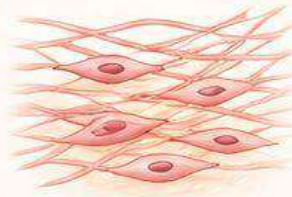
Fibroblast aktivasyonu

Anjiyogenez

Kollajen üretimi

VEGF, FGF, EGF, PDGF, TGF-β (büyüme faktörleri)

4 REMODELLING
(Haftalar – Aylar)

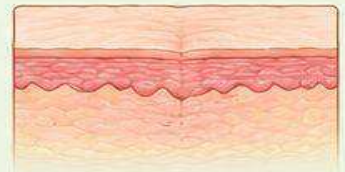


Kollajen reorganizasyonu

Skar maturasyonu

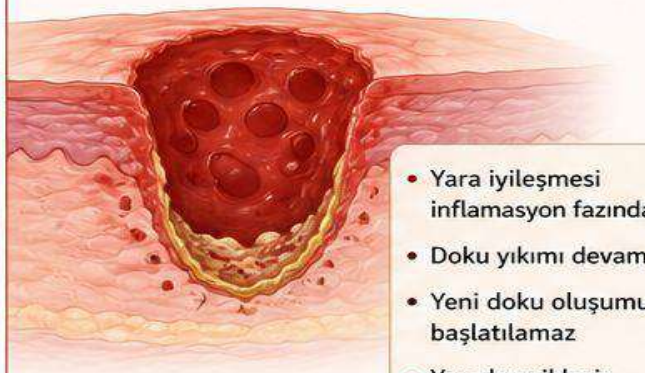
VGF-β, MMP'lerin düzenlenmesi

SONUÇ



- Doku bütünlüğü sağlanır
- Enfeksiyon kontrolü
- Fonksiyonel iyileşme

KRONİK YARA: İNFLAMATUAR FAZDA TAKILMA

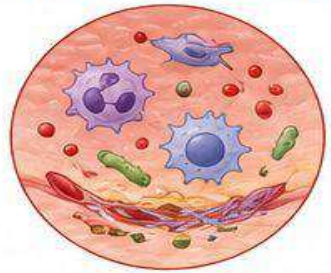


- Yara iyileşmesi inflamasyon fazında kalır
- Doku yıkımı devam eder
- Yeni doku oluşumu başlatılamaz
- Yara kronikleşir

ARTANLAR
(İNFLAMASYON DEVAM EDER)

- MMP'ler ↑↑ (Matrix Metalloproteinazlar)
- TNF-α ↑
- IL-1β ↑
- IL-6 ↑
- Proteaz aktivitesi ↑

KRONİK YARADA SİTOKİN DENGESİZLİĞİ



PERSISTAN İNFLAMASYON
(İNFLAMATUAR FAZDA TAKILMA)

DOKU YIKIMI > ONARIM
YARA KAPANMAZ

AZALANLAR
(ONARIM BAŞLATILAMAZ)

- PDGF ↓
- VEGF ↓
- TGF-β ↓
- FGF ↓
- Fibroblast aktivitesi ↓
- Kollajen ve ECM üretimi ↓

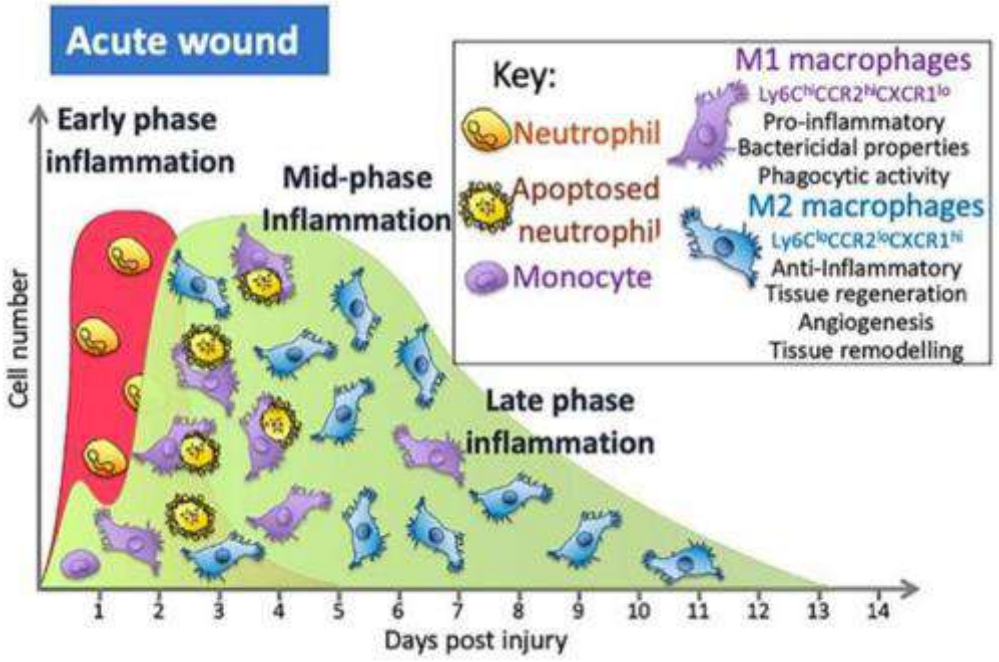
SONUÇ

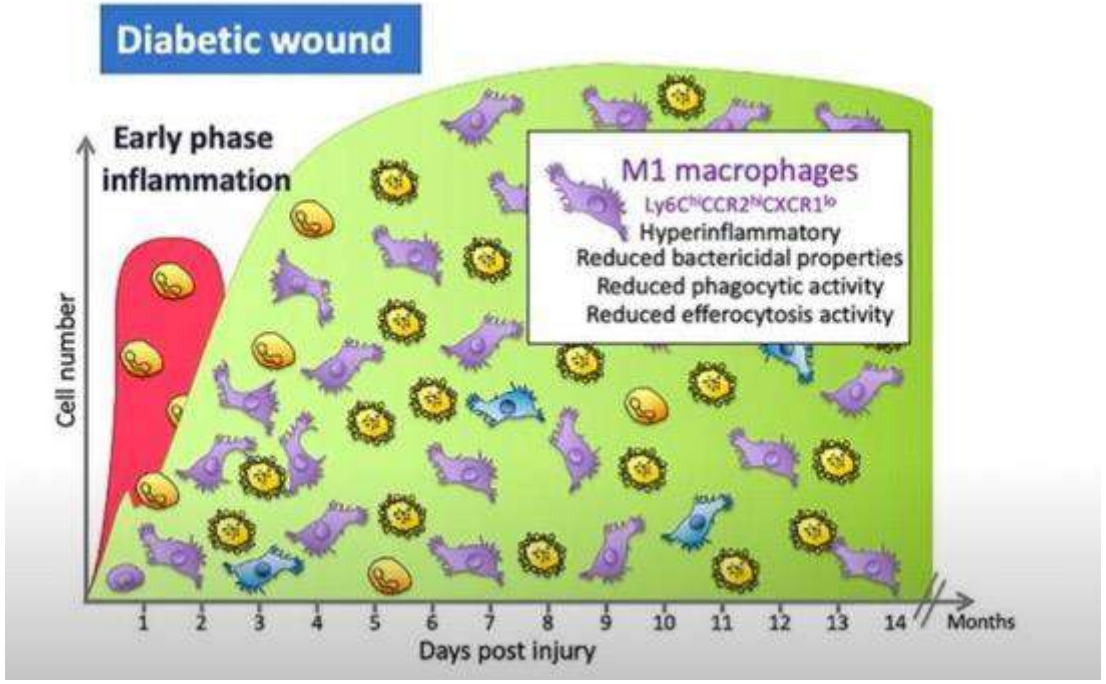
- Kollajen yıkımı artar
- Büyüme faktörleri azalır
- Anjiyogenez bozulur
- Epitelizasyon gerçekleşmez
- Enfeksiyon riski artar

Klinik sonuç:
Geç iyileşme, nüks, amputasyon riski ve yaşam kalitesinde azalma

ANA MESAJ Kronik yaralar, yalnızca yavaş iyileşen yaralar değildir; kalıcı bir inflamatuar durumda "takılı kalan" kompleks biyolojik lezyonlardır.

Kaynaklar: Schultz GS et al. Nat Rev Dis Primers. 2021;7:31.
Gurtner GC et al. Nature. 2008;453:314-321.
Sen CK. Diabetologia. 2019;62:1910-1922.

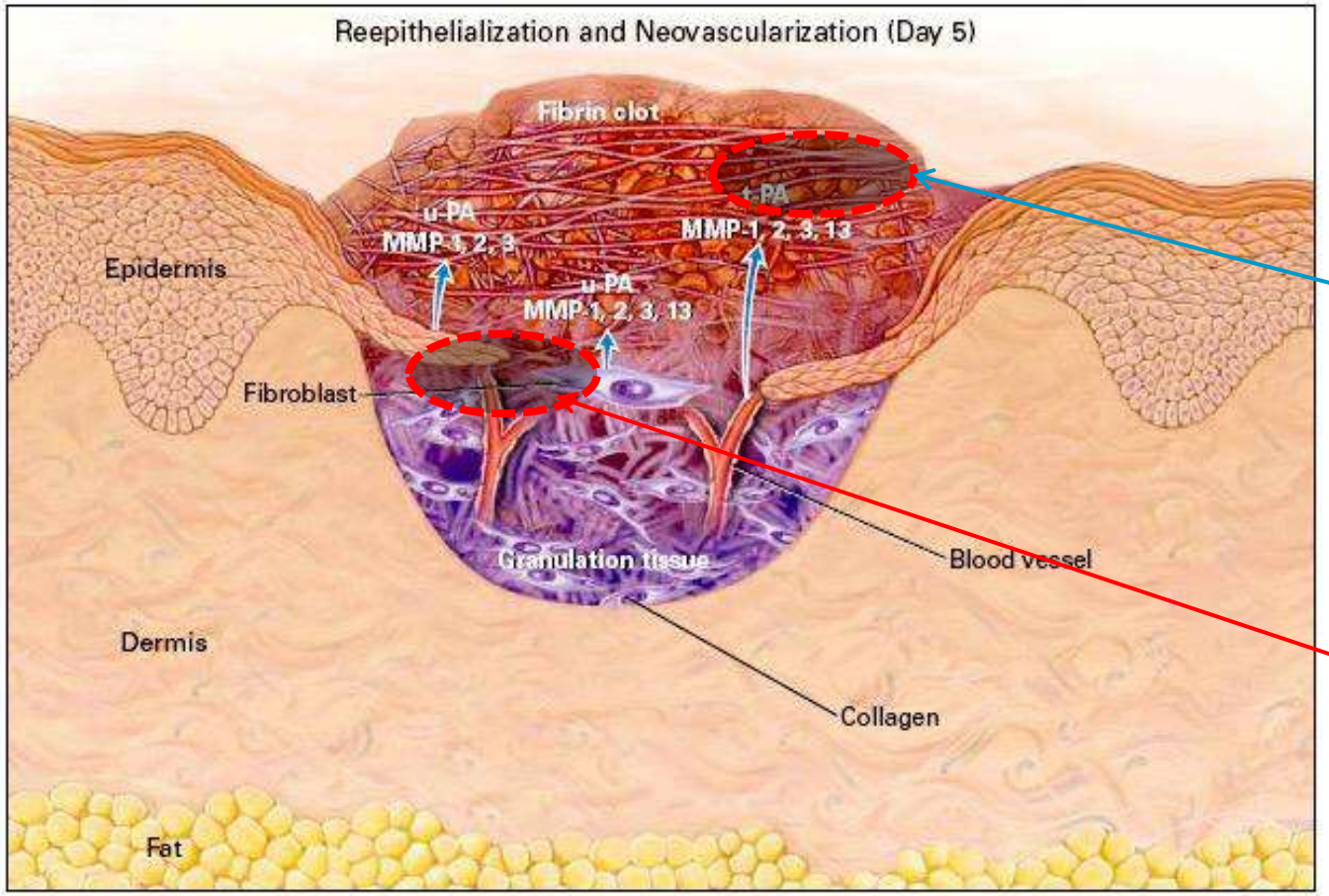




- Nötrofil, mast hücre artışı, inflamatuar yanıt artışı
- Arteriyel okluzyon ve mikrosirkulasyon yetmezliği
- Mikrosirkülasyonda kaçaklar
- Angiogenez bozulması…
- Fibroblast aktivitesi bozulması…
- Hipoksik doku hasarı… oksidatif stress
- ECM organizasyonu kötü, persistan inflamasyon
- M2 ye dönüş azalması…bozulmuş fibroblast aktivitesi

Kronik Yarada Oksijen Seviyesi Düşüktür

- Hipoksik ortam
- Biyofilm
- Fibrinöz eksüda
- Bozulmuş granülasyon
- Doku yıkım enzimleri (sitokromoksidaz, matriks metalloproteinaz, kollajenaz, hyalülonidaz)
- Yarım-yamalak oluşan kollajen lerin yıkımı…



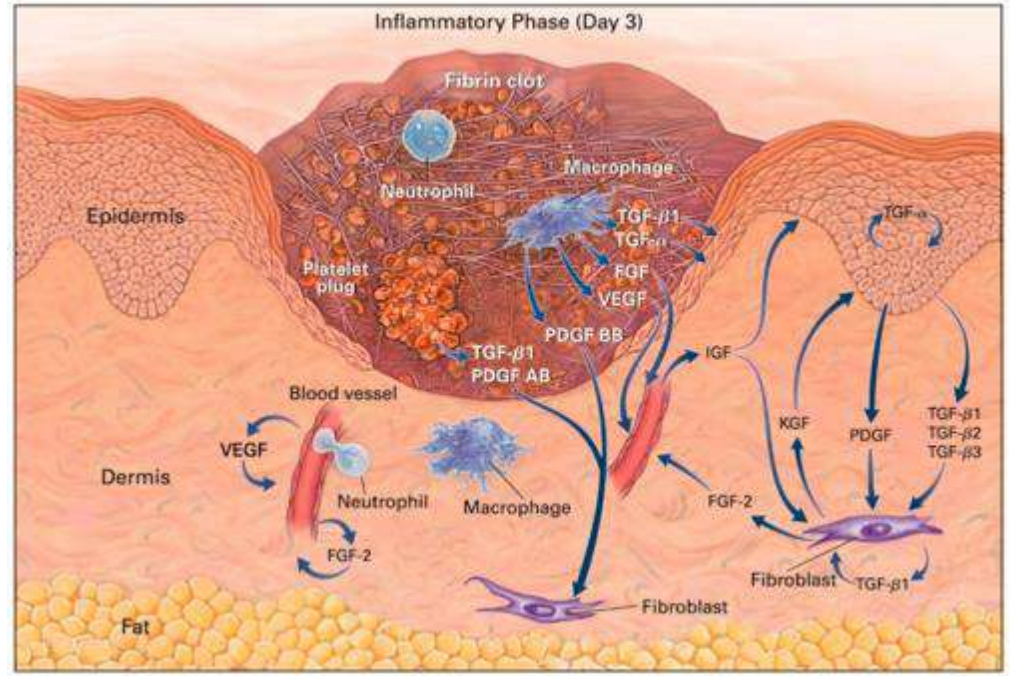
Yara yüzeyindeki pO_2 60 mmHg

Yara merkezindeki pO_2 <10 mmHg

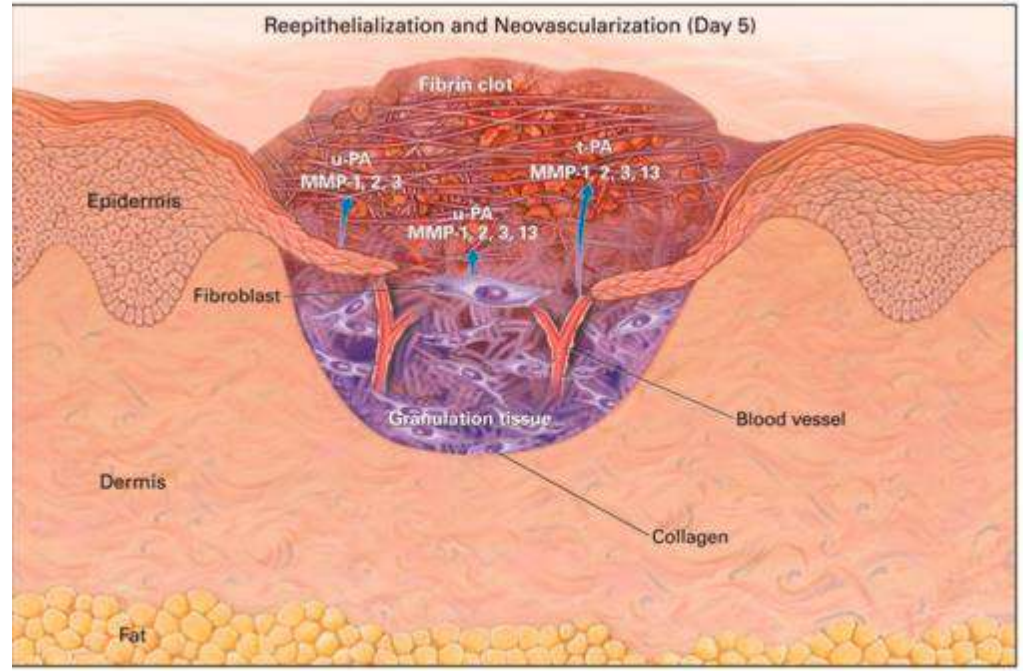
Source: Singer & Clark, N Engl J Med, 1999

Vasküler yatak normal bile olsa, vasküler yan yollar ve çalma ile doku hipoksisi kaçınılmaz

Growth Factor	Cell Source	Primary Action in Wound Healing
PDGF family		
PDGF	Platelets Fibroblasts Macrophages Vascular endothelial cells Vascular smooth muscle cells	• Chemotactically attracts fibroblasts, neutrophils, monocytes, and smooth muscle cells to the wound • Activates macrophages to release growth factors • Promotes fibroblast proliferation and production of extracellular matrix
VEGF	Platelets Fibroblasts Macrophages Keratinocytes	• Stimulates (lymph)angiogenesis • Enhances endothelial cell migration and proliferation
EGF family		
EGF	Platelets Fibroblasts Macrophages	• Stimulates the proliferation of keratinocytes, fibroblasts, vascular endothelial cells • Enhances the production of fibronectin
TGF-α	Platelets Macrophages Keratinocytes	• Similar to EGF • Induces angiogenesis
IGF family		
IGF	Fibroblasts Macrophages Neutrophils Hepatocytes	• Promotes re-epithelialization • Stimulates fibroblast proliferation
FGF family		
bFGF	Fibroblasts Macrophages Endothelial cells	• Acts as a mitogen for fibroblasts • Induces angiogenesis • Stimulates granulation tissue formation, matrix remodeling, and re-epithelialization
KGF	Fibroblasts	• Acts as a mitogen for epithelial cells
TGF-β family		
TGF-β1-3	Platelets Fibroblasts Macrophages Keratinocytes	• Acts as a potent chemoattractant for macrophages • Acts as a mitogen for fibroblasts • Stimulates or inhibits proliferation of various cells • Promotes granulation tissue formation and its tensile strength



A



B

Patogenezde en önemli noktalardan biri



Diyabetik ayak yarası = doku büyüme faktörü eksikliği

İnsan Kaynaklı Rekombinant Epidermal Büyüme Faktörü

Epidermal büyüme faktörü (epidermal growth factor) ilk kez 1922 doğumlu, 1986 yılında Nobel fizyoloji veya tıp ödülünü almış olan Stanley Cohen tarafından bulunmuştur.

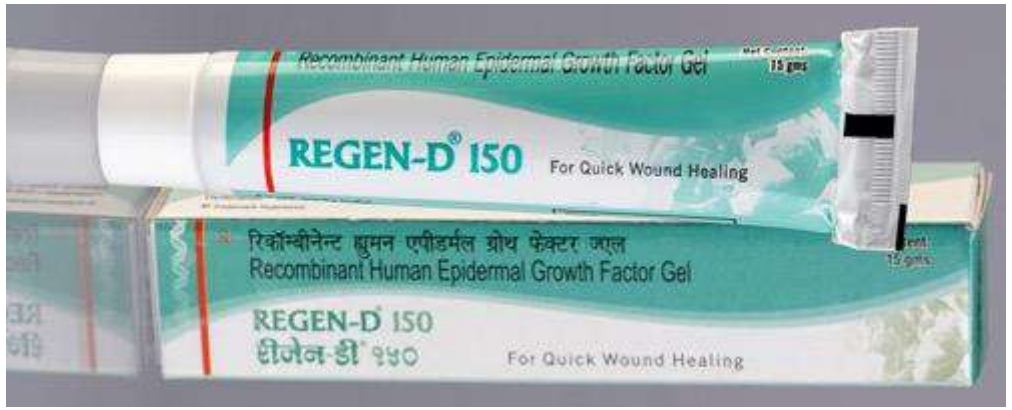


EGF evrim sırasında korunmuş eski bir polipeptid olup birçok hayvan türünde bulunur ve türler arasında benzerliği yüksek bir yapıya sahiptir. 53 amino asitten oluşan bir polipeptittir.

Vücutta hasar durumunda trombositlerden bol miktarda üretilir (diyabetik ayak ülserinde PRP uygulamasını hatırlayınız). Acil durumda hücre çoğalmasını sağlamak için vücut sıvılarında hazır halde de bulunur.

Kaynak- Heberprot-P tanıtım özetinden alınmıştır

Türkiye'deki tek topikal rhEGF 150



- Topikal jel
- Yüzeysel uygulama
- Günde iki kez

- Toz
- Jel
- Krem

- bFGF-basic fibroblast growth factor
- aFGF- acidic fibroblast growth factor
- GM-CSF
- PDGF- plateled derived growth factor

Table 6. Application parameters of topical growth factors for skin wounds

Growth factor	Dosage form	Concentration	Common dose	Frequency	References
bFGF	Powder	Adjustable preparing solution	150 IU/cm^2 or 1 μg/cm^2	Once or twice per day	4–6,8,9,13,14,16,24,27
	Gel	2100 IU/g	150 IU/cm^2	Once per day	96–99
aFGF	Powder	Adjustable preparing solution, e.g. 1000 IU/mL	100 IU/cm^2	Once per day	42–43,45
EGF	Powder or solution	Adjustable preparing solution, e.g. 2000 IU/mL or 2.5 to 5.0 μg/mL or 10.0 μg/g	400 IU/cm^2 or 80 ng/cm^2	Once per day	21,100–103
	Gel or cream	10 μg/g or 20 to 40 μg/g	1 μg/cm^2 or 50 000 IU/cm^2 or 80 ng/cm^2	Once every 1–4 days	60,67,104–107
GM-CSF	Powder	Adjustable preparing solution	5 μg/cm^2	Once per day	108
	Gel	10 μg/g	1 μg/cm^2 or 10 μg/cm^2	Once per day	80–83,89
PDGF	Powder	Adjustable preparing solution, e.g. 100 μg/mL	10 μg/cm^2	Once per day	93
	Gel	10 μg/g	10 μg/cm^2	Once per day	90–92,94–95

bFGF basic fibroblast growth factor, *aFGF* acidic fibroblast growth factor, *EGF* epidermal growth factor, *GM-CSF* granulocyte macrophage colony stimulating growth factor, *PDGF* platelet-derived growth factor

Chun-mao Han et all. Clinical guideline on topical growth factors for skin wounds. *Burns & Trauma,* 2020, 8, tkaa035

Table 3. Quality of evidence and Grading of Recommendations Assessment Development and Evaluation (GRADE) recommendations for topical application of epidermal growth factor in different types of wounds

Wound type	Quality of evidence	GRADE recommendation	References
Superficial partial-thickness burns	Moderate	Weak	47–59
Deep partial-thickness burns	Moderate	Weak	47–62
Donor sites	Moderate	Weak	47–51
Redisual granulation wounds after burns	Moderate	Weak	48,50,51,53
Diabetic foot ulcers	High	Strong	47,63–70
Venous ulcers	Moderate	Weak	71–73
CO_2 laser treated wounds	Moderate	Weak	74–76
Grafted wounds	Low	Weak	48
Chronic ulcers after burns	Low	Weak	48,53
Radiative dermatitis wounds	Low	Weak	77
Leg ulcers	Low	Weak	78

Aslında sadece diyabetik ayak ülserlerinde kanıt düzeyi yüksek bulunmuş ve kuvvetle kullanımı önerilmiş

Chun-mao Han et all. Clinical guideline on topical growth factors for skin wounds. *Burns & Trauma,* 2020, 8, tkaa035

Evaluation of the efficacy and safety of topical epidermal growth factor Regen-D® in diabetic foot wounds: a randomised, parallel group phase III study

Bulent M Ertugrul, Nur Yapar, Meltem Taşbakan, Arife Polat Duzgun, Emre Ozker, Şamil Aktaş, Başar Kaya, Murat Ilkar Gelisen, Volkan Öztuna, Işık Şenkaya Sığnak and Mevlüt Türe

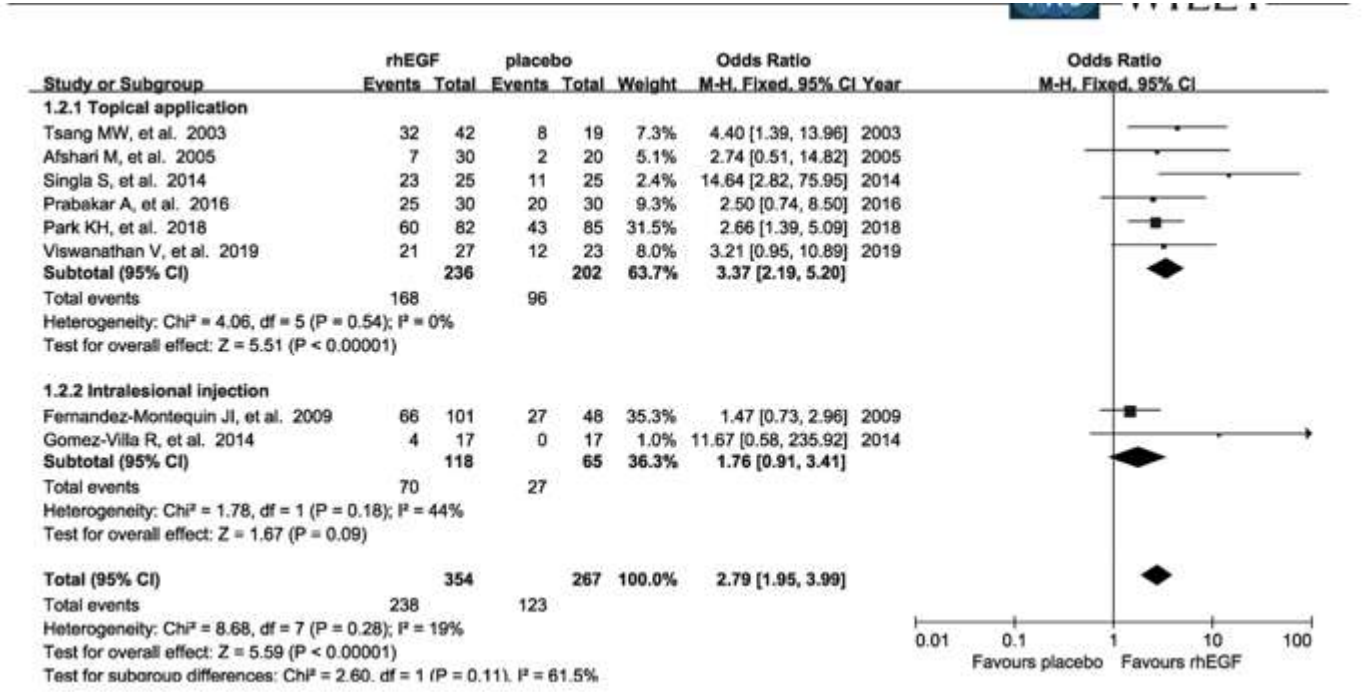
- Çalışma grubu 76 vs kontrol 66 (standart tedavi)…G1, 2…
- 1. Ay'dan itibaren etki başlamış…
- İlk ayda; kapanma 2 kat yüksek, granülasyon aynı…
- İkinci ayda; istatistiksel anlamlı fark yok,
- Dördüncü ayda- çalışma sonunda; kapanma 2 kat yüksek…
- Çalışma sonunda; yanıtsız çalışma grubunda 9 kat daha az….
- Rekürrens çalışma grubunda hiç yok- 10 ay izlem…

Table 2. Results of patient evaluations.

Month 1 evaluation	**Control group (*n*=66)**	**Study group (*n*=76)**	***P*-value**
No granulation	5 (7.6)	1 (1.3)	0.152
Existence of granulation	55 (83.3)	60 (80.0)	0.774
Wound closure	6 (9.1)	14 (18.7)	0.165
Month 2 evaluation	**Control group (*n*=50)**	**Study group (*n*=63)**	***P*-value**
No granulation	4 (8.0)	4 (6.3)	0.984
Existence of granulation	28 (56.0)	30 (47.6)	0.485
Wound closure	18 (36.0)	29 (46.0)	0.379
Month 4 evaluation	**Control group (*n*=56)**	**Study group (*n*=60)**	***P*-value**
No granulation	7 (12.5)	2 (3.3)	0.064
Existence of granulation	32 (57.1)	19 (31.7)	<0.001
Wound closure	17 (30.4)	39 (65.0)	0.006
End of study evaluation	**Control group (*n*=69)**	**Study group (*n*=76)**	***P*-value**
Wound	31 (44.9)	20 (26.3)	0.019
Wound closure	27 (39.1)	55 (72.4)	<0.001
No response	9 (13.0)	1 (1.3)	0.005
Recurrence	2 (2.9)	0 (0.0)	0.136

Gerçek yaşam verisi?

- Sistematik derleme…RCT…
- rhEGF vs placebo…
- PRİSMA sensitivite analizini geçen 9 çalışma,
- 720 katılımcı (404 çalışma, 316 placebo)
- 6 tane topikal uygulama
- 2 tane intralezyoner uygulama
- 1 bias nedeniyle değerlendirme dışı



rhEGF'ün gerek topikal, gerekse intralezyoner uygulaması iyileşmeyi olumlu etkiliyor…

Ding-Yun Zhao et all. Efficacy and safety of recombinant human epidermal growth factor for diabetic foot ulcers: A systematic review and meta-analysis of randomised controlled trials. Int Wound J. 2020;17:1062–1073.

Topikal vs İntralezyoner?

Meta-Analysis > Ann Vasc Surg. 2020 Jan;62:442-451. doi: 10.1016/j.avsg.2019.05.041. Epub 2019 Aug 5.

Topical Recombinant Human Epidermal Growth Factor for Diabetic Foot Ulcers: A Meta-Analysis of Randomized Controlled Clinical Trials

Qi Yang [1], Yonghong Zhang [2], Haiyang Yin [1], Yanjun Lu [1]

- Derleme, RCT
- 7 adet…610 katılımcı…
- Kıyaslama çalışması yok,
- Enfeksiyon kontrol altında,
- Osteomyelit olmamalı…????
- Topikal Wagner G1,2 (RR, 1.61; 95% CI, 1.32 to 1.97; I^2 = 0%)
- İntralezyonel daha derin ülserde etkili (RR, 2.06, 95%, CI 0.35 to 12.22; I^2 = 50%).

Topikal = G1,2
İntralezyoner >2

1. Güvenlik verisi yetersizliği nedeniyle çocuk, hamile, emzirenler, >65 yaş uygulanması önerilmez,
2. Debridman sonrası ve enfekte olmayan yaraya uygulanması önerilir,
3. Ciddi periferik enflamasyon durumunda uygulanması önerilmez,
4. Şimdiki verilere göre en iyi etkiyi 100-1000IU/cm2'de görülür,
5. Doz sıklığı; günde birden fazla olmalıdır,
6. Toplam süre yara yatağı graftlemeye hazır oluncaya kadar kullanılabilir,
7. Farklı EGF'lerin bir arada kullanımı ile ilgili iyi sonuçlar olsa da ileri çalışmalara ihtiyaç vardır,
8. EGF ile vakum kapama ve aljinat kombinasyonu iyi sonuçlar verdiğine dair çalışmalara olsa da yeni verilere ihtiyaç vardır,
9. EGF etkisini azaltan; etanol, hidrojen peroksid, gümüş ile kombinasyon yapılmamalıdır,
10. Uygulama bölgesinde ciltte kanser şüphesi durumunda uygulanmamalıdır,

Guideline

Clinical guideline on topical growth factors for skin wounds

Chun-mao Han[1,*], Biao Cheng[2], Pan Wu[1] and writing group of growth factor guideline on behalf of Chinese Burn Association

[1]Department of Burns & Wound Care Center, the Second Affiliated Hospital of Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, China and [2]Department of Burns & Plastic Surgery, General Hospital of Southern Theater Command, PLA, No. 111 Liuhua Road, Guangzhou 510000, China

*Correspondence. Email: hanchunmao1@126.com, zrssk@zju.edu.cn

Received 20 May 2020; Revised 03 July 2020; Editorial decision 16 July 2020

Genel sonuç…G3,4 maliyet etkin

Sadece DM ayak pratiğinde mi? Etkin….

JOURNAL OF DERMATOLOGICAL TREATMENT
2019, VOL. 30, NO. 1, 96–101
https://doi.org/10.1080/09546634.2018.1468546

Taylor & Francis
Taylor & Francis Group

SHORT REPORT

Human recombinant epidermal growth factor in skin lesions: 77 cases in EPItelizando project

Jordi Esquirol-Caussa[a,b] and Elisabeth Herrero-Vila[a,c]

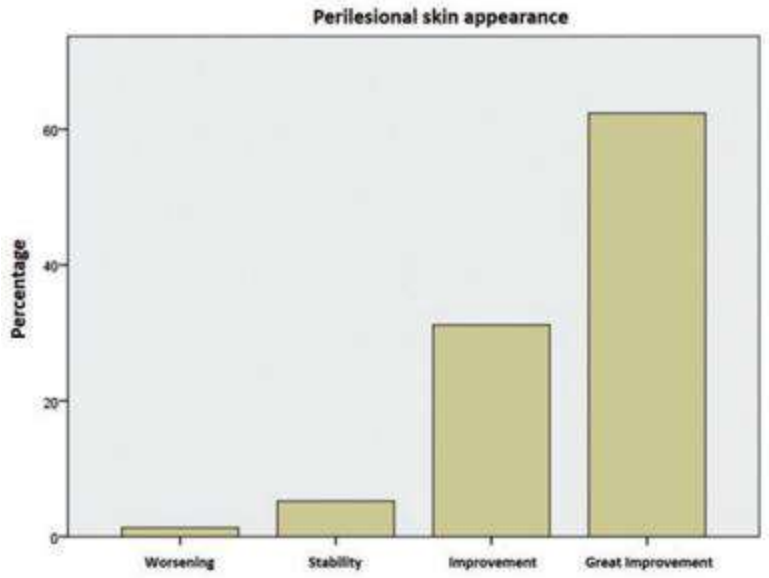
[a]Centro Médico Teknon, Barcelona, Spain; [b]Servei Universitari de Recerca en Fisioteràpia (SURF), Escoles Universitàries Gimbernat (adscrites a la Universitat Autònoma de Barcelona), Barcelona, Spain; [c]Servei de Medicina Preventiva, Àptima, Terrassa, Barcelona, Spain

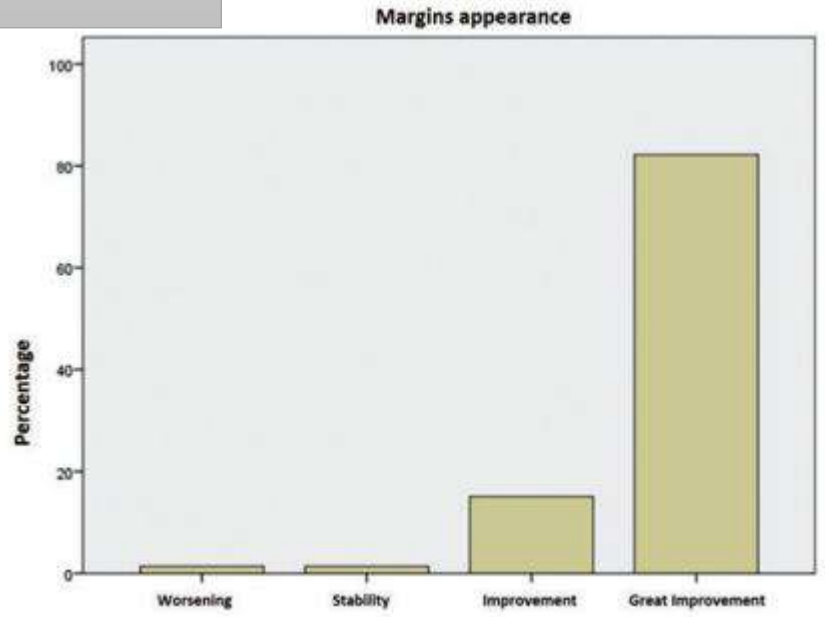
Epitelizasyon ve iyileşme

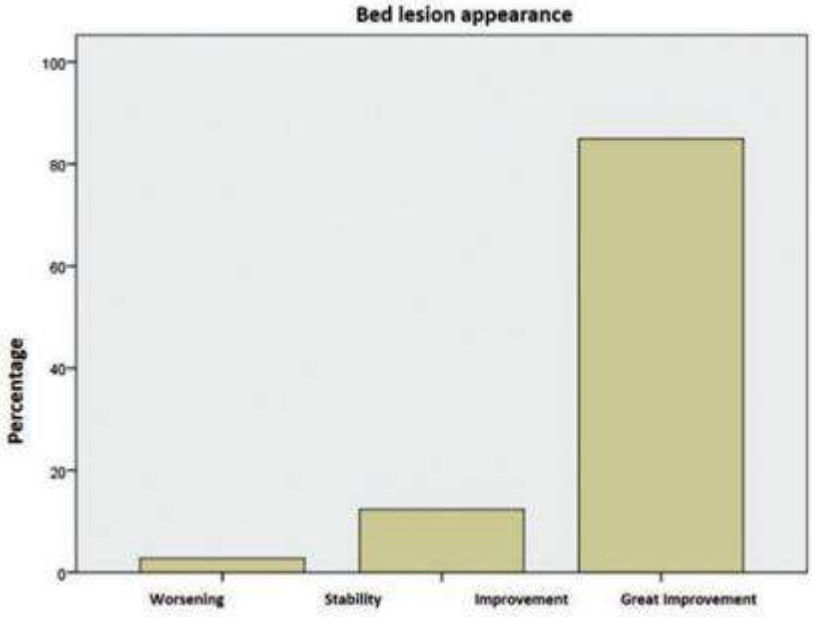
- Yara etrafında %60
- Yara sınırlarında %80
- Yara yatağında %80

Table 3. Percentage of ulcers with higher and lower than 40% healing rate in 4 weeks.

	% of healing in 4 weeks	
	<40% healing in 4 weeks *N* (%)	>40% healing in 4 weeks *N* (%)
Venous ulcer	17 (56.66)	13 (43.33)
Pressure ulcer	6 (75)	2 (25)
Diabetic foot	2 (28.57)	5 (71.43)
Posttraumatic ulcer	2 (33.33)	4 (66.66)
Vasculitis	2 (100)	–
Arterial ulcer	–	1 (100)
Hypertensive ulcer	1 (100)	–
Postgraft ulcer	1 (100)	–
Total	31 (55.36)	25 (44.64)







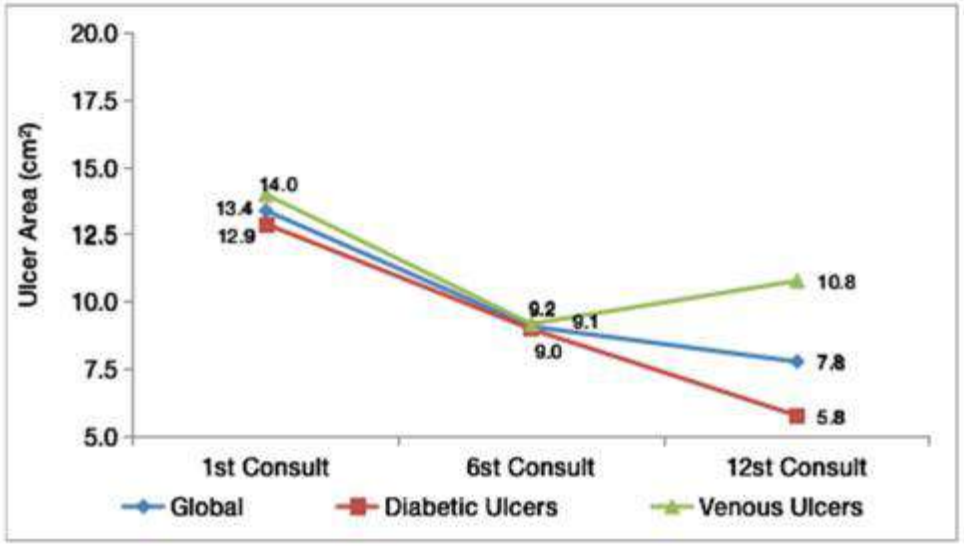
Article

rhEGF-Loaded Hydrogel in the Treatment of Chronic Wounds in Patients with Diabetes: Clinical Cases

Beatriz Guitton Renaud Baptista de Oliveira [1], Bianca Campos Oliveira [1,*], Gabriela Deutsch [2], Fernanda Soares Pessanha [3], Rossana Mara da Silva Moreira Thiré [4] and Selma Rodrigues de Castilho [2]

- Eksüdasyona etkisi?
- İyileşmeye etkisi?

- Toplam 10 hasta
- 12 hafta takip
- En hızlı düzelme venöz ülserlerde …!
- Eksüdasyonda ciddi azalma %20…Azalma olmayan yok



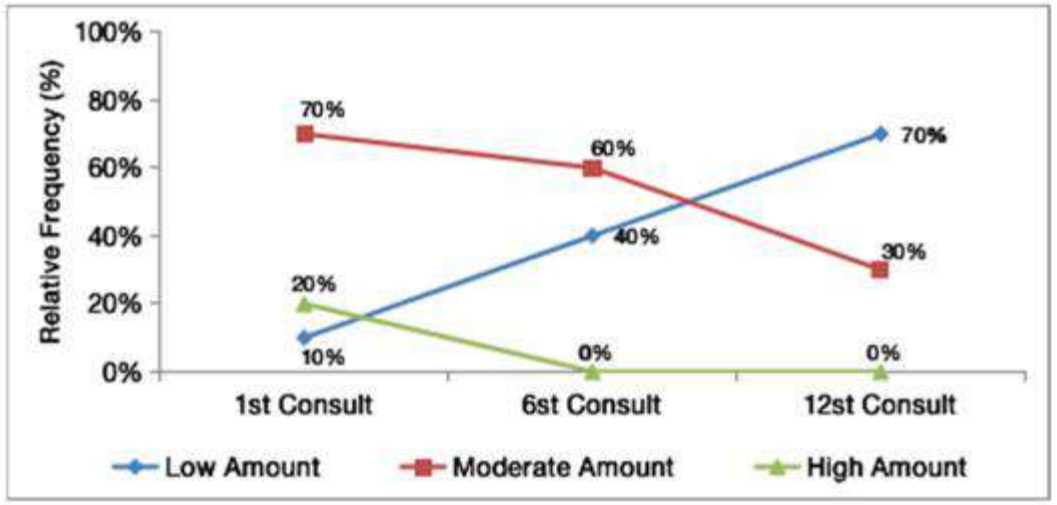


Figure 1. The evolution of the mean area of the lesion in the three evaluations.

RKÇ'larda Regen D'nin yeri?

Review Article

The Role of Recombinant Proteins and Growth Factors in the Management of Diabetic Foot Ulcers: A Systematic Review of Randomized Controlled Trials

Elahe Mahdipour[1] and Amirhossein Sahebkar[2,3,4,5]

[1]*Department of Medical Biotechnology and Nanotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Halal Research Center of IRI, FDA, Tehran, Iran*
[3]*Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*
[4]*Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[5]*Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland*

Correspondence should be addressed to Amirhossein Sahebkar; amir_saheb2000@yahoo.com

Received 23 April 2020; Accepted 29 June 2020; Published 15 July 2020

Table 4: Outcomes of RCTs that evaluated EGF safety and effectiveness.

Ref	Type of growth factor	Wound closure	Mean time to heal in treatment groups	Mechanism mentioned as complete healing		Confounders				Further outcomes	
				Granulation tissue	Reepithelialization	Sex	Baseline HbA1c	Wound size	Offloading	Recurrence rate	Amputation rate
[16]	EGF	More complete healing in the rhEGF group ($p = 0.033$); decreased in area size ($p = 0.049$); and more epithelial islands in the wound bed were present ($p = 0.025$)	8 weeks	Y	Y	NM	NM	NM	NM	NM	NM
[17]	EGF	Granulation tissue covering ≥50% of the ulcer at 2 weeks was achieved by more cases in the EGF groups ($p = 0 \cdot 000015$). Shorter time to complete healing in the 75 μg group ($p = 0.006$)	3 weeks	Y	NM	NM	NM	NM	NM	2 cases in the placebo group	29 cases in all groups
[18]	EGF	Reduced seropurulent discharge in the EGF group $p = 0.0495$ and serous discharge $p = 0.009$. More granulation tissue $p = 0.041$. More complete healing in the EGF group $p = 0.007$	17.2 ± 1.3 ($p = 0.01$)	Y	NM	NM	NM	NM	NM	NM	NM
[19]	EGF	More cases with complete healing in the 0.04% hEGF group. Patients in the 0.04% hEGF group also healed more quickly than those in the other groups ($p = 0.0003$). No significant difference in healing time between the 0.02% hEGF and control groups	6 weeks in the 0.04% hEGF group ($p = 0.0003$)	Y	Y	N	NM	NM	NM	NM	2 cases in placebo and 2 in 0.02% hEGF groups
[20]	EGF, REGEN-D150	For wounds >6 cm^2 in size treatment resulted in more healing ($p < 0.002$). A reduced healing time in the EGF group. At the end of 10 weeks, 69% of wounds healed versus 21% in placebo control	9 weeks	Y	Y	NM	NM	NM	NM	NM	NM

EGF: epidermal growth factor; Y: yes; N: no; NM: not mentioned.

- >6 cm^2 yaralarda daha etkili
- İyileşme süresinde kısalma anlamlı
- 10. Hafta sonunda %69 kapanma

rEGF gelecekteki uygulanma alanları-1

Skar tedavisinde vaka bazında etkin…



The Efficacy and Safety of Epidermal Growth Factor Combined with Fractional Carbon Dioxide Laser for Acne Scar Treatment: A Split-Face Trial

by YANISA RATANAPOKASATIT MD, MSc, and PUNYAPHAT SIRITHANABADEEKUL, MD
Both authors are with the Department of Dermatology, Chulabhorn International College of Medicine at Thammasat University in Pathum Thani, Thailand.

J Clin Aesthet Dermatol. 2022;15(7):44-48.

BACKGROUND: Epidermal growth factor (EGF) stimulates collagen production and supports the wound healing process. However, there are no studies on fractional carbon dioxide (CO_2) laser combined with EGF for acne scar treatment. **OBJECTIVE:** We sought to evaluate the efficacy and safety of fractional CO_2 laser combined with topical EGF versus fractional CO_2 laser alone in the treatment of acne scars. **METHODS:** Twenty-three patients with atrophic acne scars underwent three monthly sessions of randomized split-face application of fractional CO_2 laser combined with topical EGF or placebo twice daily for seven days following each laser session. Scar improvement was evaluated at one month and three months posttreatment by two blinded dermatologists and the Antera 3D® skin analysis system. Wound healing response and adverse events were also evaluated. **RESULTS:** Twenty-one patients completed the trial. According to dermatologist grading and skin analysis system, EGF showed significant superiority at three months posttreatment compared to placebo. The wound healing response did not differ between the groups. Surprisingly, the melanin index on the EGF side showed a significant decrease at three months posttreatment, compared to placebo. There was no allergic reaction to the topical EGF. **CONCLUSION:** Treatment with topical EGF after ablative fractional CO_2 laser improves the clinical appearance of atrophic acne scars, and EGF may help decrease skin pigmentation after laser treatment. The use of topical EGF is safe when applied to post-laser ablation. **KEYWORDS:** Epidermal growth factor, fractional carbon dioxide laser, acne scar

TABLE 1. Evaluation of scar improvement by physician and Antera 3D® system

TIME	QUARTILE GRADING SCALE BY PHYSICIAN MEAN±SD		P-VALUE (BETWEEN GROUPS)	PERCENTAGE OF IMPROVEMENT BY ANTERA 3D® SYSTEM MEAN±SD		P-VALUE (BETWEEN GROUPS)
	EPIDERMAL GROWTH FACTOR	PLACEBO		EPIDERMAL GROWTH FACTOR	PLACEBO	
1 month posttreatment	1.71±0.56	1.67±0.58	0.31	18.97±8.60	15.95±9.97	0.11
3 months posttreatment	2.76±0.54	2.57±0.51	0.04	27.40±10.50	21.28±10.50	0.01

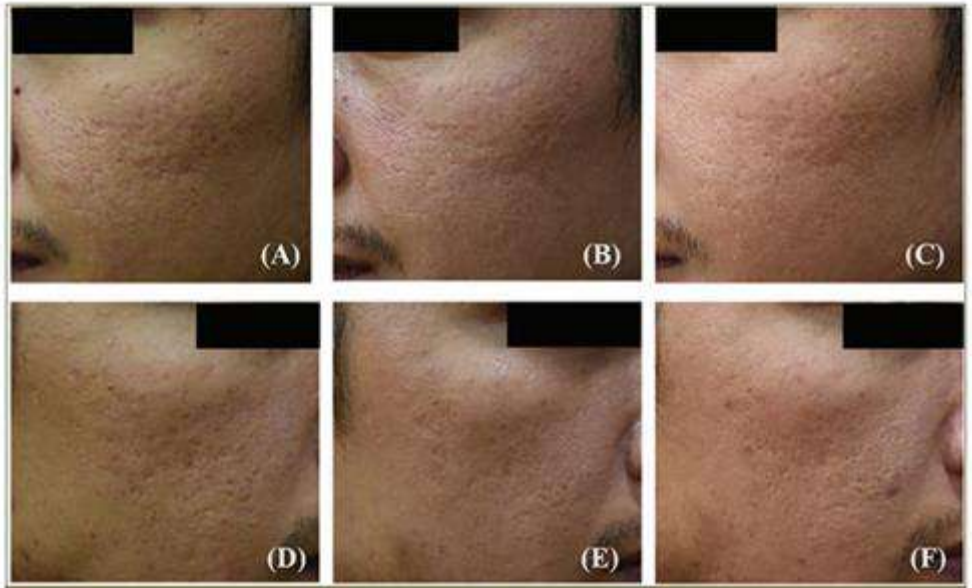


FIGURE 1. Clinical photographs of 29-year-old male; Figures 1A–1C show the side treated with the epidermal growth factor, and Figures 1D–1F show the placebo-treated side. (A) and (D) are baseline. (B) and (E) are at one month posttreatment. (C) and (F) are at three months posttreatment.

rEGF gelecekteki uygulanma alanları-2

- Atopik dermatitis…
- Deney haycanı- kulak modeli
- Enflamasyon çözülüyor
- Cilt kalınlığı artıyor
- Etki hızlı ortaya çıkıyor…

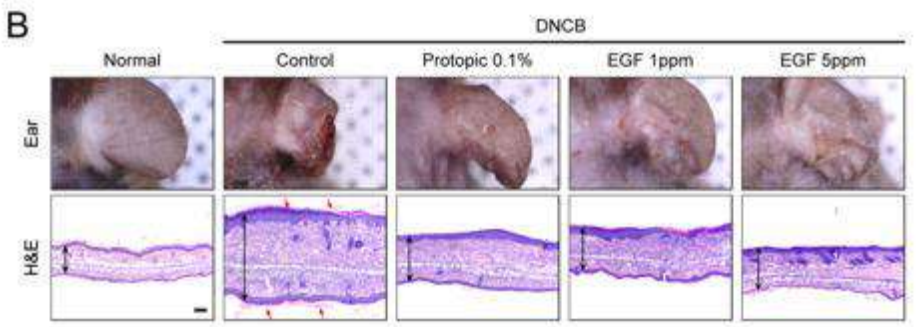
Sonuç- molekül yeniden konumlandırılmaya uygun….

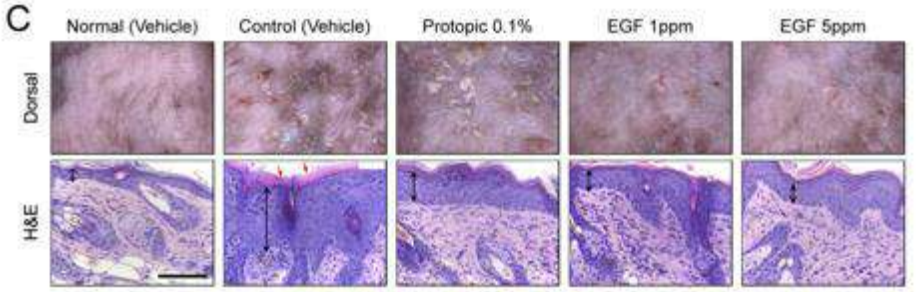
OPEN

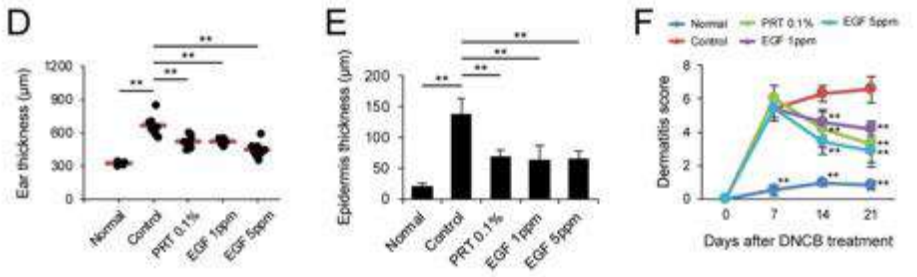
Topical administration of EGF suppresses immune response and protects skin barrier in DNCB-induced atopic dermatitis in NC/Nga mice

Received: 23 January 2018
Accepted: 30 July 2018
Published online: 09 August 2018

Young-Je Kim[1], Mi Ji Choi[1,2], Dong-Ho Bak[1,2], Byung Chul Lee[1,2], Eun Jung Ko[3], Ga Ram Ahn[1], Seung Won Ahn[4], Moo Joong Kim[5], Jungtae Na[1] & Beom Joon Kim[1,2]

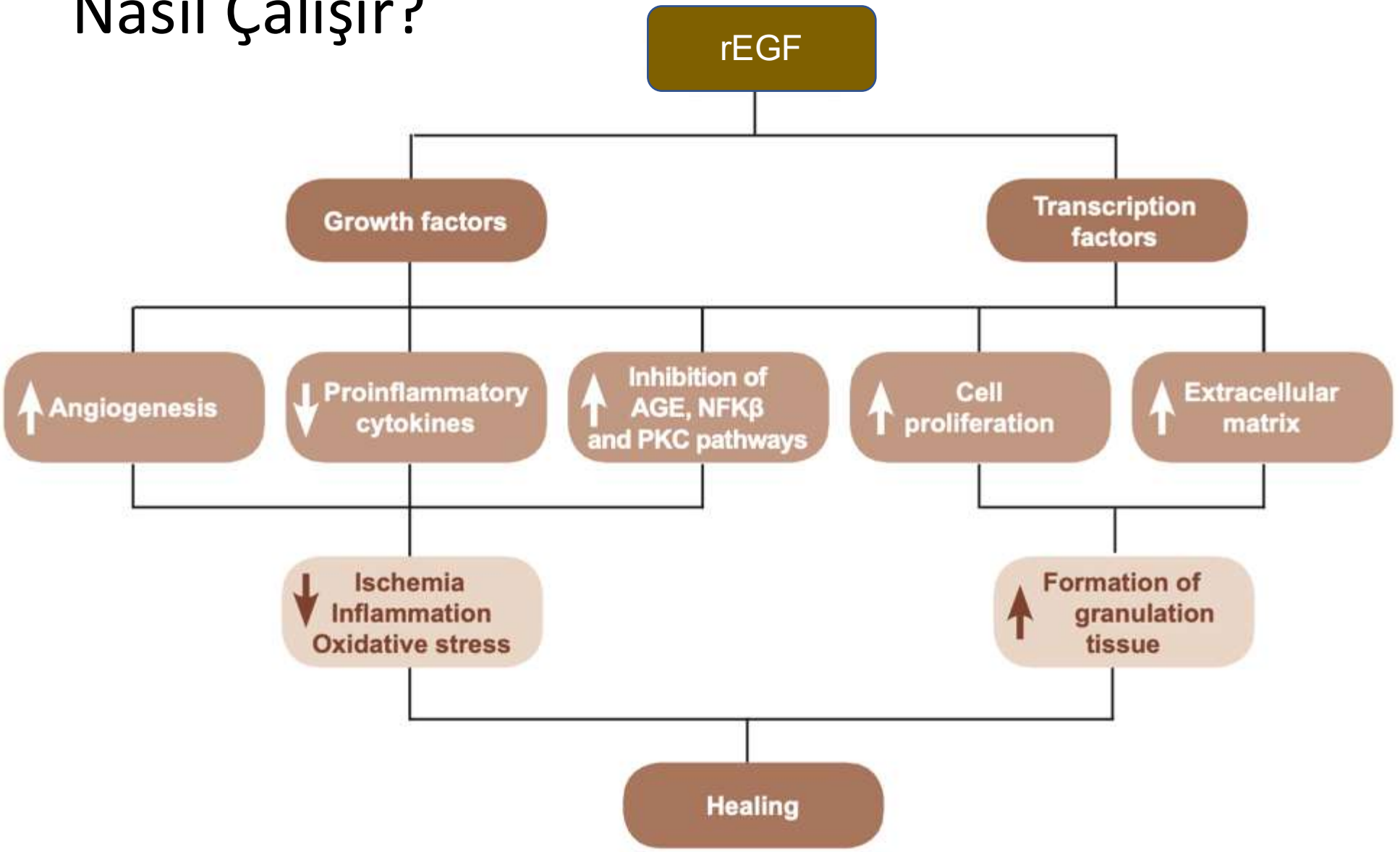






y skin disease characterized by a complex, er dysfunction, immunology, and pruritus. Although thelial homeostasis and wound healing, the effect a new therapy for AD, the anti-AD potential of EGF in NC/Nga mice using 2,4-dinitrochlorobenzene to evaluate its therapeutic effect on DNCB-induced ar thickness, epidermal hyperplasia, serum total er loss in NC/Nga mice with DNCB-induced AD. In ich as filaggrin, involucrin, loricrin, occludin, and treatment. These beneficial effects of EGF on AD may ated cytokines, mast cell hyperplasia, and protease lymphopoietin (TSLP), which are triggers of AD. Taken entially protect against AD lesional skin via regulation

Nasıl Çalışır?



Hanlet Camacho-Rodríguez et al. Heberprot-P's Effect on Gene Expression in Healing Diabetic Foot Ulcers

Sonuçta…

Anjiyogenesis ↑

ANGPT1
(Angiopoietin 1)

Enflamasyon ↓

IL-1A
TNF alfa

No.	Gene	Fold change	P-value	Direction of change*
1	AGER	−1.20	0.190	
2	ANGPT1	1.45	0.001	↑
3	CDK4	1.48	0.009	↑
4	CDKN1B	1.04	0.568	
5	COL1A1	1.67	0.005	↑
6	CTGF	−1.28	0.302	
7	FOS	1.10	0.740	
8	HIF1A	−1.25	0.088	
9	IGFBP3	1.28	0.220	
10	IL17A	−2.17	0.079	
11	IL-1A	−13.70	0.000	↓
12	IL-6	−1.78	0.207	
13	MMP2	2.21	0.000	↑
14	MMP7	1.07	0.886	
15	MMP9	1.69	0.090	
16	NFKB1	-1.37	0.002	↓
17	P21	1.54	0.009	↑
18	PDGFB	1.68	0.002	↑
19	PHB	−1.20	0.073	
20	PLCG1	−1.08	0.325	
21	TGFB1	−1.08	0.540	
22	TIMP1	1.08	0.652	
23	TIMP2	1.43	0.007	↑
24	TNFA	−1.96	0.001	↓
25	TP53	1.99	0.000	↑
26	VEGFA	1.38	0.227	

Kollajen sentezi ↑
Extra sellüler matrix ↑

COL1A1
(collagen type I alpha 1 chain)

Myelofibroblast ↑

MMP2
(matrix metalloproteinase 2

TIMP2
(Tissue inhibitor of metalloproteinases 2

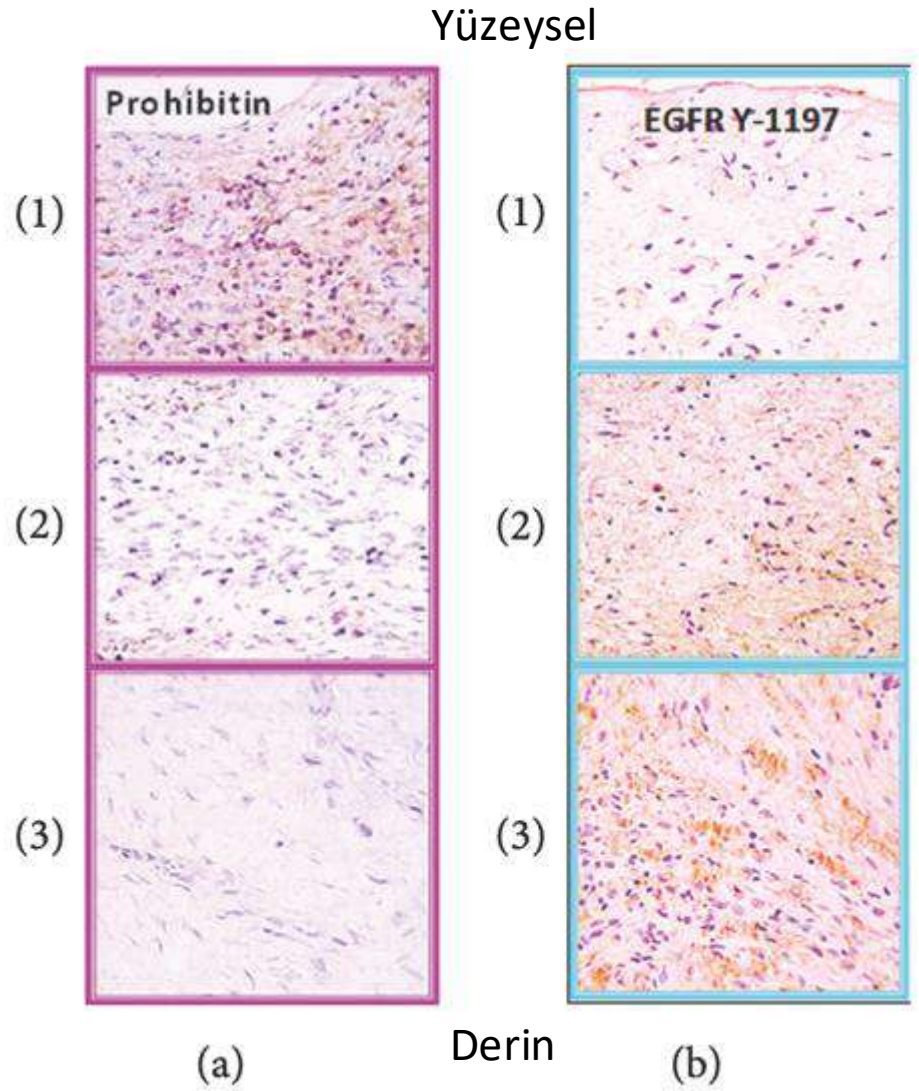
Epitelizasyon ↑

PDGFB
(Platelet Derived Growth Factor Subunit B)

Hanlet Camacho-Rodríguez et al. Heberprot-P's Effect on Gene Expression in Healing Diabetic Foot Ulcers

Prohibitin

- Aslında lipid dokuda yüksek oranda bulunur,
- Kronik ülserde; yüzeyde daha çok, derin dokuda daha az,
- Hücre siklüsü bloklajı; antimitojenik faktör
- EGF uygulandığında prohibitin doku dağılımı derine iniyor…
- Hücre siklüsünün başladığının indirekt göstergesi…

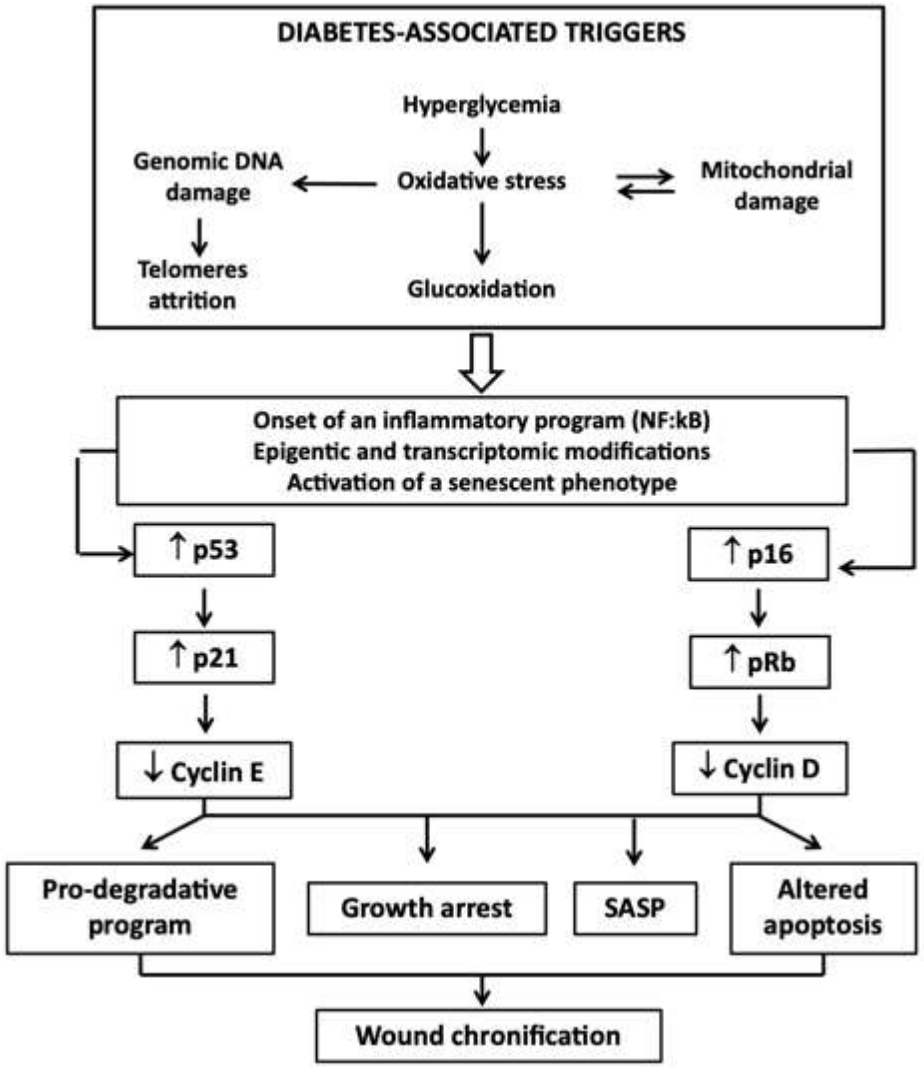


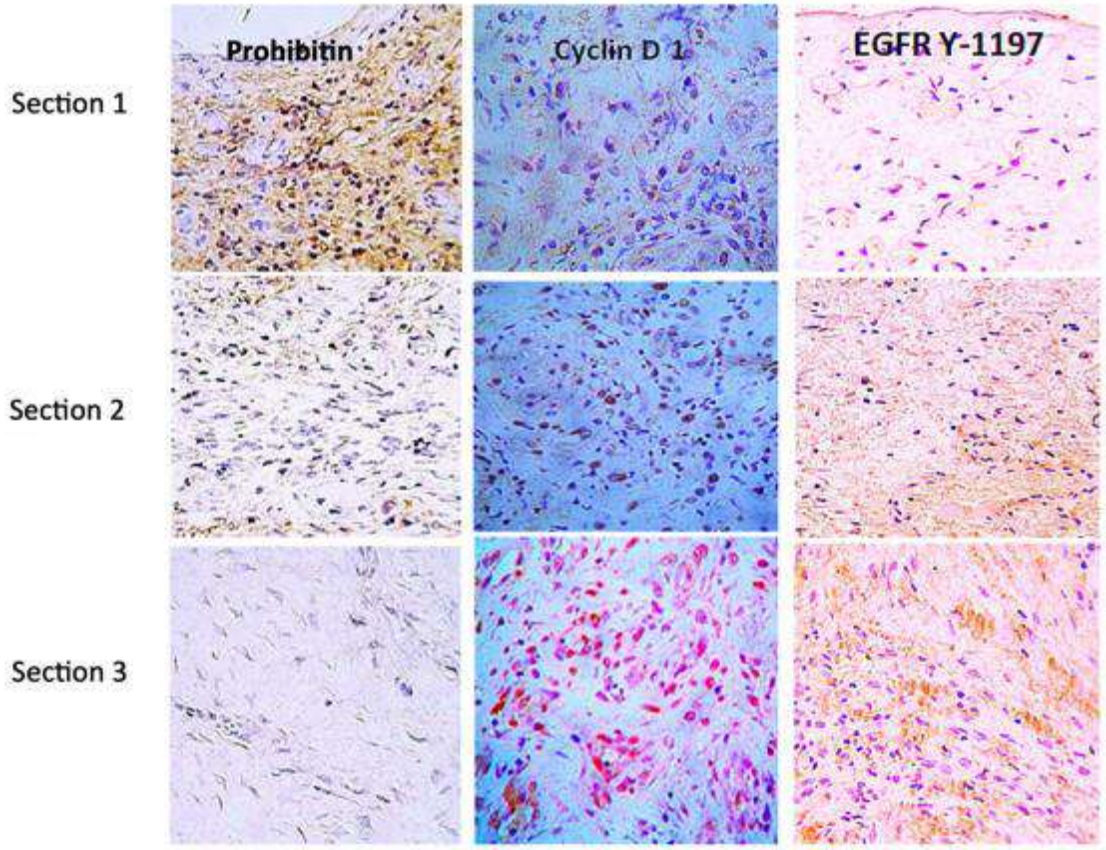
Peroksidaz boyası- prohibitin EGF sonrası her tabakaya yayılmış

2-6 mm cilt biyopsileri

Berlanga-Acosta J. Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment. Int Wound J 2011; 8:612–620

Cyclin D-azalması





rhEGF uygulaması sonrası Cyclin D artışı ile hücre proliferasyonu artar

Jorge Berlanga-Acosta et all. Epidermal Growth Factor (EGF) intralesional infiltrations: From the bench to the diabetic ulcers cells

Integr Mol Med, 2019 doi: 10.15761/IMM.1000354 Volume 6: 1-7

Uygulama sonrası moleküler düzeyde ne oluyor?

- İlk 15 dk'da: EGFR'ü membran ekspresyonu artıyor,
- rhEGF endositoz ile hücre içine giriyor,
- 15 dk-24 saat: stoplazmik translokasyon ve endoplazmik organellerin dağılımı,
- 45dk-24 saat: nükleer translokasyon ve DNA'ya bağlanma,
- 24.saatten sonra:

-Hücre proliferasyonu,

-EGFR mitokondriyal birikmesi,

-rhEGF kollajene bağlanması ve ekstasellüler matriks sentezi

V.FalconCama,M.Fernandez Mayola,Y.Mendoza-Mar ́ıetal., "Epidermal growth factor based therapy promotes intracellular trafficking and accumulation of its receptor in the nucleus of fibroblasts from diabetic foot ulcers," *Journal of Diabetic Complications & Medicine*, vol. 01, no. 03, 2016.

Sıfır noktası- rhEGF ilk dakikası

- Fibroblast benzeri hücre membranı stabil
- ER'da değişim yok…

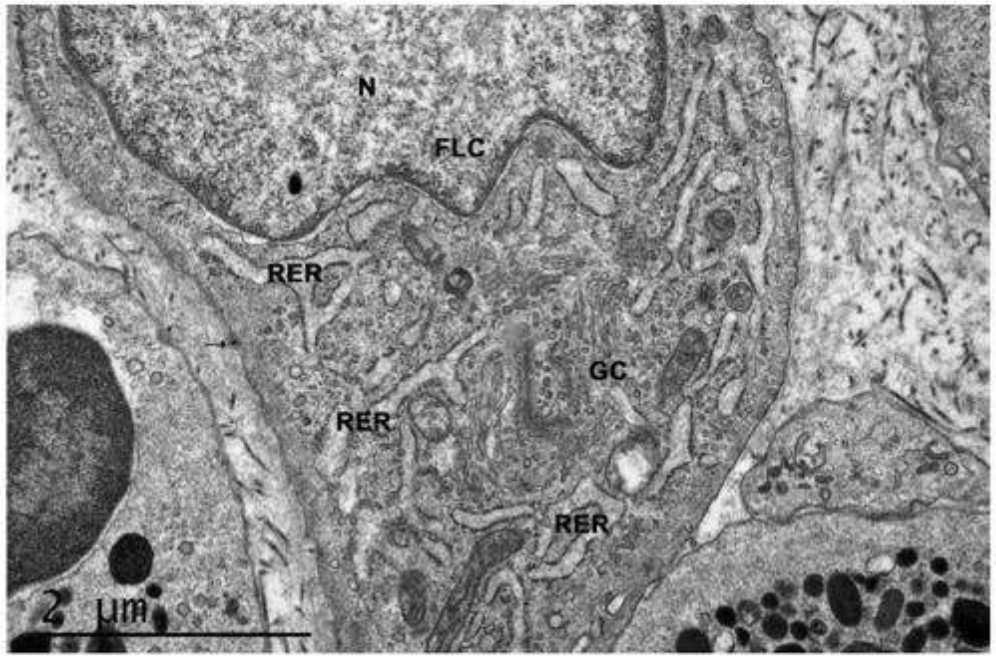


Figure 1A: Time Zero (T0) harvesting corresponds to the sample obtained minutes prior to the initial EGF infiltration. The image shows a negligible immunostaining on the plasma membrane of a Fibroblast-like cell (arrow). Rough endoplasmic reticulum (RER); Nucleus (N); Golgi complex (GC); fibroblast-like cell (FLC) (Bar=2 um).

45 dk sonrası-

- ER'da şişme,
- EGFR expresyonu (Vesikül)
- Fibroblast benzeri hücre membranında genişleme
- Kollajen matrix ve kollajen fiberde toplanma

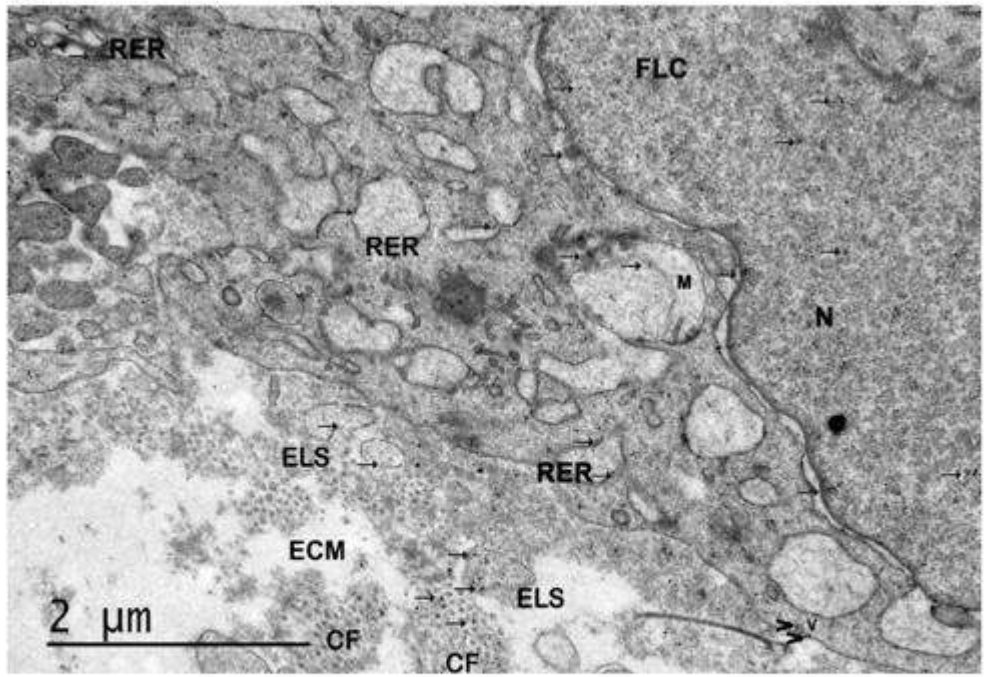
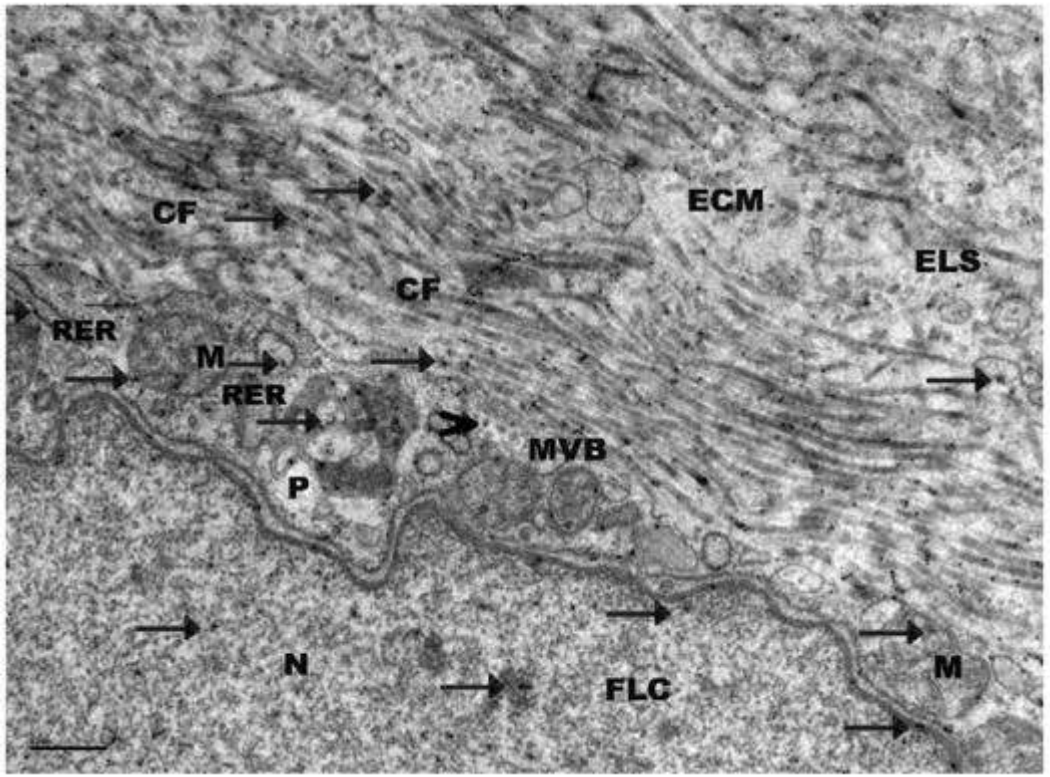


Figure 1B: Immunolabeling of EGFR (arrows) in part of a Fibroblast-like cell (FLC) from a biopsy sample obtained 45 minutes after EGF infiltration. Immunostaining appeared in mitochondria, RER and nucleus. Also note that EGFR was immunolabeled in vesicles (V) (arrowhead), on plasma membrane (arrowhead), the extracellular matrix (ECM), on collagen-like fibers (CF) and exosome-like structures (ELS) (Bar=2 um).

6 saat sonra-

- EGRF (oklar ile işaretli) yaygınlaşma ve hücre yüzeyine yayılma
- Kollajen fibrillerde çaprazlaşma ve yaygınlaşma
- MVB- multivesicular body; stoplazma içinde artar (sayıca + ebat)



24 saat sonra-

- Nükleus entegrasyonu
- rhEGF mitokondriyal birikme,
- rhEGF kollajene bağlanma, ekstrasellüler matriks sentezi

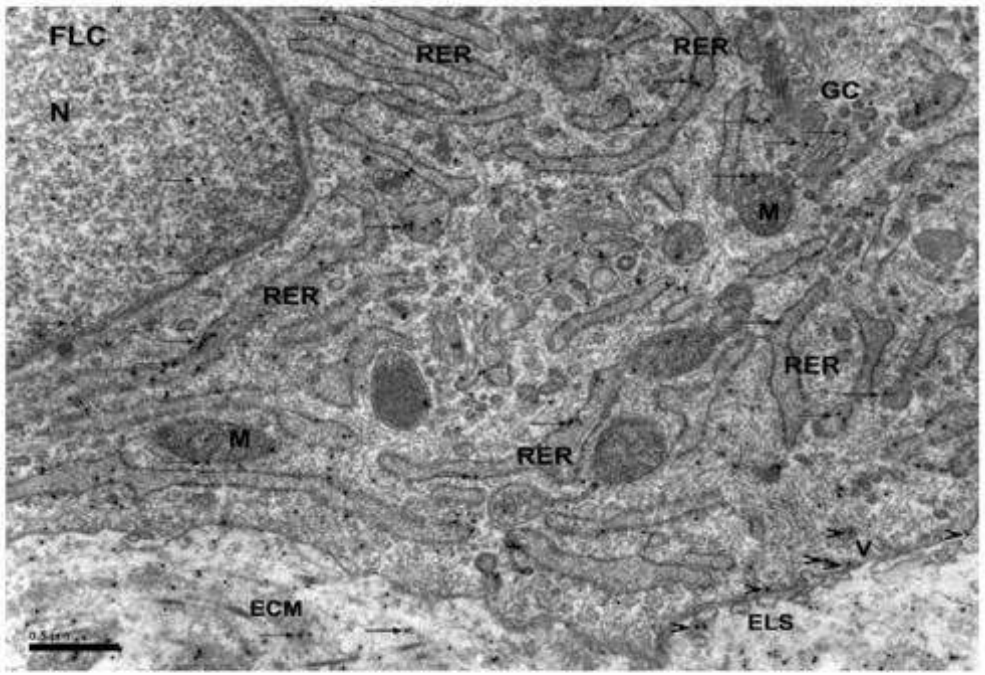


Figure 2D: Immunolabeling of PCNA in part of a fibroblast-like cell (FLC) from a biopsy of samples infiltrated with EGF at T24. Large labeling of RER, Golgi complex (GC) and mitochondria (M) were observed. Immunostaining of PCNA was also detected in nucleus (N), and extracellular matrix (ECM) (arrows). Also note immunostaining in plasma membrane, vesicles and exosome-like structures (ELS) (arrowheads) (Bar=0.5um).

Aslında prensip olarak bir replasman tedavisi uyguluyoruz….

Hasta deneyimleri-1

- 32 yaşında erkek hasta, DM, OAD, 112 kg
- Nöropatisi var…sensoriyel
- Sıcak asfalta basma sonrası ayak tabanında yanık,
- DAİ- grade 2
- Sağ ayak plantar kısmında hassasiyet, YDE?
- Ateş –üşüme –titreme
- Takip ve tedavi amaçlı yatış…
- PE abterapi- SCF

Enzimatik debridman
2 hafta







	BK (%PNL)	ESH	CRP	BUN	Kreatinin	eGFR	AST	ALT
1. gün	16,700 (%85)	18	25	18	0.5	98	21	26
3. gün	11.200 (%68)	-	-	21	0.6	91	34	39
5. gün	7.200 (%62)	-	10	17	0.7	90	27	36
7. gün	4.500 (%65)	-	-	21	0.5	99	21	45

Yüzeyel doku USG- abse, koleksiyon yok… minimal cilt altı ödem

4. Hafta

- Granülasyon kısmen var,
- Epitelizasyon nazlı…

- Yara kenarları kaba-keskin debridman
- Yara yatağına Regen D



6. Hafta



8. Hafta





Hasta deneyimleri-2

- 69 yaşında erkek hasta, DM, OAD, 74 kg
- Nöropatisi var, nefropatisi var …
- Ayakkabı vurması sonrası…
- Sağ ayak II. Parmakta DİP'da…DM enfeksiyonu…6. haftada…
- DAİ-grade 3
- PO almış…Enfeksiyon +enflamasyon kontrol altına alınmış,
- ESH, CRP (N)
- Ayak grafisinde 2. parmak distal falanks erimiş…

7. hafta

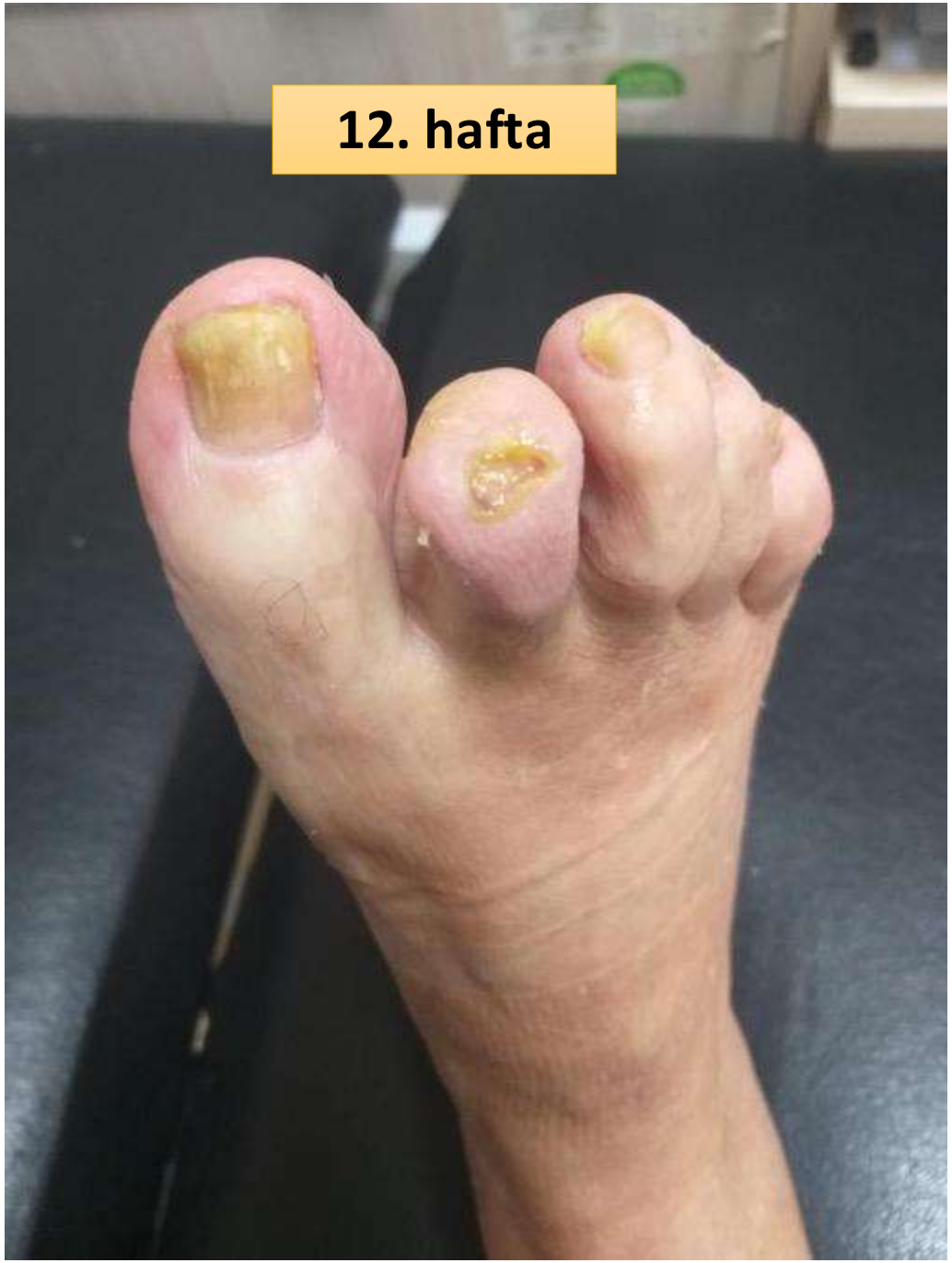
- Lokal pansuman – debridman
- Tırnak + distal falanks kendiliğinden ayrıldı





- Debridman – HOCL
- Regen D-4 hafta





Hasta deneyimleri-3

- 59 yaşında erkek hasta, DM, insülin kullanıyor, 74 kg
- Nöropati-retinopati- nefropati (HD) var …
- Sağ bacak diz altı ampütasyon…DM enfeksiyonu nedeniyle…
- Post op. 6. ayda düşme sonrası güdükte travma…açılma…
- Sonrasında YDE bulgusu- PO antibiyotik… 4 hafta…
- Ödem artmış…
- Güdükte enfeksiyon bulgusu yok,
- ESH, CRP (N)

AMPUTASYON SONRASI DİYABETİK HASTADA GÜDÜKTE YARA



KABUKLU BÖLÜME HİDROJEL,YARA İÇ KISMINA İSE YOĞUN AKINTIDAN DOLAYI GÜMÜŞ İÇERİKLİ FİBER ÖRTÜ VE BARİYER KREM İLE YARA BAKIMINA BAŞLANILDI.

AMK 1 gr tab 2x1

4 hafta sonra …YARADAKİ AKINTI DURDUĞU İÇİN FİBRİNLERİ ÇÖZMEYE YÖNELİK HİDROJEL UYGULAMASINA GEÇİLDİ



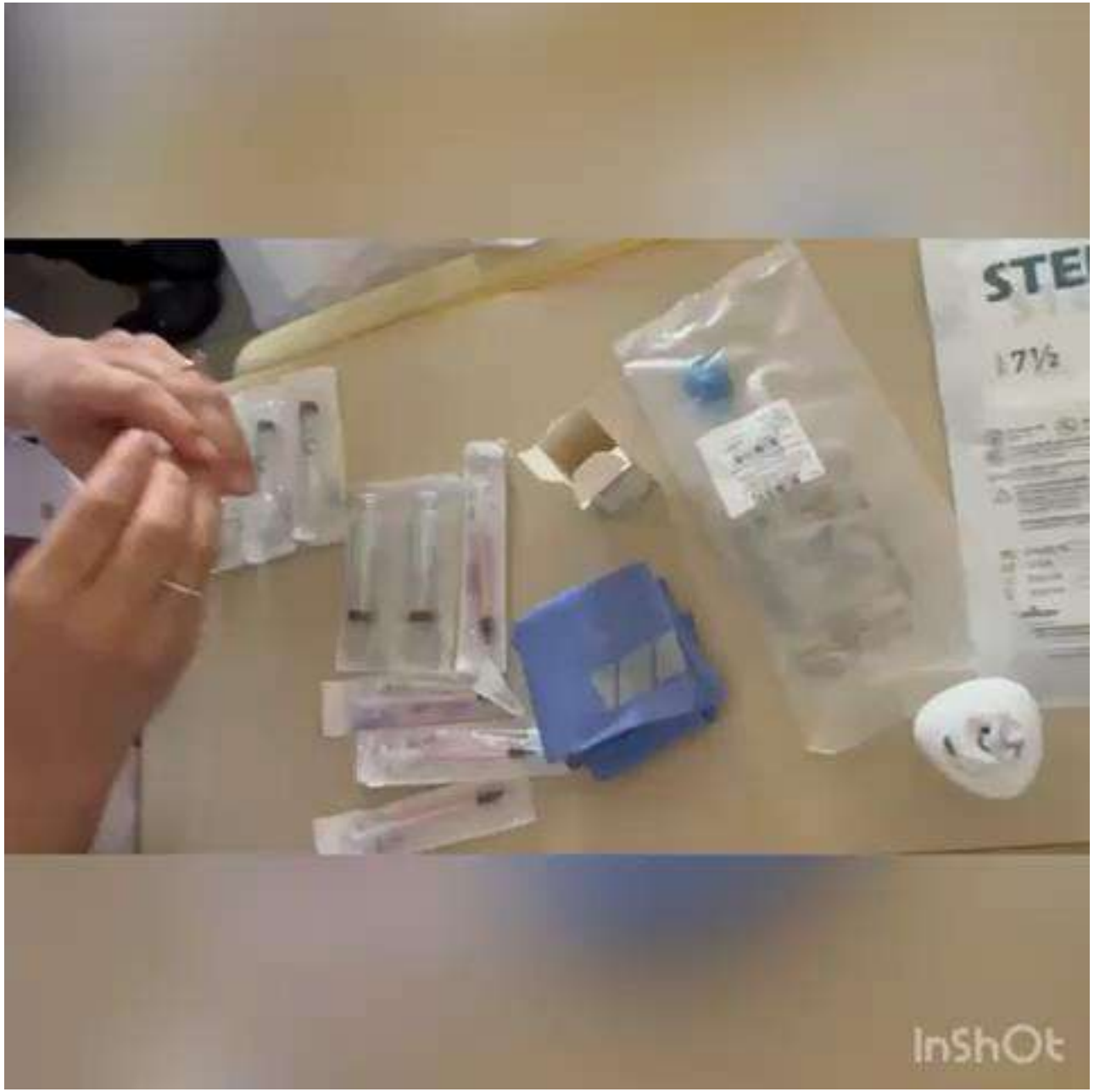


Tedavi 8. haftası…
YARA GRANÜLE VE TEMİZ OLDUĞUNDAN topikal rhEGF- 4 hf

YARANIN SON DURUMU

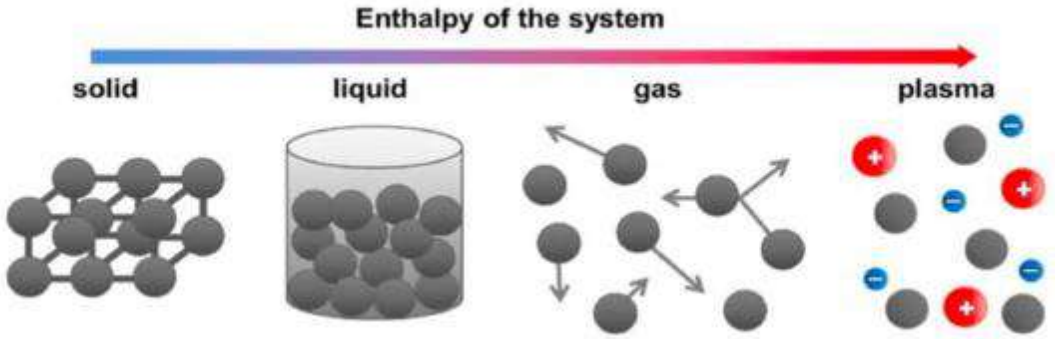


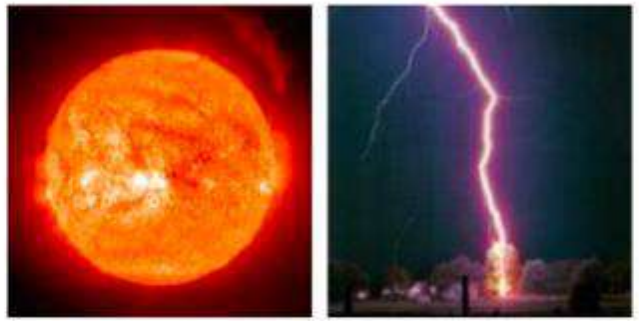

1
2
3
4


STE
7½
InShOt

Soğuk Atmosferik Plazma

Katı-sıvı-gaz-plazma

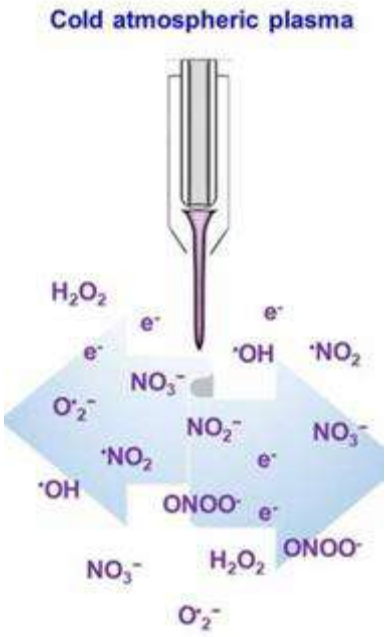




Güneşte

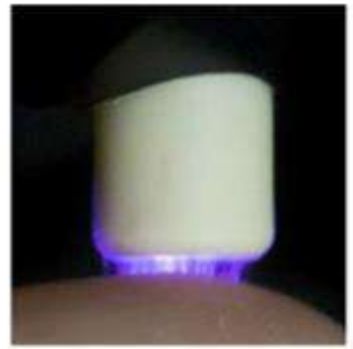
Şimşekte

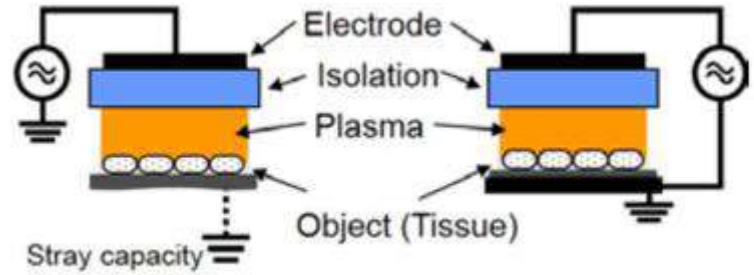
- Sıcak plazma=4000C
- Soğuk plazma=30-50C



- Havadan O_2 ve N_2 serbest radikaller
- Maddeyi iyonlarına ayırır

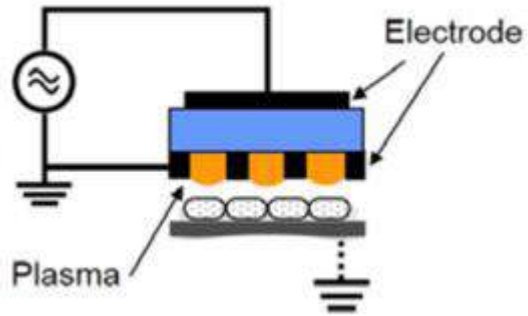
Volume dielectric barrier discharge (DBD)





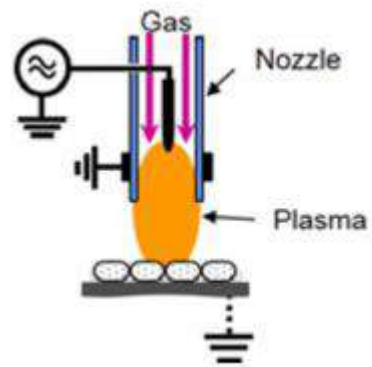
Surface dielectric barrier discharge (DBD)

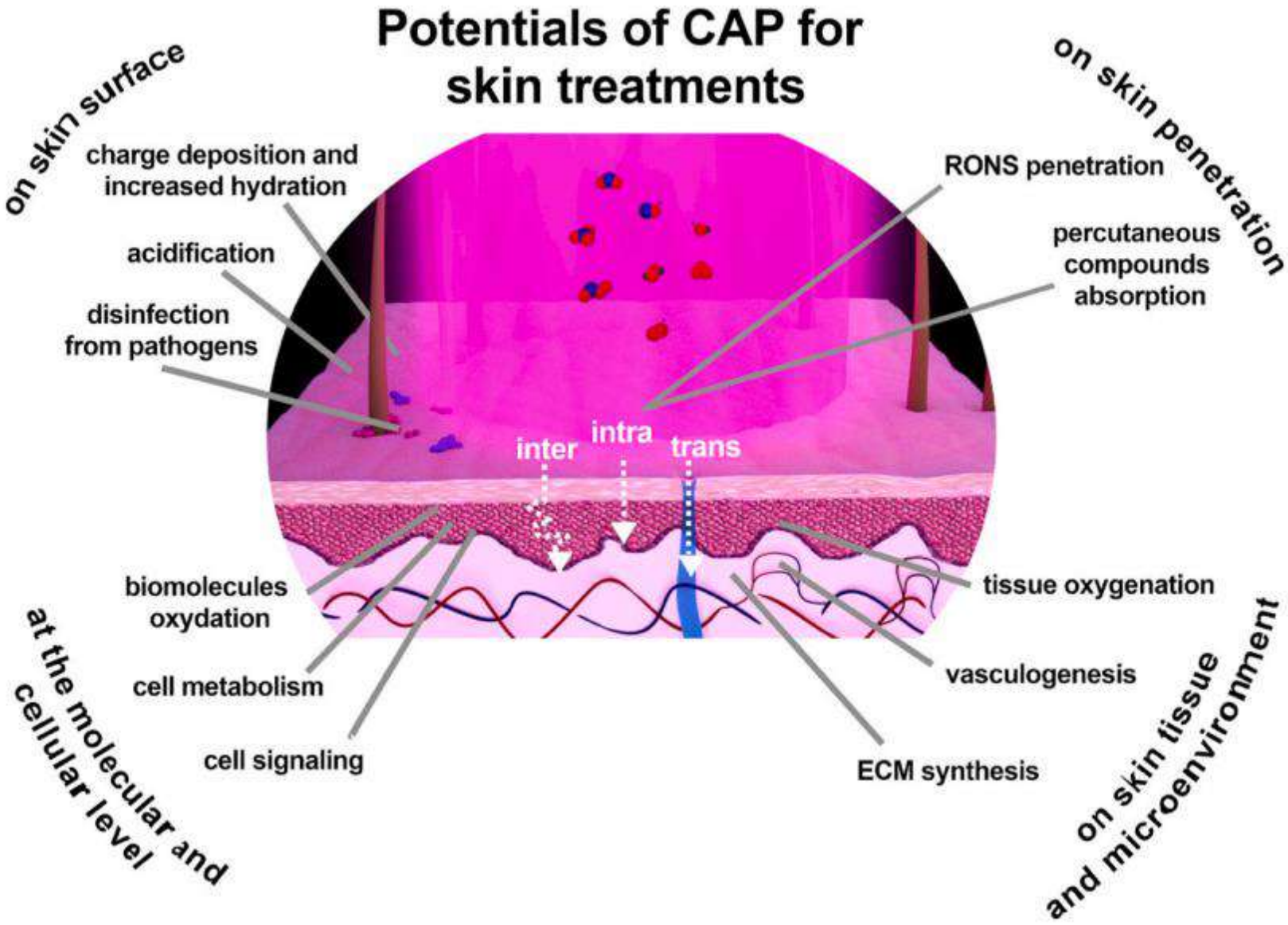




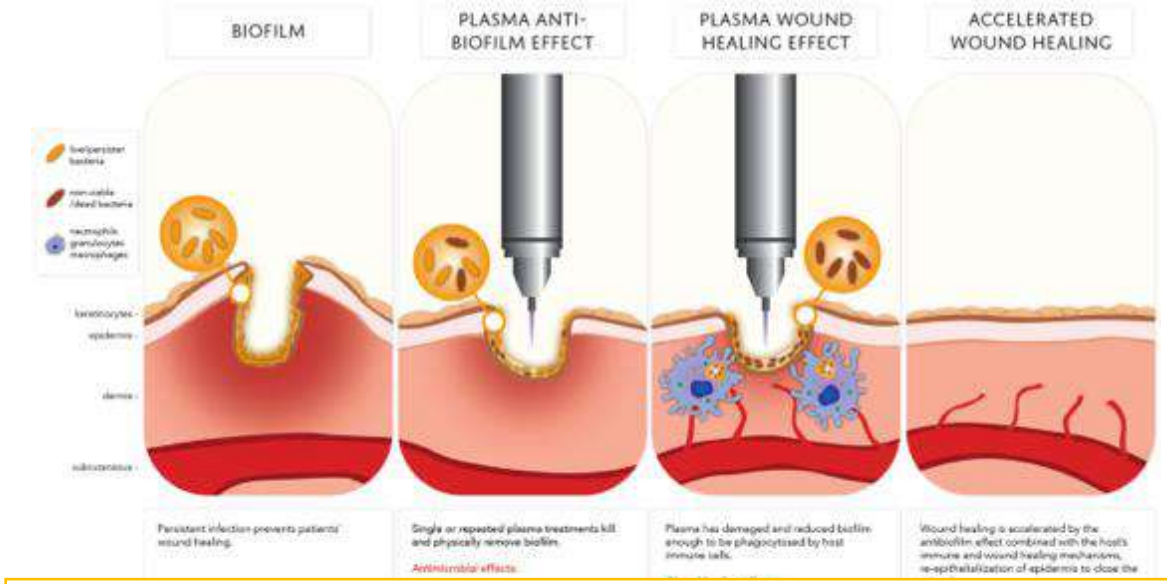
Plasma jet







Giovanni Busco, Eric Robert, Nadira Chettouh-Hammas, Jean-Michel Pouvesle, Catherine Grillon,The emerging potential of cold atmospheric plasma in skin biology, Free Radical Biology and Medicine,Volume 161,2020,Pages 290-304



- Anti bakteriyel etki
- Biyofilm parçalayıcı etki
- ROS=reaktif oksijen radikalleri
- RNS=reaktif azot radikalleri
- Anjiyogenesis
- Keratinosit göçü artışı
- Büyüme faktörü artışı
- Sitokin dengesi- M2 makrofaj aktivitesi artışı

ROS RNS

Kısa ömürlü partiküller
- Tek oksijen
- Süperoksit anyonlar
- Peroksinitrit
- Hidroksi radikaller

Uzun ömürlü partiküller
- Hidrojen peroksit
- Nitritler
- Nitratlar

Doz bağımlı sonuçlar

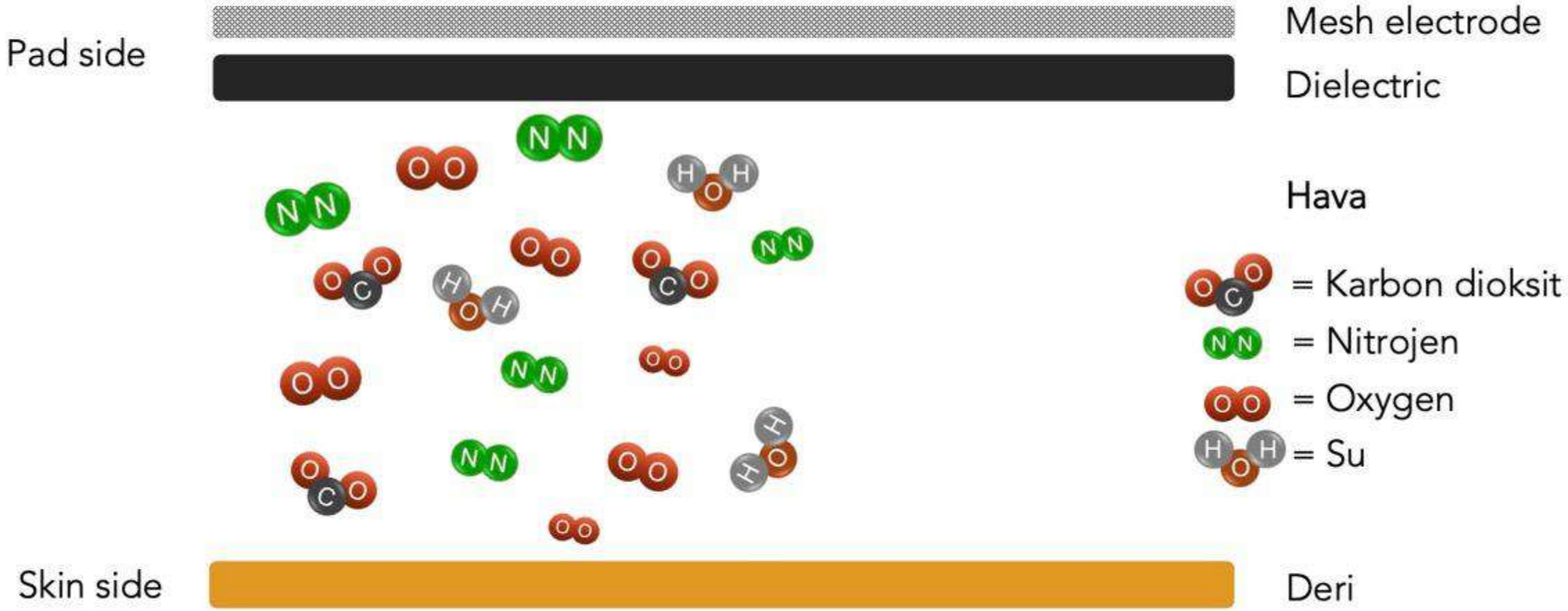
Düşük doz
- Hücre siklüsü durması
- Otofaji
- Biyolojik yaşlanma

Yüksek doz
- Hücre nekrozu
- Hücre ölümü

Bolgeo, T.; Maconi, A.; Gardalini, M.; Gatti, D.; Di Matteo, R.; Lapidari, M.; Longhitano, Y.; Savioli, G.; Piccioni, A.; Zanza, C. The Role of Cold Atmospheric Plasma in Wound Healing Processes in Critically Ill Patients. *J. Pers. Med.* **2023**, *13*, 736. https://doi.org/10.3390/jpm13050736

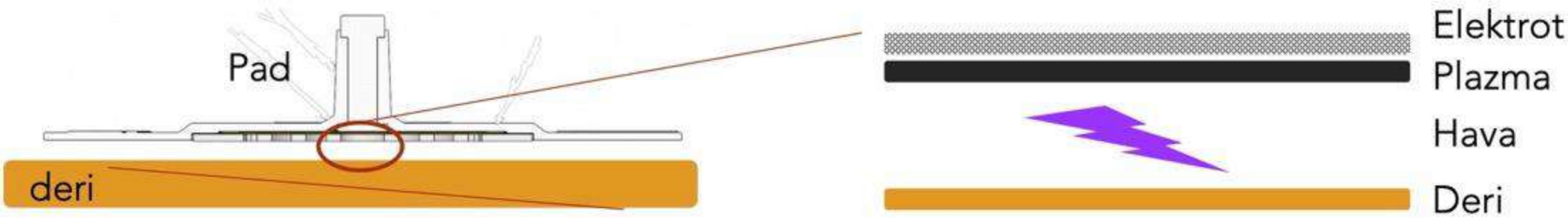
Çalışma Methodu

Oda havası sadece oksijenden daha fazlasıdır. Havada çeşitli moleküller vardır, örneğin Oksijen, Azot, Karbondioksit ve Su.

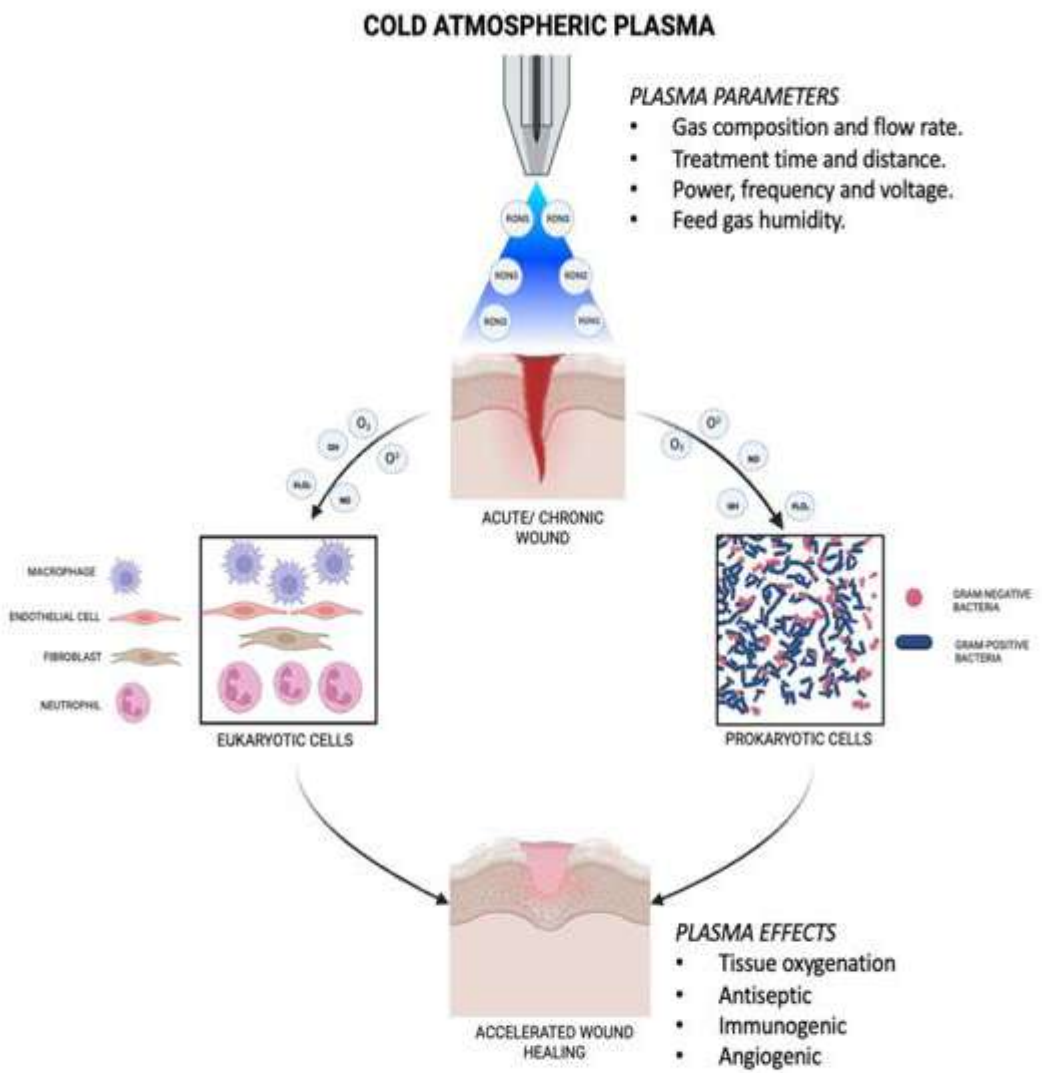


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Method of action



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Dokuda ROS ve RNS etkisi?

Gaz içeriği ve akım hızı

- Helyum, argon ve heliox (helyum+oksijen), azot
- 2.2 lt/dk argon, 2 lt/dk helyum yara iyileşmesi

Temas süresi ve mesafe

- 2-5 dk argon daha iyi yara iyileşmesi
- Mesafe <15 mm daha iyi yara iyileşmesi

Voltaj ve frekans

- Voltaj <5 kV, frekans <25 kHz (helyum için) daha iyi granülasyon
- Nemlendirme

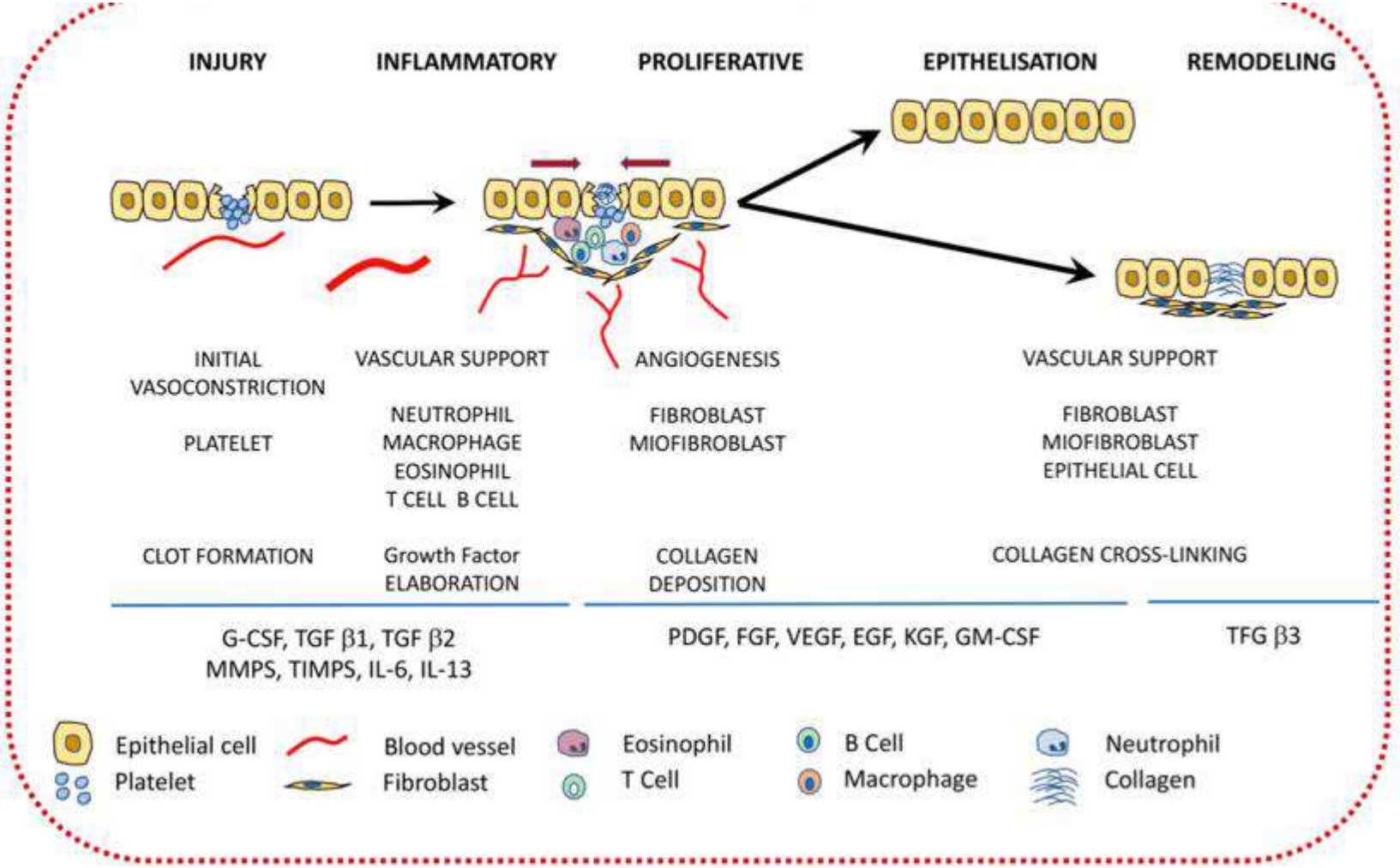
Antimikrobiyal etkinlik (standart)

- Lipid peroksidasyonu
- Protein modülasyonu
- DNA hasarı (bakteride-hidrojen peroksit)
- Anti-biyofilm etkinlik

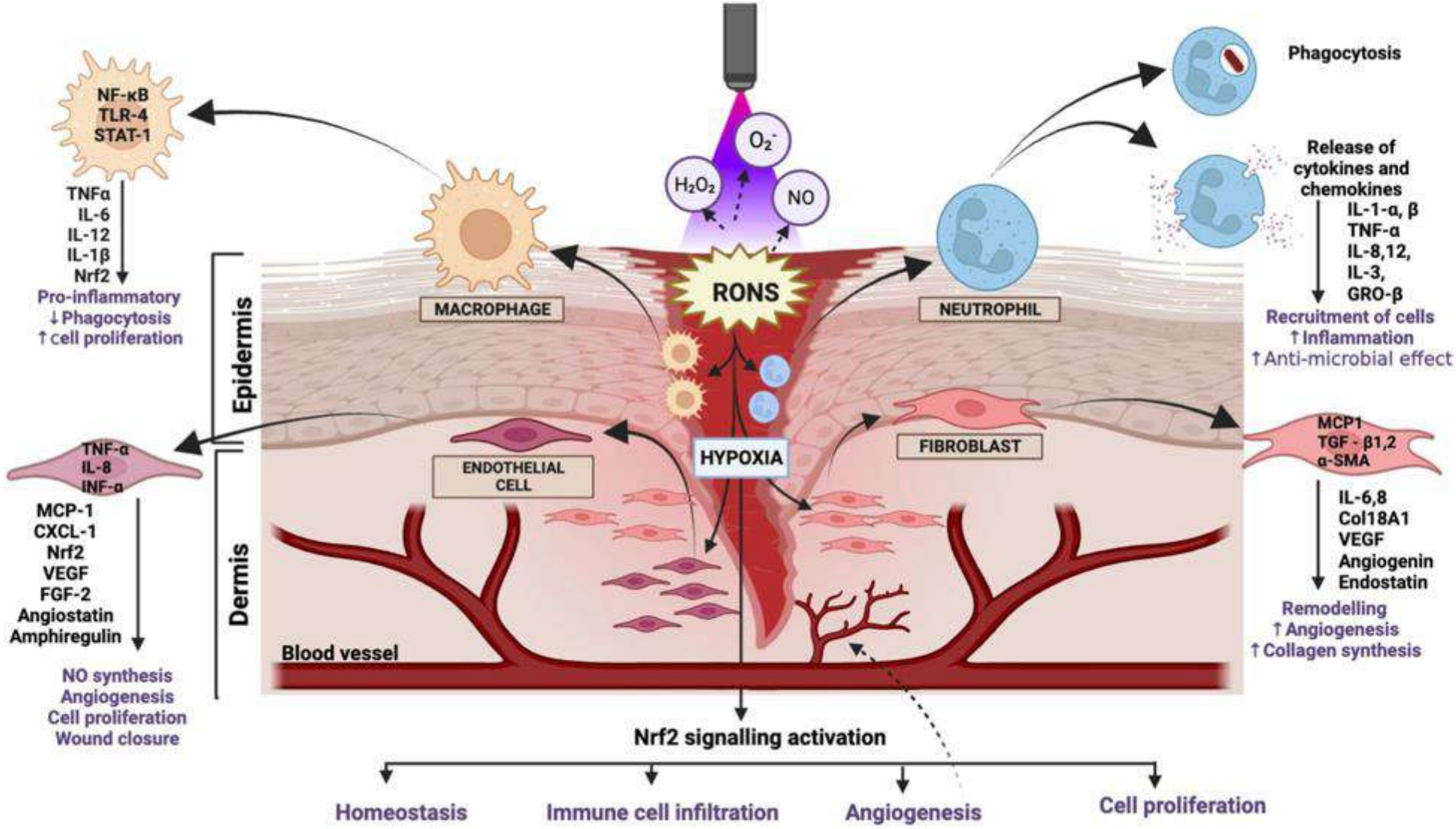
Roopak Murali Cold Atmospheric Plasma (CAP) in Wound Healing: Harnessing A Dual Edged Sword, Redox Exp. Med, 2023

Hangi aşamalarda kullanılabilir?

- Enfekte yarada
- Biyofilm olan yarada
- Granülasyonu başlamış
- Epitelizasyonu kısmi olmuş, durmuş yarada



CAP, yara iyileşmesine etkisi hangi aşamalarda?



Roopak Murali Cold Atmospheric Plasma (CAP) in Wound Healing: Harnessing A Dual Edged Sword, Redox Exp. Med, 2023

Study type	Wound type	CAP device	CAP parameters					Treatment time	Outcome	References
			Frequency	Voltage	Power	FR, slm	Distance[d]			
CT	Chronic ulcers	MicroPlaSter alpha and beta (Argon)	2.6 GHz	50–100 V	86 W	2.2		2-min exposure/day.	Reduced microbial load and increased healing rate of chronic ulcer.	Isbary *et al.* (2012), (2010)
CT	Venous ulcers	PlasmaDerm® VU-2010	50 Hz	230 VAC	8 VA			Average time of 11 min (45 s/cm^2 wound area) per exposure. 3 times a week and for 8 weeks.	Reduced microbial activity and accelerated healing of venous ulcers.	Brehmer *et al.* (2015)
Pilot Study	Atopic dermatitis	MediPL Derm	2.45 GHz ±50 MHz		1.5 W	0.6	5 mm	Plasma exposed for 3 times/day and treated at 0, 1, 2 weeks.	Improved mild and moderate atopic dermatitis and reduced proportion of *Staphylococcus aureus.*	Kim *et al.* (2021)
RCT	Pressure ulcers	Argon Plasma Jet	50 Hz		5[a]; 0.682[b] W/cm^2		5 mm	Plasma exposed at 1 min/cm^2 and once a week for 8 weeks.	Improved PUSH score and reduced bacterial load regardless of the bacterial species.	Chuangsuwanich *et al.* (2016)
RCT	Chronic wounds	SteriPlas® (Argon)	2.6 GHz	50–100 V	86 W	2.2		2-min exposure on the wound site once a week or 3 times a week.	Improved wound healing in patients with therapy-refractory chronic wounds.	Moelleken *et al.* (2020)
CCS	Superficial skin wounds	Plasma Jet		10 kV	50 mW; 5 mA[c]		10 mm	The wound was exposed to CAP for 5 min a day and the procedure was done every 2 days.	Complete healing of the superficial skin wounds irrespective of the type of lesions.	Gao *et al.* (2019)
CCS	Chronic wounds	CPTpatch	NA					2-min plasma exposure 3 times a week, for first 4 weeks and in the next 4 weeks, the plasma was exposed twice a week.	Significant improvement in rate of wound healing as well as reduction in the *Staphylococcus aureus* colony.	Landscheidt *et al.* (2022)
CCS	Psoriasis	PCC	5 kHz	7 kV			1 cm	The psoriasis plaques were exposed to plasma for 30 s for 14 days.	Gradual reduction of psoriasis plaque and complete disappearance on 14th day.	Gareri *et al.* (2020)
RCT	Wounds at donor skin graft sites	Argon Plasma Jet	2.45 GHz		86 W	2.2		The wounds were exposed to plasma for 2 min/day for 7 days.	Rapid healing rate of wounds at skin graft sites.	Heinlin *et al.* (2013)

Study type	Wound type	CAP device	CAP parameters					Treatment time	Outcome	References
			Frequency	Voltage	Power	FR, slm	Distance[d]			
CCS	Ablative CO_2 laser lesions	kINPen®MED plasma jet (Argon)	1 MHz	2–3 kV		4–6		CAP was applied 30 s intervals for 3 days.	Improved rate of wound healing and scar recovery.	Metelmann *et al.* (2013)
RCT	CO_2 laser skin wounds	kINPen®MED plasma jet (Argon)	1 MHz	2–3 kV		4–6		The wounds were exposed for a duration of 60 s to the plasma.	Improved wound healing rate with reduction in redness and roughness of the skin.	Nishijima *et al.* (2019)
CCS	2nd-degree burns	Helium Plasma Jet	13.56 MHz		10 W		5 mm	The site of the burn injury was treated using plasma for 180 s. Two treatments were performed in a single day.	Increased rate of reepithelialization with decontamination of bacteria on the wound sites without any inflammatory effects.	Betancourt-Angeles *et al.* (2017)

[a]Power intensity level; [b]Output power measurement; [c]Discharge current; [d]Distance between lesion and device.
CCS, clinical case study; CT, clinical trial; FR, flow rate; NA, not available; PCC, plasma coagulation controller; RCt, randomized controlled trial; slm, standard liter per minute.

- Kronik yarada farklı yara tiplerinde de başarılı
- Çoğunda yaraya 5mm yakınlıkta
- Çoğunda haftada 3 defa
- Her defasında 2 dk

CAP-sınırlılıkları

- Uzun dönem etkisi tam bilinmiyor?,
- Uygulama etkinliği değişken, hasta seçiminde objektiviteyi bozuyor,
- Hücresel ve doku etkinlikleri gösterilmiş ama vaka çeşitliliği gerekli,
- Argon ve helyum gibi gazların kullanımı bazı ?
- Yanıkta, amputasyon güdüğünde karsinogenezi tetikleyebilir mi?
- Ama …Melanom vb kanser tedavisinde etkin kullanılmaya başlandı?

COLD PLASMA

AN EMERGING TECHNOLOGY FOR CLINICAL USE IN WOUND HEALING



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Son nokta …

Hiçbir formu genotoksik değil …

Table 11: Overview of OECD 476 and 487 assays performed with CAP devices.

CAP source type	OECD genotoxicity assay employed	Finding	Reference
DBD operated with Ar	HPRT test	No genotoxicity	377
DBD operated in air	HPRT test	No genotoxicity	361
DBD operated in air	HPRT test	No genotoxicity	212
Atmospheric pressure Ar and neon PJ	MN test	No genotoxicity	378
Atmospheric pressure Ar PJ	MN test	No genotoxicity	379
Atmospheric pressure Ar PJ	HPRT test, MN test	No genotoxicity	380
Atmospheric pressure Ar PJ	MN test	No genotoxicity	381

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14 Mart


24 Mart






14 Mart
21 Mart





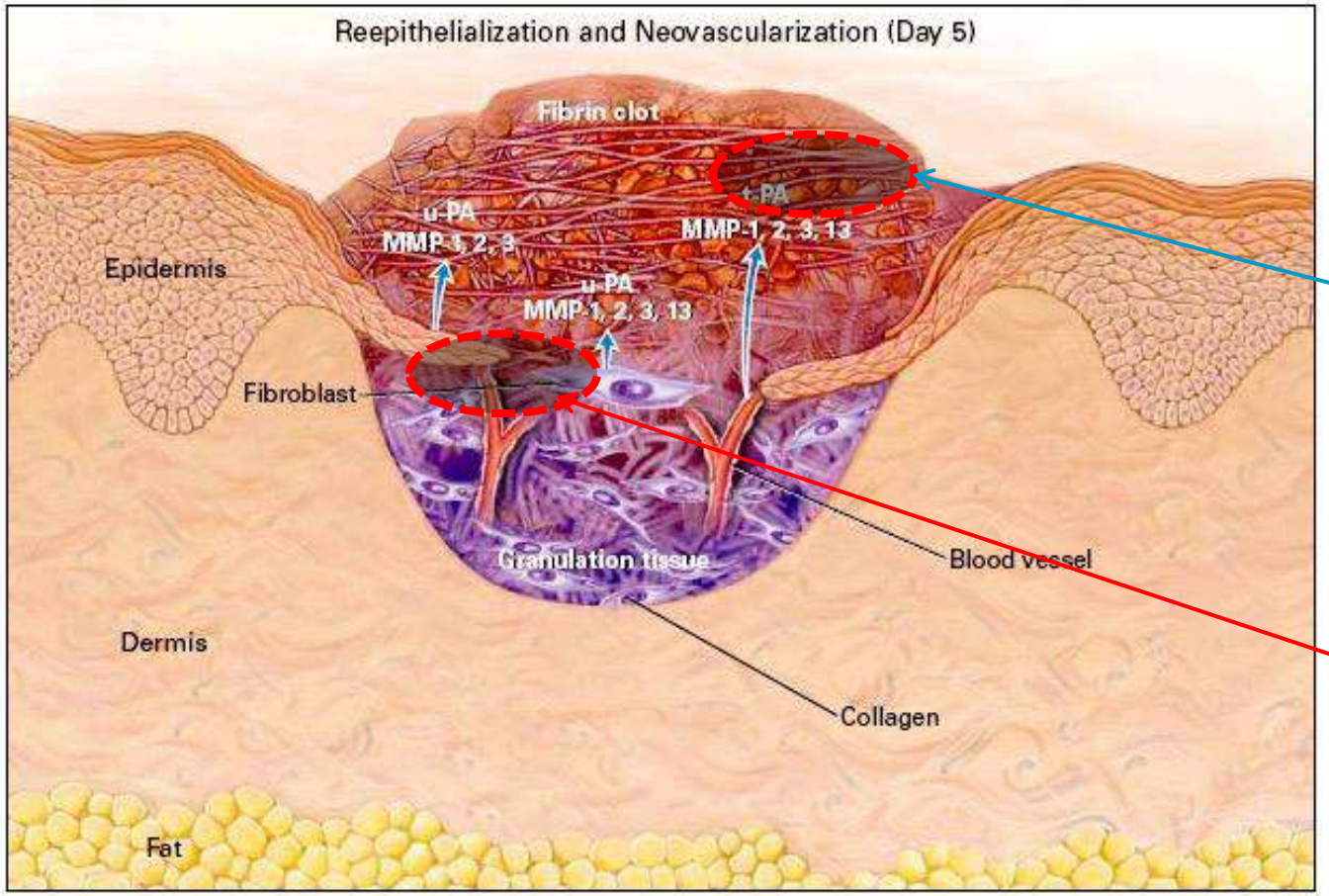





14 Mart
21 Mart

Kronik Yarada Oksijen Seviyesi Düşüktür

- Hipoksik ortam
- Biyofilm
- Fibrinöz eksüda
- Bozulmuş granülasyon
- Doku yıkım enzimleri (sitokromoksidaz, matriks metalloproteinaz, kollajenaz, hyalülonidaz)
- Yarım-yamalak oluşan kollajen lerin yıkımı…



Yara yüzeyindeki pO_2 60 mmHg

Yara merkezindeki pO_2 <10 mmHg

Source: Singer & Clark, N Engl J Med, 1999

Vasküler yatak normal bile olsa, vasküler yan yollar ve çalma ile doku hipoksisi kaçınılmaz

Topikal oksijen tedavisi ?!*

- Normal şartlar altında…
- Yaranın 3-4 mm altında, oda havası ile (%21 O_2, pO_2=159mmHg) 50mmHg O_2 içerir…
- Yara iyileşmesi için yeterli mi? Kısmen !
- AMA ne kadar sağlıklı doku oluşur?
- Hele ayak gibi yük taşıyan bir uzuvda…
- Ek basınç uygulamadan, %100 O_2 ile dokuyu buluşturursanız…yaradaki seviye 250 mmHg pO2'ye çıkıyor…



Topikal oksijen tedavisi endikasyonları?

- Diyabet
- Vasküler ülserler
- Ameliyat sonrası enfeksiyonlar
- Basınç yaraları
- Ampütasyonlar ve enfekte güdükler
- Deri greftleri
- İskemik dokular
- Yanıklar
- Donma

Dipnot…
Tüm bu endikasyonlar konservatif tedavi yaklaşımlarına ek olarak yardımcıdır.
Primer tedavide tek başına kullanımı çok sınırlıdır!

Oropallo A, Andersen CA. Topical Oxygen. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.





HBOT KONTRENDİKASYONLARI ve KOMPLİKASYONLARI

- Üst solunum yolu enfeksiyonu
- Şiddetli sinüs enfeksiyonları
- Yüksek ateş – nöbetlere yol açar
- Herhangi bir anemi veya kan bozukluğu
- Akut Hipoglisemi

- Barotravma
- Klostrofobi - kapanma Kaygısı
- Oksijen toksisitesi (akciğer ve CNS)
- Miyopi - Hafif basınçlandırma sırasında lenste geçici eğrilik nedeniyle oluşan küçük görme değişiklikleri
- Mobil olmayan hastalar için kullanılamaz

- Tüm hastalar için uygun değildir

HBOT vs Topikal Oksijen?

	HBOT	TO, aralıklı	TO, sürekli
Basınç	1.4-3.0 atm	<1.1atm	<1.1atm
Oksijen konsantrasyonu	%93-99	%87-93	>%93
Süre	1.5 s günde-haftada 3-5 kez	1.5 s günde-haftada 3-5 kez	24 s günde, haftada 7 gün
Doku oksijen ulaşımı	Vasküler yatağa, mikrovasküler dolaşıma bağlı	Direkt dokuya ulaşıyor	Direkt dokuya ulaşıyor

Topikal oksijen yara tedavisi tipleri

- TO- topikal oksijen
- TWO2-topikal yara oksijen tedavisi
- TCOT-transkütanöz oksijen tedavisi
- CTO-sürekli topikal oksijen tedavisi
- CDO-sürekli oksijen difüzyon tedavisi

Genel bakış…Topikal oksijen yara tedavi sistemleri

	TO (topikal oksijen)	**TWO2** (topikal yara oksijen tedavisi)	**TCOT** (transkütanöz oksijen tedavisi)	**CTO** (sürekli topikal oksijen tedavisi)	**CDO** (sürekli oksijen difüzyon tedavisi)
Terapi süresi	Aralıklı	Aralıklı	Sürekli	Sürekli	Sürekli
Oksijen uygulama yöntemi	Torba, bot	Torba, bot, çember	Açık uçlu kanül	ODS (Oxygen Distribution System)	ODD (Oxygen Diffusion Dressing)
Yara yatağında basınç	Kontrol dışı	Kontrollü, siklik, 0-50mmHg	Kontrol dışı	Kontrol dışı	Kontrollü, <20mmHg
Oksijen kaynağı	High flow oksijen konsantratörü	High flow oksijen konsantratörü	Elektrokimyasal oksijen jeneratörü	Elektrokimyasal oksijen jeneratörü	Elektrokimyasal oksijen jeneratörü
Oksijen akımı	Sabit, 6-10lt/dk	Sabit, 6-10lt/dk	Sabit, 3lt/dk	Sabit, 14 lt/dk	Ayarlanabilir, 3-15lt/dk
Oksijen saflığı	%87-93	%87-93	>%99	>%99	>%99

Oropallo A, Andersen CA. Topical Oxygen. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.

Topikal oksijen tedavisi, yaranın geleceği mi?

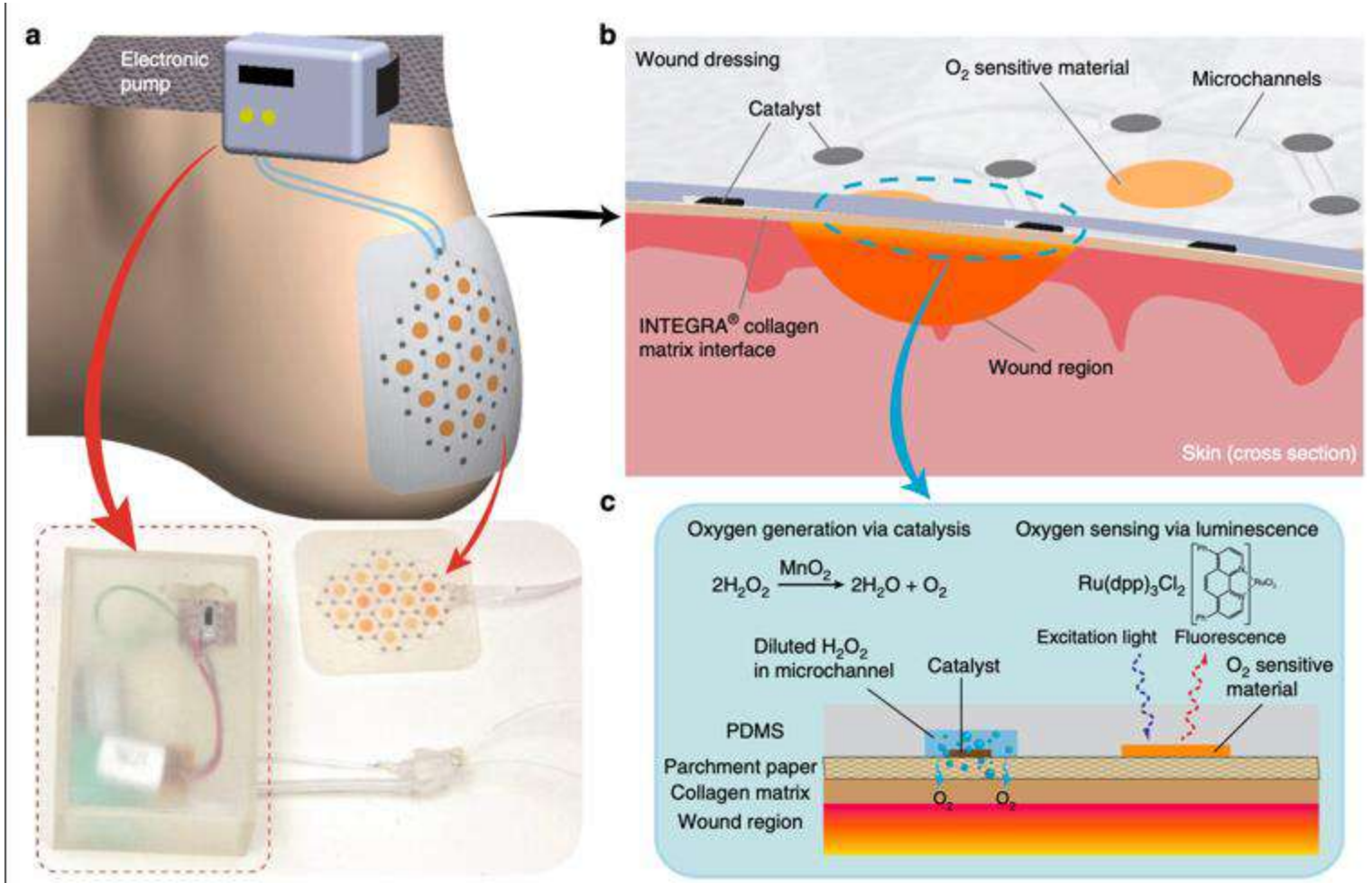


Fig. 1 Design of the integrated oxygen sensing and delivery patch. a Overview illustration of the patch in use for foot ulcer applications. **b** Cross-sectional view of smart oxygen generation and sensing patch and wound area. **c** Mechanisms for generating oxygen and for sensing it for use on a flexible smart wound dressing

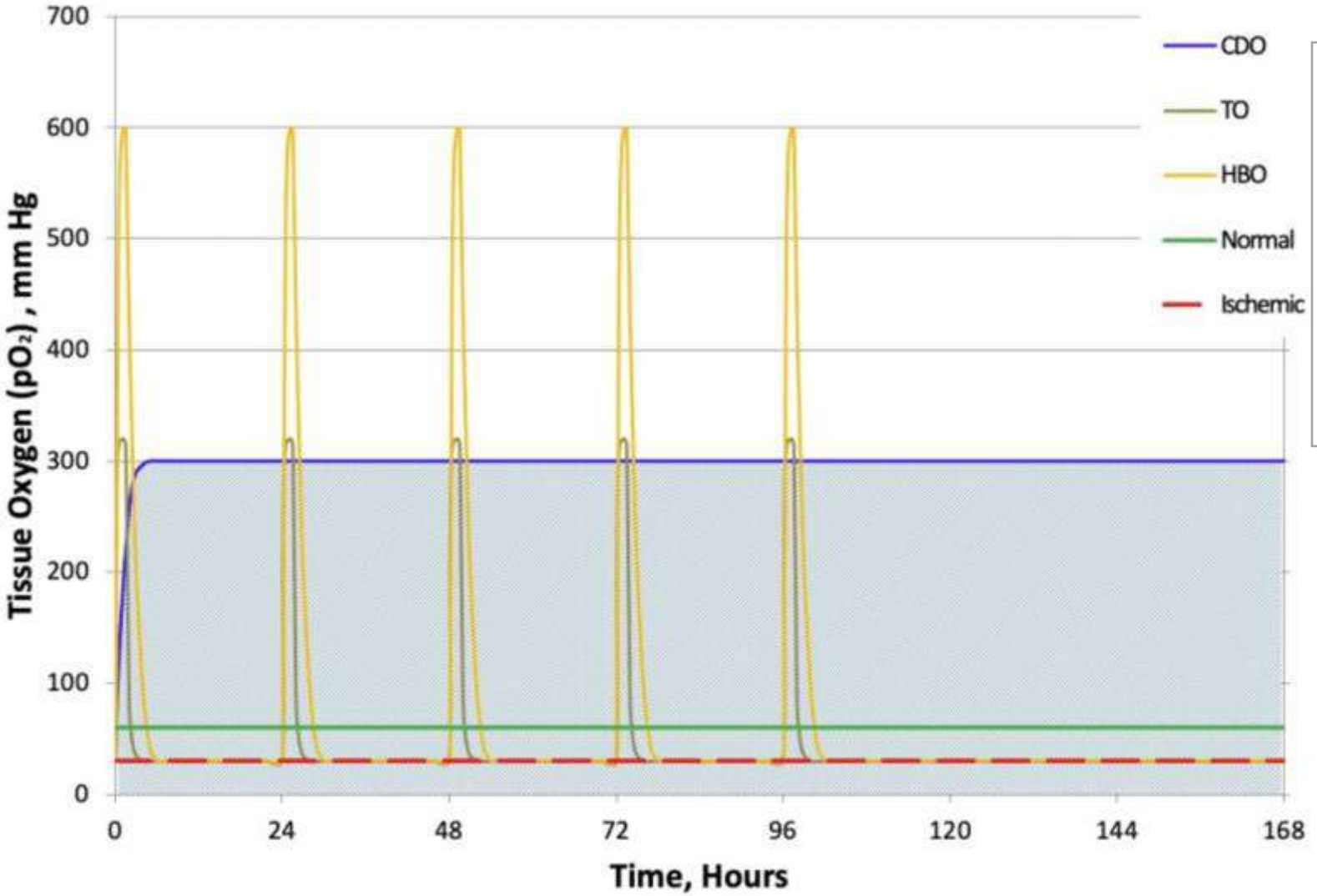
ODD
(Oxygen Diffusion Dressing)

ODS
(Oxygen Distribution System)

- Mobil
- Bataryalı
- Küçük yara
- Hidrojen peroksit, Mn…
- Oda havası…

Ochoa, M., Rahimi, R., Zhou, J. *et al.* Integrated sensing and delivery of oxygen for next-generation smart wound dressings. *Microsyst Nanoeng* **6**, 46 (2020). https://doi.org/10.1038/s41378-020-0141-7

Sürekli mi? Aralıklı mı? Daha etkili…



- Dokuda oksijen düzeyi sağlanması açısından sürekli olan…
- Yara iyileşmesi açısından ?
- Yarada mekanizmalar çok karışık…hipoksi sadece birisi…

Oropallo A, Andersen CA. Topical Oxygen. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.

Efficacy of Topical Wound Oxygen Therapy in Healing Chronic Diabetic Foot Ulcers: Systematic Review and Meta-Analysis

Marissa J. Carter,[1,*] Robert G. Frykberg,[2] Alisha Oropallo,[3] Chandan K. Sen,[4] David G. Armstrong,[5] Harikrishna K.R. Nair,[6] and Thomas E. Serena[7]

- Meta analiz
- 2010 sonrası çıkan literatürler…
- Topikal oksijen tedavisi
- E1,2 … iskemi ve enfeksiyon yokluğunda iyileşmeye etkili
- Alt grupta…iskemi yaygınlaşmasına etkisi kısıtlı…
- Enfeksiyon varlığında kontrolüne etkisi olumlu…
- Tedaviye ek uygulanması akılcı…

Objective: To conduct a systematic review and meta-analysis of recently published randomized controlled trials (RCTs) that employed the use of topical oxygen therapy (TOT) as an adjunct therapy in the treatment of Wagner 1 and 2 diabetic foot ulcers.
Approach: Following a literature search of eligible studies from 2010 onward, four RCTs were included. Studies were analyzed for patient and wound characteristics, outcomes, risk of bias, and quality of the evidence assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. A random-effects meta-analysis for complete wound healing was carried out due to statistical heterogeneity of included studies.
Results: Risk of bias judgment (RoB2 analysis) resulted in one low-risk trial and three trials with some risk. One study was determined to be the origin of the statistical heterogeneity. Pooled results showed statistical significance with a risk ratio (RR) of 1.59 (95% confidence interval [CI]: 1.07–2.37; $p = 0.021$). Sensitivity analysis, based on imputed values for missing outcomes, demonstrated that both the RR and 95% CIs changed little. The GRADE ratings for each domain were as follows: (a) risk of bias: moderate (3); (b) imprecision: moderate (2), high (1); (c) inconsistency: low (2), high (1); (d) indirectness: moderate (2), high (1); and (e) publication bias: moderate (1), high (2). Overall, the evidence was moderate.
Innovation: Our study shows that TOT is a viable diabetic foot ulcer therapy.
Conclusions: These data support the use of TOT for the treatment of chronic Wagner 1 or 2 diabetic foot ulcers in the absence of infection and ischemia.

Keywords: diabetic foot ulcer, topical oxygen therapy, systematic review, meta-analysis

TOPICAL WOUND OXYGEN THERAPY




Basınçlı saf
oksijen(100%)

Medium Chamber



- Extremity Chamber - 90 minute a day x 5 days a week



1.Oksijen geçirgen pansumanların üzerinden uygulanabilme

2.Diğer yara bakım tedavileri ile kombinasyon kolaylığı

- Extremity Chamber - 90 minute a day x 5 days a week





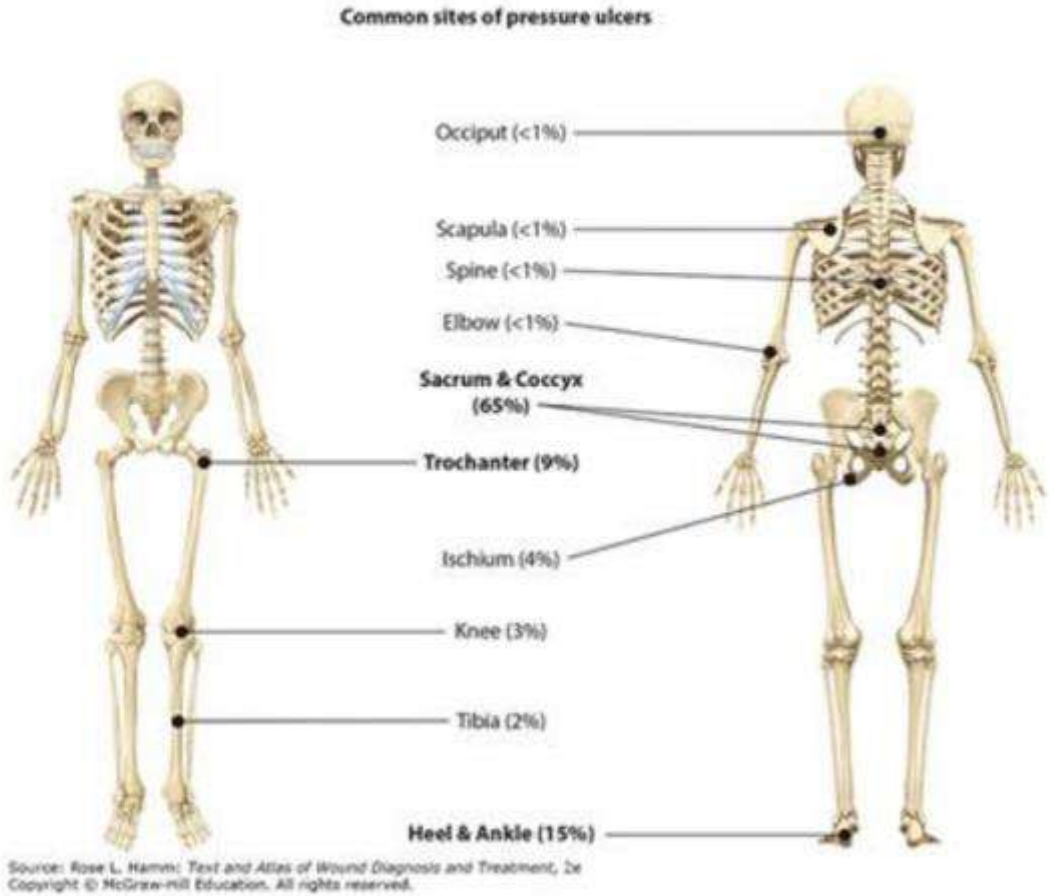


Multi-Patch

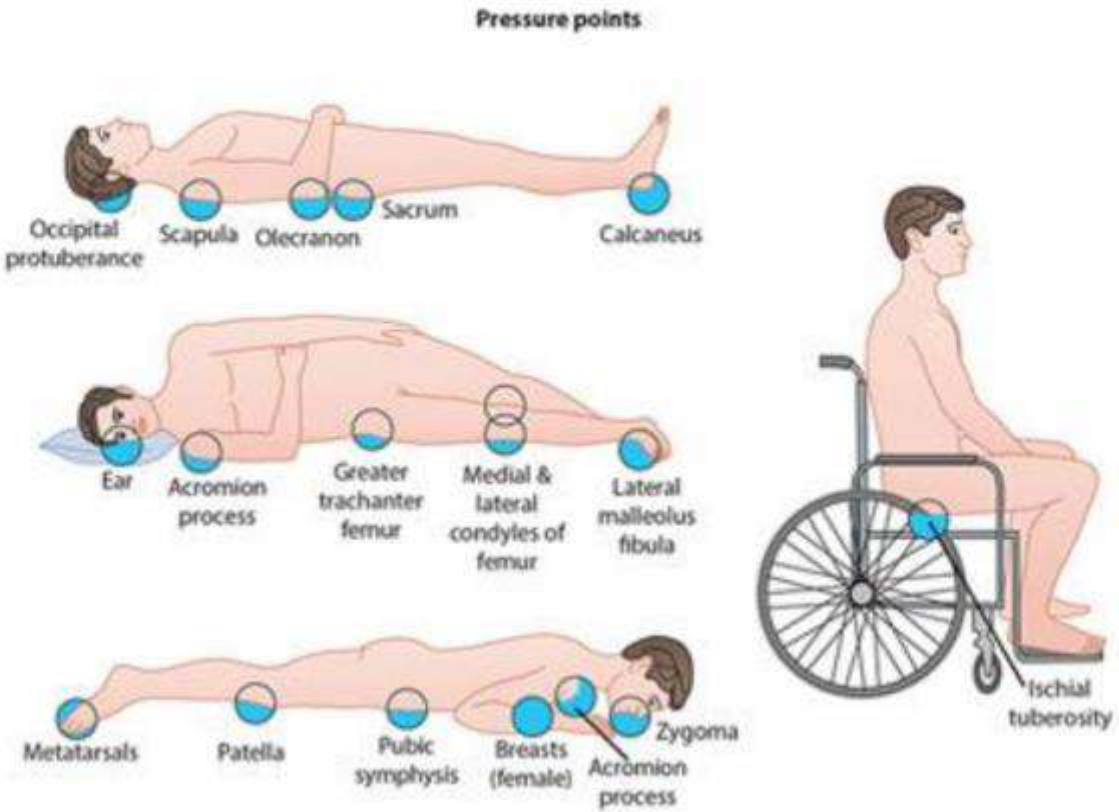
(Other Wounds)

Multi-Patch Operating: Placement Instructions

Boney Prominence



Source: Rose L. Hamm: *Text and Atlas of Wound Diagnosis and Treatment, 2e*
Copyright © McGraw-Hill Education. All rights reserved.

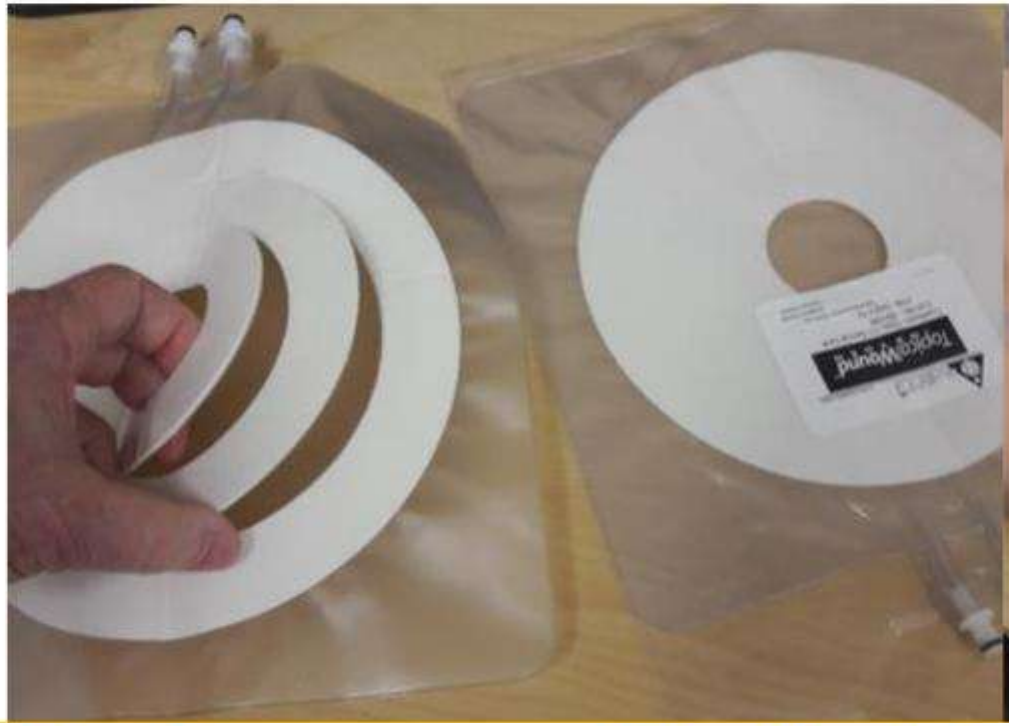


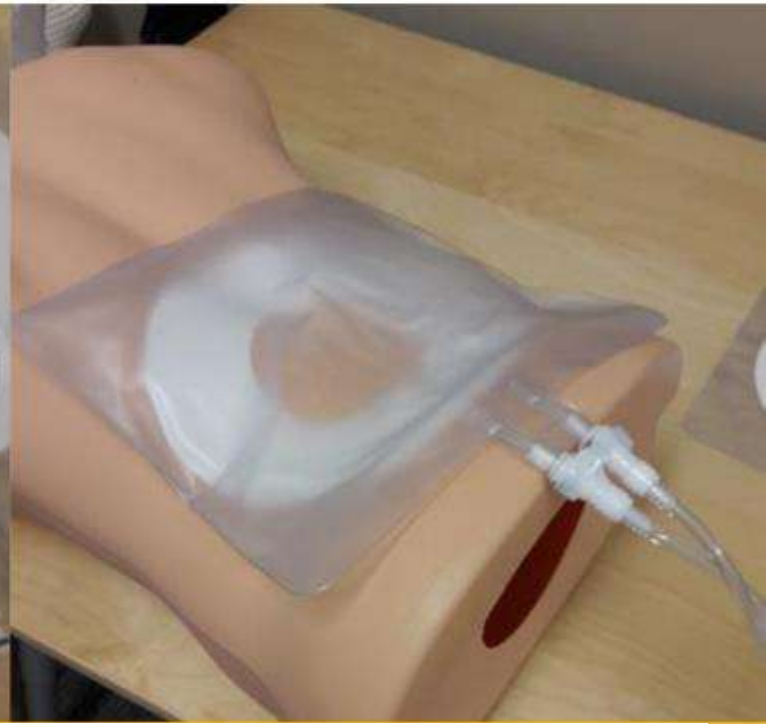
Multi-Patch Operating & Placement Instructions

Take care to place hoses so the patient is not lying or resting any part of their body on them

Maximum opening is 15cm (5.9 inches) diameter







Routine frequency and duration of therapy is:

- Multi-patch - 60 minute a day x 7 days a week

Prospektif randomize kontrollü çalışması olması…

FEATURE

Topical Wound Oxygen Therapy in the Treatment of Severe Diabetic Foot Ulcers: A Prospective Controlled Study

Eric Blackman, MD, FRCS(C), FAADEP; Candice Moore, RN; John Hyatt, MD, FRCS(C); Richard Railton, MD, FRCS(C), FACS; and Christian Frye, MD, MPH

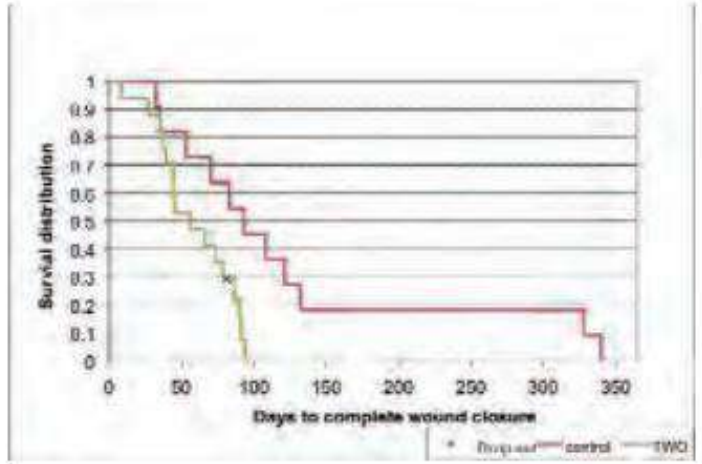


Figure 2. Kaplan-Meier estimate for time to complete wound closure.

Time to complete closure TWO_2 group = 94 days; time to complete closure control group = 340 days (P = 0.013)

two2 MULTI-MODALITY OXYGEN

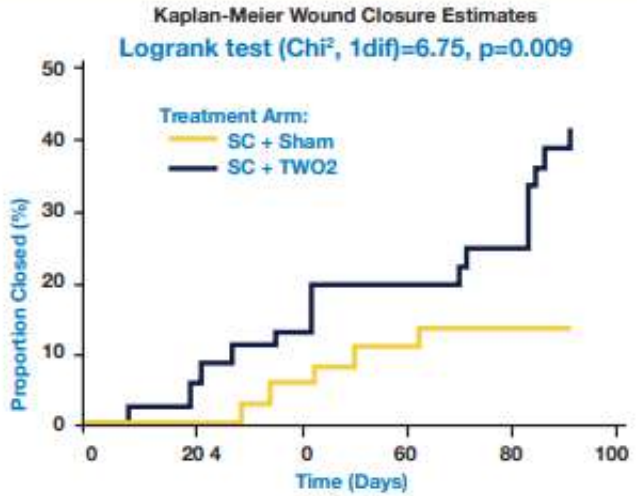
Advanced Oxygen Therapy Inc.

12 haftalık takipte 6 kat hızlı iyileşme

6X MORE LIKELY TO HEAL in 12 weeks

Primary Outcome:
Healed Ulcers at 12 Weeks

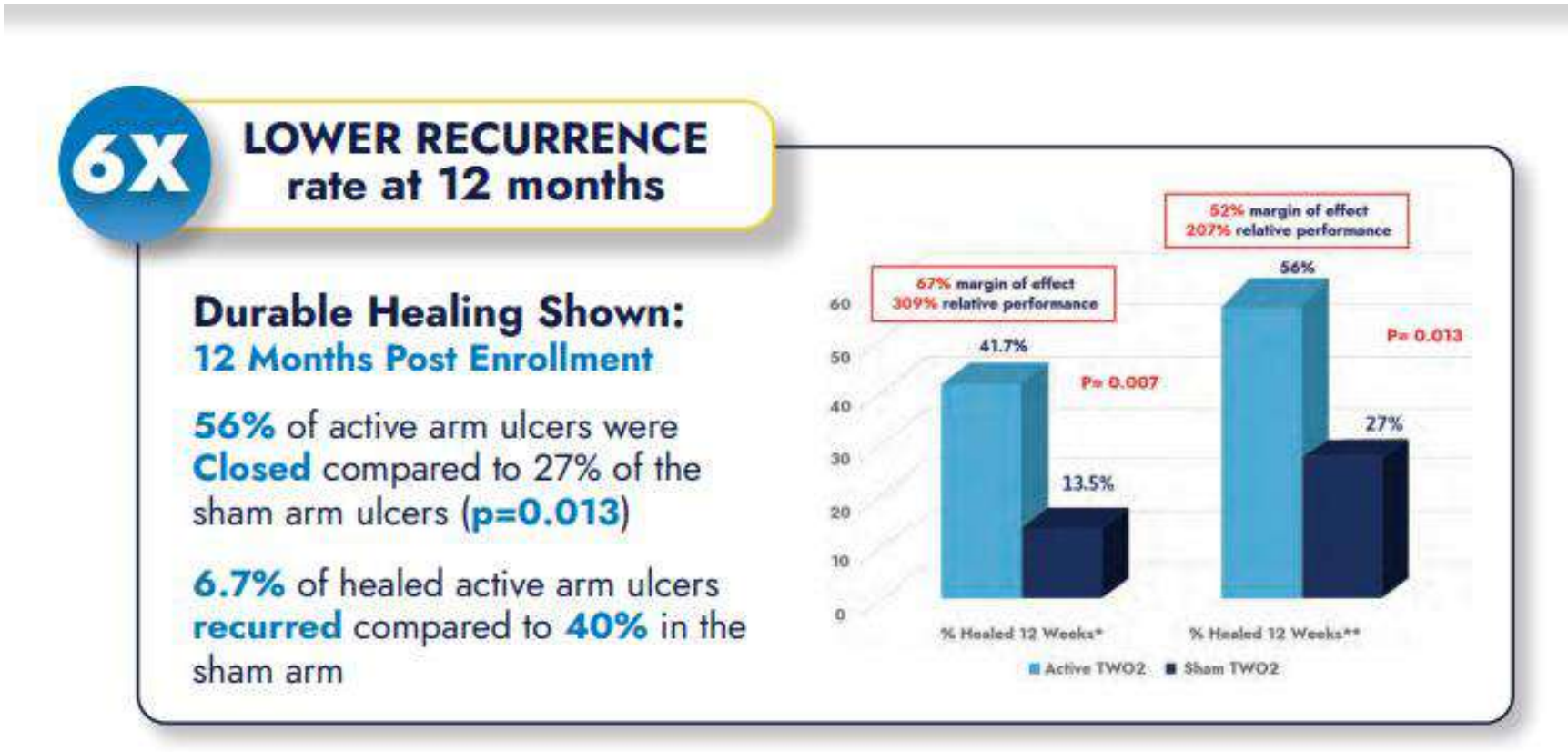
After adjusting for UTC ulcer severity, produced an odds ratio (OR) of **6.00** (97.8% CI 1.44,24.93), **P=0.004**



twO2 MULTI-MODALITY OXYGEN

Advanced Oxygen Therapy Inc.

12 aylık takipte… 6 kat daha az rekürrens



MULTI-MODALITY OXYGEN

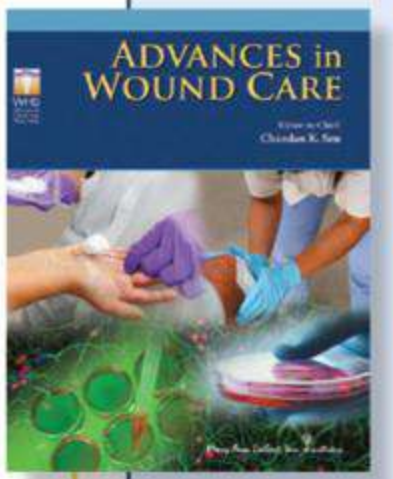
Advanced Oxygen Therapy Inc.

Gerçek yaşam verilerinin RKÇ'ları desteklemesi

Proven to deliver sustained wound healing

Supported by the highest level scientific studies, designed with integrity.

REAL WORLD EVIDENCE STUDY



88% Reduction in Hospitalizations

71% Reduction in Amputations

#1 Ranked Journal in Wound Care

RANDOMIZED CONTROLLED TRIAL

6X MORE LIKELY TO HEAL in 12 weeks

6X LOWER RECURRENCE rate at 12 months



Study Received Perfect Cochrane Score for Quality of Research

Health Canada Santé Canada

FDA CLEARED (510k)

ACHC® ACCREDITED

CE 0050

MEDICAL DEVICES
ISO 13485:2016
NSAI Certified

Quality & Regulatory Compliance Mantra

Advanced Oxygen Therapy Inc.

Uluslararası kılavuzlar

IWGDF Guidelines

The International working group on diabetic foot

JAMA Clinical Reviews JN

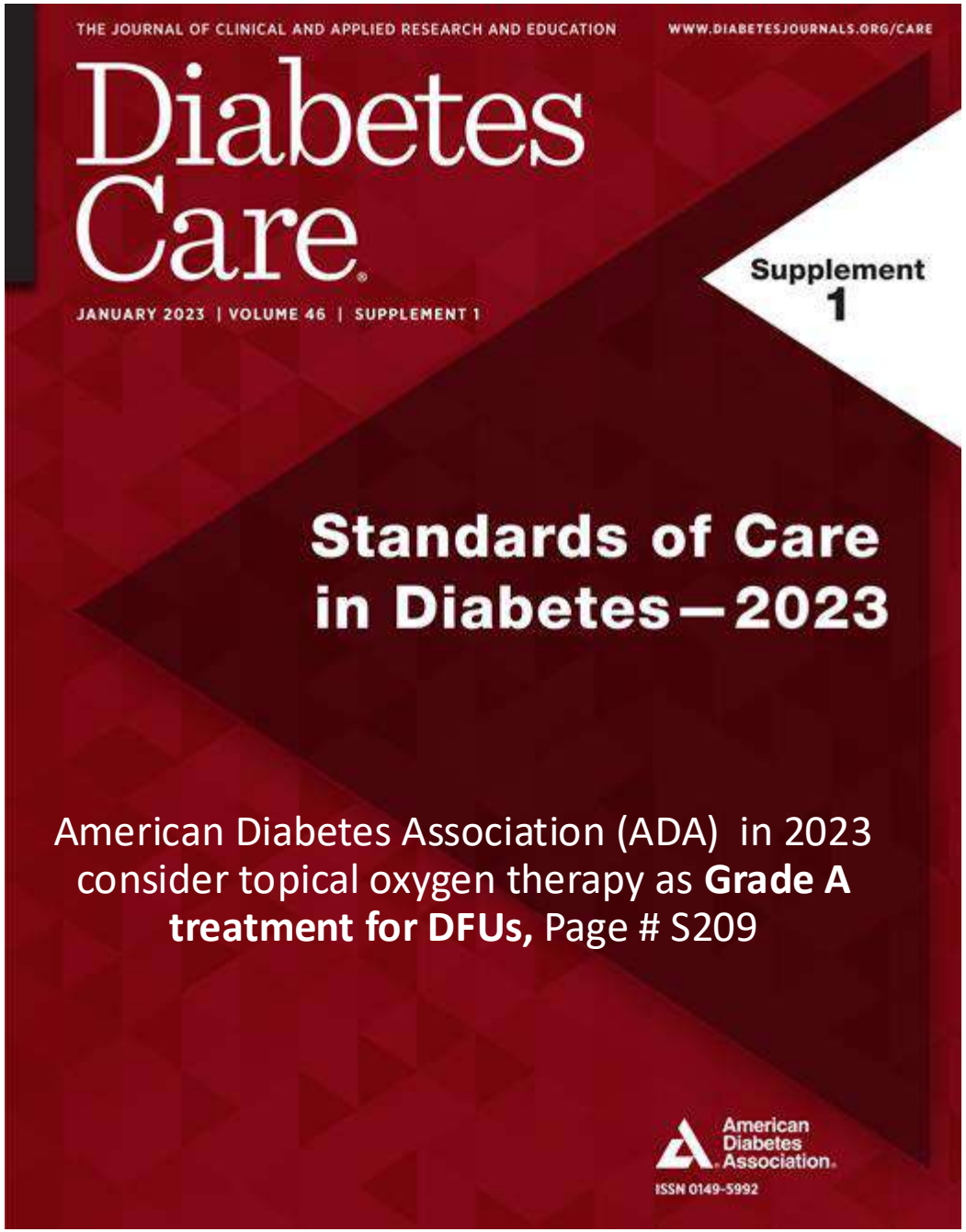
The journal of American medical association

American Diabetes Association®

IWGDF Güidelines

Topikal Oksijen Tedavisi, 2023 Diyabetik Ayak Ülseri Kılavuzlarında Uluslararası Diyabetik Ayak Çalışma Grubu…

…iyileşmeye olumlu etkisi nedeni ile tedaviye yardımcı olarak önerildi…



American Diabetes Association (ADA) in 2023 consider topical oxygen therapy as **Grade A treatment for DFUs,** Page # S209

12. Retinopathy, Neuropathy, and Foot Care: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S203–S215 | https://doi.org/10.2337/dc23-S012

12.30 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. **A**

Continuous Topical Oxygen Therapy made easy

WOUNDS | INTERNATIONAL

- Bataryalı
- Taşınabilir
- Havadaki oksijeni jeneratör aracı saflaştırıp dokuya veriyor…



Figure 2: The NATROX® O_2 system consists of three proprietary components: a) NATROX® O_2 Oxygen Generator (OG); b) two interchangeable batteries; c) NATROX® O_2 Oxygen Delivery System (ODS)

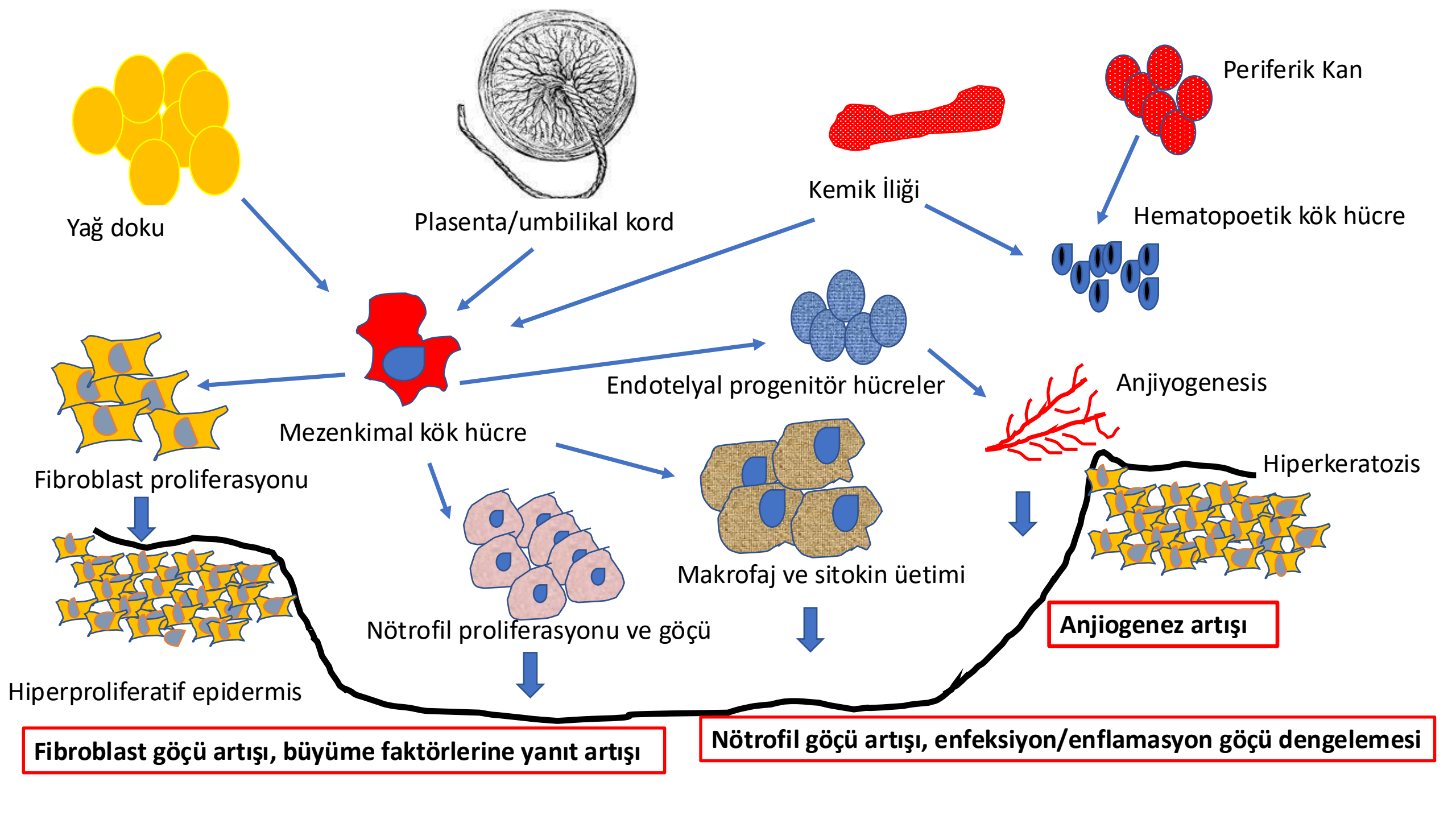
Kronik yarası olan hastalarda, NATROX® O_2 sürekli topikal oksijen tedavisi kullanıldığında, standart bakıma kıyasla iyileşme şansı %71 daha yüksektir. [1]

FDA CLEARED · CE 0197 · GSA

Table 1. Key evidence for the use of TOT	
Systematic Reviews and Meta-Analyses of RCTs	**Key outcomes**
Carter et al, 2023	A random-effects meta-analysis of four RCTs demonstrated that TOT improved wound healing at 12 weeks vs. SoC alone, supporting the use of TOT for the treatment of chronic Wagner 1 or 2 DFUs in the absence of infection and ischemia. The overall GRADE level of evidence for TOT was moderate. RR: 1.59; 95% CI: 1.07–2.37; p=0.021
Sethi et al, 2022	Meta-analysis of four RCTs demonstrated that use of adjuvant TOT significantly increased complete wound healing by approximately 60% at 12 weeks of wound healing in DFUs vs. SoC alone. RR: 1.59; 95% CI: 1.07, 2.37; p=0.02; NNT: 6.3
Sun et al, 2022	Meta-analysis of seven trials demonstrated that the TOT group had a higher healing rate with no effect on adverse events. RR: 1.63; 95% CI: 1.33, 2.00; p=0.096
Thanigaimani et al, 2021	Meta-analysis of six RCTs demonstrated that TOT significantly increased the likelihood of ulcer healing vs. controls. RR: 1.94; 95% CI: 1.19, 3.17; I^2: 57%; NNT: 5.33
Connaghan et al, 2021	Meta-analysis of five RCTs demonstrated that DFUs are >2 times more likely to heal with TOT vs. SoC alone. OR: 2.49; 95% CI: 1.59–3.90; p=0.00001
RCTs	**Key outcomes**
Serena et al, 2021 Multi-centre RCT, n=145 DFU	**Complete healing:** significantly more patients in the cTOT group healed by 12 weeks vs. the SoC group (36/81 [44.4%] vs. 18/64 [28.1%] respectively [p=0.044]) **Wound reduction:** significantly higher wound reduction reported in the cTOT group vs. the SoC group, achieving a mean reduction of 70.1% vs. 40% respectively (p=0.005) **Pain:** measured using the Visual Analogue Scale — majority of patients reported no pain in either group initially. Therefore, no significance was seen between the groups
Yu et al, 2016, RCT, n=20 DFU	**Complete healing:** Grade II ulcers: 100% cTOT-treated wounds healed vs. zero in the control group, Grade III ulcers: 50% cTOT-treated vs. zero in the control group **Wound reduction:** significant decrease in mean wound area size from baseline over 8 weeks (p<0.001) in the cTOT group and with the exception of week 1, significant reduction at every week (W2-8). Wound exudate increased significantly (in the first two weeks); treatment significantly increased rate of wound closure
RCT follow-up	**Key outcomes**
Al-Jalodi et al, 2022 Follow-up to Serena et al (2021) RCT	**Recurrence:** 85% of the cTOT patients remained healed at 1 year vs. 60% of the SoC patients **Amputation:** 1 major amputation in a SoC patient

https://woundsinternational.com/wp-content/uploads/2024/03/INO24_ME_Natrox_WINT_web.pdf

HÜCRESEL TEDAVİLER


Yağ doku
Plasenta/umbilikal kord
Kemik İliği
Periferik Kan
Hematopoetik kök hücre
Endotelyal progenitör hücreler
Anjiyogenesis
Mezenkimal kök hücre
Fibroblast proliferasyonu
Hiperkeratozis
Makrofaj ve sitokin üetimi
Nötrofil proliferasyonu ve göçü
Hiperproliferatif epidermis
Anjiogenez artışı
Fibroblast göçü artışı, büyüme faktörlerine yanıt artışı
Nötrofil göçü artışı, enfeksiyon/enflamasyon göçü dengelemesi

ADSC: adipose tissue derived mesenchymal stem cells
BM-MSC: Bone marrow-derived mesenchymal stem cells
PB- MSC: peripheral blood derived mesenchymal stem cells
hUC-MSC: human umbilical cord mesenchymal stem cells

Table 2 Stem cell types advantages, disadvantages and use in clinical and preclinical studies

Stem cell type		Advantages	Disadvantages	Clinical studies		Preclinical studies	
Adult stem cells	BM-MSC	• Donor-specific therapy • Lower malignancy risk • Cell-lineage committed (targeting differentiation) • No ethical conflict	• Cell lineage committed (limited differentiation potential) • Biopsy high surgical risk • Nondisposable tissue • Low stem cell concentration • Cell concentration and performance influenced by comorbidities	19	(52.8%)	27	(50.0%)
	PB-MSC	• Donor-specific therapy • Lower malignancy risk • Cell-lineage committed (targeting differentiation) • No ethical conflict • Relatively disposable tissue • Vein puncture has low surgical risk • Simple cell harvesting protocol	• Cell lineage committed (limited differentiation potential) • Cell concentration and performance influenced by comorbidities • G-CSF administration needed	11	(30.5%)	2	(3.7%)
	hUC-MSC	• Future donor-specific therapy • Lower malignancy risk • Cell-lineage committed (targeting differentiation) • Disposable tissue • UC tissue harvesting has low surgical risk • Donor UCB banking storage	• Cell lineage committed (limited differentiation potential) • Immunoincompatibility • Ethical conflict • Low stem cell concentration • Need for UCB banking	4	(11.1%)	12	(22.2%)
	ADSC	• Donor-specific therapy • Lower malignancy risk • Cell-lineage committed (targeting differentiation) • No ethical conflict • Disposable tissue • Liposuction has low surgical risk	• Cell lineage committed (limited differentiation potential) • Cell concentration and performance influenced by comorbidities	3	(8.3%)	11	(20.4%)
Embryonic stem cells		• High differentiation potential (pluripotent)	• Increased malignancy risk • Ethical conflicts	0	(0.0%)	1	(1.9%)
Induced pluripotent stem cells		• High differentiation potential (pluripotent) • Somatic-cell memory (targeting differentiation) • Donor-specific therapy • No ethical conflict • Disposable tissue • Low cell harvesting procedure risk	• Increased malignancy risk • Complex induction protocol • Somatic-cell memory (biased differentiation)	0	(0.0%)	0	(0.0%)

ADSC adipose tissue-derived mesenchymal stem cells, *BM-MSC* bone marrow-derived mesenchymal stem cells, *G-CSF* granulocyte-colony stimulating factor, *hUC-MSC* human umbilical cord mesenchymal stem cells, *PB-MSC* peripheral blood-derived mesenchymal stem cells, *UC* umbilical cord, *UCB* umbilical cord blood

En yaygın

En kolay

En popüler

Hücresel tedaviler fihristi…

Lokal veya sistemik enjeksiyon (IM/IV)

- Kök hücre…

A. Otolog

1.BMMSc: Kİ kökenli mesenkimal kök h.

2.BM-NCs:Kİ mononükleer h.

3.PBSCs: Periferik kan kökenli kök h.

4. PBMNCs: Periferik kan mono nükleer h.

5. ASCs: yağ doku kökenli kök h.

6. BMTRCs: Kİ ile zenginleştirilmiş doku onarım h.

7. SVF: otolog stromal vasküler faktör

B. Allojenik

1. HUCMSCs: İnsan göbek bağı mezenkimal kök h.

2. PDMSCs: Plasenta kökenli mezenkşmal kök h.

3. ESCs: Embriyonik kök h.

Klinik tercihe bağlı

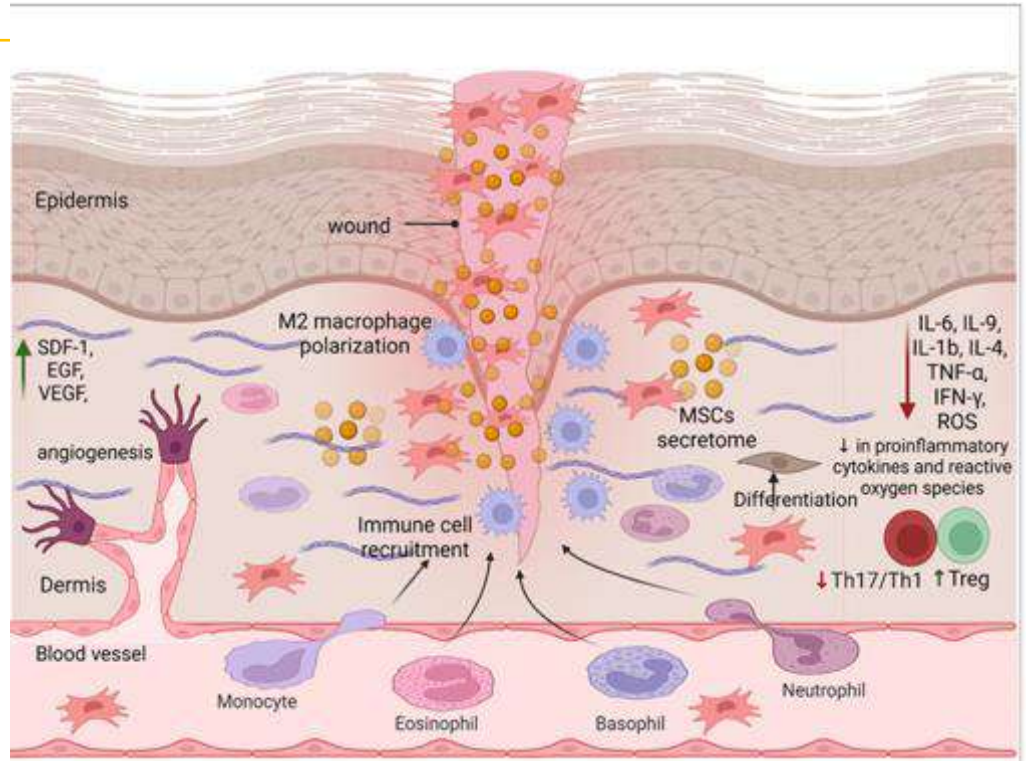
\+ Büyüme faktörleri …GMCSF, EGF, PDGF

El Hage R, Knippschild U, Arnold T, Hinterseher I. Stem Cell-Based Therapy: A Promising Treatment for Diabetic Foot Ulcer. Biomedicines. 2022 Jun 25;10(7):1507. doi:

Otolog vs Allojenik
(Mezenkimal vs Embriyonik)

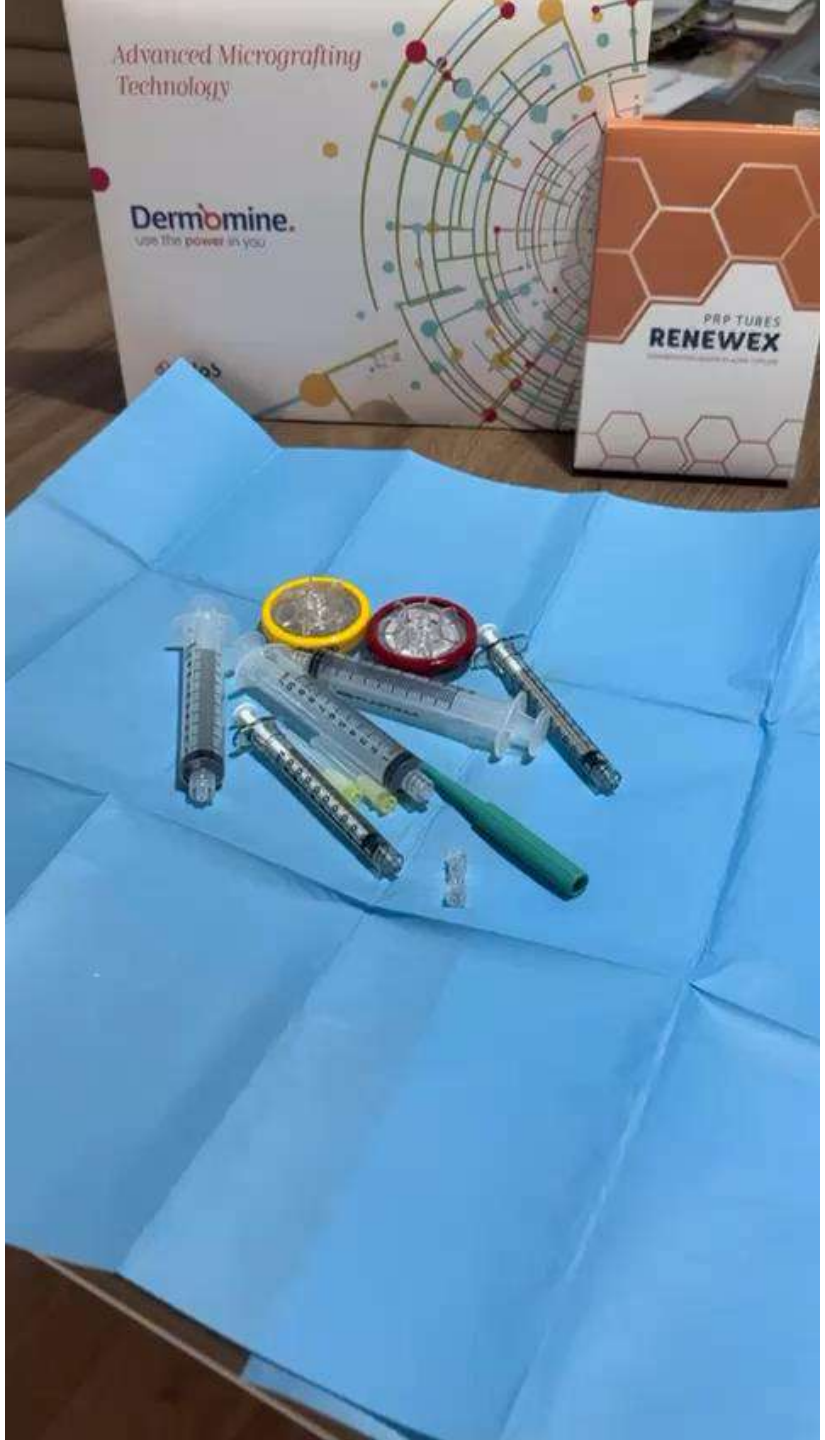
- Terapotik kullanım ile ilgili etik kurallar sıkı değil,
- Kendi dokusu olduğu için immün reaksiyon riski yok,
- Temini daha kolay,

- Etik kurallar yeni oluşuyor,
- İmmün rejeksiyon riski var,
- Temini daha zor,
- Viral patojen geçişi?
- Kanser gelişimi?

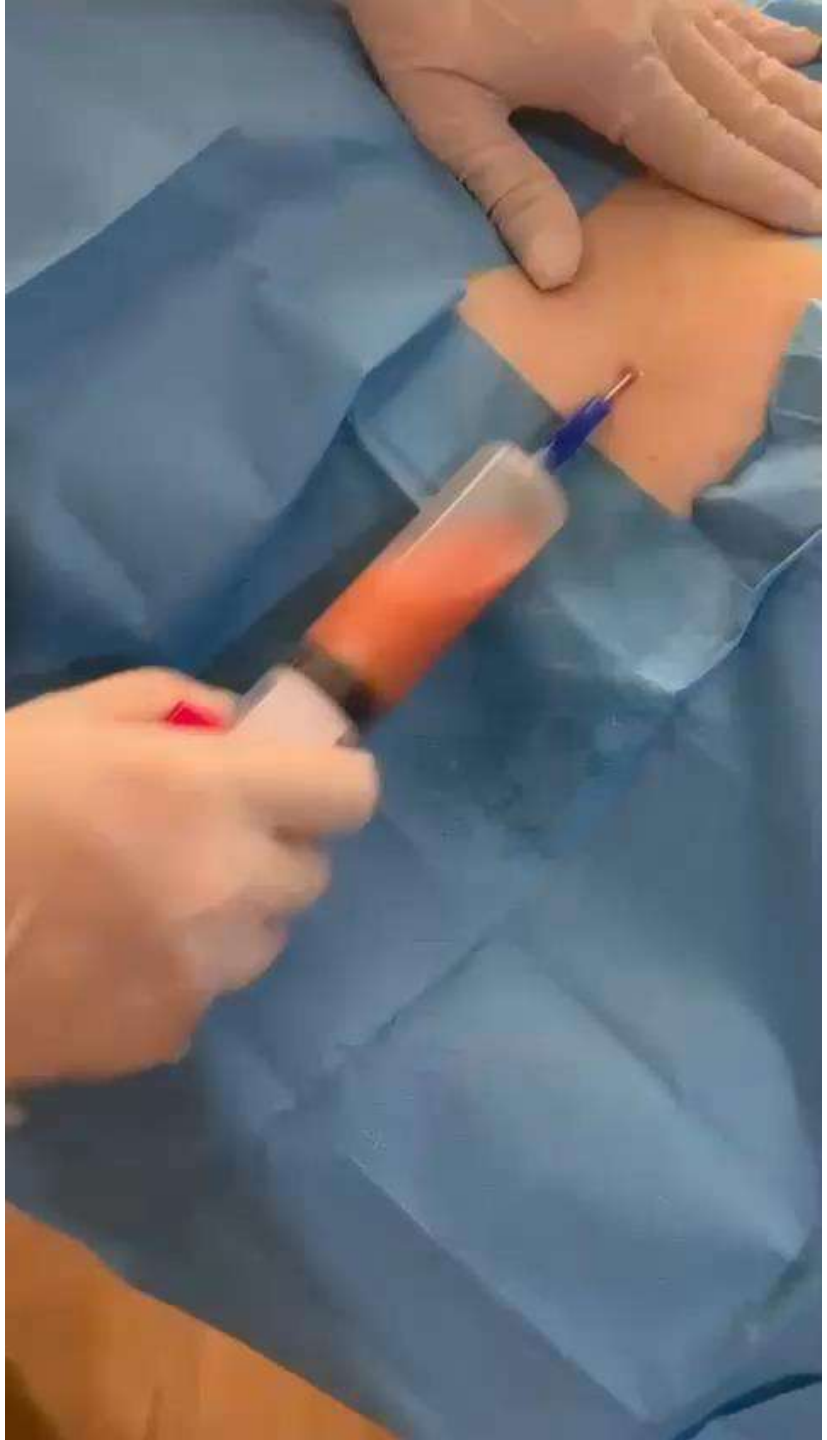


1. M2 makrofaj yanıtı artışı…polarizasyon
2. Sekrotom salınımı artışı
3. EGF,VEGF artışı
4. ROS azalma
5. Fibroblast ve keratinosit artışı

Hetta HF, Elsaghir A, Sijercic VC, Akhtar MS, Gad SA, Moses A, Zeleke MS, Alanazi FE, Ahmed AK, Ramadan YN. Mesenchymal stem cell therapy in diabetic foot ulcer: An updated comprehensive review. Health Sci Rep. 2024 Apr 21;7(4):e2036. doi: 10.1002/hsr2.2036. PMID: 38650719; PMCID: PMC11033295


Advanced Micrografting
Technology
Dermomine.
use the power in you
PRP TUBES
RENEWEX


Lipomine
50ml
60
40
30
20
10





Neden Göbek Kordonu Warton Jeli Mezenkimal Kök Hücre

- **Yüksek hücresel içerik**
- **Kolay çoğaltılabilme**
- **İnvaziv olmayan toplama prosedürleri**
- **Düşük Patojenik Enfeksiyon Riski**
- **Daha Yüksek proliferasyon faktörü**
- **Daha düşük immünojenite**
- **Düşük Maliyet**
- ***Dış etmenlerden en az etkilenen ve genetik yapısı en stabil olduğu düşünülen mezenkimal kök hücrelerdir.***

Kordon Matriksinden

MKH

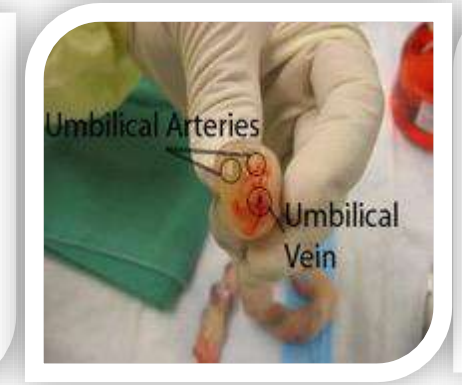


Bu grup hücrelerin en önemli özelliği embriyonik kök hücrelere benzer **telomer enzim** aktivitesi taşımalarıdır.

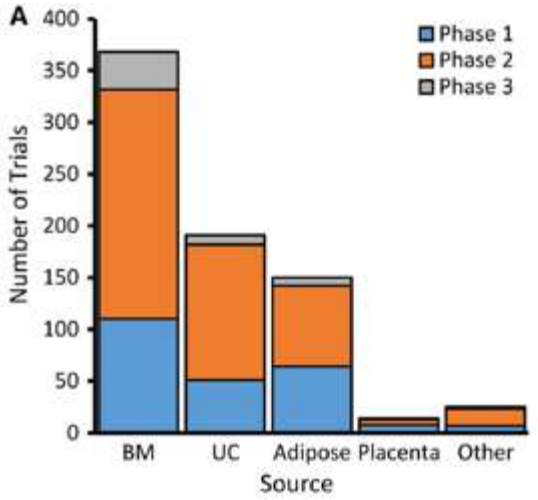
- **Adipojenik**, **osteojenik**, **kondrojenik** ve **nöronal** hücrelere farklılaşabilir.







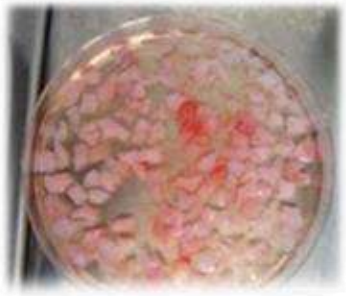




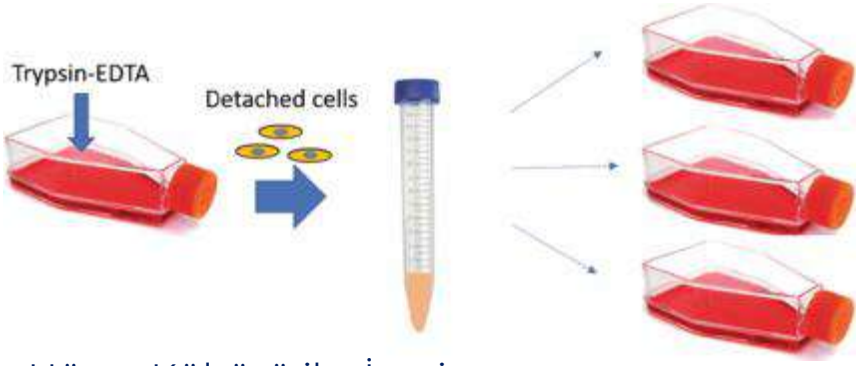
İzolasyon ve Pasajlama







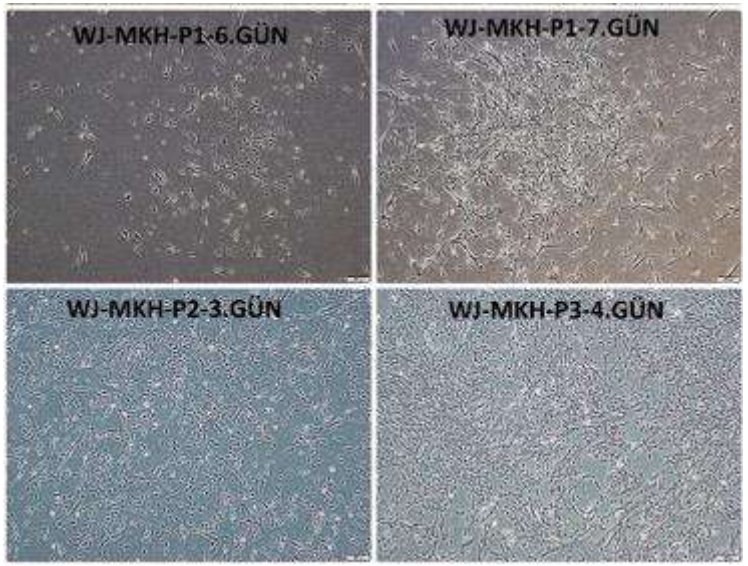
Primer kültür



Hücre Kültürü ile İn-vitro koşullarda hücre çoğaltma işlemi

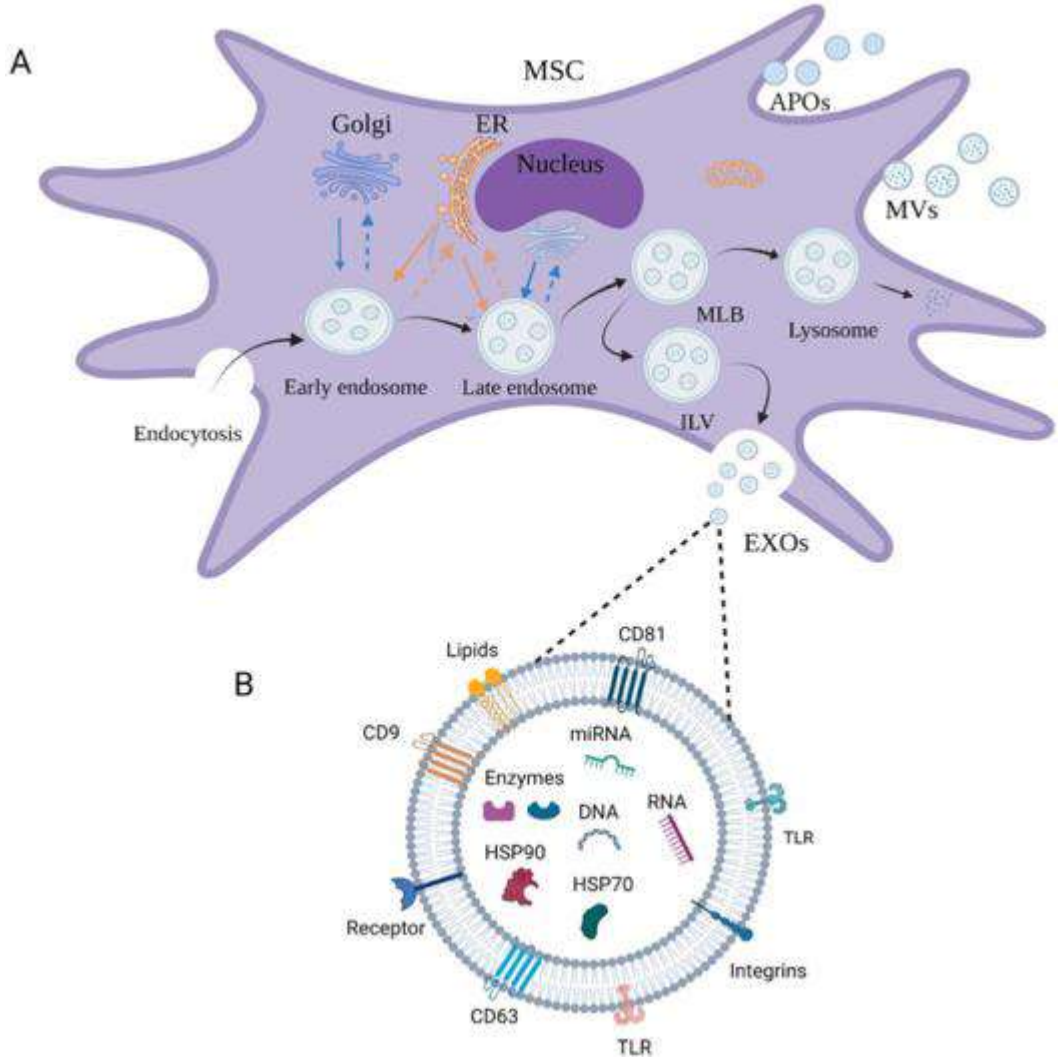


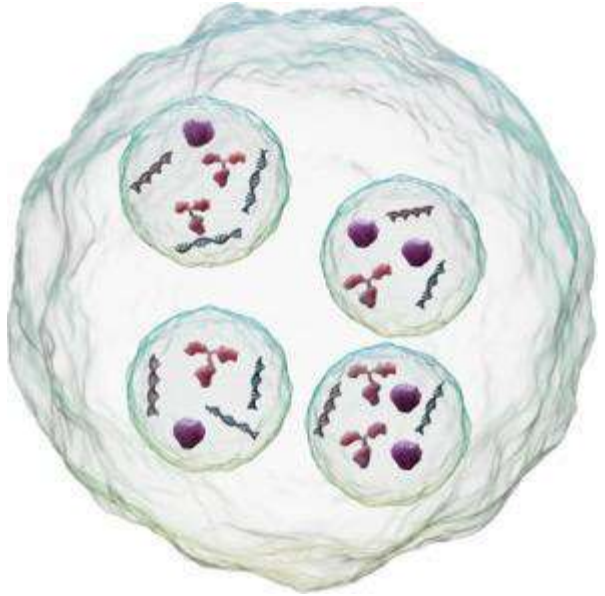
Enzimatik Ayrıştırma – **Eksplant Kültür**



Pasaj 3'e kadar çoğaltılmış hücrelerde kalite kontrol testleri

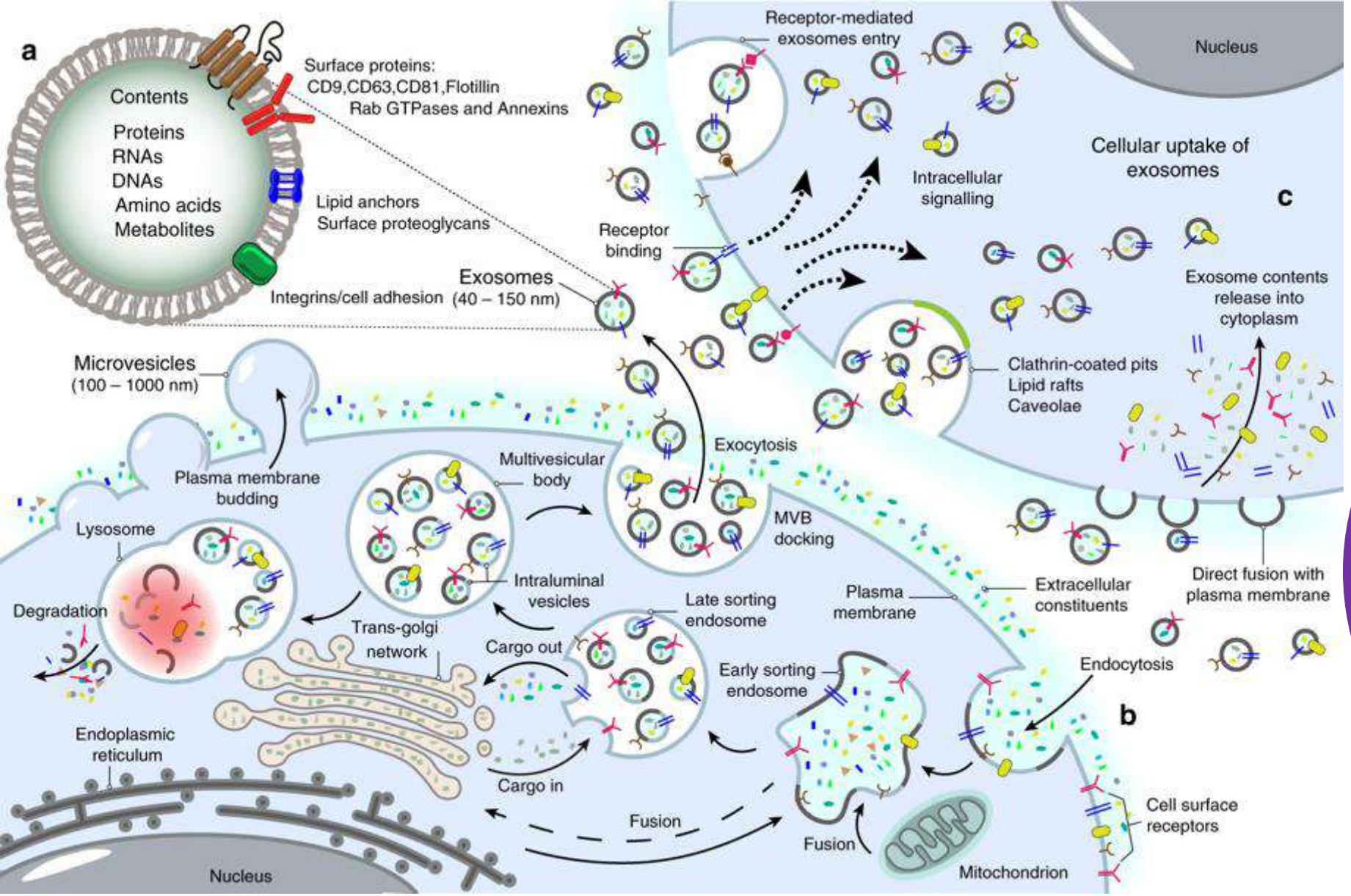
- Flow Sitometri-Karakterizasyon
- **Gen Ekspresyon Analizi**
- **Telomeraz Enzim Aktivitesi**
- Hücre Sayısı-Canlılık
- Sterilite Analizleri
- Mikoplazma





Eksozomlar; tüm hücrelerden salınan lipid yapıda zara sahip, genetik bilgiler, büyüme faktörleri ve proteinleri taşıyan, **40-150** nanometre çapında çok küçük keseciklerdir, Hücreler arası iletişimi sağlar, yakın ve uzak hücreler arasında hücre içi bilgilerin önemli düzenleyicileri olan molekülleri taşırlar.

Cell Death and Disease (2022) 13:580 ; https://doi.org/10.1038/s41419-022-05034-x



ExoCarta‘ da **1.500’** lerin üzerinde **Protein** sayısı

http://exocarta.org/index.html

Proteinler

Büyüme faktörleri

Lipidler

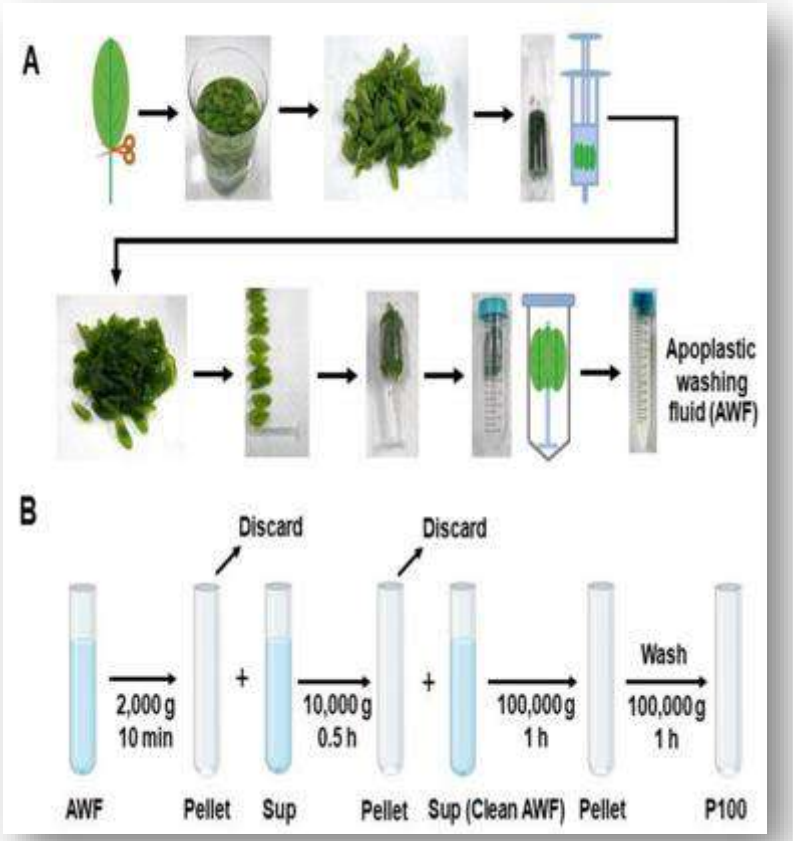
mRNA

miRNA

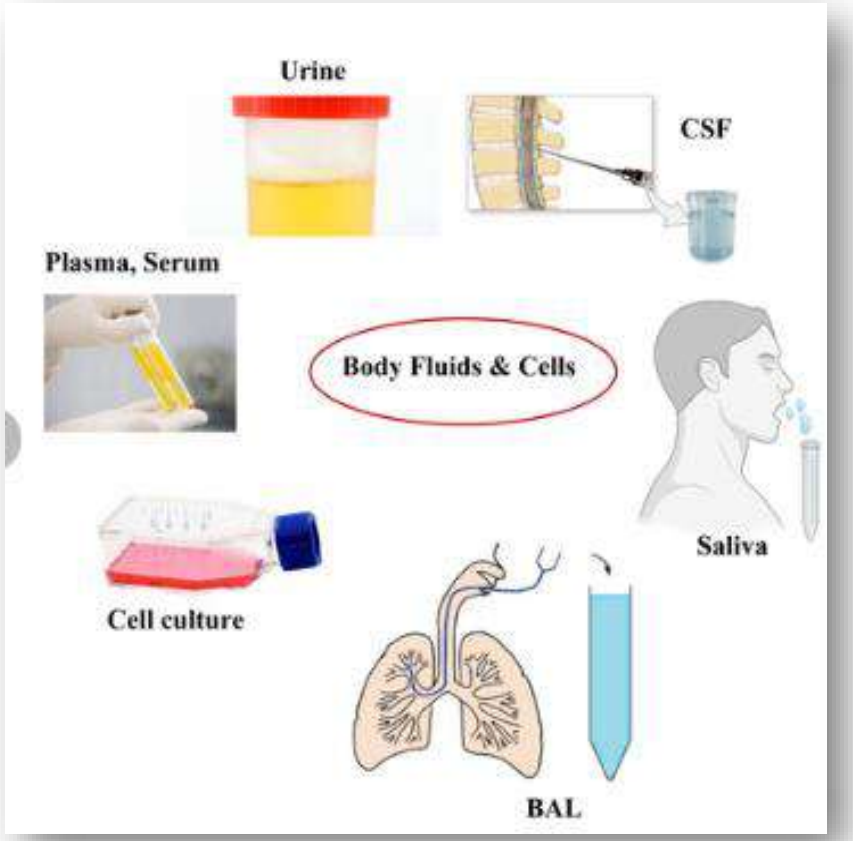
Sitokinler

Amino asitler

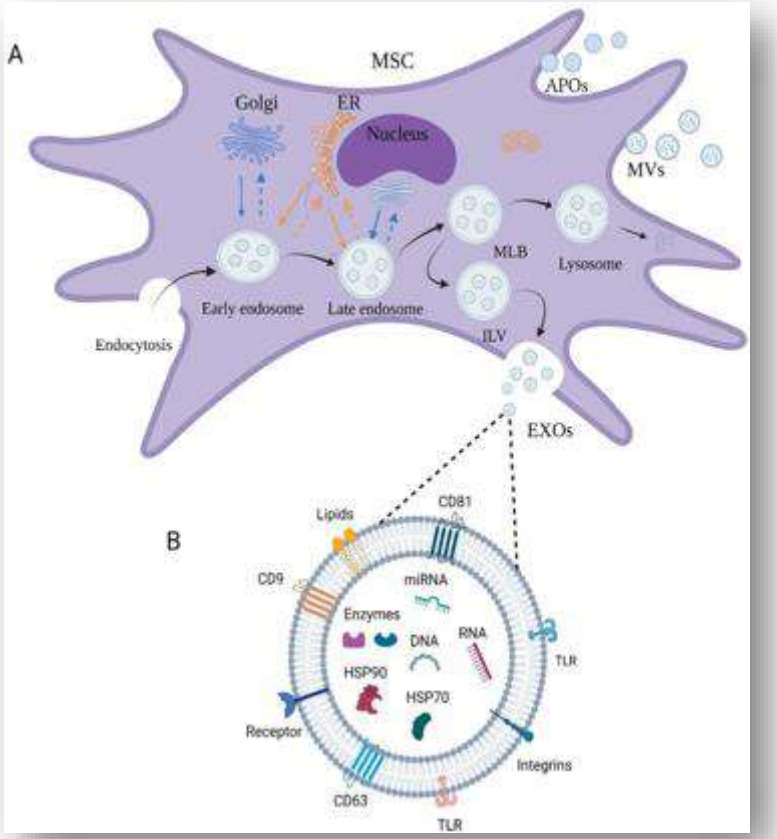
BİTKİ ve HAYVAN KAYNAKLI



OTOLOG ERİŞKİN SIVILARI



MEZENKİMAL KÖK HÜCRELER

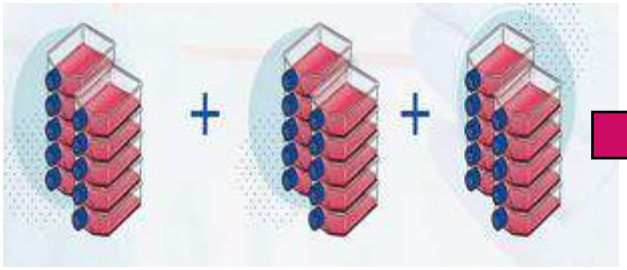


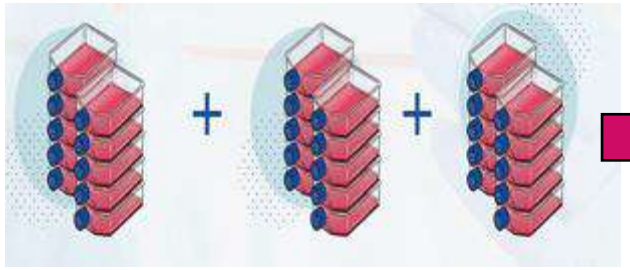
Eksozom Kaynakları

Eksozom İzolasyon Teknikleri

1. Ultrasanrifüj
2. Boyut Dışlama Kromatografisi
3. Polimer Esaslı Çöktürme
4. İmmünoafinite Yöntemiyle İzolasyon
5. Ultrafiltrasyon / SINIRLILIKLAR Hücre dışı veziküller, hücrenin en küçük moleküler bileşenleridir. Bu doğrultuda, hangi vezikülün ne amaçla elde edileceği ilk belirlenmesi gereken parametredir. Çünkü, izolasyon, saflaştırma ve elde edilen vezikülün doğrulanması için etkin tekniğin seçilebilmesi bu şarta bağlıdır.

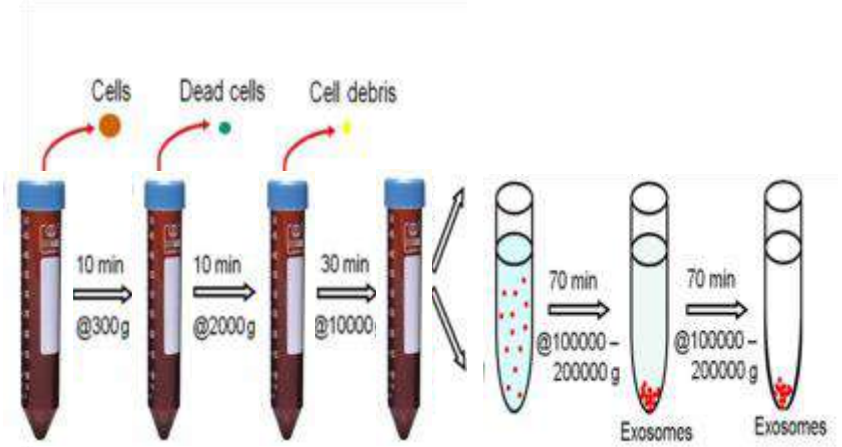
conditioned medium





Exosome Üretim Yöntemi









Ultrasantrifügasyon ile eksozom izolsyonu, hedef hücre ayrımında yüksek güvenirlikli teknolojilerin başında gelmektedir. **DOI:https://doi.org/10.51123/jgehes.2023.90**

Yeni trend…

Sekretom tedavileri

EXOSOM

Exosome

EGF ile başlayan süreç…

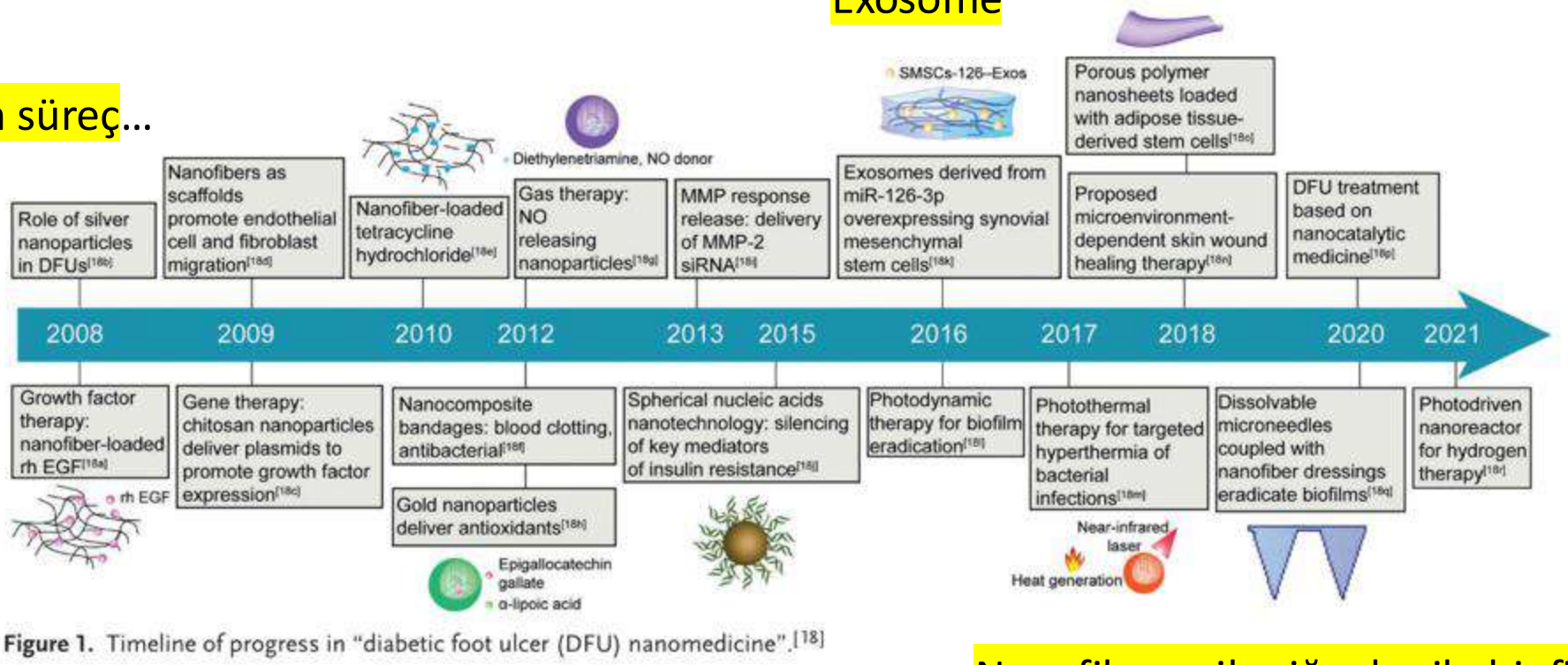


Figure 1. Timeline of progress in "diabetic foot ulcer (DFU) nanomedicine".[18]

Nanofiber mikroiğneler ile biofilm eradikasyonu

Huang F, Lu X, Yang Y, Yang Y, Li Y, Kuai L, Li B, Dong H, Shi J. Microenvironment-Based Diabetic Foot Ulcer Nanomedicine. Adv Sci (Weinh). 2023

Sun et al. Stem Cell Research & Therapy (2022) 13:416
https://doi.org/10.1186/s13287-022-03110-9

Stem Cell Research & Therapy

RESEARCH Open Access

Effectiveness and safety of stem cell therapy for diabetic foot: a meta-analysis update

Yuming Sun[1], Jinhong Zhao[2], Lifang Zhang[1], Zhexuan Li[1*] and Shaorong Lei[1*]

- Meta analiz,14 çalışma, toplam 683 hasta havuzu
- Ülser iyileşme oranı ve hızına olumlu etki
- Ağrısız hareket ve yaşam kalitesi artışı
- Doku oksijenizasyon artışı, mikro/makro sirkülasyona olumlu etki
- Amputasyona etkisi?
- Heterojenite?...takip süreleri…
- Kök hücre terminolojisi çalışmalarda karışık?
- Çalışmalarda metodoloji sorunu… genelde…
- RKÇ ihtiyaç var…

Türkiye

Intralesional allogeneic adipose-derived stem cells application in chronic diabetic foot ulcer: Phase I/2 safety study

Erdal Uzun[a,*], Ahmet Güney[a], Zeynep Burçin Gönen[b], Yusuf Özkul[c], İbrahim Halil Kafadar[a], Mahmut Günay[d], Mahmut Mutlu[a]

[a] Department of Orthopedics and Traumatology, Faculty of Medicine, Erciyes University, Kayseri, Turkey
[b] Oral and Maxillofacial Surgery, Genome and Stem Cell Center, Erciyes University, Kayseri, Turkey
[c] Department of Medical Genetics, Faculty of Medicine, Erciyes University, Kayseri, Turkey
[d] Department of Orthopedics and Traumatology, Kanuni Training and Research Hospital, Trabzon, Turkey

- Allojenik- bağışçı yağ doku kökenli kök hücre faz ½ güvenlik çalışması, vaka kontrol
- 20 hasta, Wagner 1-2, yüzey alanı 10-35 cm^2, ortalama
- Yaş= 57.3 +/- 6.6, kadın/erkek = 8/12
- 10 hasta kontrol-strandart bakım, 10 hasta deney grubu-dermoepidermal bileşke enjeksiyon,
- Takip, 4,10,20,60,90.gün
- Ortalama yüzey alanı=24.5 +/-5.5 cm^2
- %55 Wagner 1, %45 Wagner 2
- 17/20…%85 tam kapanma
- Deney grubu 9/10 (%90)… Kontrol 8/10 (%80)
- Üç hastada minör ampütasyon …Bir deney grubu, iki kontrol grubu…
- Gözlenen yan etki YOK

Exosom Deneyimler

Sürekli akıyor…

- 61 y, E, DM, 96 kg, VKI=31
- Periferik venöz yetmezlik (doppler)
- Sol ayak lat malleolde 4x4 cm ülser,
- Daha önceki tedaviler…kremler, kompresyon bandajları, köpük örtüler….
- Almanya…dönerci…
- Enfekte görünümde değil…
- Ağrı –hassasiyet belirgin değil…



Exosom =5 milyar hücre
Amniyotik fresh membran
Bactigras- spunch
Baskısız kapatma



7. gün



Gözlem

- Hafif çekilmeler var
- Membranın bir kısmı hala yerinde
- Merkezde epitel adacıkları
- Periferde epitel yürümesi
- Ebatı kısmen küçülmüş

10.gün



Gözlem

- Yara üstü kısmi granülasyon başlamış
- Derinliği azalmış
- Yara etrafındaki çekilmeler kaybolmuş

Dipnot…
Hasta ilk pansuman sonrası Almanya’ya gitti…
Resimleri kendi çekip atıyor

17.gün



Gözlem

- Yara kapanmaya devam ediyor
- Epitelizasyon hızlanmış
- Yara yeniden çekilmeler-yıldız şeklini almış

21.gün

Gözlem

- Yara kapanmaya devam ediyor
- Epitelizasyon hızlanmış
- Tabanı dolmaya devam ediyor
- Yıldız şekli devam…



28.gün



24.gün



Gözlem

Tam kapanma oldu – olacak

Yara tabanı dolmaya devam ediyor

34.gün




Filtreler



Kapanmayan ameliyat yeri…



- 70y, E, CABG, DM, Graft yerinde akıntılı yara…
- Sağ bacak graft yerinde… en geniş yeri 4 cm… uzunluğu 17 cm…
- VKI=28
- HbA1C=9.5
- 6 aydır devam ediyor…
- Her şey denenmiş?...
- Hasta Şanlı Urfa'lı…'Kapanmayan yarasın'



- 10 milyar exosom…
- Amniyotik membran…
- Bactrigras…
- Spunch…
- Orta basınçta sargı…



24.gün

Gözlem

- Yara kenarlarında hafif kabarma
- Akıntıda artış
- Refleks…PO antibiyotik



31.gün

Gözlem

- Akıntı daha az…
- Kapanma durdu?



34.gün

Gözlem

- Akıntı daha az…ama var
- Hareket yeniden başladı



49.gün



59.gün

Gözlem…

- İyi gidiyor
- İşaretli alan hariç…





Amniyotik membran







SAĞLIK

Kapanmayan yaralarından kök hücre tedavisiyle kurtuldu

İzmir'de, bacağına 10 milyar kök hücre enjekte edilen 70 yaşındaki hasta, iyileşip eski günlerine döndü.

Tezcan Ekizler |

24.01.2024 - Güncelleme : 24.01.2024



Tek seans Amniyotik membran +5 milyar Exosom



Tek seans amniyotik membran + 5 milyar eksozom









Amniyotik membran 5 milyar eksozom X 3











Platelet-Rich Plasma (PRP)

- Mekanizma… Trombositler büyüme faktörlerini çevresinde toplar…
  - -PDGF
  - -TGF-β
  - -VEGF
  - -EGF
- Etki…
  - -fibroblast proliferasyonu uyarılması
  - -angiogenesis artışı
  - -granulasyon dokusu oluşumu artışı
- Klinik kullanım alanı…tüm yara tipleri…enfekte olmamak kaydı ile…

How to Prepare Platelet-Rich Plasma (PRP)

1 Blood Collection

- Draw blood from a peripheral vein
- Anticoagulant (eg, citrate) in tube
- Usually 15–30 mL collected



2 Centrifugation

- Blood is centrifuged at **3,500 RPM**
- Spin for **5–10 minutes**
- Blood separates into three layers



3 Isolation

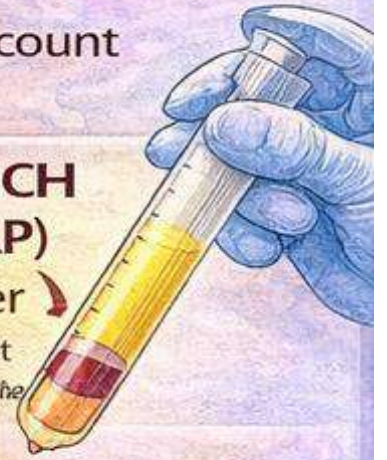
- Extract PRP layer into a syringe

Platelet-Poor Plasma (PPP)

- Upper layer
- LOW platelet count

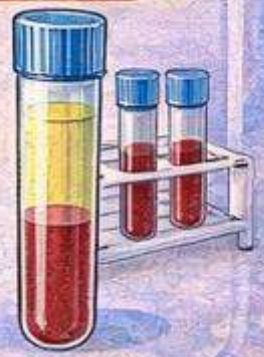
PLATELET-RICH PLASMA (PRP)

- Middle layer
- **HIGH** platelet count (4–5δ glamhe



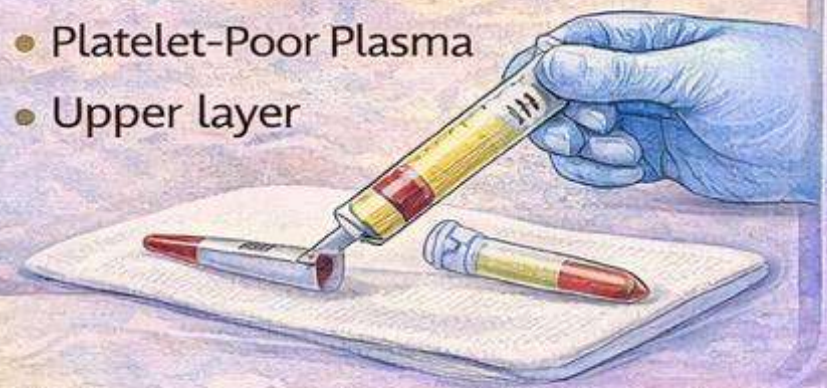
2 Centrifugation

- Blood is centrifuged at **3,500** RPM
- Spin for 5–10 minutes
- Blood separates into three layers



Layers after centrifugation:

- Platelet-Poor Plasma
- Upper layer



PLATELET-RICH PLASMA (PRP)

- **HIGH** platelet count (3–5x baseline)

Red Blood Cells (RBCs)

- Lower layer

Key Clinical Benefits:

- PRP is rich in growth factors that promote tissue repair and regeneration.

Platelet-Rich Fibrin (PRF)

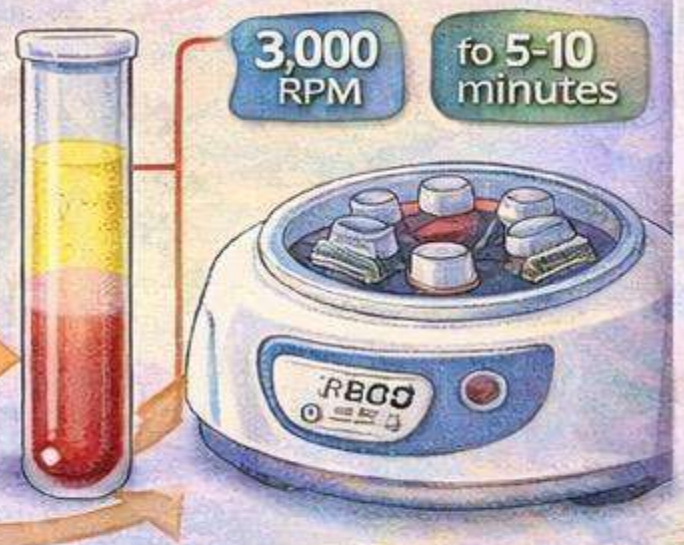
Platelet-rich fibrin (PRF) is an advanced autologous biomaterial with applications in regenerative medicine and dentistry.

1 Blood Collection

- Blood locetall from pegiocagant-free* tubes
- Centrifuged immediately* after draw.
- Usually 15-30 ↄ. collected

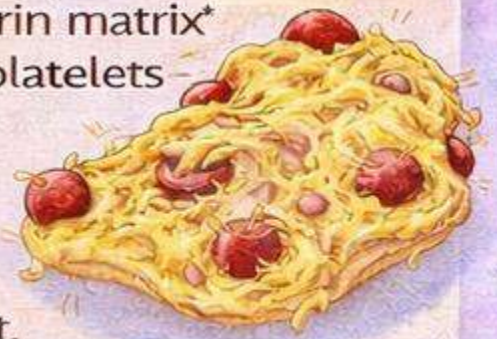


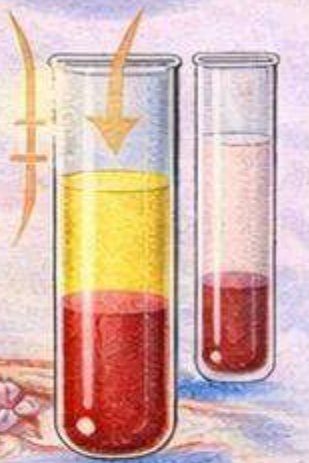
2 Centrifugation



Platelet-Rich Fibrin

- Concentrated fibrin matrix* with embedded platelets + growth factors
- Slow release of growth factors
- No anticoagulant, no additives
- Clinical uses*:
  - perioolontal surgery,
  - dental implants,
  - wound healing,
  - orthopeoie procedures.





Advantages of PRF

- No chemical additives
- Simple and cost-effective,
- Higher concentration of Key growth factors.

Mechanism of Action

- PRF *secretes growth factors.
- Stimulates *angiogenesis.
- Promotes tissue regeneration.

PRP is rich in growth factors















PRP-PRF handikaplar…kişisel gözlem

-Uygulama hatalarına açık

-Kontaminasyona açık

-PRP kiti içeriği otolog ürünün saflığını çok etkiliyor

-Bu hastaların zaten büyüme faktörleri üretim sorunları var…

-Kombinasyon daha iyi sonuç veriyor

Biomühendislik ürünü deri benzerleri

Ürün	Yapısı	Endikasyonları
Apligraf	İki tabakalı (keratinocytes + fibroblasts)	Diyabetik ayak ülseri, venöz ülser
Dermagraft	Dermal fibroblast iskelet	Diyabetik ayak ülseri

Epidermal tabaka
- Keratinosit içerir
- Re-epitelizasyonu uyarır

Dermal tabaka
- Fibroblast içerir
- Kollajen matriks
- Anjiogenezi ve doku remodelingi destekler

Çalışma mekanizmaları?

1 **Hücresel sinyal iletimi**

Büyüme faktörleri fibroblast ve keratinosit aktivitesini arttırır

2 **Extracellular matrix desteği**

Hücre göçü için iskelet Provides scaffold for cell migration.

3 **Angiogenezis uyarımı**

Yeniden damar oluşumu Promotes formation of new blood vessels.

4 **Enflamasyon azalması**

Yarada micro çevreyi destekler



Dermal graft +Ballı örtü







Apligraft +Ballı örtü

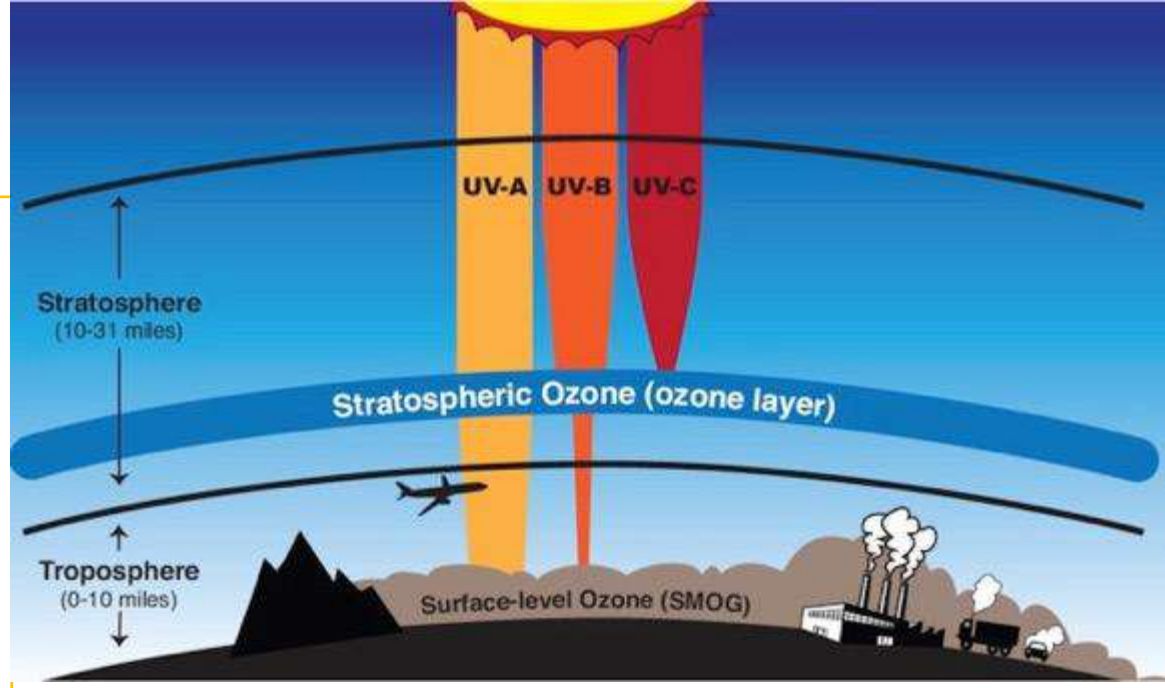
GETAT

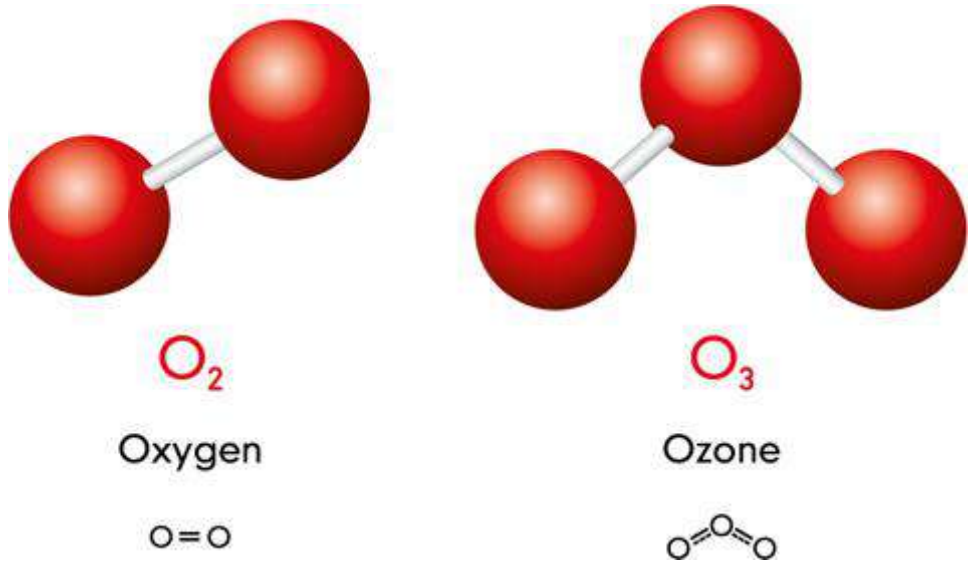
- Ozon
- Magotterapi-larva tedavisi

Ozon…

Dünya üzerinde iki ozon katmanı var…
1. Kötü ozon…<2 km'de
-Yeryüzüne yakın olan toksik etkili,
-Her yıl 1-1,2 milyon insanın ölümüne sebep olduğu düşünülüyor…
-Uzun dönem maruziyet KVS, KOAH sebebi…
-Nitroz oksit, CO ve hidrokarbon ile oluşuyor…sıcakta daha çok

2. İyi ozon…>15km'de
UV'yi tutan…





Ozon terapi tarihçesi

- 1785 Martinus von Marum …Hollandalı…Ozonun keşfi…elektrostatik makineler etrafında oluşan koku
- 1840 C.Friedrich Schönbein…ozon sentezi- keşfi…ozonize oksijen
- 1873 Fox…Mikroorganizma eliminasyon kabiliyetinin keşfi…
- 1893 Hollanda…su dezenfeksiyonunda kullanımı…
- 1896 Nicola Tesla…ilk ozon jeneratörü patenti…ozon=O3
- 1911 Dr. Noble Eberhart …ilk ozon uygulamaları…Tbc, anemi, astım, pnömoni, DM, gut, Sy
- 1913 Almanya'da ilk ozon terapi cemiyeti…Dr. Blass…
- 1914-1918 Birinci Dünya Savaşı…antiseptik…yarada…
- 1932 Erwin Payr…cerrah…kendisinde deniyor…lokal uygulama –yara iyileşmesi
- 1940 FDA- Ozon jeneratörlerinin kullanımını yasakladı…
- 1950 E.A. Fisch…diş hekimi uygulaması…patent…
- 1957 Dr Haensler…ilk modern ozon jeneratörü…ozon dirençli materyel kavramı…
- 1961 Dr Haensler…ilk majör ve minör otohemoterapiyi tanımlıyor…
- 1972 Dr.Haensler ve Wolff…. Uluslararası Tıbbi Ozon Derneği
- 2010 Madrid Deklerasyonu…Dr. Bocci …ISCO3 (International Scientific Committee on Ozone Therapy)

Tıpta ozonun bilenen/araştırılan etki mekanizmaları

1. Anti mikrobiyal…membran permaabilite artışı
2. Anti oksidan …H2O2 oluşumu, aldehid ve lipid oksidasyonu
3. Anti enflamatuvar…nükleer faktör kappa B yolu inaktivasyonu…IL-1,IL-2, IL-6 ve TNF-alfa üretimi azalması…
4. Eritrositte glikoliz artışı…oksijen taşıma kapasitesi artışı…
5. Glutatyon peroxidaz, superoksit dismutaz ve katalaz aktivitesi artışı ile doku artıklarının uzaklaştırılması…antiageing?
6. Kanser …adjuvan?...Tümör içi…
7. Kozmetik…?

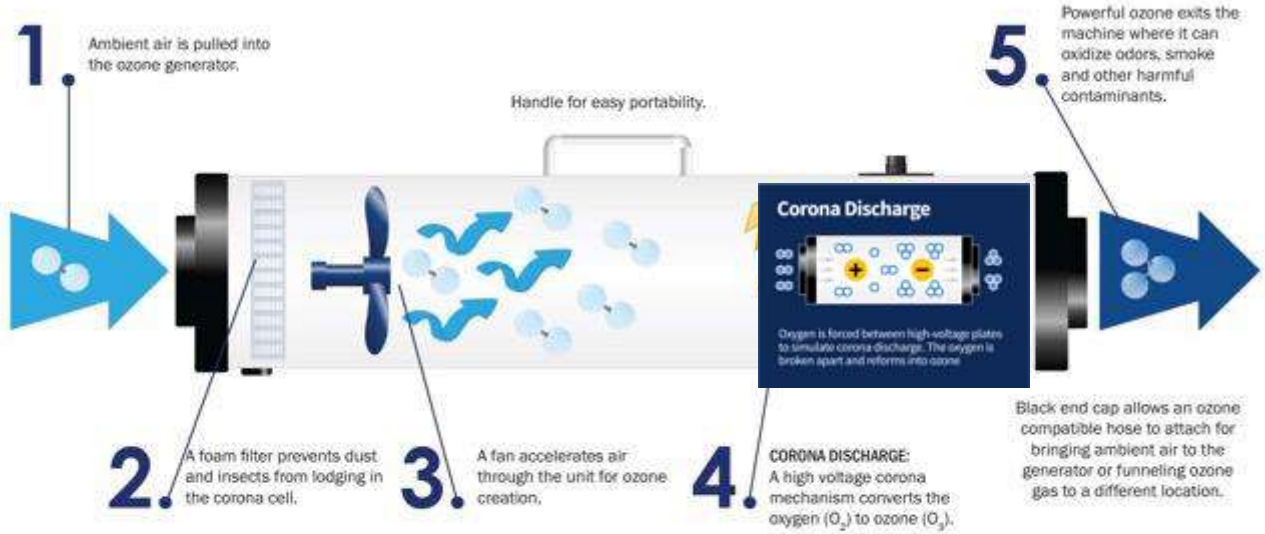
Ozon uygulamaları ?

- Major/ minör otohemoterapi
- Lokal enjeksiyon…eklem içi…disk etrafına…tetik nokta…
- Rektal insuflasyon…
- Ozonize su (enteral, mesane/vajen yıkama), zeytin yağı (lokal) vb…
- Cilt altı…kozmetik uygulamalar…
- Torba uygulama…yara için…
- Extracorporeal blood oxygenation and ozonation (EBOO)

Medikal Ozon nasıl elde ediliyor?

Yüksek voltaj ile Oksijen atomlarına ayrılır

Oksijen



Enerji kesilince ‘0’ iyonları birleşir 0_3 olur…



Yüksek basınç ve fan ile stabilizasyonu bozulur

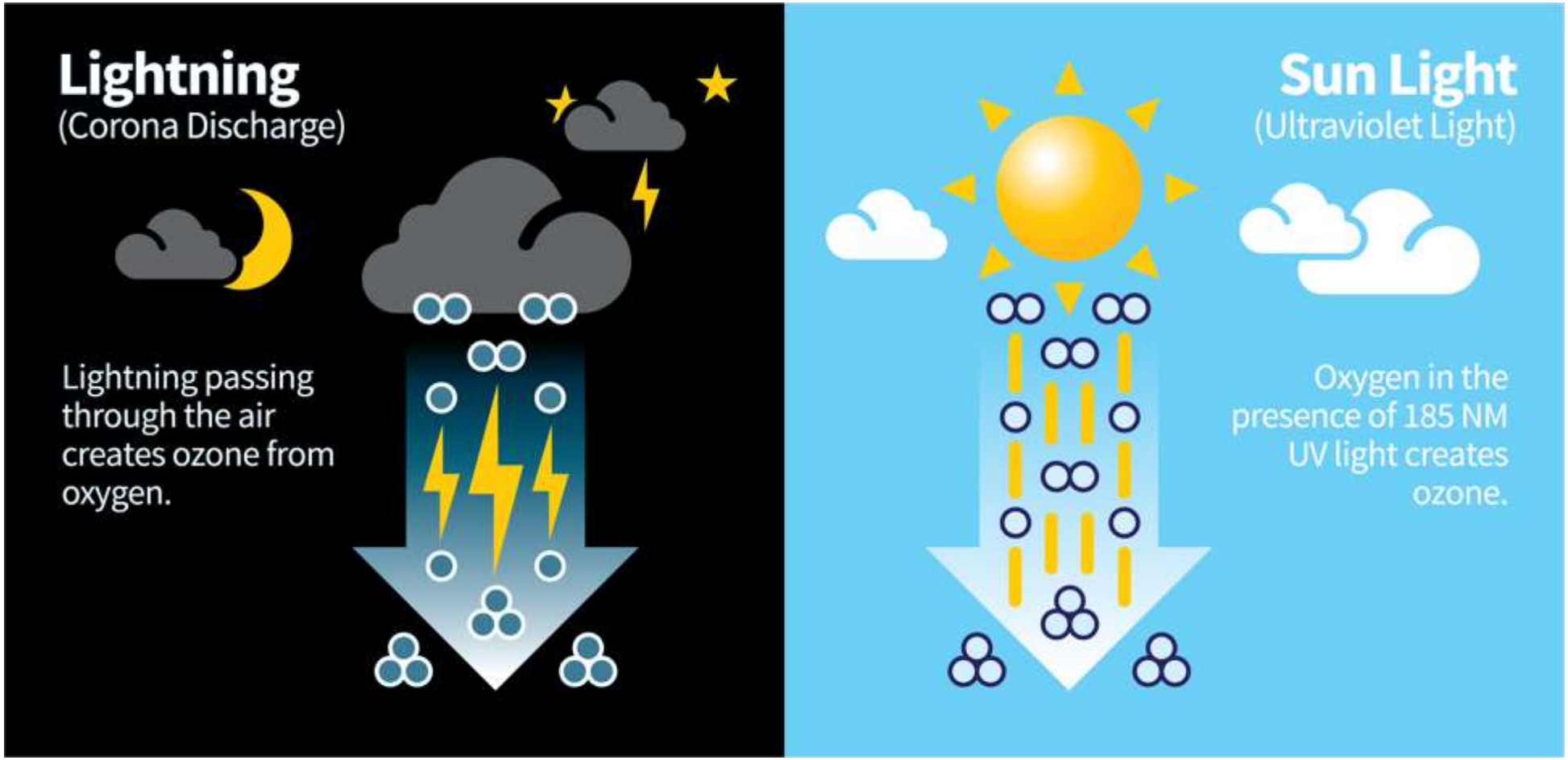
OZON KAOSTAN DOĞAR…

Tıbbi –saf 0_2

Aslında doğayı taklit ediyoruz…
Yıldırım-şimşek enerjisi ile 0_2---0_3

Sanayide –0_2 +hava karışımı

Aslında doğayı taklit ediyoruz…
UV ile 185 nm ile 0_2---0_3



Ozon kanıt düzeyi?

Review > Front Public Health. 2023 Jan 16:10:1112296. doi: 10.3389/fpubh.2022.1112296. eCollection 2022.

The role of ozone treatment as integrative medicine. An evidence and gap map

Maria Emilia Gadelha Serra [1], José Baeza-Noci [2], Carmen Verônica Mendes Abdala [3], Marilia Moura Luvisotto [1], Charise Dallazem Bertol [1], Ana Paula Anzolin [1]

References	Title	Study Topic	Country	AMSTAR confidence level	Database
Cochrane (18)	Ozonioterapia no tratamento da úlcera crônica de membros inferiores: revisão sistemática de literatura	Wounds	Brazil	High	LILACS
Liu et al. (20)	Ozone therapy for treating foot ulcers in people with diabetes	Wounds	China	High	MEDLINE
Fitzpatrick et al. (21)	Ozone therapy for the treatment of chronic wounds: A systematic review	Wounds	Australia	Moderate	MEDLINE
Wen et al. (19)	A systematic review of ozone therapy for treating chronically refractory wounds and ulcers	Wounds	UK	High	MEDLINE

Ozon terapinin tıbbi uygulamalarının yara tedavisi metaanalizleri güvenli bulunmuş… AMA…

References	Country	Patients number	Population studied	Methodology	Results and conclusions
Cochrane (18)	Brazil	190	>18 years old with chronic lower-limbs ulcer	SR according to the Cochrane methodology. Randomized clinical trials that tested OT or associated with placebo or other active treatment option were included.	Three studies were included, one of OT in ischemic ulcer and two for diabetic ulcers. The studies were heterogeneous, making it impossible to perform meta-analyses. There is poor methodological evidence that OT may be effective and safe in the treatment of chronic ulcers related to DM and peripheral arterial insufficiency. No evidence was found on the effectiveness of OT in the treatment of venous ulcers.
Liu et al. (20)	China	212	Any age with DM and foot ulcers	Search databases: COCHRANE WOUNDS GROUP SPECIALIZED REGISTRY, COCHRANE CENTRAL REGISTRY OF CONTROLLED TRIALS (CENTRAL), OVID MEDLINE (IN PROCESS AND OTHER UNINDEXED CITATIONS), OVID EMBASE, EBSCO CINAHL, SCIENCE WOUNDS CITATION INDEX, CHINESE BIOMEDICAL LITERATURE DATABASE and THE CHINESE CLINICAL REGISTRY. Without restrictions on the language, date, or configuration of the study. RCT comparing OT with placebo or any other interventions for foot ulcers in people with DM. The methodological quality of the included studies and the level of evidence of the results were evaluated using cochrane's bias risk tool and the GRADE (Evaluation of classification, development and evaluation) approach, respectively.	Three studies were included in the review. The overall risk of polarization was high for two trials. No side effects were observed. OT was associated with a greater reduction in ulcer area from baseline to the end of the study than treatment with antibiotics (DM −20.54 cm^2, 95% CI −20.61–−20.47), and a shorter duration of hospitalization (MD −8.00 days, 95% CI −14.17–−1.83), but did not appear to affect the number of ulcers healed over 20 days (RR 1.10, 95% CI 0.87–1.40). The other two trials ($n = 111$) comparing OT plus usual care with usual care for foot ulcers in people with DM. The meta-analysis showed no evidence of a difference between groups for the outcomes of reduction of ulcer area (DM −2.11 cm^2, 95% CI −5.29–1.07), the number of ulcers healed (RR 1.69, 95% CI 0.90–3.17), adverse events (RR 2.27, 95% CI 0.48–10.79), or amputation rate (RR 2.73, 95% CI 0.12, 64.42). The available evidence was three small RCT with unclear methodology, so we cannot draw reasoned conclusions about the efficacy of OT for foot ulcers in people with DM.
Fitzpatrick et al. (21)	Australia	453	Any age with chronic wounds	Search databases: GOOGLE SCHOLAR, PUBMED, COCHRANE LIBRARY and reference lists. English language studies, RCT and trials that reported the use of OT in the topical treatment of chronic wounds were included. The level of bias and quality of the studies were evaluated.	Nine studies were selected and submitted to meta-analysis. There was a significant improvement in the wound with OT, especially in the treatment of chronic wounds. Compared to standard treatment, OT can improve the proportion of chronic wounds healed in a shorter period of time, and further scientific research is needed.

Kanıt düzeyi düşük

Etkili…Tek başına bağımsız değil

Daha kısa sürede iyileşiyor, ek çalışmaya ihtiyaç var

Wen et al. (19)	UK	1.055	Wound of second- or third-degree actinic ulcers following a radiotherapy cycle, chronic venous leg ulcers, digital ulcers in systemic sclerosis, critical limb ischemia and diabetic foot ulcers	Search databases: COCHRANE LIBRARY, PUBMED, OVID EMBASE, WEB OF SCIENCE and CHINESE BIOMEDICAL LITERATURE. RCTs about participants with chronic wounds were included. Risk of bias assessment was performed by the Cochrane risk-of-bias tool. A randomized-effects model was applied to pool results according to the types of wounds or ulcers.	Twelve included studies, ozone was implemented by topical application (ozone gas bath, ozonated oil, ozone water flushing) and systematic applications including autologous blood immunomodulation and rectal insufflation. Compared with standard control therapy for diabetic foot ulcers, OT regardless of monotherapy or combined control treatment markedly accelerated the improvement of the wound area SMD = 66.54%, 95% CI = [46.18, 86.90], $P < 0.00001$ and reduced the amputation rate RR = 0.36, 95% CI = [0.24, 0.54], $P < 0.00001$. But there is no improvement in the proportion of participants with completely healed wounds and length of hospital stay. No adverse events associated with OT have been reported. The efficacy of OT for other wound types is still uncertain because of no sufficient studies. More high-quality randomized controlled trials are needed to confirm the efficacy and safety of OT for chronic wounds or ulcers.

- Hastanede kalış süresi ve tam iyileşme üzerinde etkisi net değil
- Gruplar heterojen
- RKÇ ihtiyaç var

Ozon – yara iyileşmesi -RKÇ

Randomized Controlled Trial > Diabetes Metab Syndr. 2019 Jan-Feb;13(1):822-825.
doi: 10.1016/j.dsx.2018.11.060. Epub 2018 Dec 1.

Efficacy of comprehensive ozone therapy in diabetic foot ulcer healing

Morteza Izadi [1], Ramin Kheirjou [2], Roya Mohammadpour [3], Mohammad Hassan Aliyoldashi [3], Saeedreza Jamali Moghadam [4], Farzin Khorvash [5], Nematollah Jonaidi Jafari [6], Shahram Shirvani [7], Nahid Khalili [6]

Affiliations – collapse

Affiliations

1 Ozone Therapy Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.

Abstract

Background: Diabetic foot ulcer is one of the common complications of diabetes disease that is costly and difficult to treat. This problem can lead to morbidity and even mortality. Ozone is a gas that can optimize cellular metabolism and, because of its antioxidant and antibacterial effects, can help the better healing of diabetic foot ulcer.

Method: Two hundred patients, aged 18-85 with diabetic foot ulcers ranging from grade 1 to 4 according to Wagner classification in two groups were studied. Group 1 was treated by full ozone therapy besides the standard regular DFU treatment while group two just was received routine diabetic foot care. Wound size, wound grade, healing time, Fasting blood sugar and inflammatory biomarker before and after treatment were checked.

Results: All patients have had complete wound closure in the ozone group. The mean age of the patients included in the results was 59.03 ± 12.593 and 53.5 ± 10.212 for ozone group and control group. The baseline average surface area of ulcers was 13.41 ± 14.092 cm^2 (range 1-70 cm^2) in ozone group and 12.72 ± 0.911 (range 1_64 cm^2) in the control group. Average healing time was 69.44 ± 36.055 days (range 15-180 days), which is significantly lower than the median healing time measured in the control group and some previous studies.

Conclusion: Our study results support the efficacy of ozone therapy especially in its comprehensive use in DFU healing and reduction in the chances of infection and amputation.

The ozone therapy controversy and the need for science-based health policies in the Brazilian context

Heslley Machado Silva

State University of Minas Gerais (UEMG) and University Center of Formiga (UNIFORMG), Brazil

The Lancet Regional Health - Americas
2024;34: 100745
Published Online 10 April 2024
https://doi.org/10.1016/j.lana.2024.100745

OZON SİYASAL –BİLİMSEL POLEMİK

- Bolsanaro bilinen bir bilim karşıtı
- Lula ise yerine büyük ümitler ile geldi ama, ‘pseudoscience’ kurbanı oluyor…
- Lula hükümeti ozon terapiyi sağlık alanında onaylamaya ve uygulamaya hazırlanıyor…
- Hiçbir bilimsel dayanağı olmayan, randomize kontrollü çalışmalarca bilimsel olarak insan sağlığına faydası olduğu gösterilmemiş bir uygulama hükümetin sağlık politikasında nasıl yer alır …akıl dışı…
- Üstelik bu durum Lula’nın ilk denemesi değil…2003-2006 yılında hükümette olduğu dönemde, alternatif tıbbı Brezilya Sağlık Sistemine tanımlatmıştı…
- Daha önceki deneyimlerden neden ders alınmıyor…Dilma Roussef hükümetinde de mucizevi kanser ilacı olduğu iddia edilen ‘fosfoetanolamin’ ile ilgili yaşanmış sorunlar hale aklımızda iken…
- Bilimsel temeli olan sağlık uygulamalarına ihtiyacımız var…



Türkiye’de Ozon deyince ilk akla gelen…



Ozon…Özet

- Doz bağımlı etkisi net değil…5-100 mcg/ml ? değişken- sebep?
- Ozon dokuda dağılımı-taşınımı kişinin eritrosit dağılımına …
- Mikrovasküler dolaşıma…vb bir sürü faktöre bağlı…

LİSTE ÇOK UZUN VE TARTIŞMAYA AÇIK

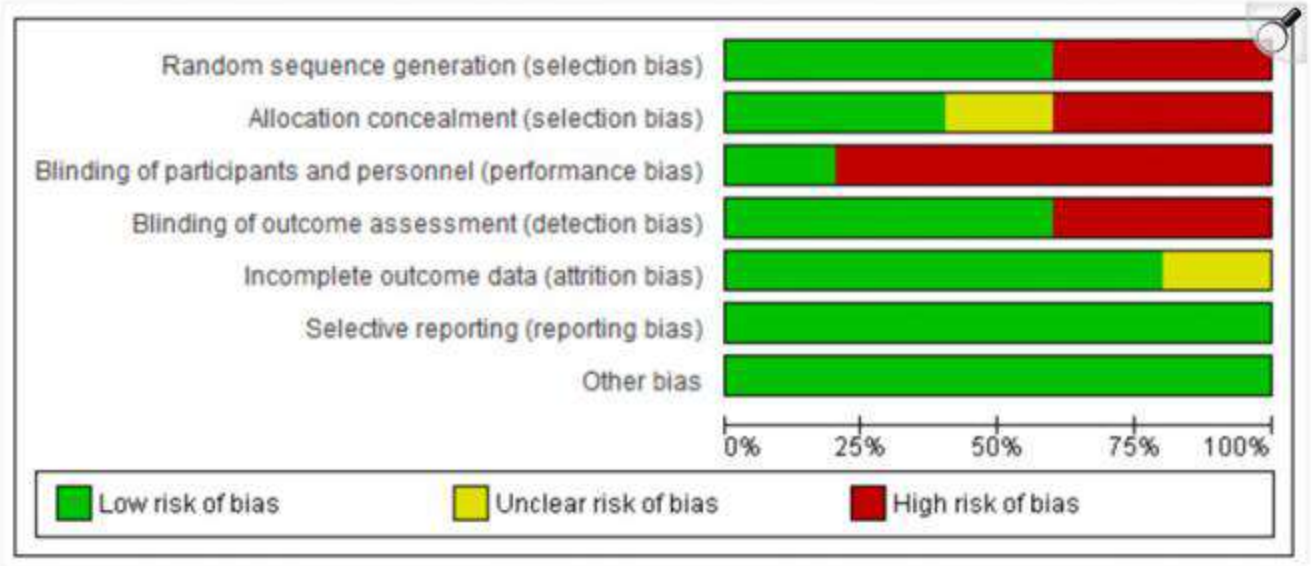
AMA

Vaka kontrol bazlı yanıt alınan hasta sayısı takdire şayan…

Bilimsel metodolojiye uygun çalışmalar yapmak lazım…

Medyatik olması bilim camiasının bakış açısını etkiliyor…

Larva tedavisi…?



- Gerçekten bir tedavi mi?
  -Debridman
  -Granülasyonu uyarma?
- Başarı oranı?
  -Debridmanda yeterli
  -Granülasyon?
- Enfeksiyonu kontrol altına alma, lokal AB etkisi?
- Fakir ülkelerin yöntemi!
- Kıyaslamalı çalışma eksik?
- Yanlılık?

Mohd Zubir MZ, Holloway S, Mohd Noor N. Maggot Therapy in Wound Healing: A Systematic Review. Int J Environ Res Public Health. 2020 Aug 21;17(17):6103. doi: 10.3390/ijerph17176103. PMID: 32825736; PMCID: PMC7504313.



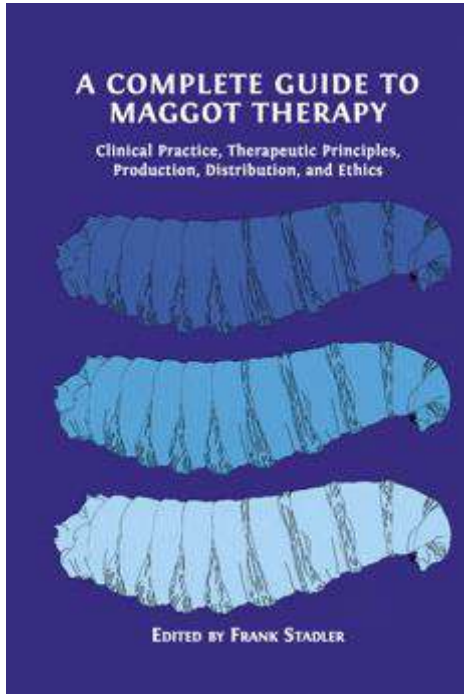


Figure 3.1 Chronic wounds amenable to maggot therapy: a) pressure ulcer, b) venous stasis ulcer, c&d) diabetic foot ulcers, e) burn, f) surgical wound dehiscence, g) orthopaedic wound, h) malignancy. Photos: © Steve Thomas, www.medetec.co.uk.

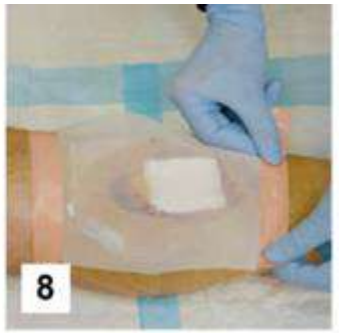
Endikasyon	Kontraendikasyon ve uyarılar
Debridman gereken kronik yara	Septik hasta
Enfeksiyon (lokal)	Yaygın ağrı varlığı (artabilir)
Granülasyonu uyarmak	Yaygın kanama öyküsü varlığı (debridman sonrası artabilir, yakın takip)
	Uygulama sonrası lokal veya sistemik allerji
	Doku invazyonu (larva türü kontrol edilmeli)

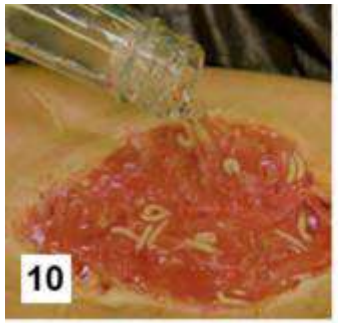
Uygulama















- Cm^2'ye 5-10 larva…Lucilia sericata
- Dokuya direkt yerleştirme veya biyobag
- Sızıntıyı kontrol etme-günlük
- Maksimum 48-72 sonra kontrol
- İhtiyaç durumuna göre haftada 2-3 defa uygulama tekrarı…
- İkincil kapama… larva kaçamayacak, hava alacak, sıkı olmayacak …

Frank Stadler (ed.), A Complete Guide to Maggot Therapy: Clinical Practice, Therapeutic Principles, Production, Distribution, and Ethics. Cambridge, UK: Open Book Publishers, 2022, https://doi.org/10.11647/OBP.0300



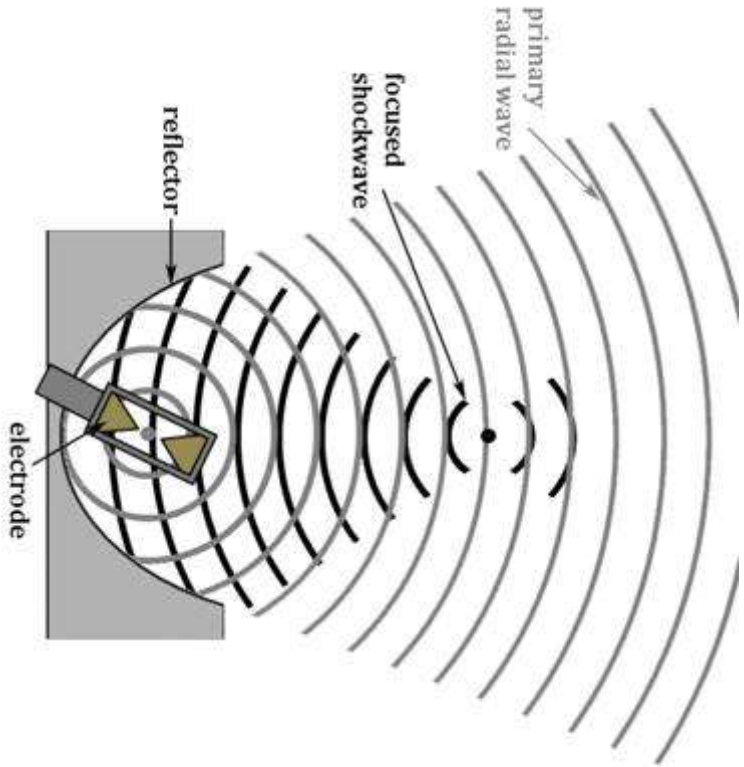
Değişken	Derecelendirme
Yara tiplerine uyumu	*****
Hedefe yönelik etkinlik	****
Uygulama kolaylığı	*****
Kısa süre eğitim ile uygulanabilme kolaylığı	*****
Düşük maliyet	*****
Düşük yan etki profili	*****
Hasta tarafından kabul edilebilirlik	****
Sağlık çalışanı tarafından kabul görme	*
Ürüne ulaşım	*

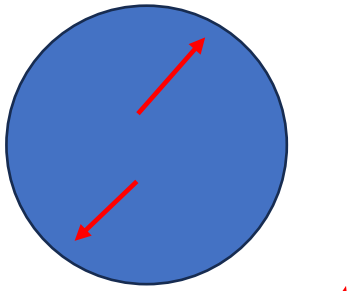
Frank Stadler (ed.), A Complete Guide to Maggot Therapy: Clinical Practice, Therapeutic Principles, Production, Distribution, and Ethics. Cambridge, UK: Open Book Publishers, 2022, https://doi.org/10.11647/OBP.0300

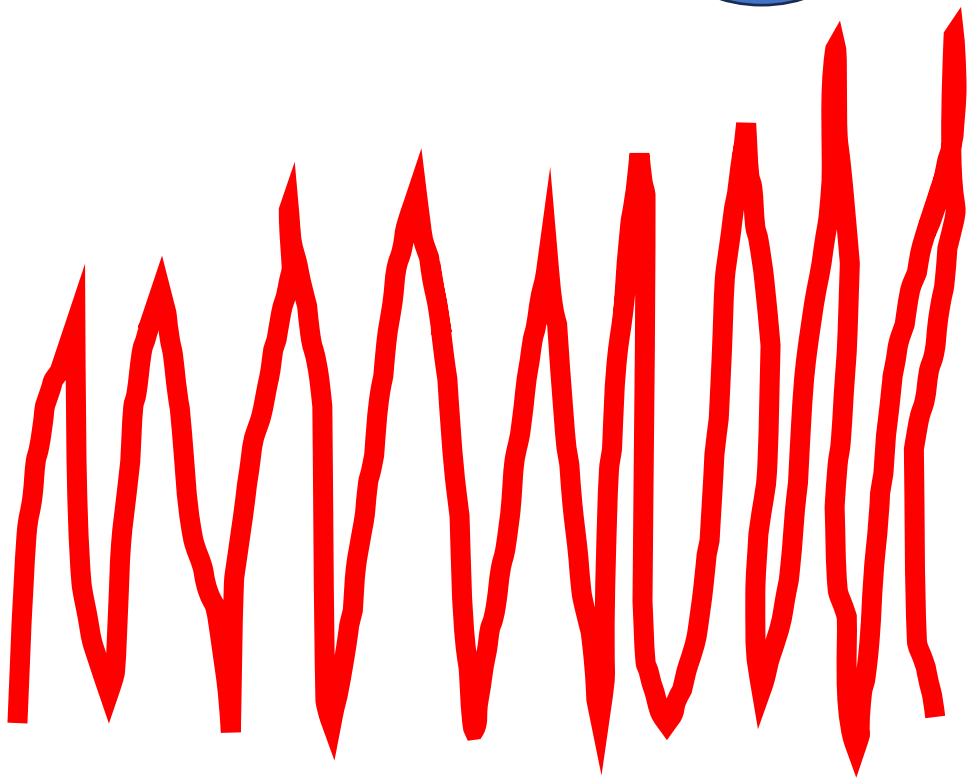
Korsan konu-ESWT

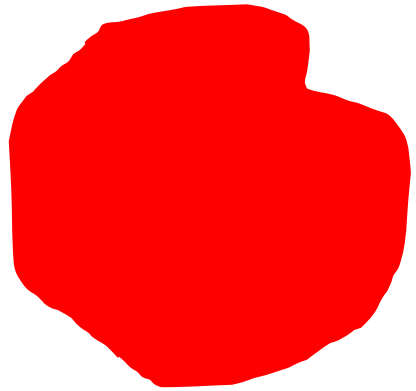
Extracorporal Shock Wave Treatment

ESWT…hücresel mikrotravma









fESWT → Daha güçlü, daha derine etki eder, daha hassas ama daha maliyetli ve ağrılı

rESWT → Daha yüzeyel, daha konforlu, daha ucuz ve yaygın kullanılır

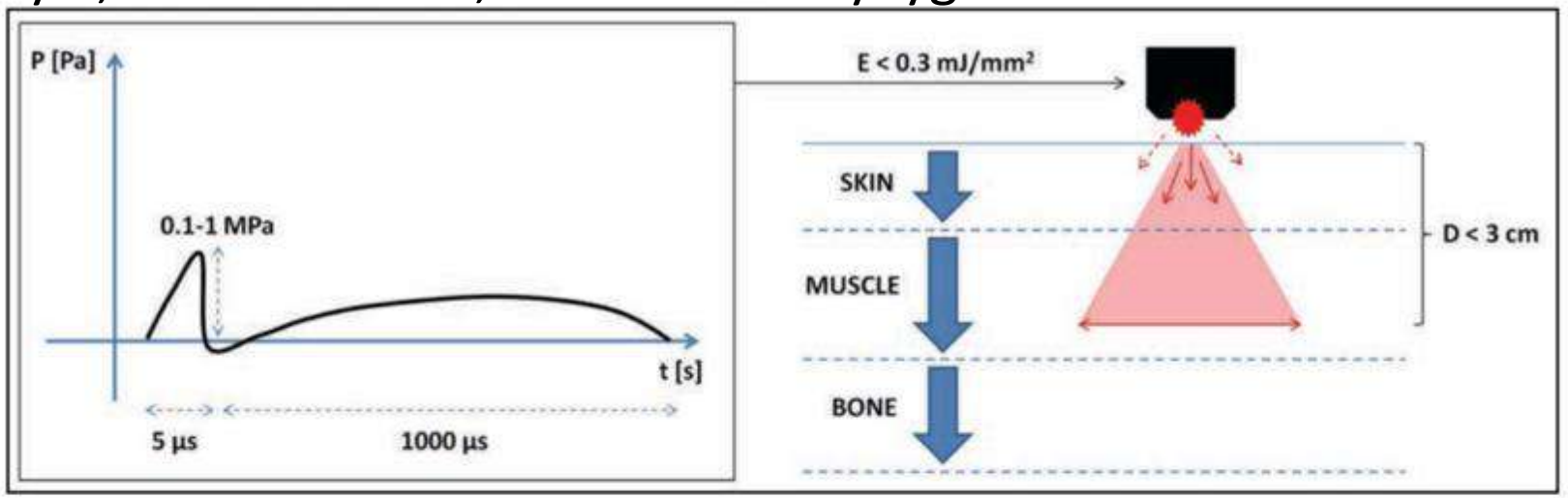


Figure 1. Schematic illustration of wave propagation with physical characteristics of radial extracorporeal shock wave therapy (ESWT).

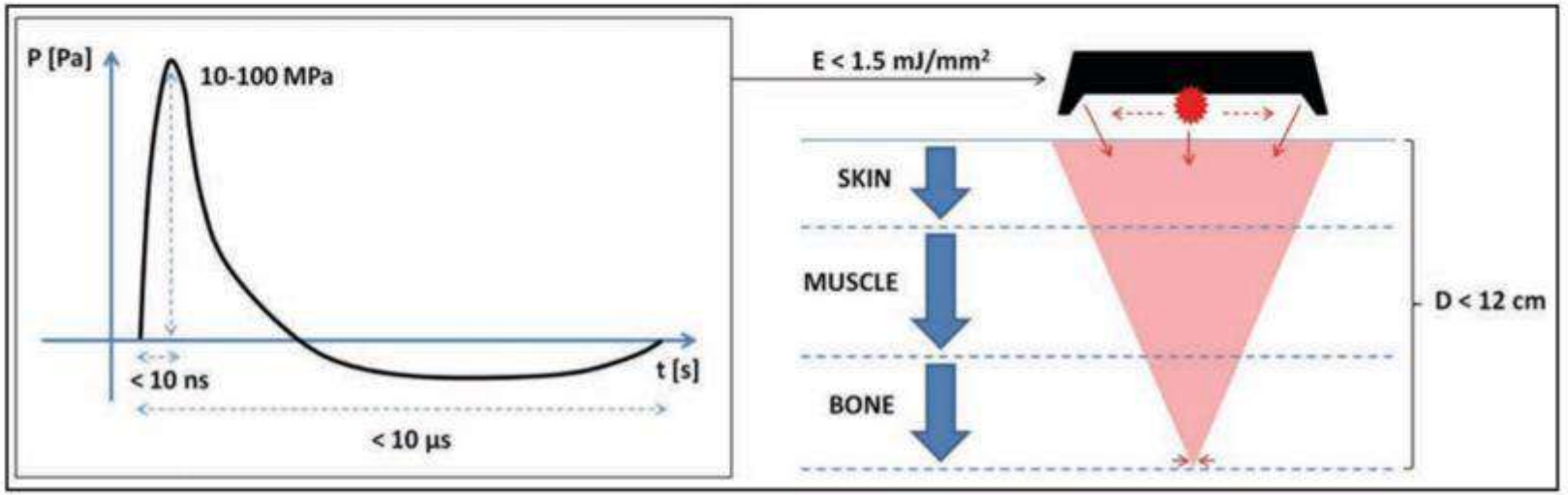
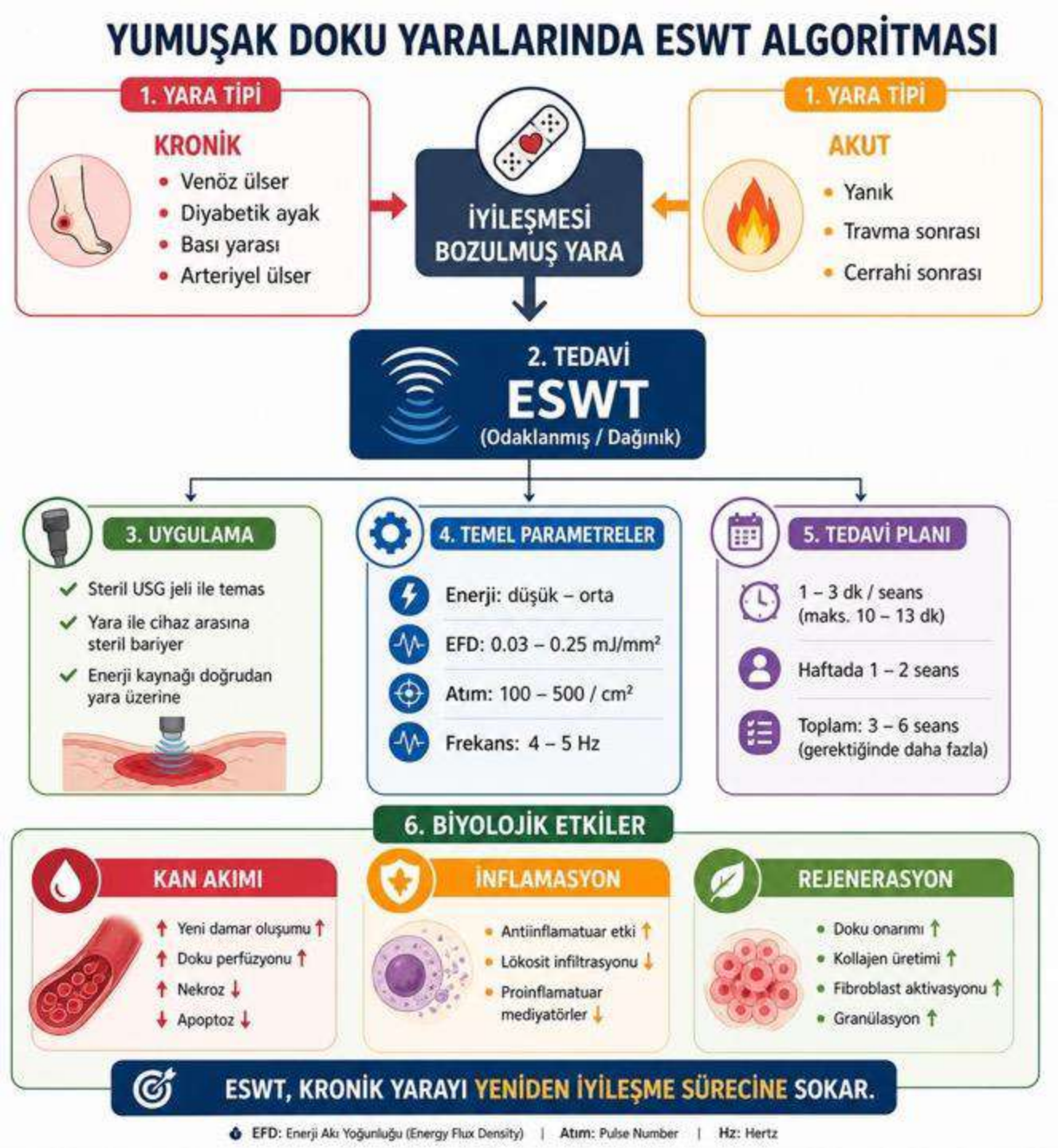


Figure 2. Schematic illustration of wave propagation with physical characteristics of focused ESWT.

Özellik	fESWT (Odaklanmış)	rESWT (Radyal)
Cihaz tipi	Elektromanyetik, elektrohidrolik, piezoelektrik	Pnömatik
Dalga tipi	Odaklanmış (planar)	Dağınık
Enerji düzeyi	Yüksek (0.01–1.50 mJ/mm²)	Düşük (0.01–0.50 mJ/mm²)
Basınç gücü	Çok yüksek (100–1000 bar)	Düşük (1–10 bar)
Etkili derinlik	Derin (0–12 cm)	Yüzeyel (0–5 cm)
Etki alanı	Küçük ve hedefe odaklı	Geniş ve yüzeyel
Seans sayısı	Az (1–3 seans)	Daha fazla (3–5 seans)
Hassasiyet	Yüksek (hücre düzeyi)	Daha düşük (doku düzeyi)
Kullanım alanı	Ortopedi, üroloji, kardiyoloji, **yara tedavisi**	Kas-iskelet sistemi
Ağrı	Daha fazla (lokal anestezi gerekebilir)	Daha az
Yan etki riski	Daha yüksek	Daha düşük
Uygulama	Daha pahalı	Daha ucuz
Cihaz yapısı	Büyük, daha sessiz	Küçük, daha gürültülü

Dymarek R, Halski T, Ptaszkowski K, Slupska L, Rosinczuk J, Taradaj J. Extracorporeal shock wave therapy as an adjunct wound treatment: a systematic review of the literature. Ostomy Wound Manage. 2014 Jul;60(7):26-39. PMID: 25019247.

Kronik yarada önerilen algoritma…



Dymarek R, Halski T, Ptaszkowski K, Slupska L, Rosinczuk J, Taradaj J. Extracorporeal shock wave therapy as an adjunct wound treatment: a systematic review of the literature. Ostomy Wound Manage. 2014 Jul;60(7):26-39. PMID: 25019247.

Meta-Analysis > Wound Repair Regen. 2017 Aug;25(4):697-706. doi: 10.1111/wrr.12566. Epub 2017 Oct 18.

Extracorporeal shock wave therapy for chronic wounds: A systematic review and meta-analysis of randomized controlled trials

Li Zhang [1], Changshui Weng [1], Zhanbo Zhao [2], Xiaobing Fu [3]

> Int Wound J. 2017 Feb 15;14(6):898–908. doi: 10.1111/iwj.12723

Extracorporeal shockwave therapy for the treatment of chronic wound of lower extremity: current perspective and systematic review

Mohammed TA Omar [1,2,✉], Rehab FM Gwada [2,3], Afaf AM Shaheen [2,4], Raoul Saggini [5]

Meta-Analysis > Med Sci (Basel). 2025 Oct 2;13(4):219. doi: 10.3390/medsci13040219.

Efficacy of Extracorporeal Shockwave Therapy in the Management of Chronic Diabetic Foot Ulcer: A Systematic Review and Meta-Analysis

Maria Ruiz-Muñoz [1], Lidia Rueda-Zapata [1], Francisco-Javier Martinez-Barrios [1], Tereza Nováková [2], Eva Lopezosa-Reca [1], Manuel Gonzalez-Sanchez [3], Raul Fernandez-Torres [1], Alejandro Galan-Mercant [4]

> J Wound Care. 2025 Dec 1;34(Sup12a):S5-S16. doi: 10.12968/jowc.2024.0113.

Use of extracorporeal shock wave therapy for wounds and musculoskeletal treatment: a systematic review

Tanner J Howard [1], Leah Amir [1], Matthew J Regulski [2 3], John D Mullins [4 5]

- ESWT tedavisi kronik yara iyileşmesinde etkili
- Çalışmalar ve meta analizler bunu destekliyor
- Daha çok RKÇ çalışmaya ihtiyaç var …

ESWT Guidelines

English version

Updated and agreed from the ISMST Managing Board, in close cooperation with the Germanspeaking Society for Extracorporeal Shockwave Therapy (DIGEST)

Daegu, South Korea July 20th, 2023

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ISMST

Indications

1. Approved standard indications
1.1. Chronic Tendinopathies
1.1.1. Calcifying tendinopathy of the shoulder
1.1.2. Lateral epicondylopathy of the elbow (tennis elbow)
1.1.3. Greater trochanter pain syndrome (GTPS)
1.1.4. Patellar tendinopathy
1.1.5. Achilles tendinopathy
1.1.6. Plantar fasciitis, with or without heel spur
1.1.7 Trigger finger
1.2. Bone Pathologies
1.2.1. Delayed bone healing
1.2.2. Bone Non-Union (pseudarthroses)
1.2.3. Stress fracture
1.2.4. Avascular bone necrosis without articular derangement
1.2.5. Osteochondritis Dissecans (OCD) without articular derangement
1.3. Skin Pathologies
1.3.1. Delayed or non-healing wounds
1.3.2. Skin ulcers
1.3.3. Non-circumferential burn wounds
1.3.4. Cellulite
1.4 Spasticity

Osteomyelit?

Terapötik Beklenen Etki	Olası Biyolojik Yolak (Özet)
Ağrı giderici etki	• Uygulama bölgesinde Substance P azalır • Miyelinsiz sinir liflerinde seçici azalma • CGRP (kalsitonin ilişkili peptid) ekspresyonu azalır • Serotonerjik sistem aktivasyonu
Doku onarımı	• Tenosit (tendon hücresi) artışı • Hasarlı matriksin temizlenmesi (katabolik süreçler) • **Mikrodoku uyarımı (mikrohasar)** • **Yeni damar oluşumu (anjiyogenez) artışı** • **Kollajen üretimi ve olgunlaşma artışı** • **Fibrozis azalması (skar düzenlenmesi)**
Kemik oluşumu (osteojenik etki)	• **Osteoblast aktivasyonu ve artışı** • **VEGF** ve HIF-1α artışı • Kıkırdak ve kemik rejenerasyonu artışı • Kalsiyum metabolizması düzenlenmesi • **Periost uyarımı, osteoklast aktivitesi azalması** • **NO, BMP-2, TGF-β gibi faktörlerle kemik oluşumu artışı**

Mittermayr, R., Antonic, V., Hartinger, J., Kaufmann, H., Redl, H., Téot, L., Stojadinovic, A. and Schaden, W. (2012), ESWT in wound healing. Wound Repair Regen, 20: 456-465. https://doi.org/10.1111/j.1524-475X.2012.00796.x

Dymarek R, Halski T, Ptaszkowski K, Slupska L, Rosinczuk J, Taradaj J. Extracorporeal shock wave therapy as an adjunct wound treatment: a systematic review of the literature. Ostomy Wound Manage. 2014 Jul;60(7):26-39. PMID: 25019247.

De la Corte-Rodríguez H, Román-Belmonte JM, Rodríguez-Damiani BA, Vázquez-Sasot A, Rodríguez-Merchán EC. Extracorporeal Shock Wave Therapy for the Treatment of Musculoskeletal Pain: A Narrative Review. Healthcare (Basel). 2023 Oct 26;11(21):2830. doi: 10.3390/healthcare11212830. PMID: 37957975; PMCID: PMC10648068.

Yöntemler arasında kanıt düzeyi kıyaslaması?

Klasik vs hücresel

Tedavi	**Kanıt düzeyi**
Debridman	güçlü
Off-loading	güçlü
rhEGF	orta
PRP	orta
Stem cell	düşük-orta
Exosome	deneysel

Kronik yara tedavisinde temel mesajlar

1 Kronik yara biyolojik bir iyileşme yetmezliğidir.

2 En önemli tedaviler hala klasik yaklaşımlardır: **TİMERS**

- Debridman
- Enfeksiyon kontrolü
- Yükten kurtarma
- Revaskülarizasyon

3 Rejeneratif tedaviler standart tedavinin yerine değil, tamamlayıcısıdır.

4 En güçlü kanıt diyabetik ayakta büyüme faktörleri ve PRP için vardır.

5 Exosome ve kök hücre tedavileri umut verici ancak daha fazla RCT gereklidir.

Kronik yara bakımı ekip işidir…
Ekip sağlam ise, liderlik kolay…



Sabrınız için teşekkür ederim.