Iran Endocrine Society | Research Insititute for Endocrine Sciences | Shahid Beheshti University of Medical Sciences | Iran University of Medical Sciences | Institute of Endocrinology and Metabolism

THE 14th INTERNATIONAL CONGRESS OF
ENDOCRINE DISORDERS
22nd - 24th November 2023

Epidermal and platelet-derived Growth Factors in Diabetic Foot Ulcer

By: Mahboobeh Nazari

Endocrine Research Center
Institute of Endocrinology and Metabolism

IRAN UNIVERSITY OF MEDICAL SCIENCES

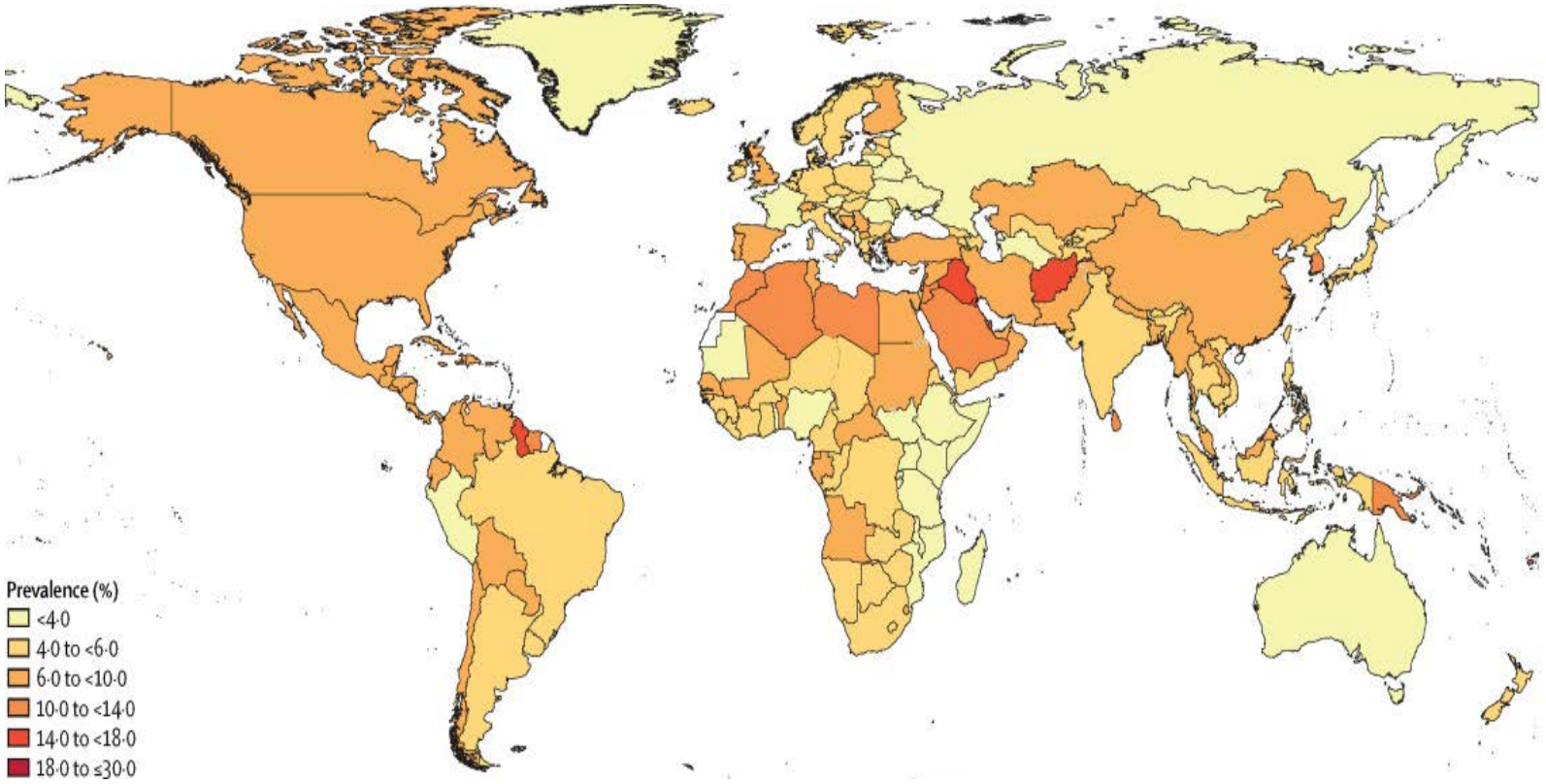
Agenda

- Introduction: (Epidemiology and Economic Burden of DFU)
- Wound healing process
- Growth factors in wound healing process (E.g. PDGF, EGF)
- Clinical evidence related to growth factor therapy

Epidemiology of Diabetes

- ✓ In 2021, there were 529 million
- ✓ By 2050, more than 1.31 billion
- ✓ Nationwide prevalence of diabetes among Iranian adults: 15%

Age-standardized total diabetes prevalence rates in 2021



Diabetes Therapy, 2021; 12, 2921-2938

Diabetic foot ulcer prevalence

- Globally: 6.3% ≈ 33 million people
- In males: 4.5%
- In females: 3.5%
- In T2DM: 6.4%
- In T1DM: 5.5%

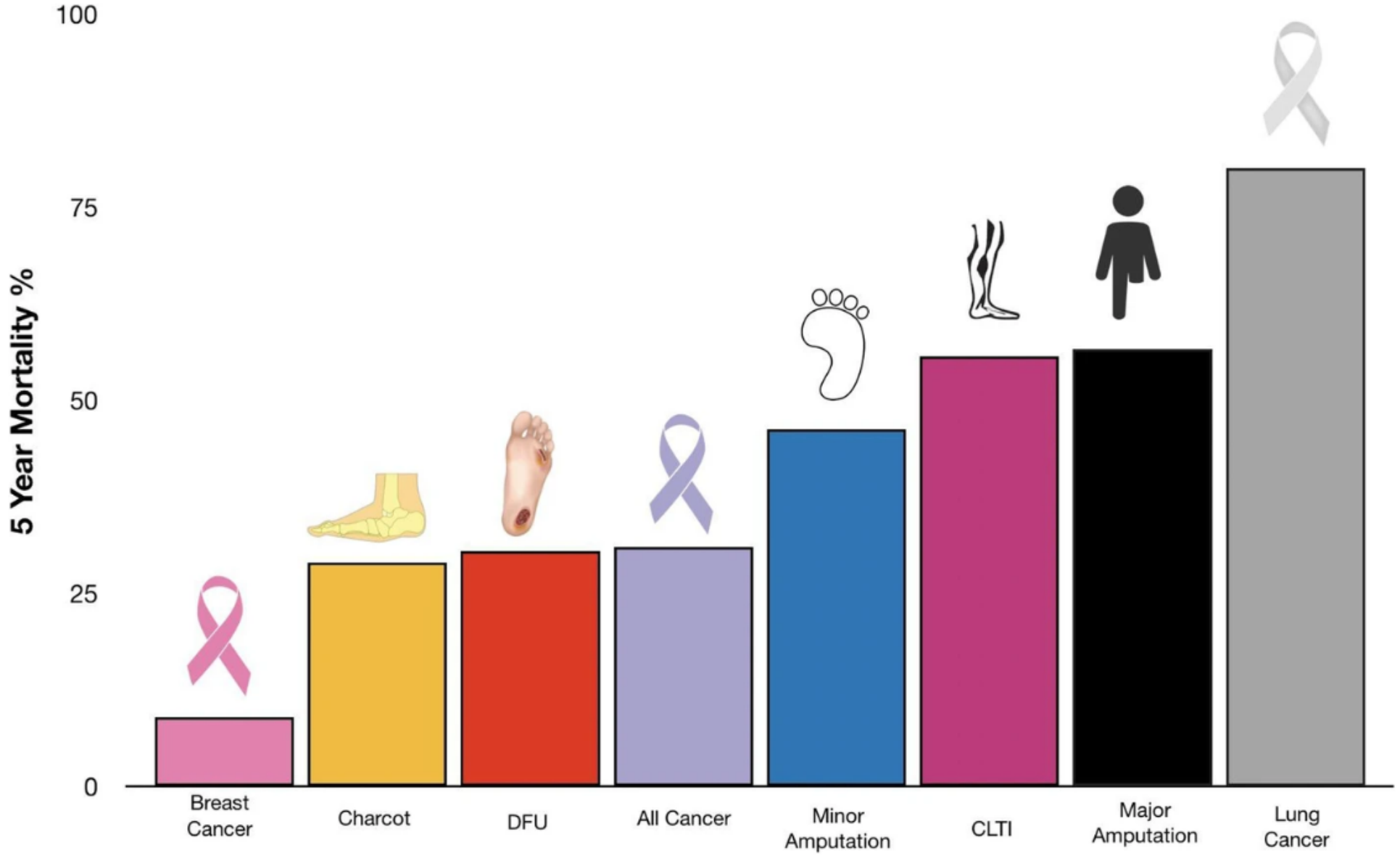
Ann Med. 2017 Mar;49(2):106-116

BURDEN and Economic Burden OF DFU

- 50%–70% of all the limb amputations are because of diabetic wounds.
- In every 30 s, one leg is amputated due to diabetic wounds in worldwide
- Cost of Diabetes care in the U.S. annually : $363 billion
- Added cost of DFU: 50% to 200% above the baseline cost of diabetes-related care

National Diabetes Statistics Report. Centers for Disease Control and Prevention 2022, Diabetes Care 2014;37:651–658, Biomedicine & Pharmacotherapy 112 (2019) 108615, Journal of Vascular Surgery 2018;67:1455–1462

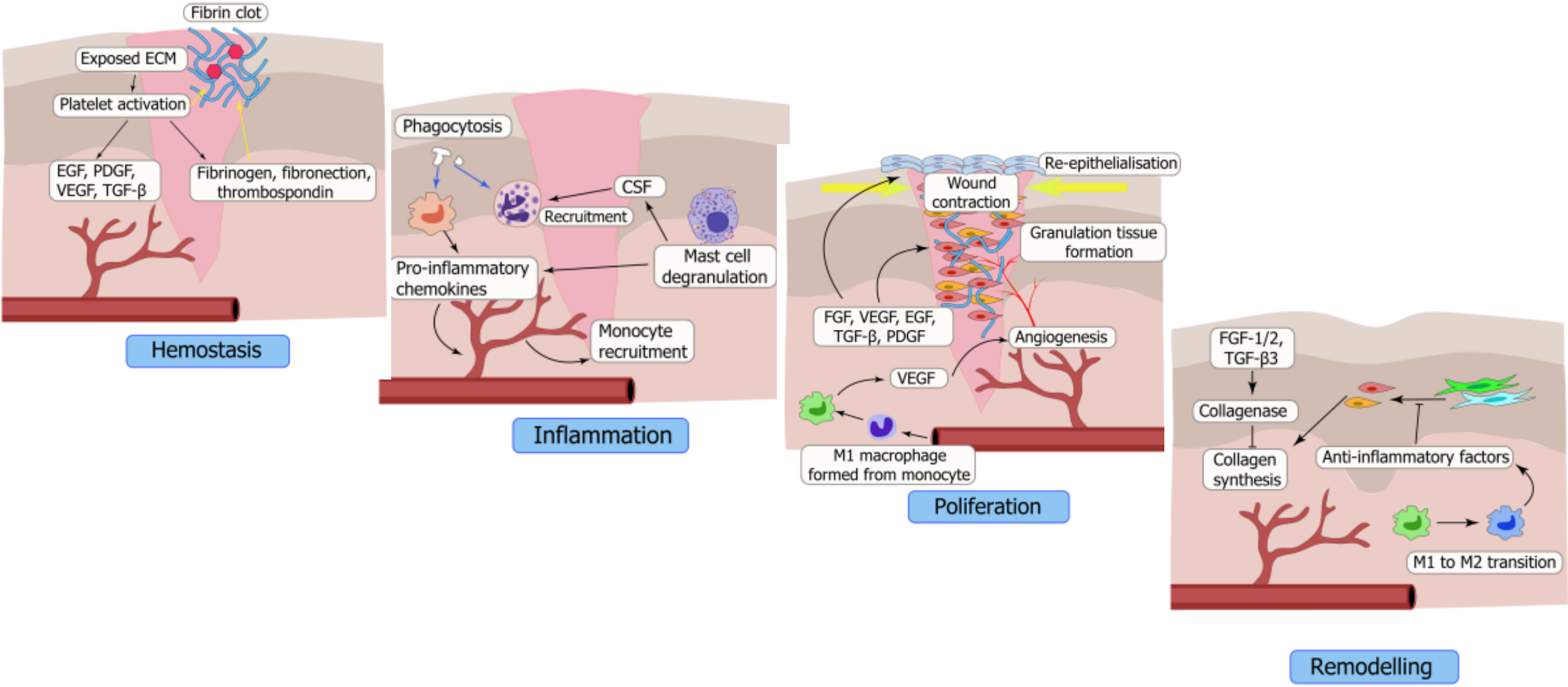
Five year mortality rate



Journal of Foot and Ankle Research (2020) 13:16

Wound Healing process

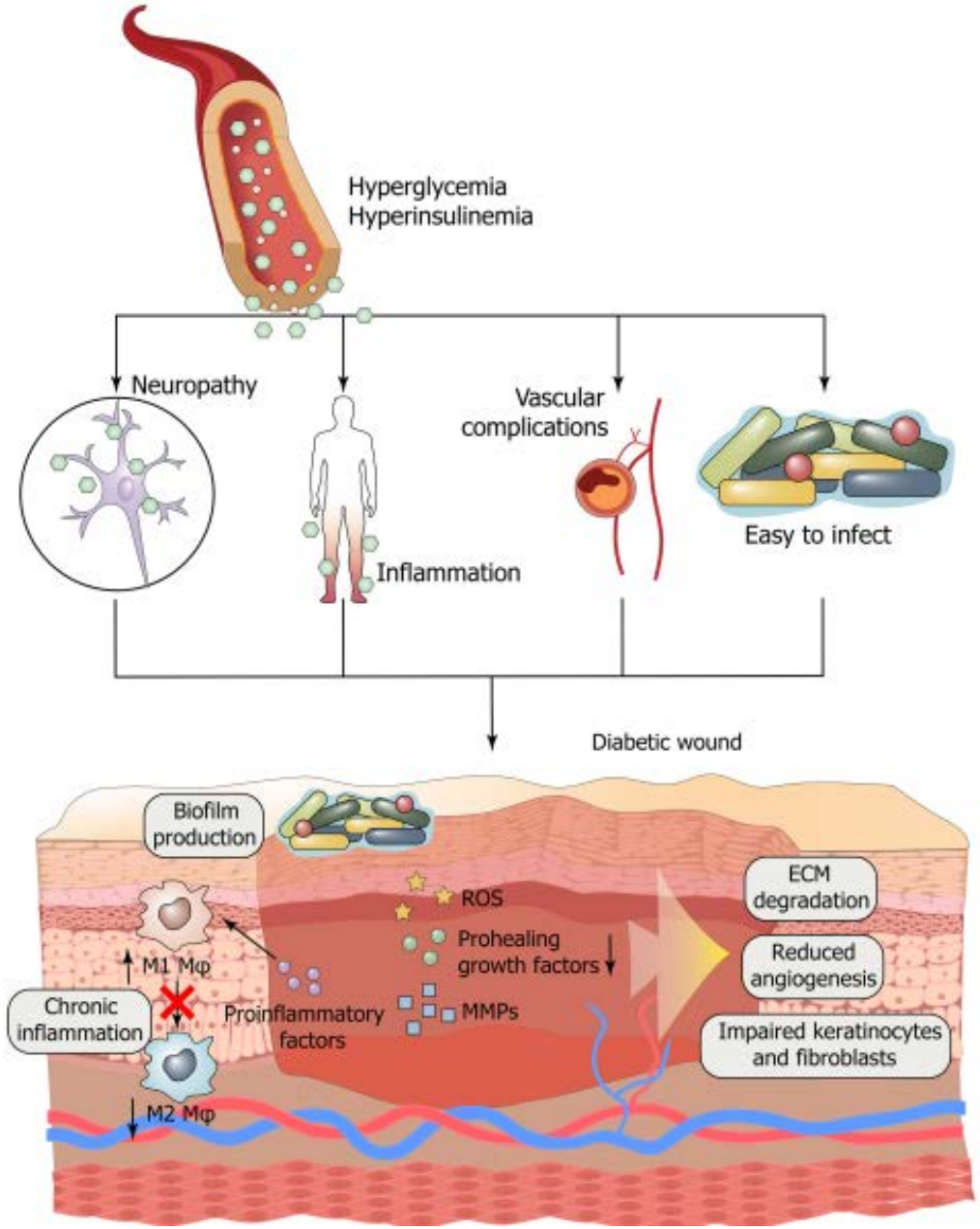
The phases of wound healing



Int. J. Mol. Sci. 2023, 24, 15109

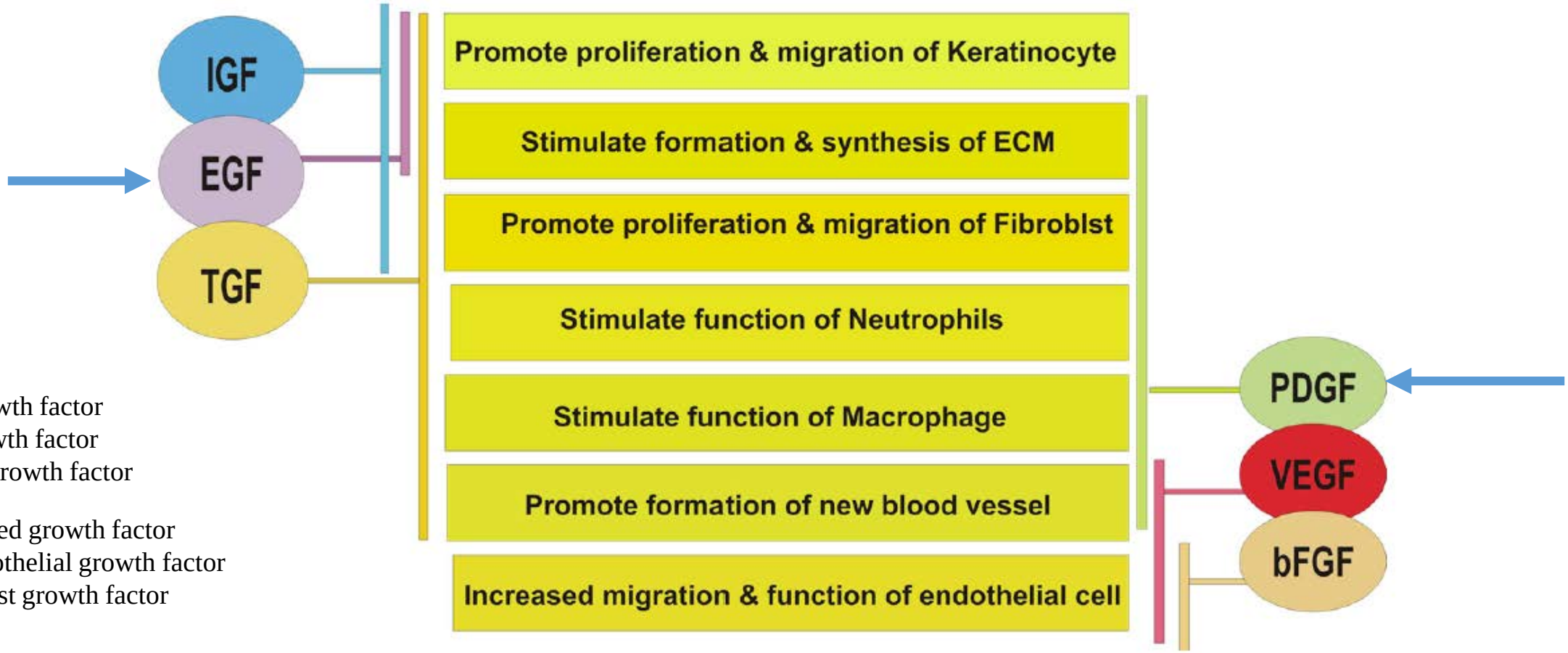
Problems in diabetic wounds healing

- Excessive formation of AGEs (advanced glycation end-products),
- insufficient neovascularization,
- insufficient concentration of GFs,
- imbalance between metabolism and nutrient delivery,
- abnormal regulation of gene expression,
- impaired vascularization



World J Diabetes 2023 April 15; 14(4): 364-395

Role of major Growth Factors on different cells and process involved in wound healing



IGF: Insulin-like growth factor
EGF: Epidermal growth factor
TGF: Transforming growth factor

PDGF: Platelet-derived growth factor
VEGF: Vascular endothelial growth factor
bFGF: Basic fibroblast growth factor

Biomedicine & Pharmacotherapy (2019); 112: 108615

Main growth factors in wound healing

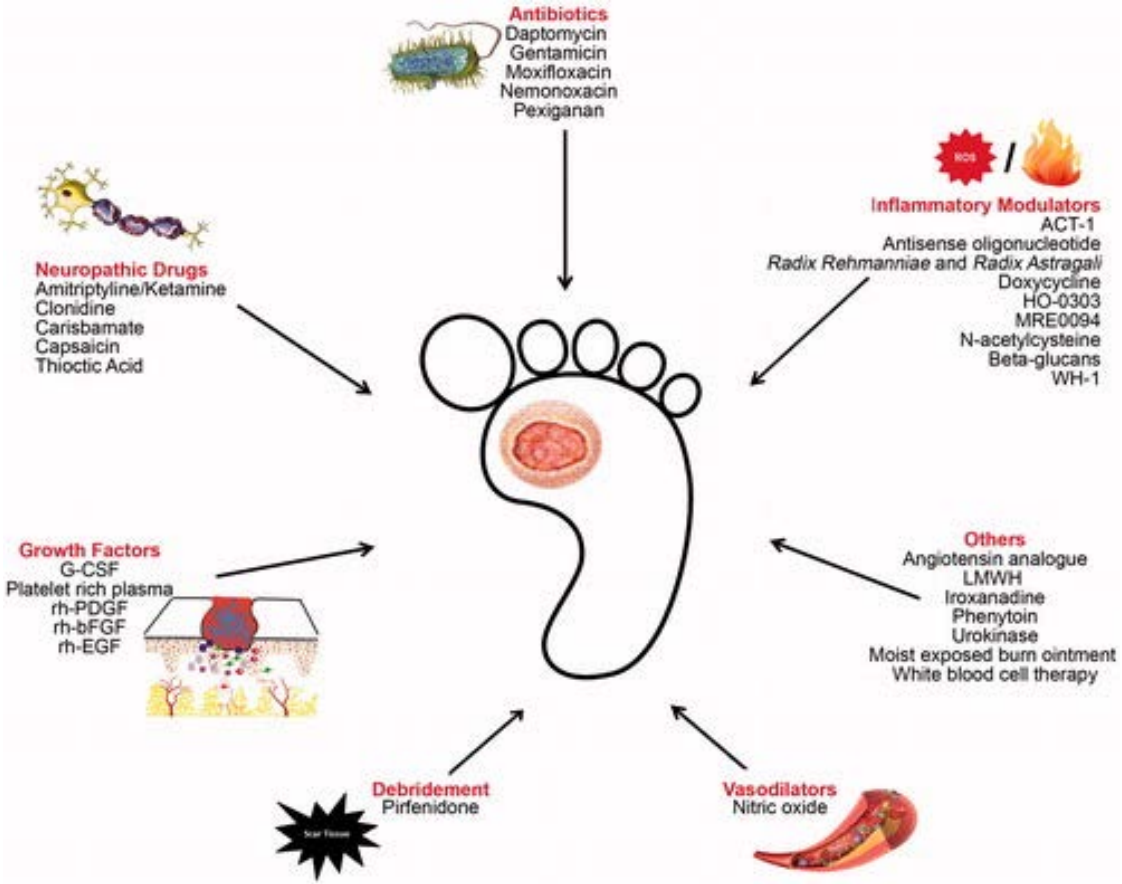
- ✓ change of their expression,
- ✓ decreased production,
- ✓ decreased release,
- ✓ trapping and excessive degradation

Type of GF	Source cells	Target cells	Receptor/signaling protein	Involved wound healing process	Acute wound	Chronic wound
VEGF	Keratinocytes, fibroblasts, macrophages, endothelial cells	Endothelial cells, macrophages	ICAM-1, VCAM-1, PLCγ/PKC/Ras/Raf/MEK/ERK	Inflammation, angiogenesis	Increased	Decreased
TGF-β	Fibroblasts, keratinocytes, macrophages, platelets	Fibroblasts, keratinocytes, macrophages, leukocytes, endothelial cells	TGF-βRI-II, Smad 2-4, α-SMA, MAPK, integrins	Inflammation, angiogenesis, granulation tissue formation, collagen synthesis, matrix formation and remodeling, leukocyte chemotactic function	Increased	Decreased
PDGF	Platelets	Leukocytes, macrophages, fibroblasts	PDGFR, Ras/Erk1/2/MAPK, PI3K	Inflammation, re-epithelial-ization, collagen deposition, tissue remodelling	Increased	Decreased
HGF	Fibroblasts	Endothelial cells, keratinocytes	c-Met, ERK1/2, Akt, PAK-1/2, Gab1	Suppression of inflam-mation, granulation tissue formation, angiogenesis, re-epithelialization	-	-
bFGF	Keratinocytes, fibroblasts, endothelial cells	Keratinocytes, fibroblasts, endothelial cells	ERK2	Angiogenesis, granulation tissue formation	Increased	Decreased
FGF-7, FGF-10	Fibroblasts, keratinocytes	Keratinocytes	Peroxiredoxin-6, Nrf2, Nrf3	Re-epithelialization, detoxi-fication of ROS	-	-
EGF, HB-EGF, TGF-α	Platelets, macrophages, keratinocytes	Fibroblasts, endothelial cells, keratinocytes	EGFR, STAT3, AP1, PI3K, ERK	Tissue formation, re-epithelialization	Increased	Decreased

World J Diabetes 2023 April 15; 14(4): 364-395

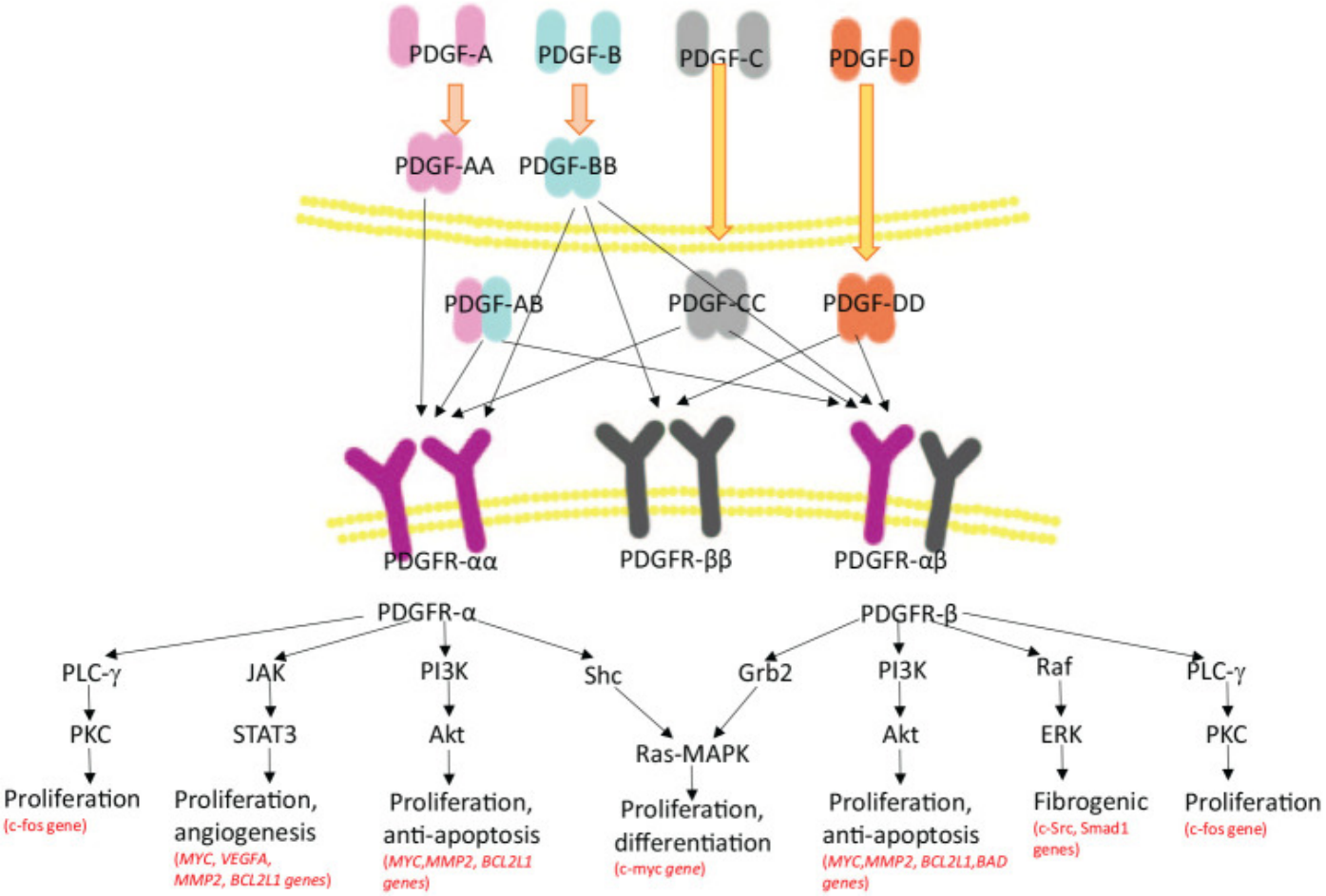
Treatment of DFU

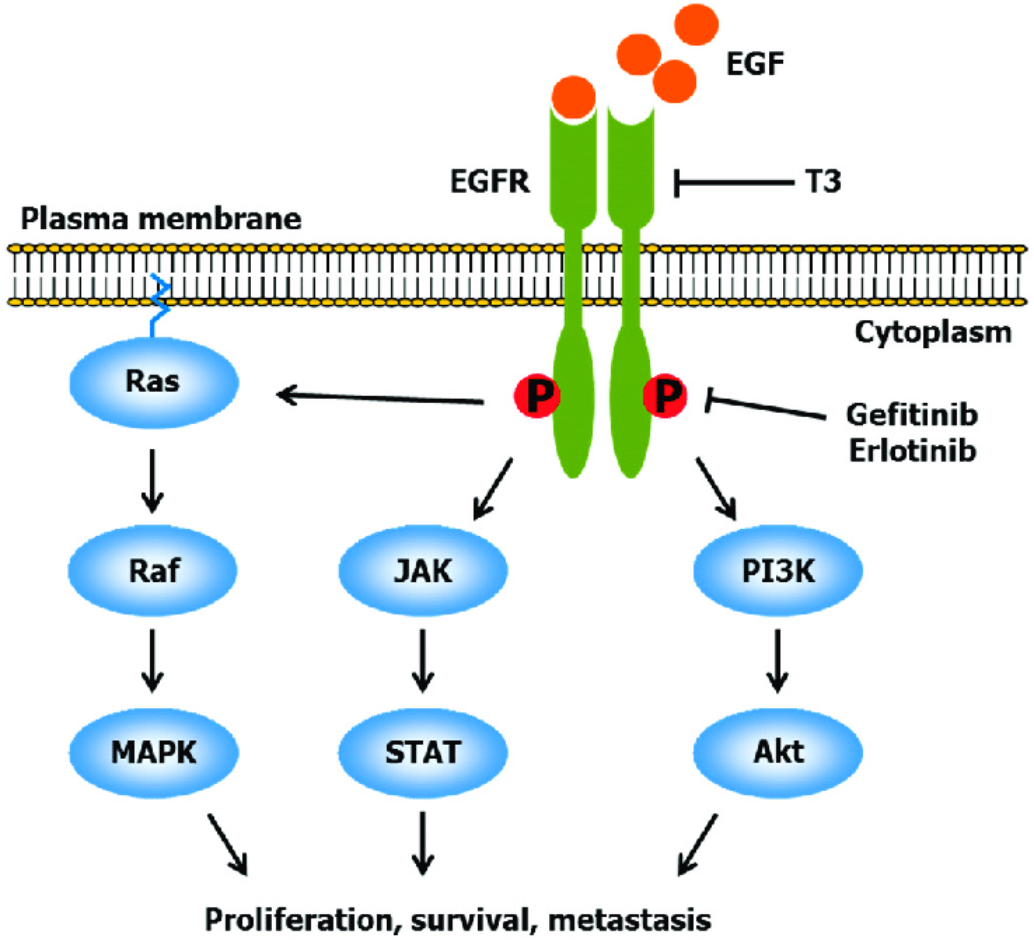
- ✓ Off-loading
- ✓ Antibiotics in the Presence of Infection
- ✓ Repeated Debridement of Necrotic Tissue



Diabetes Therapy (2012): 4. 3.1
Current Medical Research and Opinion. 2016; 32 (3): 519-542.

The signalling pathways of PDGF and EGF





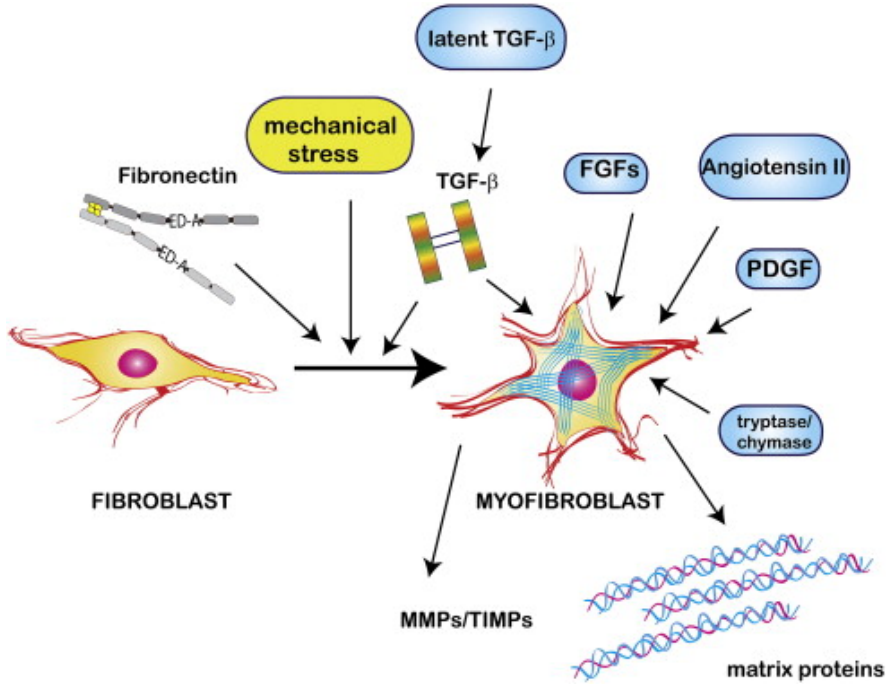
Diab Vasc Dis Res. 2020; 17(4): 1479164120942119.

Int. J. Mol. Sci. 2016, 17, 1605, Clin Podiatr Med Surg.1991; 8:937–953
Plast Reconstr Surg. 1991; 88:189–196

Platelet-Derived Growth Factor (PDGF)

PDGF activity

- PDGF acts as a cellular chemoattractant
- promotes the migration of various cells (fibroblasts, neutrophils, and monocytes) to the site of injuries.
- responsible for the differentiation of fibroblast cells into myofibroblast
- supporting the contraction of collagen fibers and the wound



CRC Press, Boca Raton, 1988; 149–162

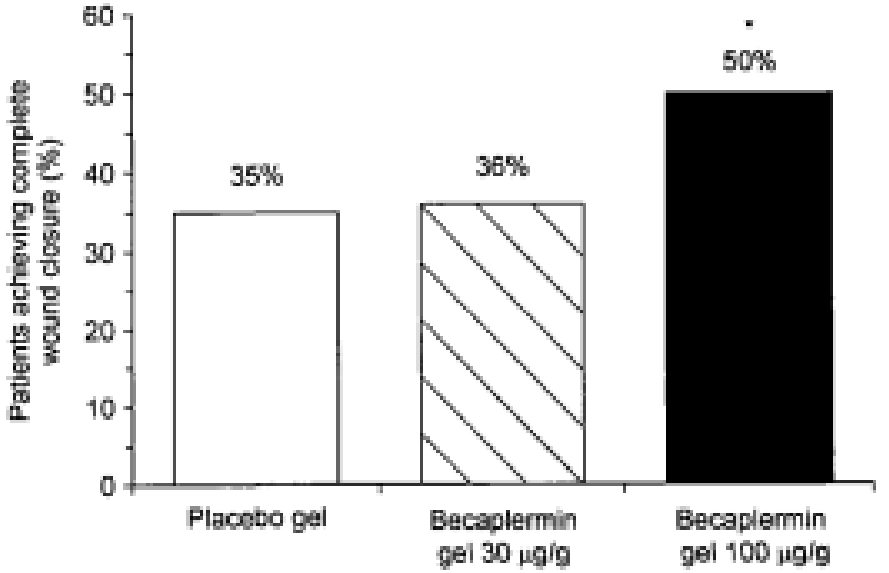
A phase III randomized placebo-controlled double-blind study

Patient demographics and target ulcer characteristics

Characteristic	Placebo gel	Becaplermin gel (µg/g) 30	100	Total
n	127	132	123	382
Sex				
Male	91 (72)	82 (62)	82 (67)	255 (67)
Female	36 (28)	50 (38)	41 (33)	127 (33)
Race				
White	100 (79)	108 (82)	101 (81)	309 (81)
Black	18 (14)	15 (11)	14 (11)	47 (12)
Asian	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Hispanic	7 (5.5)	9 (6.8)	8 (6.5)	24 (6.3)
Other	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Age (years)	58 ± 11.8	58 ± 11.3	57 ± 11.5	58 ± 11.5
Target ulcer				
Area (cm^2)	2.8 ± 4.14	2.6 ± 2.69	2.6 ± 3.41	2.7 ± 3.45
*n**	127	132	123	382
Depth (cm)	0.5 ± 0.54	0.5 ± 0.48	0.4 ± 0.46	0.5 ± 0.49
*n**	122	129	117	368
Duration (weeks)	46 ± 52.1	56 ± 80.3	46 ± 54.7	49 ± 64.0
*n**	119	123	113	355
$TcPO_2$ (mmHg)				
Foot dorsum	55.5 ± 19.61	54.1 ± 20.94	55.0 ± 22.60	54.9 ± 21.02
*n**	127	132	123	382

Data are *n*, *n* (%), or means ± SD. *Reduced *n* values reflect the number of patients with missing baseline data.

Effect of becaplermin gel on complete wound closure in patients receiving becaplermin gel 100 ug/g (n = 123), becaplermin gel 30 ug/g (n = 132), and placebo gel (n = 127). *P = 0.007 vs. placebo gel.



Diabetes Care 1998;21(5):822–827

clinical use of PDGF Approved by (FDA) in December 1997
topical interventions are used for the Treatment of neuropathic diabetic foot ulcers.

becaplermin gel 100 μg/g
increased the complete wound closure 43% (50 vs. 35%, P = 0.007)
decreased the time of wound closure 32% (86 vs. 127 days; estimated 35th percentile, P = 0.013).

Diabetes Care 1998;21(5):822–827

Characteristics of RCTs evaluated PDGF safety and effectiveness

Ref	Study	Intervention	Type of control	Size and the old of the wound	# of patients	Antibiotics application during the treatment period (if needed)	Baseline HbA1C	Types of wound and grade of wound	Dressing type	Offloading	Treatment duration	Follow up period posttherapy
[8]	Phase III RCT	Becaplermin® gel (Regranex) 100 and 30 μg/g vehicle gel once daily	Placebo	>2cm^2 for a period of at least 8 weeks	382	Y	6.5-7.2	Stage III or IV (IAET guide)	Moist saline-soaked gauze dressings	Y	20 weeks	3 months
[9]	RCT	30 μg PDGF per g of gel once a day	Placebo	1-100 cm2 at least 8-week duration	118	N	NM	NM	Non adherent saline soaked gauze	Y	20 weeks	NM
[10]	RCT	PDGF gel once daily	Placebo hydrogel	1-16 cm^2	46	N	Y	Wagner grade I	Saline moistened gauze and nonadherent wound dressing	Y	4 months	6 months
[11]	RCT	0.01% rhPDGF-BB gel once a day	Standard wound care	14.6 ± 13.2 at least 4-week duration	20	N	8.05 ± 0.84	Wagner's grade II	Moist saline and casting	Y	20 weeks	NM
[12]	RCT	PDGF gel 7 μg/cm^2 of ulcer per day	Two active controls: antiseptics and hyperbaric oxygen therapy	8-week duration	60	Y	NM	Equals to Wagner grade II, III	Saline moistened gauze	NM	10 weeks	NM
[13]	RCT	rhPDGF gel 0.01%	Active: KY Jelly (Ethnor)	26-30 cm^2 at least 4-week duration	50	Y	NM	IAET stage III and IV	Moist dressing	Y	10 weeks	NM
[14]	RCT (phase III)	0.01% PDGF gel containing 100 μg/g	Placebo	1-40 cm2 at least 4 weeks	111	Y	<12%		Moist saline gauze	Y	20 weeks	NM
[15]	RCT	Regranex (PDGF) 0.01% plus TheraGuaze	Active (TheraGuaze)	1-8 cm^2	32	NM	<10%	Wagner grade I/II	TheraGuaze	Y	NM	Study period: 20 weeks

J Diabetes Res. 2020; 6320514.

Outcomes of RCTs that evaluated PDGF safety and effectiveness

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
PDGF-Becaplermin®	50%, 35%, and 36% of complete healing in 100 μg/g Becaplermin® gel and placebo and 30 μg/g Becaplermin® gel, respectively	86 days for 100 μg/g Becaplermin® gel (decreased time by 32%)	NM	NM	NM	N	N	Y(+)	30% in all groups	NM
rhPDGF-BB gel	48% complete healing in the PDGF group compared with 25% in the placebo group $p = 0.01$	30 days in the PDGF and 40 days in the placebo group. $p = 0.01$	NM	NM	NM	NM	NM	NM	26% in PDGF treated versus 46%	NM
Topical PDGF	52% of healing in the test group versus 57% of healing in the control group (not significant)	16 weeks	NM	Y	NM	N	Y(-)	Y(+)	NM	3 cases in total
rhPDGF-BB gel	All ulcers in both groups had healed by the end of the study period	50.10 ± 23.38 days 41.8% reduction in healing time ($p = 0.02$)	NM	NM	NM	NM	N	Y(+)	NM	NM
PDGF	Percentage of patients with complete wound contraction was significantly ($p = 0.03$) higher in the PDGF group compared to the other groups	6.75-7.6 weeks Not significant	NM	NM	NM	NM	N	NM	NM	NM
PDGF	18 (72%) ulcers had healed in the control group and 15 (60%) in the test group ($p > 0.05$). Three ulcers in the control group showed >75% reduction in size compared to 2 in the test group ($p > 0.05$).	10 weeks	NM	NM	NM	NM	NM	NM	NM	NM
PDGF gel	A significantly higher ($p < 0.01$) percentage of patients in the rhPDGF-based gel-treated group achieved complete healing	46 days ($p < 0.001$)	NM	Y	NM	NM	Y(-)	NM	NM	NM
PDGF	The rates of wound closure with TheraGauze and TheraGauze + Becaplermin® were 0.37 and 0.41 cm2/week, respectively ($p = 0.34$)	12 weeks	NM	Y	NM	NM	NM	NM	NM	N

J Diabetes Res. 2020; 6320514.

Safety and adverse effects

- studies report : no adverse event
- safety of Becaplermin® gel:
- six RTCs suggests: the gel is safe for the treatment of diabetic ulcers (1998).
- A cohort study (1622 patients): no increased risk of cancer

J Diabetes Res. 2020; 6320514.

American Journal of Surgery. 1998; 176 (2): 68S–73S.

Epidermal growth factor (EGF)

Meta-Analysis > Int Wound J. 2020 Aug;17(4):1062-1073. doi: 10.1111/iwj.13377.
Epub 2020 Apr 28.

Efficacy and safety of recombinant human epidermal growth factor for diabetic foot ulcers: A systematic review and meta-analysis of randomised controlled trials

Ding-Yun Zhao [1], Ya-Na Su [2], Yong-Hong Li [2], Tian-Qi Yu [2], Jing Li [2 3], Chong-Qi Tu [1]

Meta-Analysis > F1000Res. 2023 Mar 10:11:773. doi: 10.12688/f1000research.121712.2.
eCollection 2022.

Epidermal growth factor outperforms placebo in the treatment of diabetic foot ulcer: a meta-analysis

Fazal Rahim [1], Xie Yan [2 3], Jawad Ali Shah [4], Nida Bibi [5], Zafar Ullah Khan [6], Shah Nawaz [7], Yao Ming [1]

General characteristics of included trials

Author/year	Country	Study design/ Number of cases	Intervention Type	Route	Type of DM	Apply frequency	Duration of treatments (weeks)	Number of patients	Age/ Ulcer location	Wagner grade	Complete healing/ Ulcer duration	Diabetic duration
Fernandez-Montequin, 2019	Cuban	RCT/20	rhEGF 75 µg (n = 53) rhEGF 25 µg (n = 48)	Intralesional Injection	Type 1 and 2	3 times per week	8 weeks	149	65.5/Foot	Grades 3 or 4	60%/ 4.3 weeks	15 years
Sanjeev Singla, 2014	India	RCT/1	Betadine/Urogastrone (rhEGF) gel 15	Topically	Type 1 and 2	Once every two weeks	8 weeks	50	55-58/Foot	Grade 1 or 2	22.46%/ NA	NA
Kwang Hwan Park, 2018	South Korea	RCT/6	EGF 0.005%/Normal saline	Topically	Type 1 and 2	Twice a day	12 weeks	167	56-59/Foot	Grades 1 or 2	62%/NA	NA
Thambi Durai David, 2018	India	RCT/NA	EGF Cream 150 g	Topically	NA	NA	4 weeks	50	25-75/Foot	Grade 1-2	78%/ 4 weeks	NA
Prabakar, 2016	India	RCT/1	rhEGF/saline	Topically	NA	NA	14 weeks	60	20-70/Foot	Grades 2	75%/NA	NA
Viswanathan, 2019	India	RCT/1	hEGH gel (Regen-D)/ Placebo	Topically	Type 1 and 2	NA	4 weeks	50	55-57/Foot and thigh	Grades 1 and 2	45%/NA	NA
Ajay Kundal, 2020	Indian	RCT/1	(EGF)/Conventional Betadine dressing	Topically	NA	NA	8 weeks	60	30-71/Foot	NA	58%/8	NA
Gomez-Villa, 2014	Mexico	RCT/2	rhEGF (75 µg)/Placebo	Intralesional Injection	Type 1 and 2	3 times per week	8 weeks	34	58.6/Foot	Grades 1, 2 and 3	12%/8	16.3 years

Eight randomized control trials:
620 patients (337 in EGF group, 283 in placebo group)

F1000Research 2023, 11:773 Last updated: 19 OCT 2023

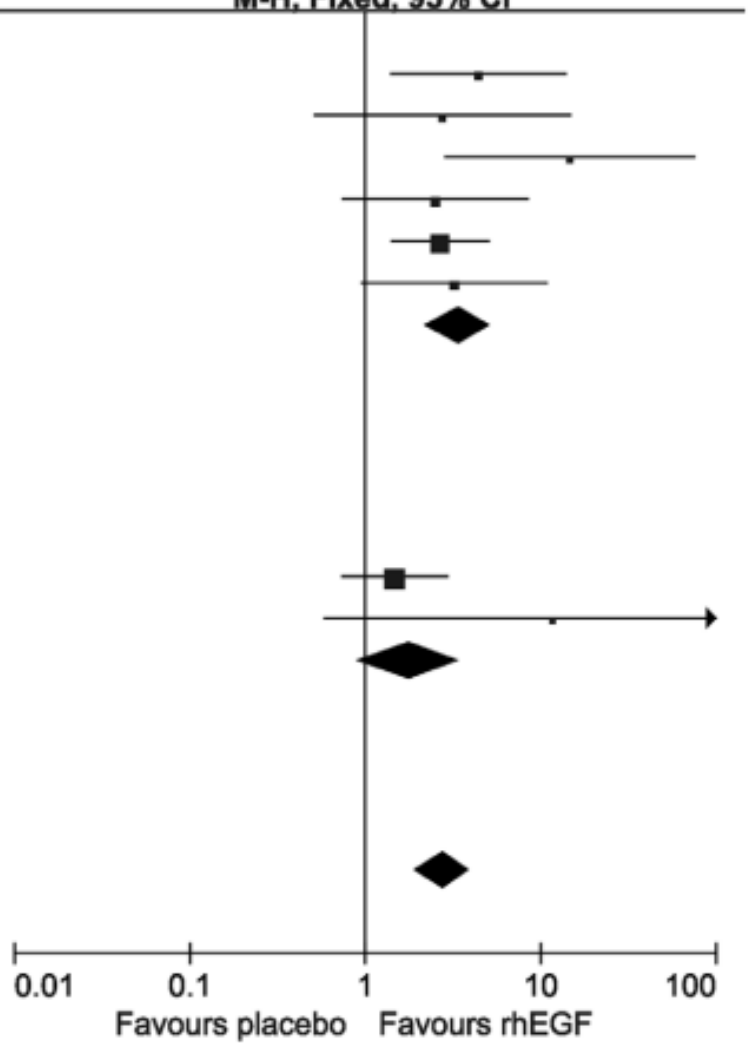
Int Wound J . 2020;17(4):1062-1073.

Interventional details of included trials

Author/year	Intervention	Control	Route	Apply frequency	Treatment duration	Evaluation time	Duration of follow-up	Complete healing rate	Mean time to complete healing (d)
Viswanathan et al. 2019	hEGH gel (Regen-D) ($n = 27$)	Placebo ($n = 23$)	Topical application	NA	30 d	NA	30 d	I = 78% (21/27) C = 52% (12/23)	I = 45 ± 12 C = 72 ± 18
Xu et al. 2018	rhEGF 40 IU/cm^2 ($n = 50$)	placebo (saline) ($n = 49$)	Topical application	Once a day	60 d	NA	NA	NA	I = 38.51 ± 1.46 C = 47.52 ± 1.82
Park et al. 2018	rhEGF 0.005% (50 lg/ml) ($n = 82$)	placebo (saline) ($n = 85$)	Topical application	Twice a day	Until ulcer healing or up to 12 wk	Weekly	12 wk	I = 73.2% (60/82) C = 50.6% (43/85)	I = 56.00 C = 84.00
Prabakar et al. 2016	rhEGF ($n = 30$)	placebo (saline) ($n = 30$)	Topical application	NA	14 wk	NA	18 mo	I = 83.3% (25/30) C = 66.67% (20/30)	Reported patient-level data
Singla et al. 2014	rhEGF (Urogastrone) gel 15 g ($n = 25$)	betadine dressing ($n = 25$)	Topical application	NA	8 wk	Every 2 wk	8 wk	I = 92.0% (23/25) C = 44.0% (11/25)	Illustrated with Kaplan-Meier curve
Gomez-Villa et al. 2014	rhEGF 75 mg/ml ($n = 17$)	placebo ($n = 17$)	Intralesional injection	Thrice per week	8 wk	Every 2 wk	8 wk	I = 23.5% (4/17) C = 0% (0/17)	NA
Fernandez-Montequin et al. 2009	I1 = rhEGF 75 µg ($n = 53$) I2 = rhEGF 25 µg ($n = 48$)	placebo ($n = 48$)	Intralesional injection	Thrice per week	8 wk	Weekly	12 mo	I1 = 77·4% (41/53) I2 = 52·1% (25/48) C = 56·2% (27/48)	I1 = 98 ± 37.8 I2 = 84 ± 60.2 C = 140 ± 172.3
Afshari et al. 2005	rhEGF 1 mg/1000 mg ($n = 30$)	Placebo ($n = 20$)	Topical application	Once a day, every day	4 wk	Weekly	4 wk	I = 23.3% (7/30) C = 10% (2 /20)	NA
Tsang et al. 2003	I1: rhEGF 0.02% ($n = 21$) I2: rhEGF 0.04% ($n = 21$)	Actovegin 5% cream ($n = 19$)	Topical application	NA	12 wk	Every other week	24 wk	I1 = 57.1% (12/21) I2 = 95.0% (20/21) C = 42.1% (8/19)	Illustrated with Kaplan-Meier curve

Proportion of complete healing

Study or Subgroup	rhEGF Events	rhEGF Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
1.2.1 Topical application							
Tsang MW, et al. 2003	32	42	8	19	7.3%	4.40 [1.39, 13.96]	2003
Afshari M, et al. 2005	7	30	2	20	5.1%	2.74 [0.51, 14.82]	2005
Singla S, et al. 2014	23	25	11	25	2.4%	14.64 [2.82, 75.95]	2014
Prabakar A, et al. 2016	25	30	20	30	9.3%	2.50 [0.74, 8.50]	2016
Park KH, et al. 2018	60	82	43	85	31.5%	2.66 [1.39, 5.09]	2018
Viswanathan V, et al. 2019	21	27	12	23	8.0%	3.21 [0.95, 10.89]	2019
Subtotal (95% CI)		**236**		**202**	**63.7%**	**3.37 [2.19, 5.20]**	
Total events	168		96				
Heterogeneity: Chi² = 4.06, df = 5 (P = 0.54); I² = 0%							
Test for overall effect: Z = 5.51 (P < 0.00001)							
1.2.2 Intralesional injection							
Fernandez-Montequin JI, et al. 2009	66	101	27	48	35.3%	1.47 [0.73, 2.96]	2009
Gomez-Villa R, et al. 2014	4	17	0	17	1.0%	11.67 [0.58, 235.92]	2014
Subtotal (95% CI)		**118**		**65**	**36.3%**	**1.76 [0.91, 3.41]**	
Total events	70		27				
Heterogeneity: Chi² = 1.78, df = 1 (P = 0.18); I² = 44%							
Test for overall effect: Z = 1.67 (P = 0.09)							
Total (95% CI)		**354**		**267**	**100.0%**	**2.79 [1.95, 3.99]**	
Total events	238		123				
Heterogeneity: Chi² = 8.68, df = 7 (P = 0.28); I² = 19%							
Test for overall effect: Z = 5.59 (P < 0.00001)							
Test for subgroup differences: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.5%							



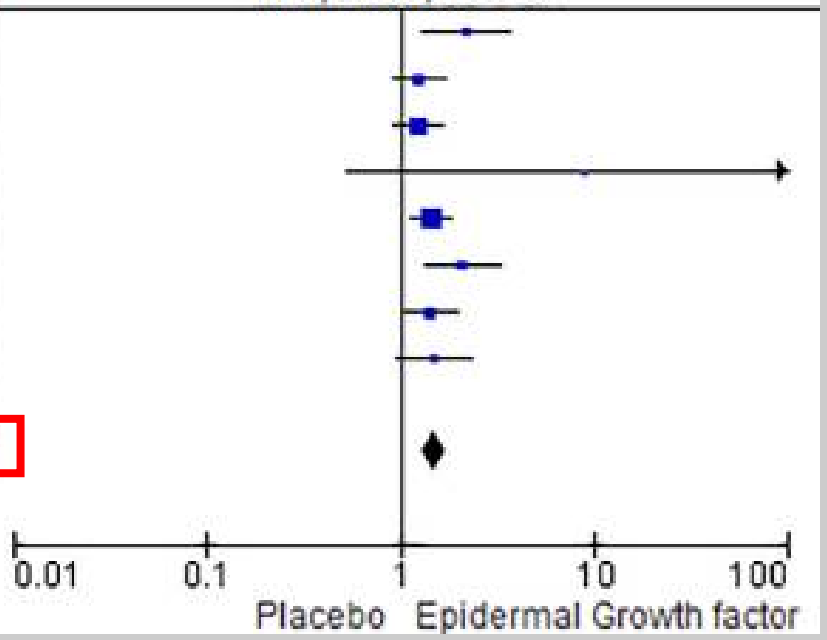
Int Wound J . 2020;17(4):1062-1073. *F1000Research 2023, 11:773 Last updated: 19 OCT 2023*

Complete healing rate of EGF and placebo in diabetic foot ulcer patients.

Study or Subgroup	Epidermal Growth Factor Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ajay Kundal	24	30	11	30	7.5%	2.18 [1.32, 3.61]
Antony Prabakar	25	30	20	30	13.6%	1.25 [0.93, 1.69]
Fernandez Montequin	65	101	25	48	23.0%	1.24 [0.91, 1.68]
Gomez-Villa	4	17	0	17	0.3%	9.00 [0.52, 155.24]
Kwang Hwan Park	60	82	43	85	28.6%	1.45 [1.13, 1.85]
Sanjeev Singla	23	25	11	25	7.5%	2.09 [1.32, 3.30]
Thambi Durai David	23	25	16	25	10.8%	1.44 [1.05, 1.97]
Vijay Viswanathan	21	27	12	23	8.8%	1.49 [0.96, 2.32]
Total (95% CI)		**337**		**283**	**100.0%**	**1.50 [1.32, 1.71]**
Total events	245		138			

Heterogeneity: $Chi^2 = 8.81$, $df = 7$ ($P = 0.27$); $I^2 = 21\%$

Test for overall effect: $Z = 6.10$ ($P < 0.00001$)



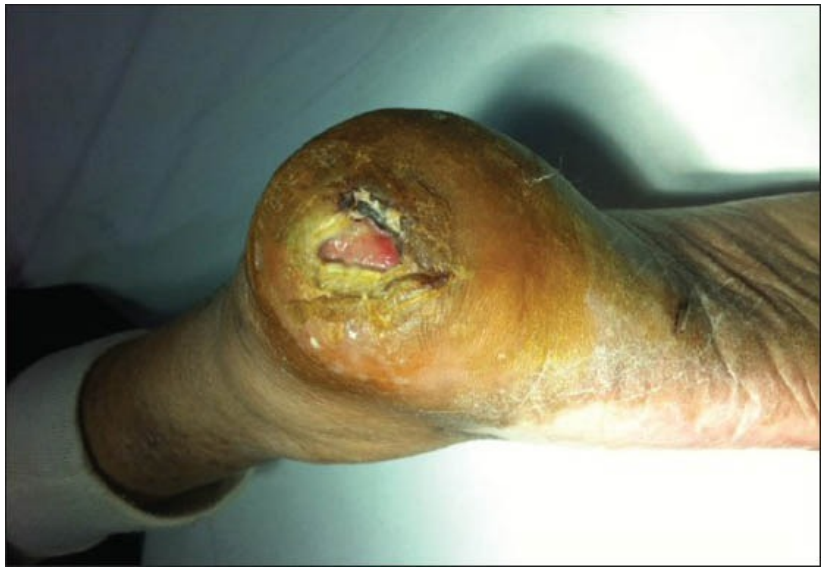
F1000Research 2023, 11:773 Last updated: 19 OCT 2023

Adverse events

Author/year	Proportion of adverse events	Serious adverse events (rhEGF group)	Serious adverse events (placebo group)	Wound-related infections	Possible product-related adverse Events	Amputation
Viswanathan et al. 2019	NA	NA	NA	NA	NA	NA
Xu et al. 2018[17]	NA	NA	NA	NA	NA	NA
Park et al. 2018	I = 7.3% (6/82); C = 8.2% (7/85)	I: 6 cases (7.3%) 1 superficial infection, 1 cellulitis, 1 acute myocardial infarction, 1 diarrhoea, 1 gastrointestinal haemorrhage, 1 acute renal failure	C: 7 cases (8.2%) 3 superficial infections, 1 cellulitis, 1 diarrhoea, 1 idiopathic thrombocytopenic purpura, 1 coronary artery disease	I = 2.4% (2/82); C = 4.7% (4/85)	I = 0%; C = 0%	I = 0%; C = 0%
Prabakar et al. 2016	NA	NA	NA	NA	NA	NA
Singla et al. 2014	NA	NA	NA	I = 60% (15/25); C = 80% (20/25)	NA	I = 4% (1/25); C = 0% (0/25)
Gomez-Villa et al. 2014	NA	0	0	I = 0%; C = 0%	I = 0%; C = 0%	I = 0%; C = 0%
Fernandez-Montequin et al. 2009	I1 = 69.8% (37/53); I2 = 58.3% (28/48); C = 64.5% (31/48)	I1: renal failure, cellulitis I2: renal failure (lethal), myocardial infarct, pneumonia	C: acute pulmonary, 2 oedema (1 lethal), cellulitis, knee abscess	I1 = 7.5% (4/53); I2 = 8.3% (4/48); C = 4.2% (2/48)	I1 = 0%; I2 = 0%; C = 0%	I1 = 13.2% (7/53); I2 = 20.8% (10/48) C = 25% (12/48)
Afshari et al. 2005	I = 0%; C = 0%	I = 0%; C = 0%	I = 0%; C = 0%	I = 0%; C = 0%	I = 0%; C = 0%	I = 0%; C = 0%
Tsang et al. 2003	NA	NA	NA	NA	NA	I1 = 9.5% (2/21); I2 = 0% (0/21); C = 10.5% (2/19)

Int Wound J . 2020;17(4):1062-1073.

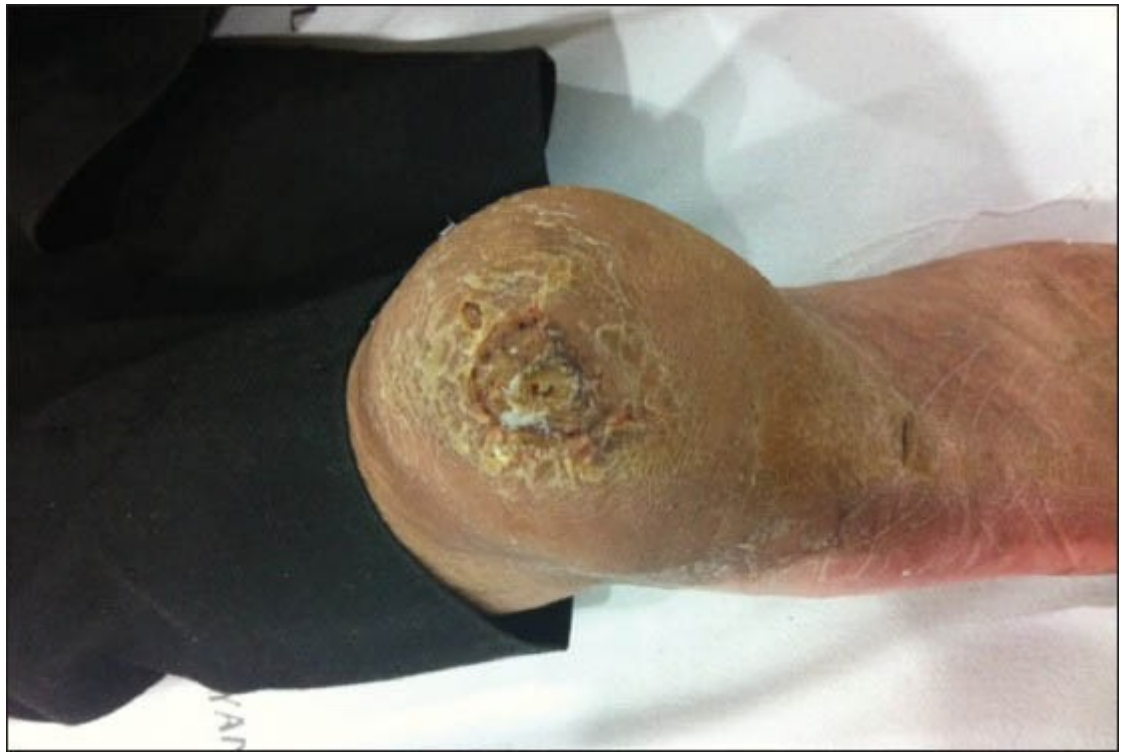
F1000Research 2023, 11:773 Last updated: 19 OCT 2023



Diabetic foot ulcer prior to start of therapy

The application of rhEGF

- ✓ shortens the wound healing time significantly
- ✓ the mean closure was significantly higher in the EGF group compared with placebo 34%.
- ✓ .



Ulcer healed completely after 6 weeks of application of recombinant human epidermal growth factor

Int Wound J . 2020;17(4):1062-1073.

J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 273–277.

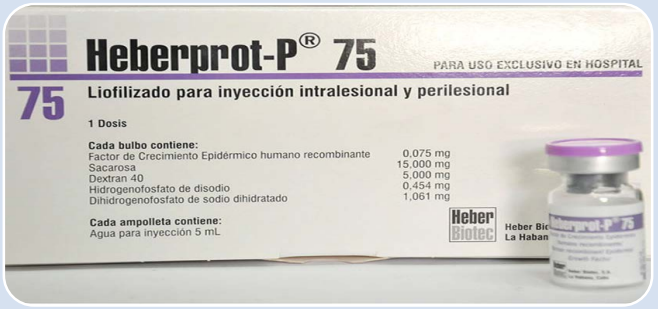
F1000Research 2023, 11:773 Last updated: 19 OCT 2023

Overview of diabetic foot management strategies

Treatment modality	Level of evidence	Strength of recommendation
Non-invasive modalities		
Wound dressing	High	Strong recommendation
Antibiotics	Low to moderate	Strong recommendation
Total-contact casting and pressure offloading techniques	High	Strong recommendation
Maggot therapy	Low	Weak recommendation
Hyperbaric oxygen	Low	Weak recommendation
Topical growth factors	Moderate	Could be beneficial
Cell therapy	Low (more studies required)	Weak recommendation
Invasive modalities		
Debridement	Moderate to high	Strong recommendation
Skin grafting	Moderate	Could be beneficial
Revascularization	Moderate	Strong recommendation

World J Clin Cases. 2023 Mar 16; 11(8): 1684–1693.

EGF



Easyef

Heberprot

REGEN-D

Clinical trials of growth factors in diabetic wounds

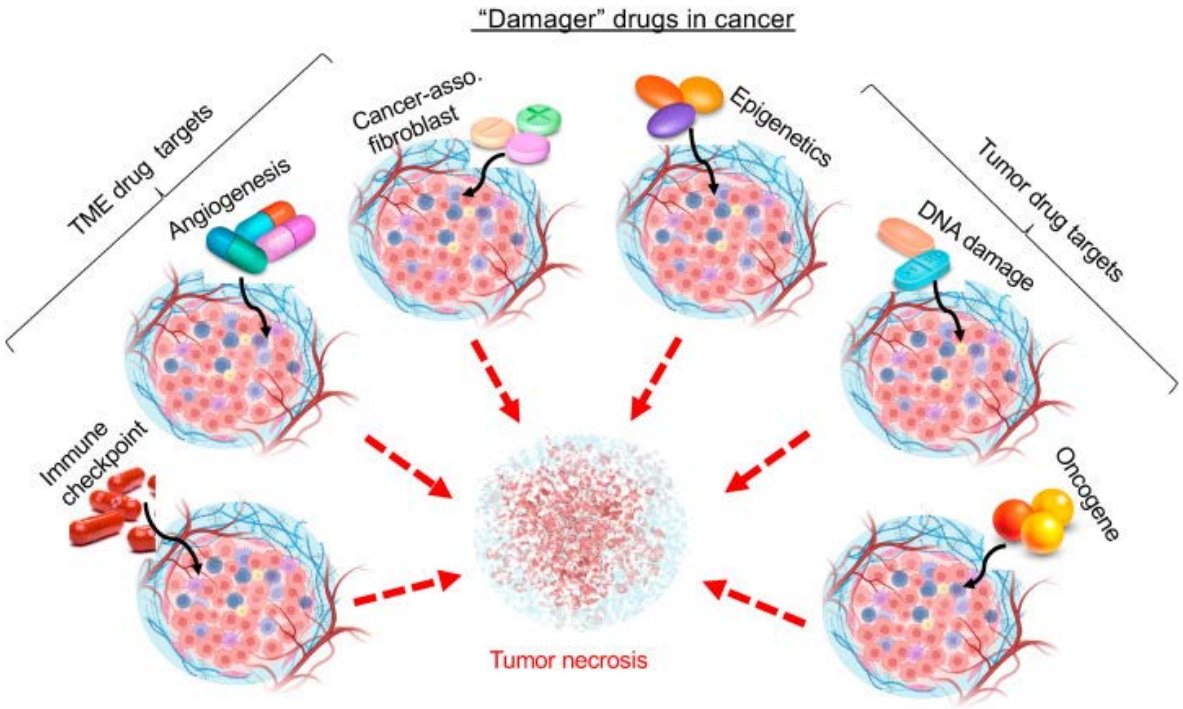
Therapeutic agents	Delivery system and route	Response on wound closure
EGF	Cream	Significantly improve wound healing rates and reduced the risk of amputation
bFGF	CGS/suture to surrounding skin	Significant wound improvement within 14 d
PDGF	Topical gel wound dressing	Reduce healing time by 30%
PDGF	Topical becaplermin gel	Improve wound healing by 35%
bFGF	0.0005% benzalkonium chloride in saline/spray on the wound	Significantly reduce wound area
rhVEGF	Methylcellulose gel/apply evenly to wounds and edges	Significantly increase incidence of complete wound healing
PDGF	Becaplermin gel/topical apply	The incidence of complete closure was significantly increased by 43%
EGF	Intralesional injection	Reduced wound area and increased re-epithelialization rate
EGF	Topical spray	Faster healing velocity and higher complete healing rate
EGF	Topical hydrogel	78% of wounds healed after 30 d

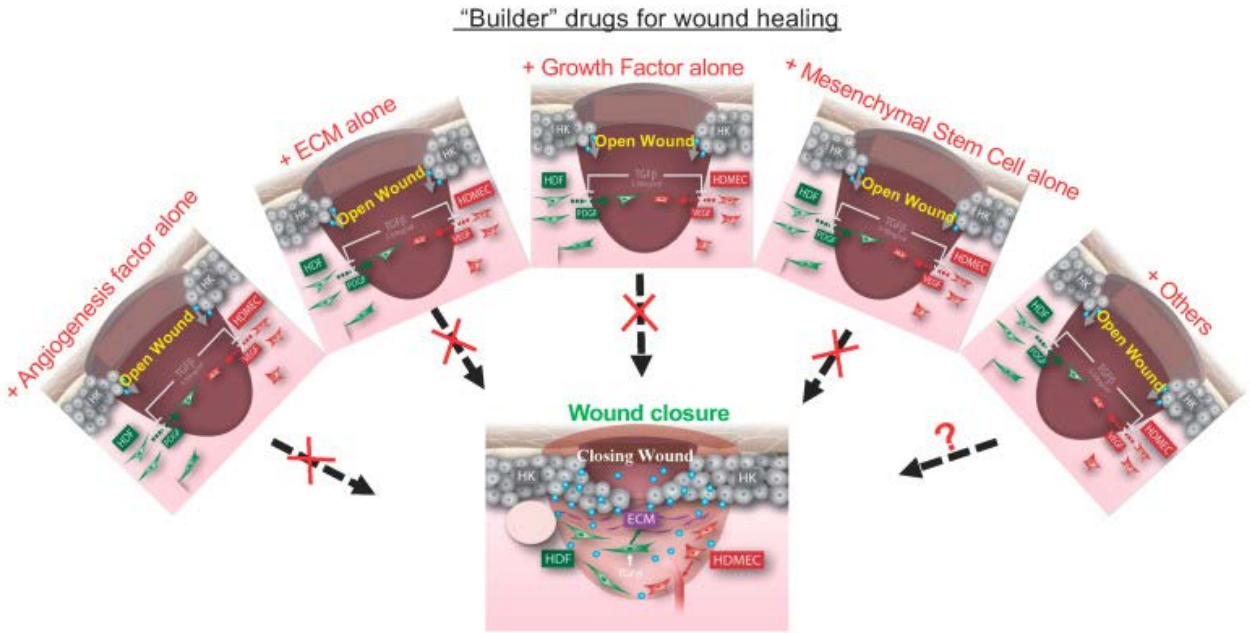
World J Diabetes 2023 April 15; 14(4): 364-395

Why Are There So Few FDA-Approved Therapeutics for Wound Healing?

Easier to make a “damager” drug in cancer.

Impossible to make a “builder” drug for wound healing from a single molecule.





Damaging is far easier than re-building

Int. J. Mol. Sci. 2023, 24, 15109.

Take-home message

- Proper wound care is a key component during the treatment, but it is not sufficient.
- GFs can be regarded as a direct and effective agent in managing and treating diabetic wounds
- GF shortens the wound healing time significantly
- the mean closure was significantly higher in the GF groups compared with placebo.


Thank
you

Efficacy of topical application of beta urogastrone (recombinant human epidermal growth factor) in Wagner's Grade 1 and 2 diabetic foot ulcers: Comparative analysis of 50 patients

Sanjeev Singla, Ramneesh Garg[1], Abhishek Kumar[2], Chiranjiv Gill

Departments of General Surgery, and [1]Plastic Surgery, Dayanand Medical College and Hospital, Ludhiana, [2]Department of General Surgery, Government Medical College and Hospital, Chandigarh, Punjab, India

Address for correspondence:
Dr. Ramneesh Garg, 127 – E, Kitchlu Nagar, Ludhiana - 141 001, Punjab, India.
E-mail: ramneeshgarg@yahoo.com

J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 273–277.

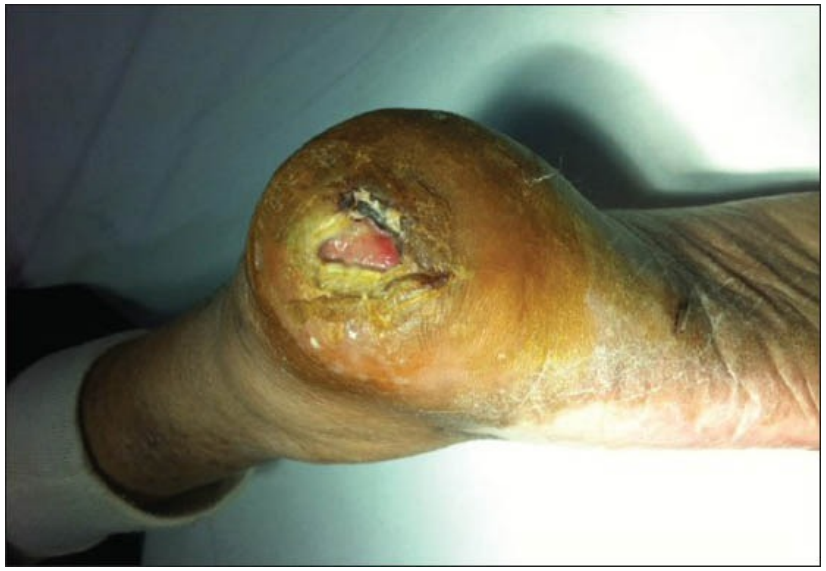
The study was conducted in the Department of Surgery,
Dayanand Medical College and Hospital, Ludhiana.

- Number of participants: 50
- Mean age:18-65 years
- ulcer size: between 2 and 50 cm^2
- Group 1(25 patients): received (rhEGF) gel.
- Group 2 (25 patients): control group, betadine dressing.
- **Follow-up:** every two weeks for eight weeks
- Free of ulcer: 13 patients in group A
- incomplete healing : 2 individuals

Table 2: The trends in granulation tissue formation

Weeks	2		4		6		8	
Granulation	Group I (%)	Group II (%)	Group I (%)	Group II (%)	Group I (%)	Group II (%)	Group I (%)	Group II (%)
Resistant	2 (8)	12 (48)	1 (4)	9 (36)	2 (8)	7 (28)	1 (4)	6 (24
Increasing	22 (88)	13 (52)	17 (68)	12 (48)	8 (32)	13 (52)	2 (8)	9 (36)
Decreasing	0	0	0	0	0	1 (4)	0	0

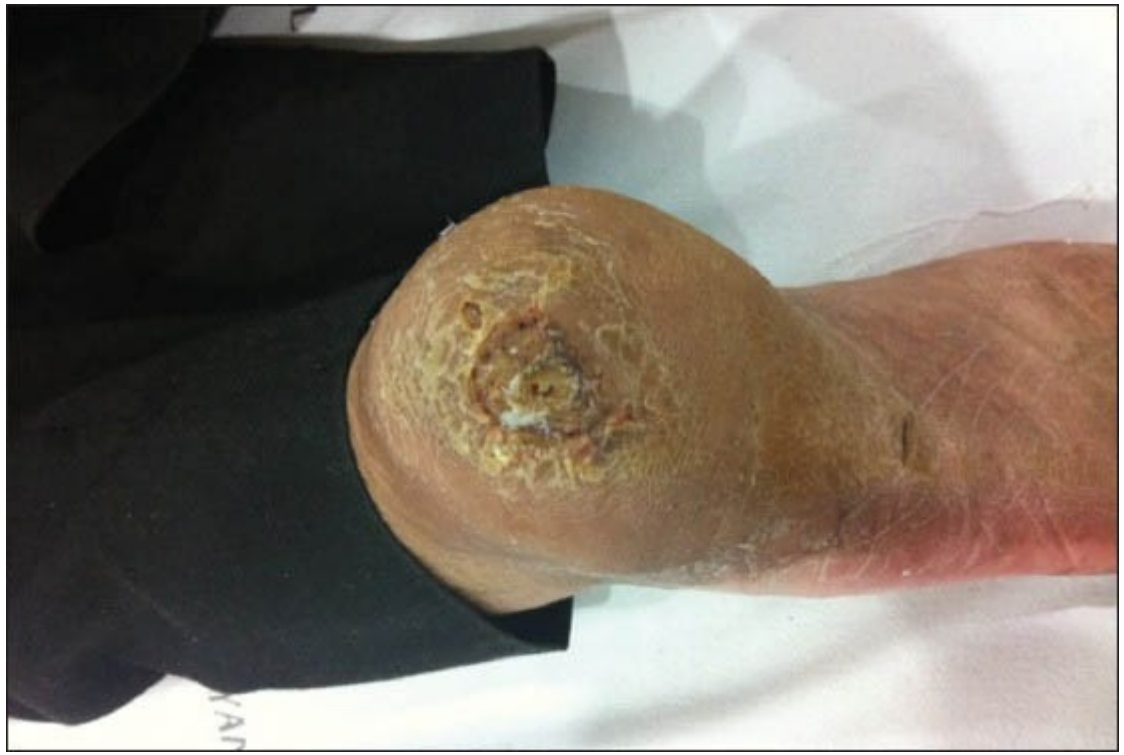
J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 273–277.



Diabetic foot ulcer prior to start of therapy

The application of rhEGF

- ✓ shortens the wound healing time significantly
- ✓ the mean closure was significantly higher in the EGF group compared with placebo.



Ulcer healed completely after 6 weeks of application of recombinant human epidermal growth factor

J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 273–277.

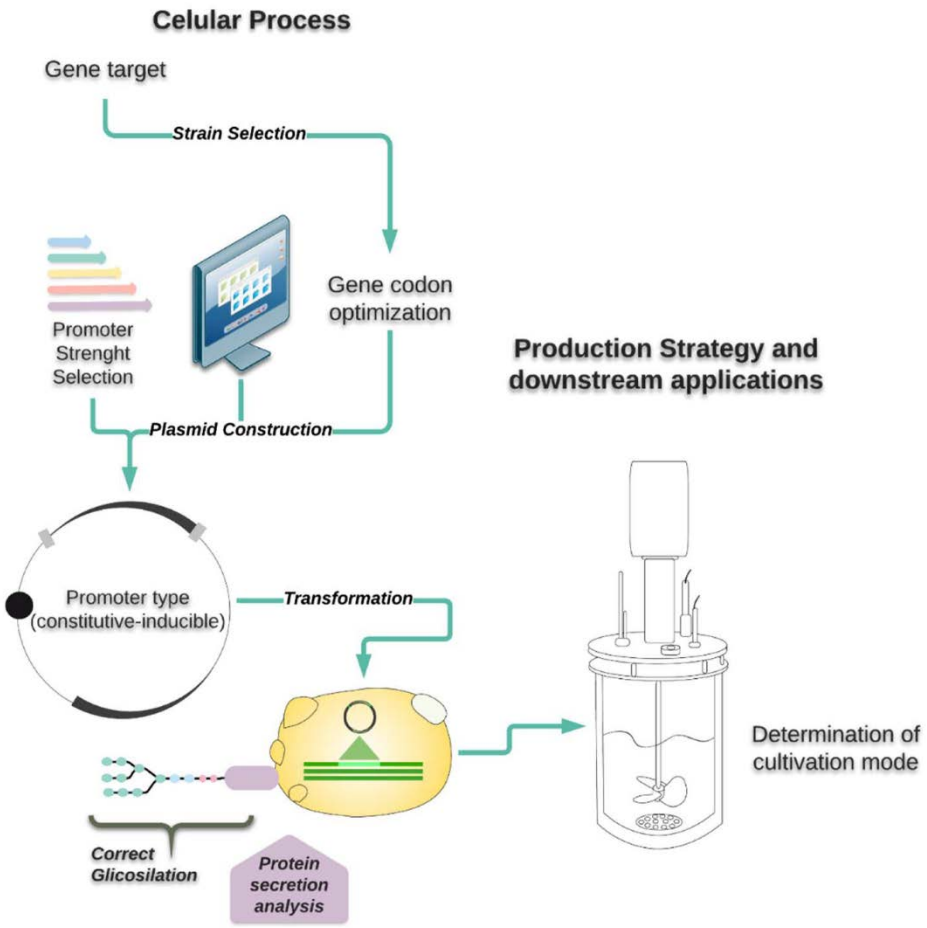
Biomaterial systems applied for the delivery of growth factors in diabetic wounds

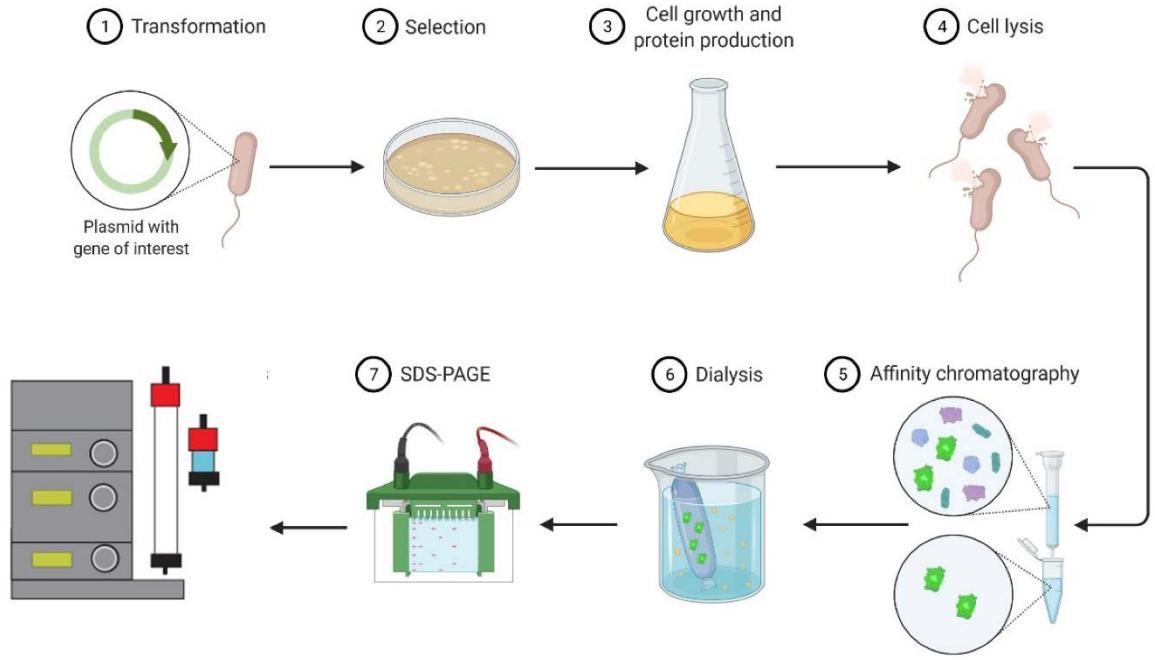
Therapeutic agents	Delivery system and route	Animal type	Wound size	Response on wound closure	Ref.
PDGF/TGF-α	Gel/topical spraying to wound bed	C57BL/KsJ-db/db mouse	Full-thickness wound measuring 1.5 cm × 1.5 cm	Accelerated wound closure at 15-21 d	[262]
bFGF	Chitosan film/topical using	C57BL/KsJ-db/db mice	Full-thickness wound (1.6 cm diameter)	Reduced wound area and increased ECM formation	[318]
bFGF	Chitosan/hydrogels implant	C57BL/KsJ-db/db mice	Full-thickness wounds (about 100 mm^2)	80% wound closure by 12 d	[319]
pDNA TGF-β1	PEG-PLGA-PEG/hydrogels implant	C57BKS.Cg-m +/+ Leprdb female mice	Full-thickness wounds (7 mm × 7 mm)	Accelerated wound closure at 5 d	[280]
bFGF	Chitosan, hydrogel/topical using	C57BL/KsJ-db/db mice	Full-thickness circular wounds (about 100 mm^2)	Accelerated tissue filling rate of wounds and increased number of CD-34-positive vessels	[320]
PDGF-BB	Carboxymethyl cellulose hydrogel/topical using	C57/Bl6 wild-type mice and lep/r db/db homozygous diabetic mice	Either a 0.6 cm^2, 1.0 cm^2, or 1.5 cm^2 full-thickness area of skin	Accelerated healing by enhanced granulation tissue formationand angiogenesis	[321]
bFGF	Collagen, PGA/porous scaffolds implant	C57BLKS/J Iar- + Leprdb/ + Leprdb	Full-thickness wounds (6 mm diameter	NA	[322]
rhPDGF	Gel/topical spraying to wound bed	Wistar diabetic rats	Full-thickness dermal wounds of 2.54 cm^2 (1.8 cm diameter)	Outstanding re-epithelialization within the first 7 d	[323]
bFGF	Chondroitin-6-sulfate, heparin/hydrogels implant	C57BLKs/J-m1/db, db/db mice, hetero-zygous (m1/db)	Full-thickness wounds (1.6 cm diameter)	89% wound closure by 2 wk	[324]
rhEGF	PCL, PCL-PEG/non-woven mesh (electrospun) implant		Ful-thickness wounds (0.8 cm diameter)	Accelerated wound closure at 7 d	[325]
PDGF	5% polyethylene glycol gel/intradermal injection	Wistar rats	Full-thickness wounds (1.8 cm diameter)	Significant wound improvement within 14 d	[237]
aFGF	Collagen, chitosan/porous scaffolds implant	SD rats	Whole skin layer round wounds (1.8 cm diameter)	Complete healing at 14 d	[326]
rhEGF	PLGA microspheres	SD rats	Full-thickness dermal wounds (2.54 cm^2, 1.9 cm diameter)	90% healing rate on the 14^{th} day	[327]
Collagen-binding domain (CBD)-VEGF	Collagen domain/praye onto the traumatic surface	SD rats	Full-thickness wounds (2 cm × 2.5 cm)	95% healing rate basically reached after 21 d	[328]

rhEGF	Dextrin conjugated/topical using	BKS.Cg-m a/a +/+ Leprdb/J db/db mice	Full-thickness wounds (10 mm × 10 mm)	Accelerated wound closure, neo-dermal tissue formation, increased granulation tissue deposition and angiogenesis	[331]
EGF	Collagen, hyaluronic acid/porous scaffolds implant	BKS.Cg-+Leprdb/+Leprdb (db/db) mice	Full-thickness wounds (15 mm × 20 mm)	N/A	[332]
pDNA bFGF	PELA/electrospun mesh implant	Male SD rats	Full-thickness wounds (about 250 mm^2)	Complete wound closure by 3 wk	[333]
bFGF	Collagen, gelatine/porous scaffolds implant	BKS.Cg- + Leprdb/+ Leprdb/Jcl	8 mm diameter and 3 mm thickness	NA	[334]
VEGF/bFGF	PLGA nps, fibrin/porous scaffolds implant	BKS.Cg-m+/+ Lepr, db/db	Full-thickness dermal wound (0.8 cm in diameter)	85% wound closure at 15 d	[335]
rhEGF	PLGA-alginate microspheres/intralesional	Wistar rats	Full-thickness dermal wound (1 cm in diameter)	90% wound closure at 11 d	[336]

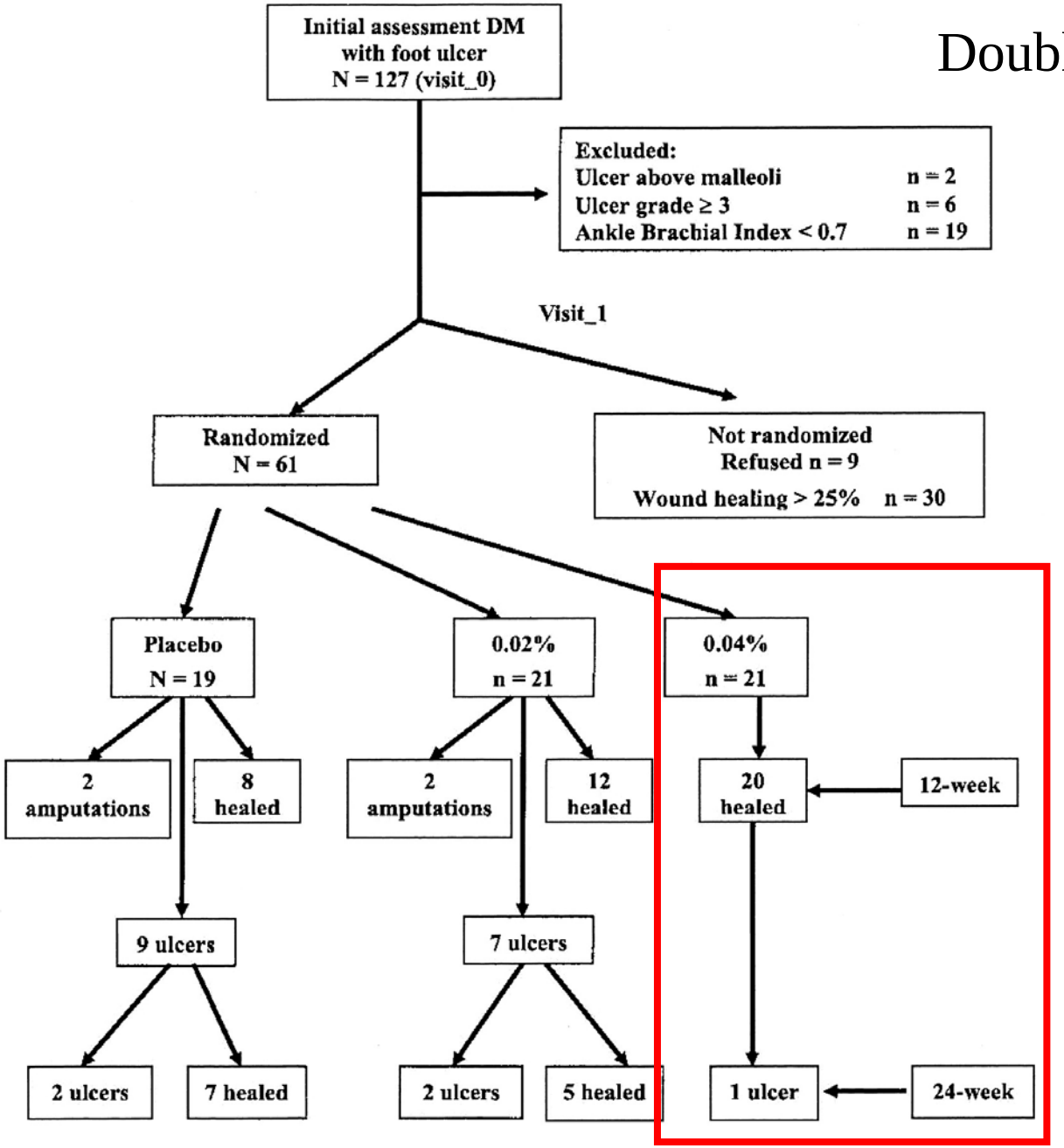
	injection				
rhEGF	Lipid nanocarriers/topical application to wound bed	BKS.Cg-m+/+Lepr 286 db/J	Full-thickness wounds 0.8 cm in diameter	95% wound closure at 15 d	[337]
VEGF, bFGF, EGF, PDGF	Collagen, hyaluronic acid, gelatine nps/non-woven mesh (electrospun) implant	SD rats	Full thickness wound (diameter of 15 mm)	Complete wound closure by 4 wk	[338]
pDNA VEGF	Hyaluronic acid/hydrogels implant	db/db mice	Full-thickness wounds were then generated using a 6 mm biopsy punch (4 mm for wounds on smaller balb/c mice)	Induction of wound closure by day 8-10	[339]
VEGF	PLGA nanoparticles/intradermal injection	db/db mice	Full thickness excisional wounds, two (8 mm diameter) and four (6 mm diameter)	Complete wound closure by 19 d	[340]
VEGF, PDGF	Poly (β-amino esters), poly (acrylic acid), heparan sulfate/woven nylon mesh implant	db/db mice	Full-thickness skin wound	Accelerated wound closure at 14 d	[341]
rhEGF	NaCMCh-rhEGF/hydrogels implant	SD rats	Full-thickness wounds (2 cm diameter, 3.14 cm^2 circular area)	Wound healed in day 15	[342]
rhEGF	PU/porous scaffolds implant	SD rats	Full-thickness wounds (dimensions of 2 cm × 2 cm)	97% wound closure at 21 d	[343]
VEGF	PEG, heparin/hydrogels implant	Cg-m +/+ Leprdb/J (db/db) mice	Full-thickness punch biopsy wound	-	[344]
rhPDGF	PLGA/Non-woven mesh (electrospun) implant	SD rats	Full-thickness excision (8.0 mm in diameter)	Complete wound closure by 14 d	[345]
bFGF	Chitosan, hydrogel + heparin/topical using	C57BL/KsJ-db/db mice	-	Significant angiogenesis and collateral circulation construction	[346]
bFGF	Gelatin hydrogel microspheres/topical injection	C57BL/KsJ-db/db mice	Full-thickness wounds (10 mm in diameter)	Accelerated diabetic skin wound healing and reduced scarring	[347]
bFGF	Acidic gelatin sheet/topical coverage	C57BL/KsJ-db/db mice	Full-thickness wound (1.5 cm × 1.5 cm)	Promoted neoepithelialization, granulation, neovascularization, and wound healing	[348]

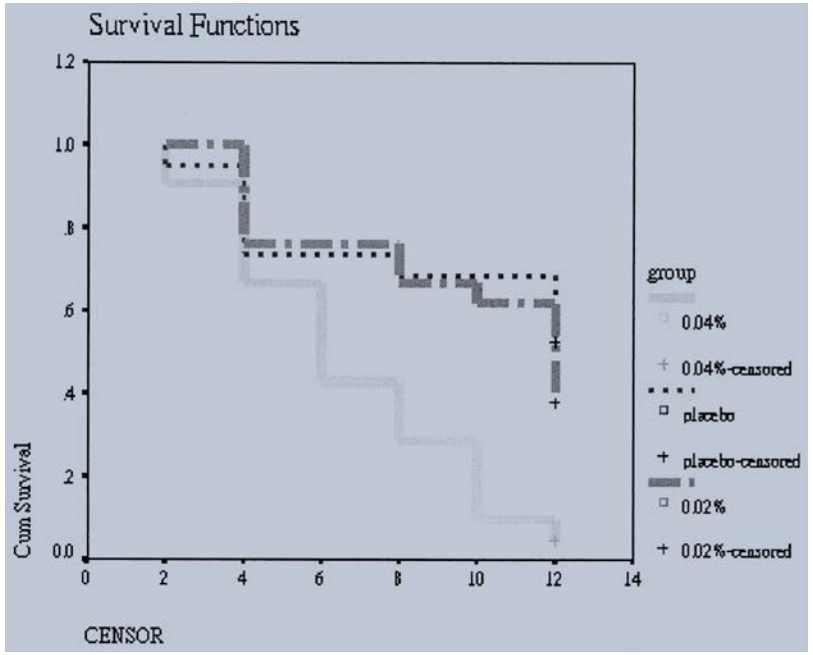
The recombinant PDGF-BB expression in the yeast, *Saccharomyces cerevisiae*





Double-blind randomized controlled study





Ulcer healing among different groups with respect to time (in weeks).
Solid line, 0.04% (wt/wt) hEGF;
interrupted line, 0.02% (wt/wt) hEGF;
dotted line, placebo (P = 0.0003).

Diabetes Care. 2003 Jun;26(6):1856-61.

Meta-Analysis > Int J Low Extrem Wounds. 2016 Jun;15(2):120-5.
doi: 10.1177/1534734616645444. Epub 2016 May 5.

Efficacy of Topical Recombinant Human Epidermal Growth Factor for Treatment of Diabetic Foot Ulcer: A Systematic Review and Meta-Analysis

Shaowei Yang [1], Zhijun Geng [2], Kui Ma [2], Xiaoyan Sun [3], Xiaobing Fu [4]

Affiliations + expand

PMID: 27151755 DOI: 10.1177/1534734616645444

Table 1. Characteristics of Included Studies.

Author (Year)	Study Type	Baseline Condition of Ulcers: Location	Severity (Wagner Grade)	Ischemia	Infection	Treatment Groups	Administration of rhEGF	Duration of Treatment
Tsang et al (2003)[14]	RCT	Below the ankle	I or II	ABPI ≥0.7	NA	Placebo + SOC 0.02% rhEGF + SOC 0.04% rhEGF + SOC	Topical application	12 weeks
Fernandez-Montequin et al (2009)[13]	RCT	Foot	3 or 4	Hemoglobin ≥100 g/L	NA	Placebo + SOC 25 µg rhEGF + SOC 75 µg rhEGF + SOC	Intralesional injection	8 weeks
Gomez-Villa et al (2014)[12]	RCT	Foot	I, II, or III	ABPI ≥0.6	NA (osteomyelitis excluded)	Placebo + SOC 75 µg rhEGF + SOC	Intralesional injection	8 weeks
Singla et al (2014)[11]	RCT	Foot	1 and 2	ABPI >0.75	NA	Beta-urogastrone (rhEGF) gel Placebo (betadine dressing)	Topical application	8 weeks

Abbreviations: ABPI, ankle brachial pressure index; rhEGF, recombinant human epidermal growth factor; NA, not available; RCT, randomized controlled trial; SOC, standard of care.

Int J Low Extrem Wounds 2016; 15:120–125

Table 2. Summary of Participants in Included Studies.

Author (Year)	Treatment Groups	Number of Patients	Mean age (Years)	Female/ Male	Type of DM	Duration of DM (Years), Mean	Area of Ulcer (cm^2), Mean ± SD	Complete Healing Rate (%)
Tsang et al (2003)[14]	Placebo + SOC	19	64.37	10/9	Type 1 or 2	10.11	3.48 ± 0.82	8 (42.1%)
	0.02% rhEGF + SOC	21	68.76	13/8	Type 1 or 2	9.85	2.78 ± 0.82	12 (57.1%)
	0.04% rhEGF + SOC	21	62.24	6/15	Type 1 or 2	9.05	3.40 ± 1.1	20 (95.3%)
Fernandez-Montequin et al (2009)[13]	Placebo + SOC	53	63	28/25	Type 1 or 2	19.5	28.5	40 (75.5%)
	25 µg rhEGF + SOC	48	65.5	21/27	Type 1 or 2	15	20.1	25 (52.1%)
	75 µg rhEGF + SOC	48	64	27/21	Type 1 or 2	15	21.8	25 (52.1%)
Gomez-Villa et al (2014)[12]	Placebo + SOC	17	55.1	12/5	Type 1 or 2	15.3	11.9 ± 11.8	0
	75 µg rhEGF + SOC	17	62.1	9/8	Type 1 or 2	17.3	19.2 ± 15.7	4 (23.5%)
Singla et al (2014)[11]	Placebo (betadine dressing)	25	58.8	21/4	Type 1 or 2	NA	2-50	23 (92%)
	Beta-urogastrone (rhEGF) gel	25	55.84	23/2	Type 1 or 2	NA	2-50	11 (44%)

Int J Low Extrem Wounds 2016; 15:120–125

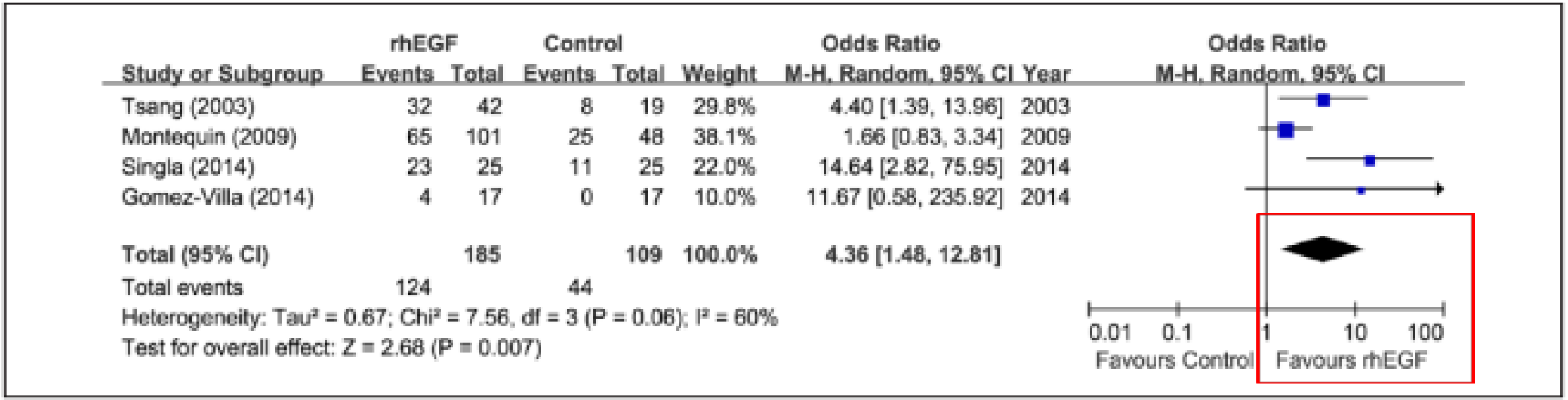


Figure 2. Meta-analysis for complete healing rate in patients with diabetic foot ulcers compared between rhEGF and control groups. CI, confidence interval; df, degrees of freedom; rhEGF, recombinant human epidermal growth factor.

Int J Low Extrem Wounds 2016; 15:120–125

Table 3. Summary of Adverse Events.

Author (Year)	Treatment Groups	Number of Patients	Adverse Events			
			Infection	Pain	Cellulitis	Osteomyelitis
Tsang et al (2003)[14]	Placebo + SOC	19	—	—	—	1
	0.02% rhEGF + SOC	21	—	—	—	1
	0.04% rhEGF + SOC	21	—	—	—	—
Fernandez-Montequin et al (2009)[13]	Placebo + SOC	48	2	20	—	
	25 µg rhEGF + SOC	48	4	13	—	
	75 µg rhEGF + SOC	53	4	13	—	
Gomez-Villa et al (2014)[12]	Placebo + SOC	17	—	16	—	—
	75 µg of rhEGF + SOC	17	—	14	—	—
Singla et al (2014)[11]	Betadine dressing	25	—	—	2	—
	Beta-urogastrone (rhEGF) gel	25	—	—	1	—

Abbreviations: rhEGF, recombinant human epidermal growth factor; SOC, standard of care.

Table 2 Clinical trials of PDGF in diabetic foot ulcers.

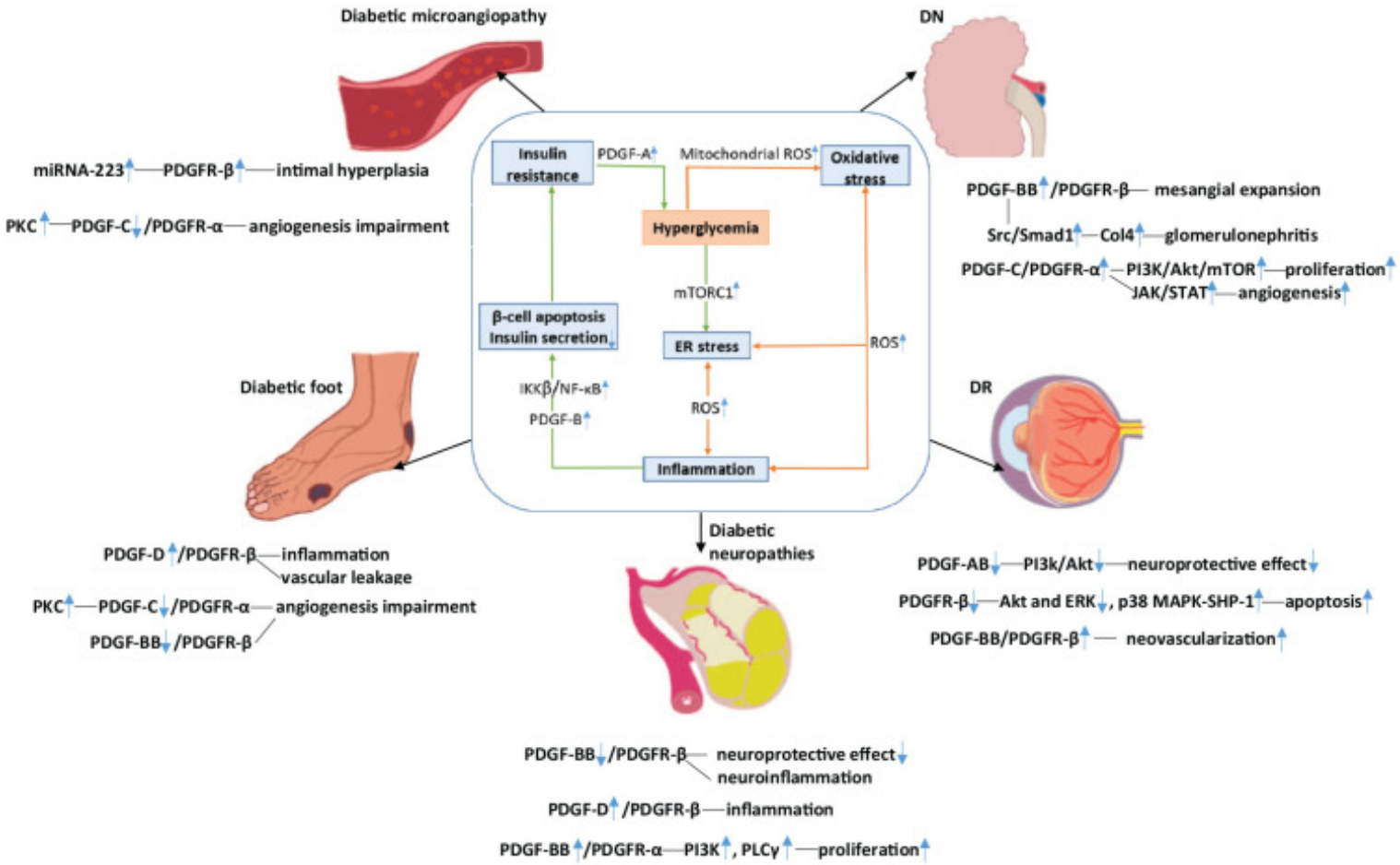
Platelet-derived growth factor

Author	Year	Study design	Comparison	Main findings
Steed	1995	Double blind placebo controlled	Topical PDGF gel 30 µg/g vs. placebo	Complete ulcer closure at 20 weeks: 48% vs. 25%, p = 0.01
Wieman	1998	Double blind placebo controlled	Topical PDGF gel 100 µg/g vs. 30 vs. µg/g vs. placebo	Complete ulcer closure: 49.5% vs. 36% vs. 35%, p = 0.007 Mean time to heal: 86 days (100 µg/g) vs. 127 days (placebo)
D'Hemercourt	1998	Randomized double-blind placebo-controlled	Topical PDGF gel 100 µg/g vs. carboxymethylcellulose gel vs. good ulcer care	Complete ulcer closure: 44.1% vs. 35.7% vs. 22%
Embil	2000	Phase IIIB open-label	Safety of topical PDGF gel 100 µg/g	Complete ulcer closure: 57.5% Mean time to heal: 63 days
Smiell	1999	Meta-analysis*	Topical PDGF gel 100 µg/g vs. placebo	Complete ulcer closure: 50% vs. 36%, p = 0.0007 Mean time to heal: 14.1 weeks vs. 20.1 weeks, p = 0.01

Notes: *Meta-analysis of the studies by Steed (1995), Wieman (1998), D'Hemercourt (1998), and Embil (2000).

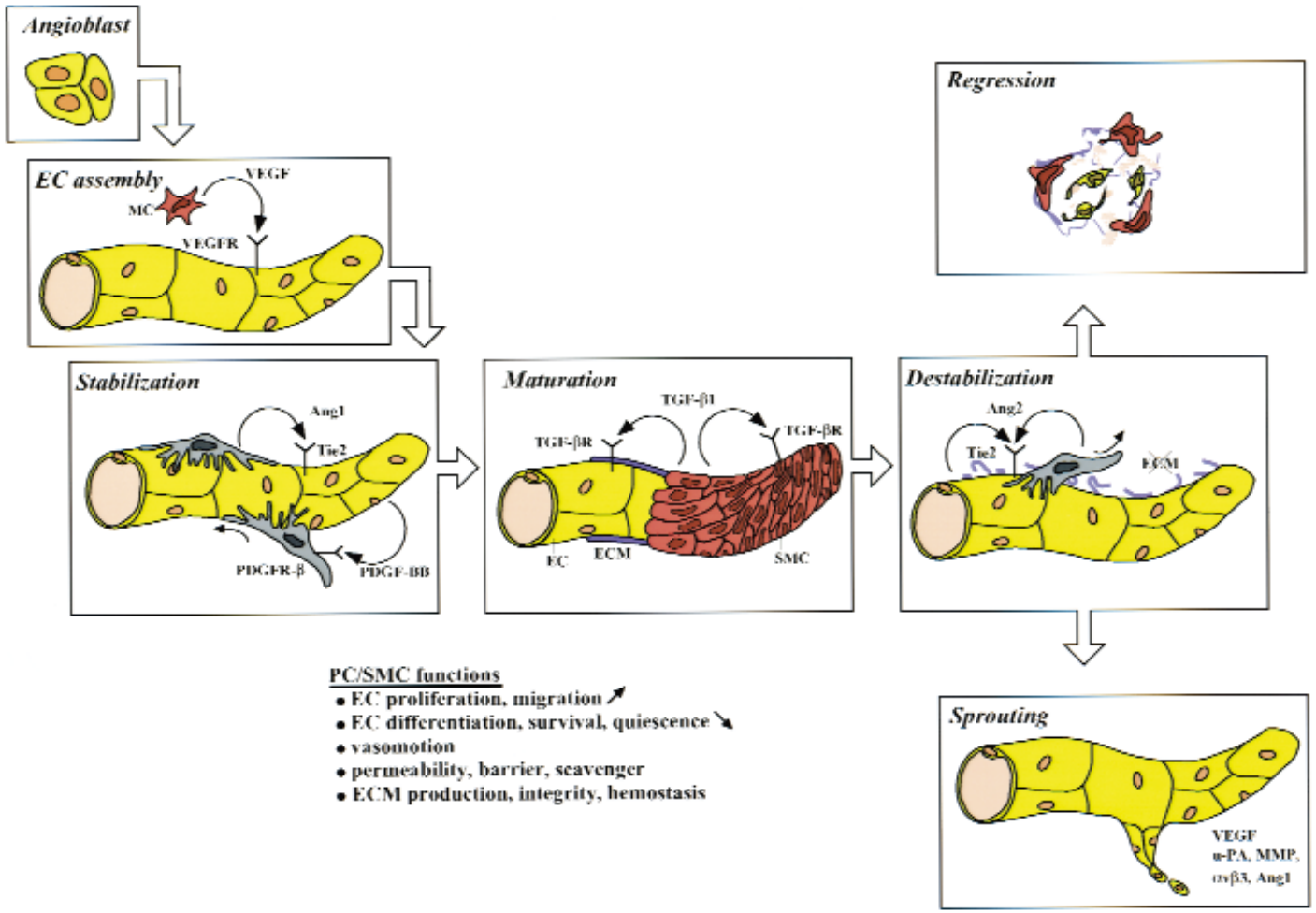
Expert Opin Biol Ther 2:211–218

Diverse signalling pathways targeting PDGFs-related diabetes mellitus



Diab Vasc Dis Res. 2020; 17(4): 1479164120942119.

PDGF and angiogenesis



Nature Medicine . 2000;6(3); 389-394

Approaches to solve the clinical problems

- Single/ dual growth factors
- cytokine stimulators/inhibitors
- cytokine matrix metalloproteinase inhibitors
- gene and stem cell therapy
- extracellular matrix and angiogenesis stimulators

- ✓Increase healing velocity rate
- ✓Decrease recurrence rate
- ✓safe and effective

- EGF achieved a significantly higher complete healing rate than placebo after four weeks of treatment, with relative risk (RR): 3.04 (0.50, 18.44) and heterogeneity (Chi2 = 6.46, df = 2 (P = 0.04) I2 = 69 %).
- Notably, the healing frequency in the placebo group was 17%, whereas the healing frequency in the epidermal growth factor group was 34%.
- Likewise, after eight weeks of treatment, the relative risk and heterogeneity were RR: 2.59 (1.42, 4.72) and (Chi2 =7.92, df= 4 (p= 0.09): I2= 49%), respectively.
- Moreover, the risk ratio at 12 weeks was RR: 1.01 (0.42, 2.46), and heterogeneity was (Chi2 =8.55, df= 2 (p= 0.01): I2= 77%)

Int Wound J . 2020;17(4):1062-1073. *F1000Research 2023, 11:773 Last updated: 19 OCT 2023*