Palermo-Mondello 19 Ottobre 2012

Update in Aferesi Terapeutica:
AFERESI e PIEDE DIABETICO

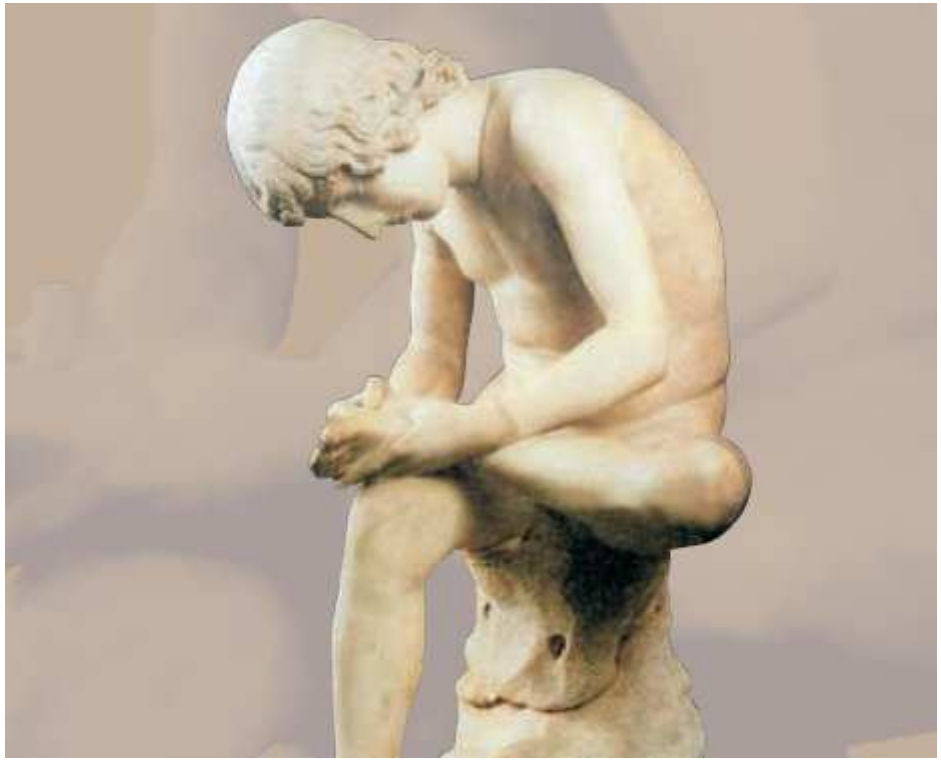
Maria Grazia Zenti

Endocrinologia e Malattie Metaboliche

AOUI Verona

- Piede diabetico: meccanismi patogenetici

- LDL-aferesi nel trattamento del piede diabetico



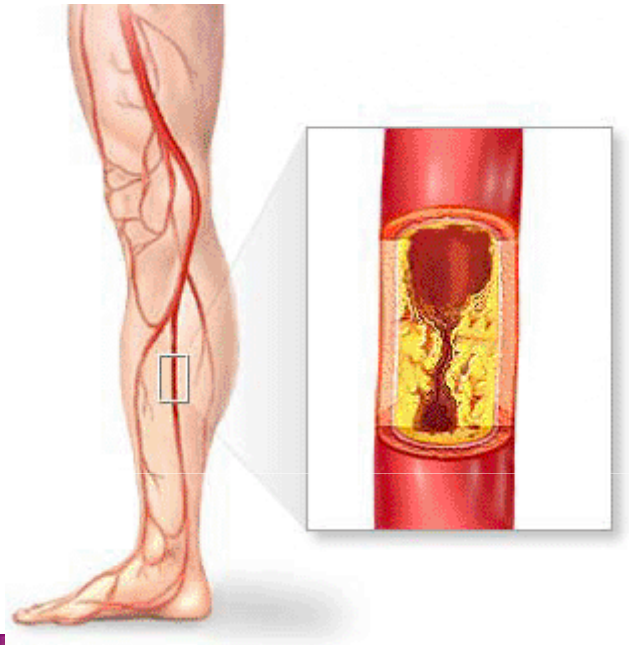
Pathophysiology of ischemic lesion in diabetic foot syndrome

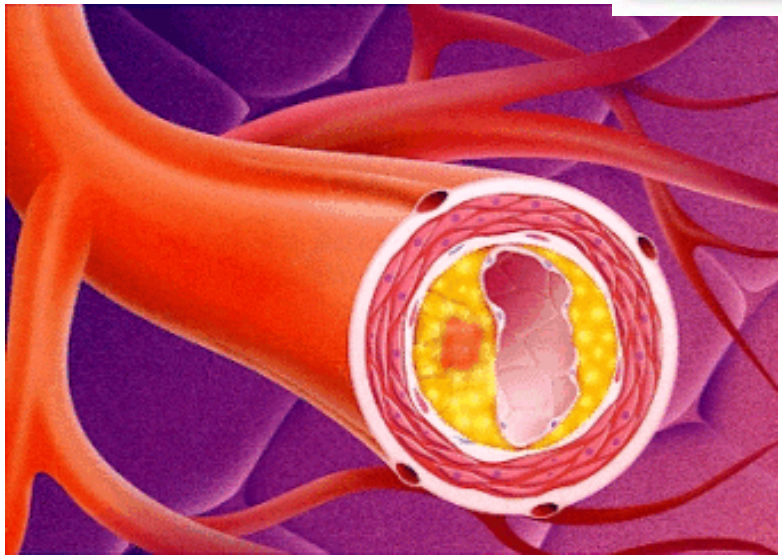
Macrovascular PAD

↓perfusion pressure

↓endothelial function

↓shear rate





Pathophysiology of ischemic lesion in diabetic foot syndrome

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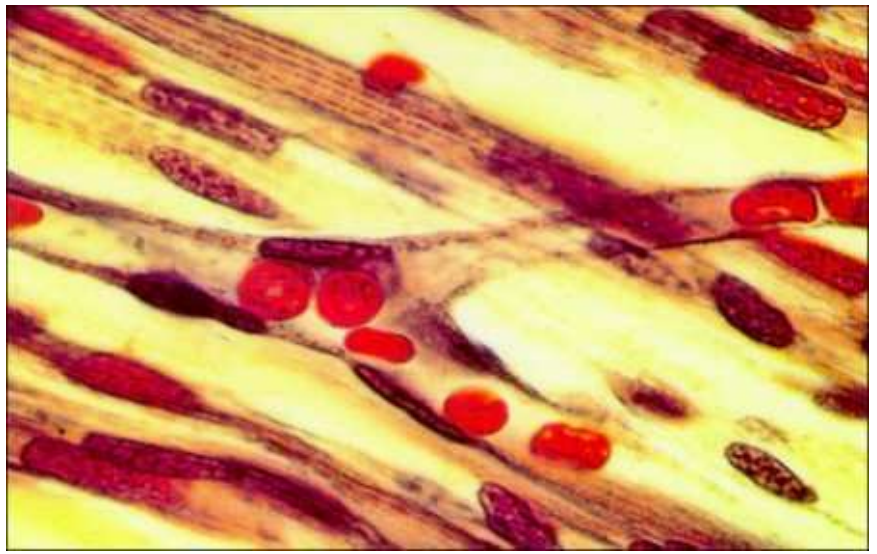
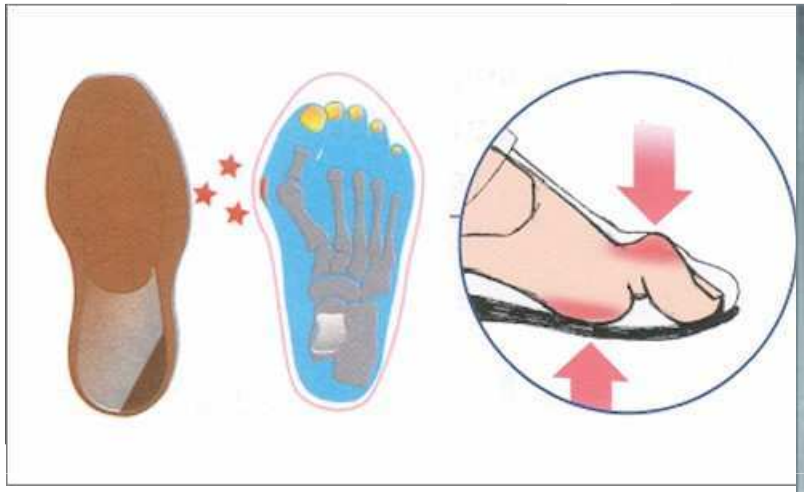
Microvascular disease of skin and muscle

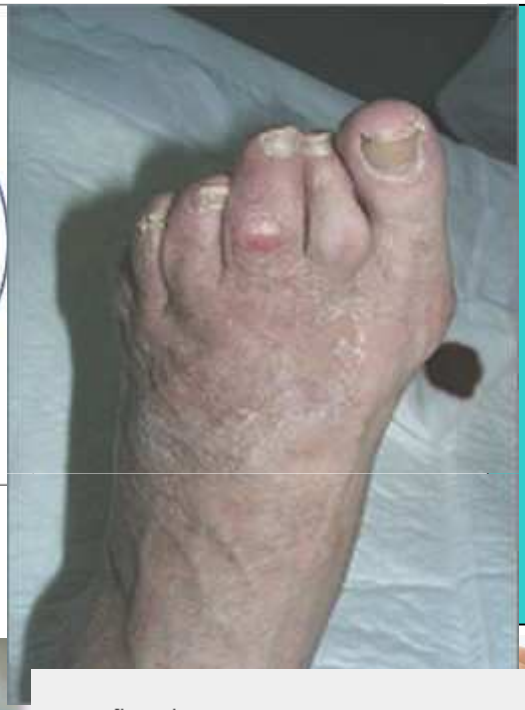
↓perfusion pressure & shear rate

↑plasma viscosity



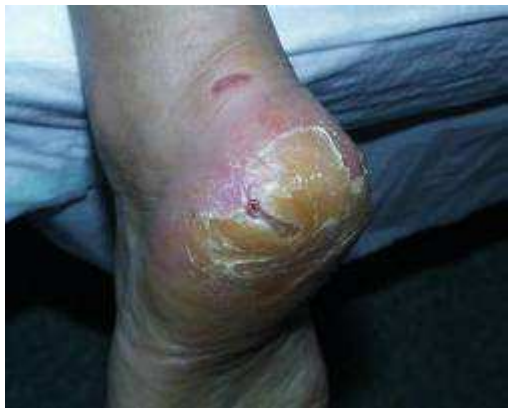
Pathophysiology of ischemic lesion in diabetic foot syndrome

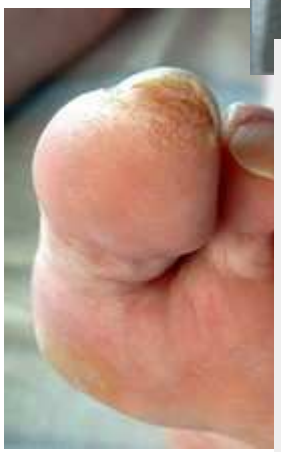


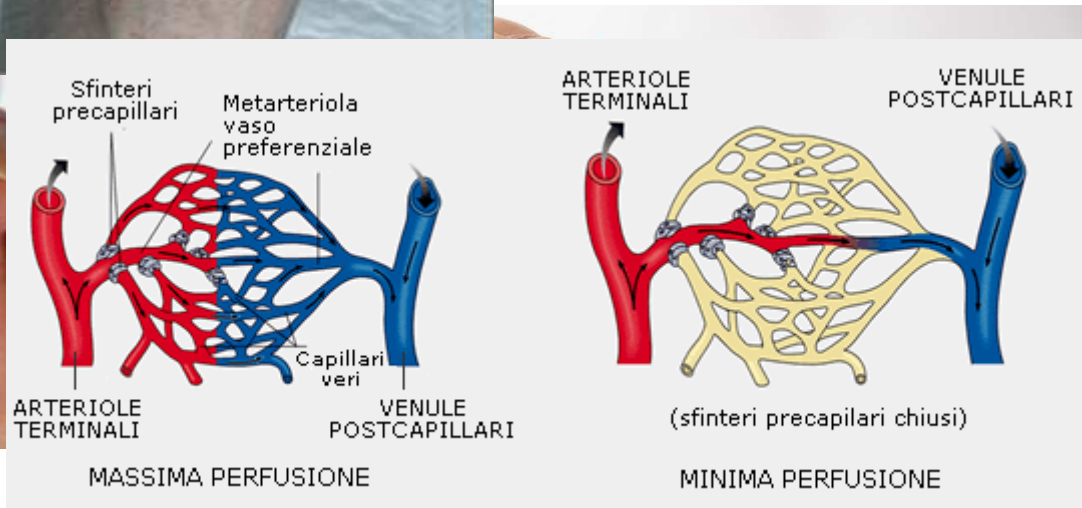


Peripheral Neuropathy

- loss of protective sensation
-structural foot Deformity
- loss of sweating, dry fissured skin and increased arteriovenous shunting







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↑plasma viscosity

Peripheral Neuropathy

- loss of protective sensation

-structural foot Deformity

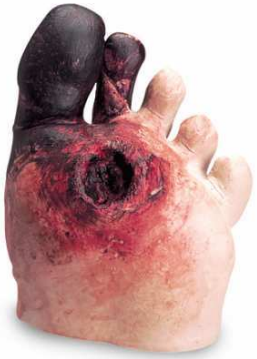
- loss of sweating, dry fissured skin and increased arteriovenous shunting

infection

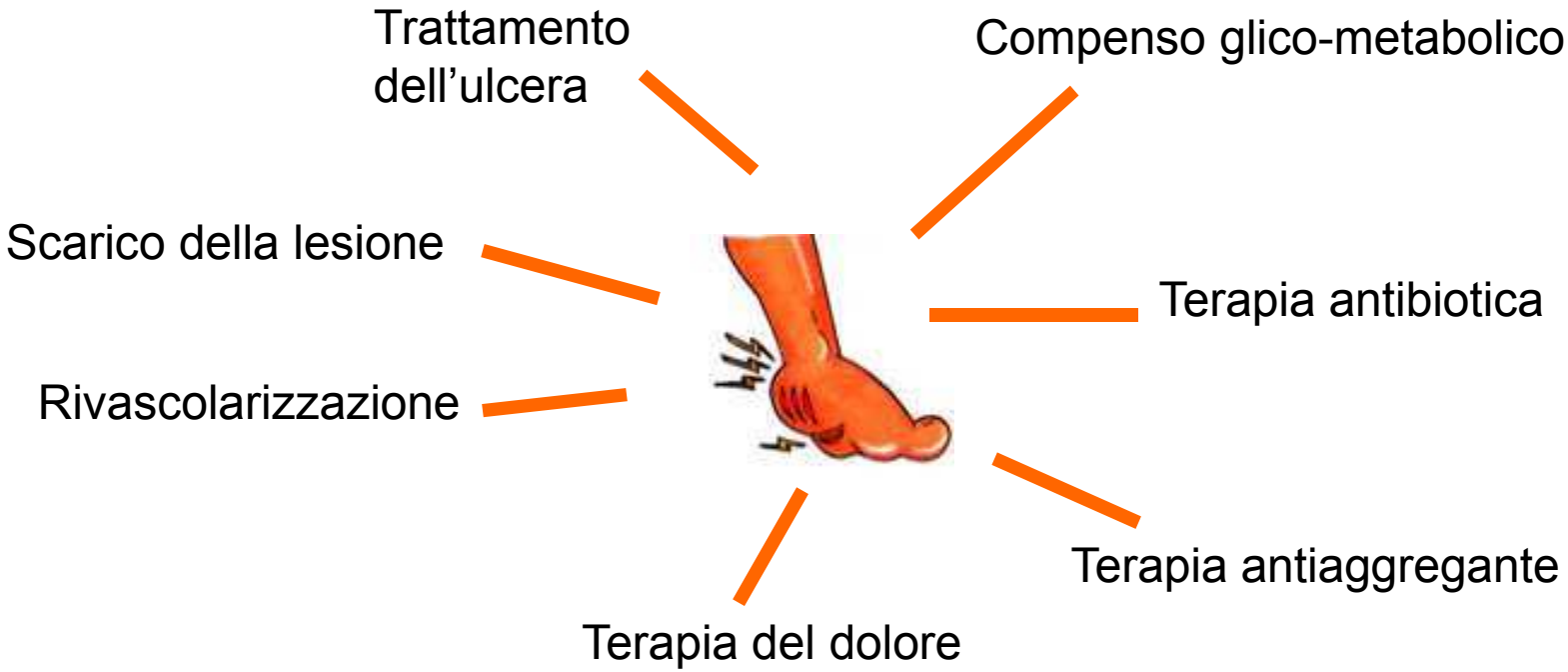
↓capillary blood flow

↓oxygen and nutritional supply

→Ischemic lesion



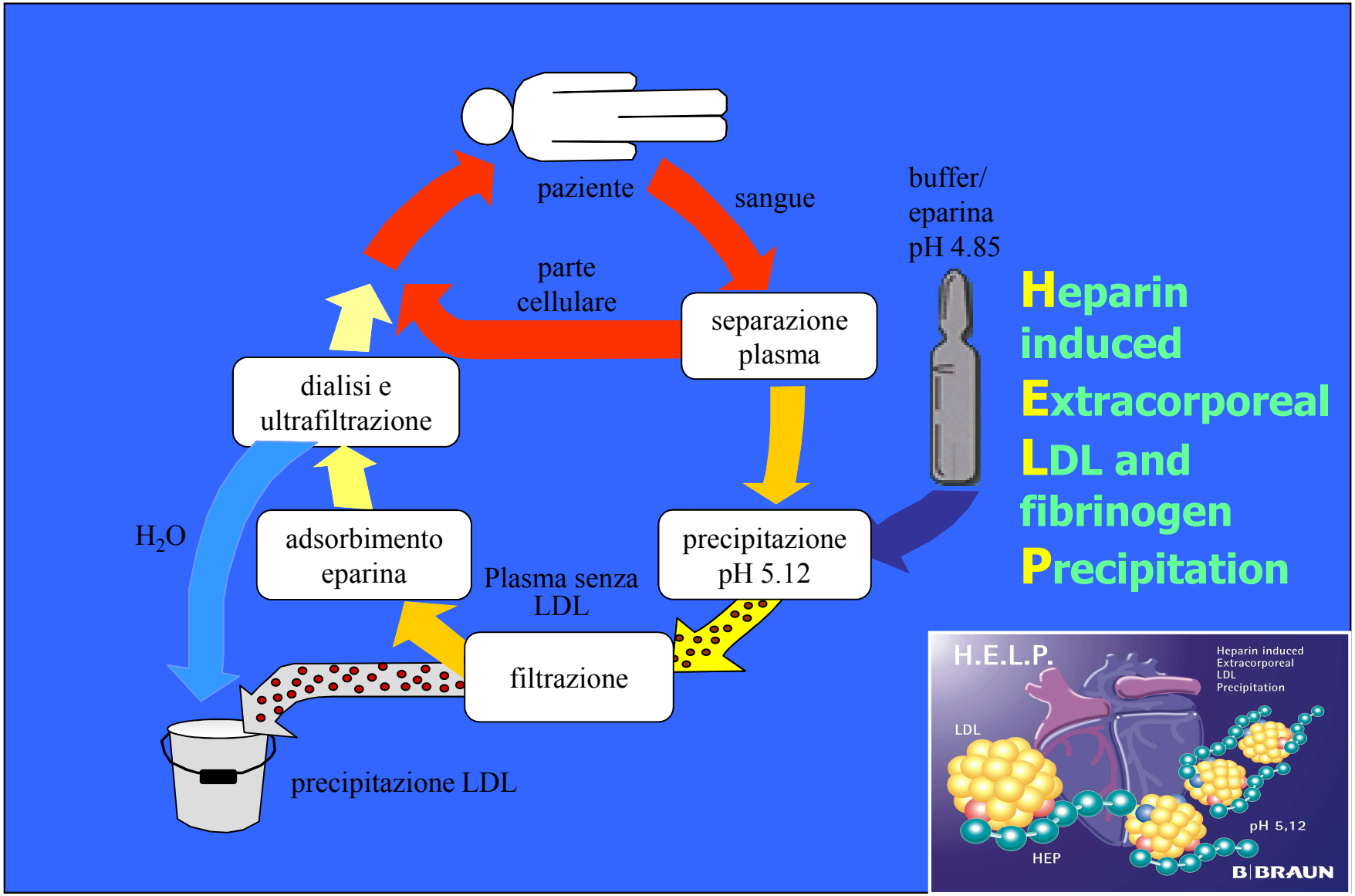
Trattamento del piede diabetico



LDL-Aferesi

Trattamento Multidisciplinare

Schema dei flussi dell'LDL-aferesi, sistema H.E.L.P.



Effetti of a single HELP apheresis on vascular homeostasis

Lipid metabolism		Coagulation		Hemorheology	
Total cholesterol	–52%	Fibrinogen	–56%	Plasma viscosity	–14%
LDL cholesterol	–56%	Thrombin	–55%	Erythrocyte aggregability	–60%
HDL cholesterol	+14%	Factor V	-57%	Thrombocyte aggregability	–66%
VLDL cholesterol	–52%	Factor VII	-35%	Peripheral muscle oxygenation	+43%
Lp(a)	–52%	vWF	–56%	Coronary flow reserve	+14%
Triglycerides	–50%	AT III	–25%	Cerebral CO_2 reactivity	+14%

Da B. R. Jaeger Therapeutic Apheresis 2001.

Acute and chronic effects of lipid apheresis in atherosclerotic vascular disease

Immediate affects:

improvement of endothelial function in macro- and microcirculation

- ►activation of vasodilatory substances and increase in the bioavailability of endogenous vasodilators
- ►reduction in susceptibility of LDL to oxidation and suppression of oxidative stress
- ►inhibition of activation of the coagulation system

Chronic affects:

reduction of cardiovascular event rate

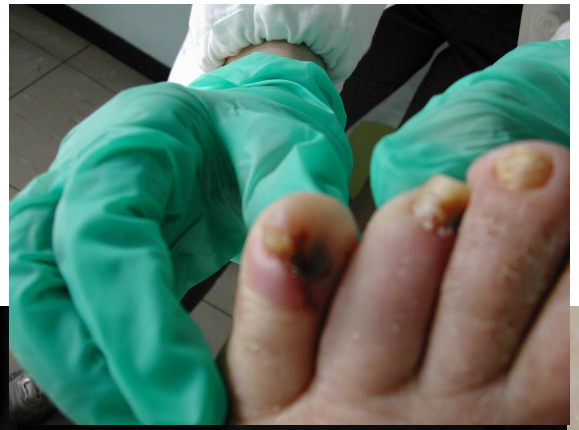
- ►suppression of progression of atherosclerotic lesions
- ►regression of atherosclerotic lesions
- ►development of new collaterals by stimulation of neoangiogenesis

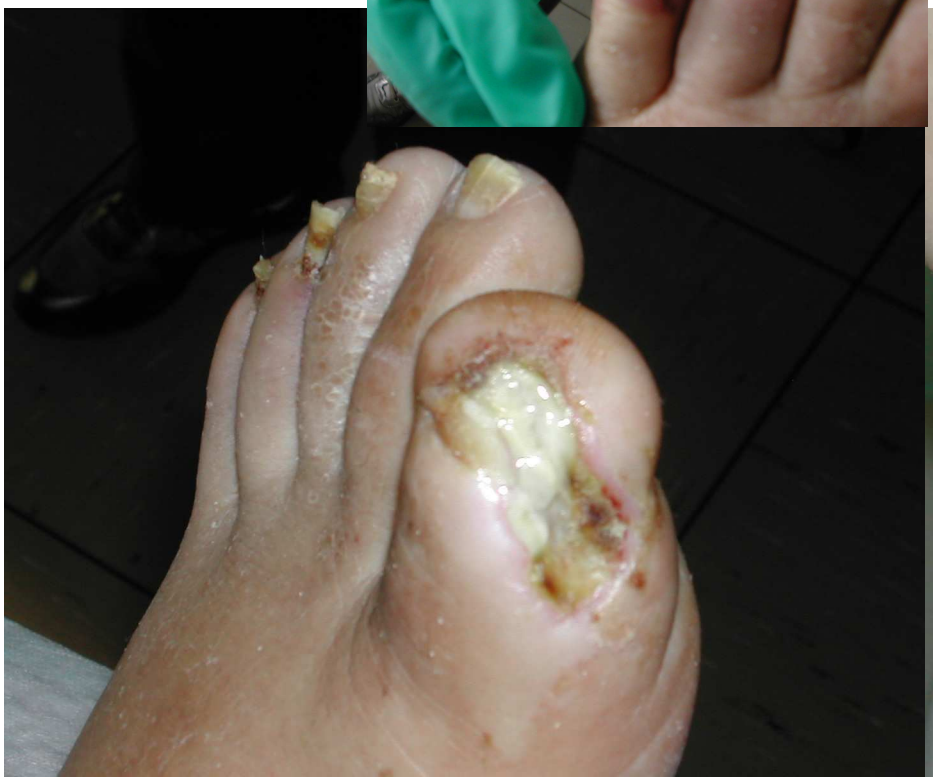
HELP-aferesi nel trattamento del piede diabetico:

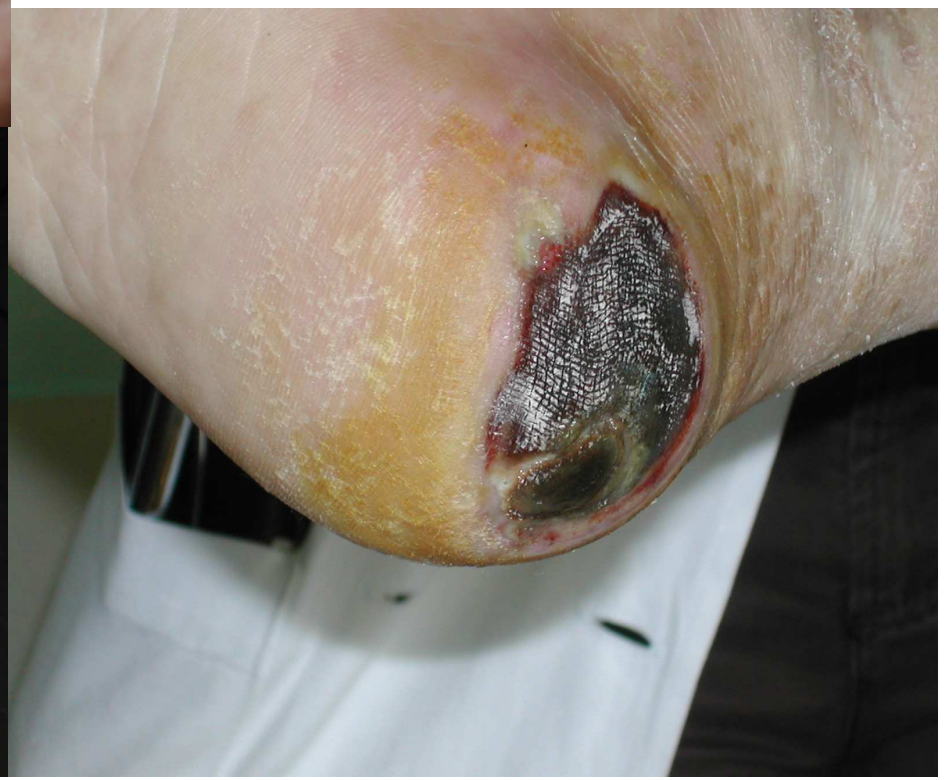
La nostra esperienza….

M, 65 anni, BMI 26 kg/m^2
PAO 110/70 mmHg, Ex fumatore
Diabete tipo 2 noto da 5 aa (insulino-trattato da 3 aa)
CHD nota da 3 aa (IMA e successivo triplice by-pass Aorto-coronarico)
Vasculopatia arti inferiori nota da 3 aa

left







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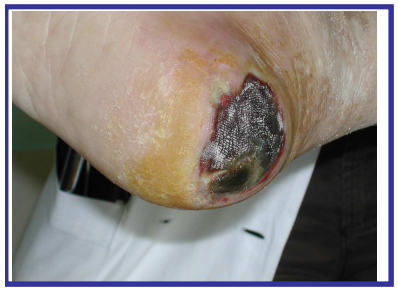

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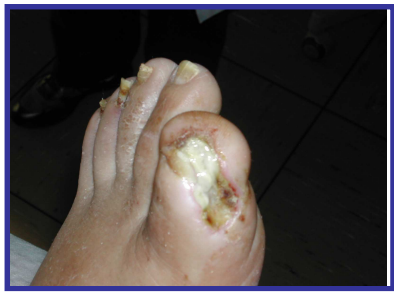
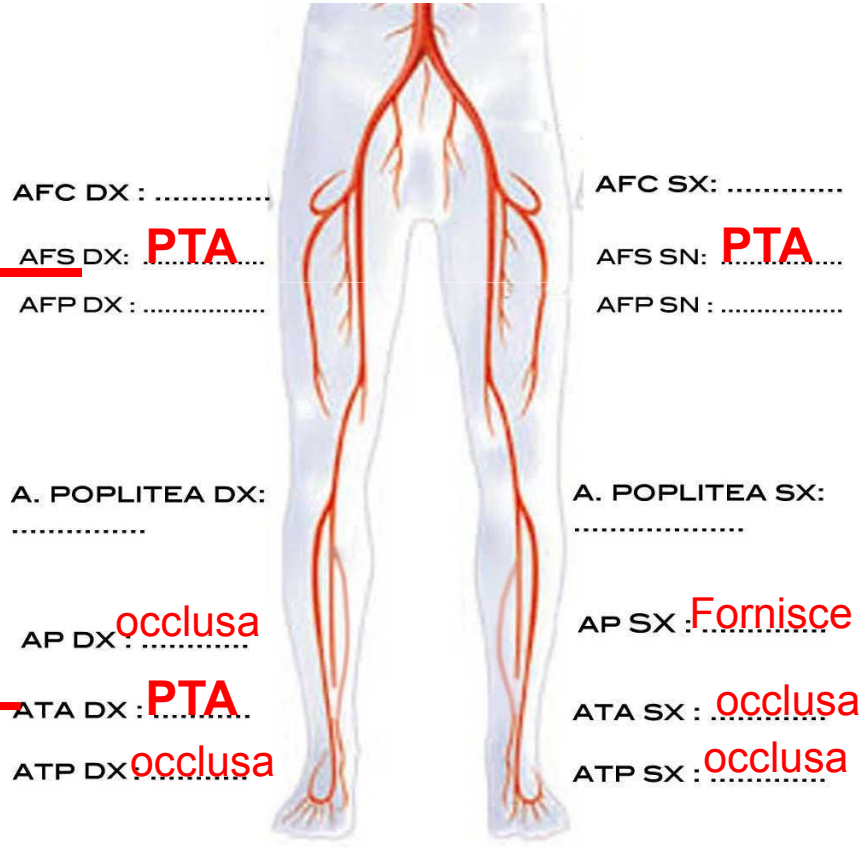


plurime stenosi nel tratto prossimale, l'a. si occlude per breve tratto al canale degli adduttori.



multiple steno-occlusioni, più evidenti nel tratto prossimale

Occlusa la pedidia risultando il piede vascolarizzato da collaterali

Trattamento

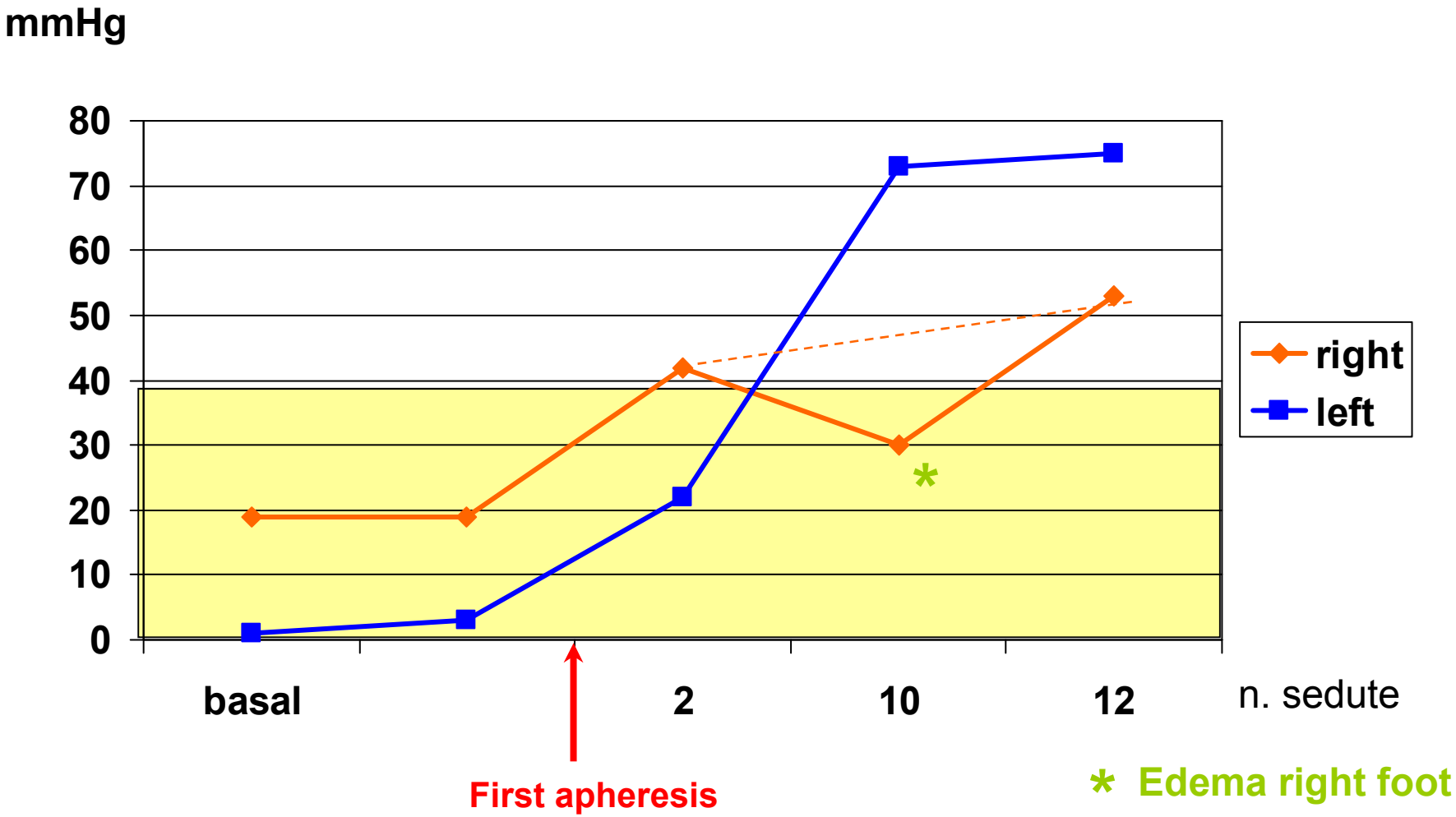
- rivascolarizzazione percutanea periferica bilaterale
- amputazione falange distale dell'alluce sx ed escarectomia del tallone dx
- terapia antibiotica mirata (sulla base dei tamponi)
- stretto controllo glicemico
- terapia medica-nutrizionale di supporto
- medicazioni delle ulcere presso l'ambulatorio dedicato per la cura del piede diabetico

progressivo peggioramento di entrambe le lesioni

LDL aferesi:

2 trattamenti la prima settimana seguiti da 1 trattamento/settimana per un totale di 12 sedute

$TcPO_2$ before, 2, 10 and 12 weeks after initiating LDL-apheresis.



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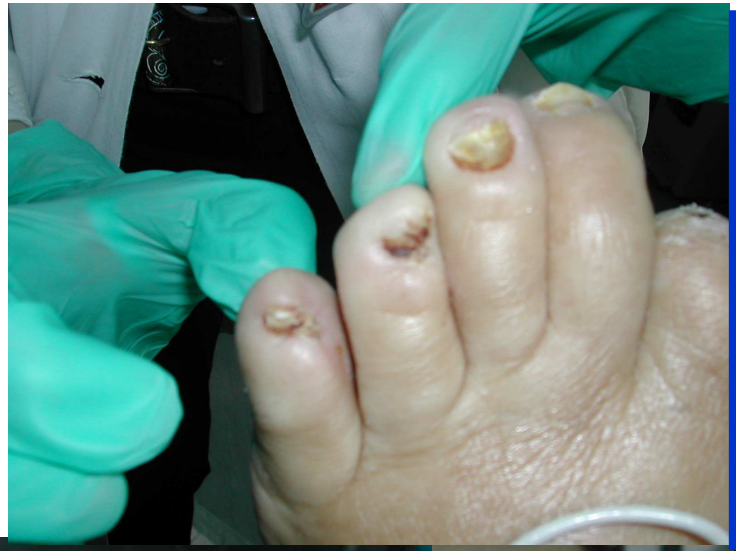
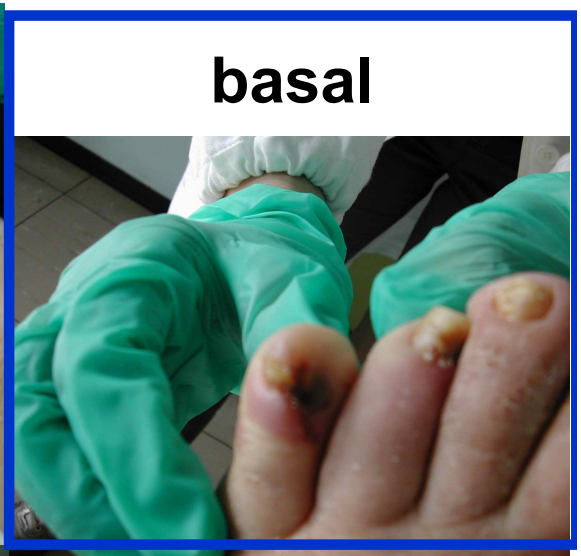
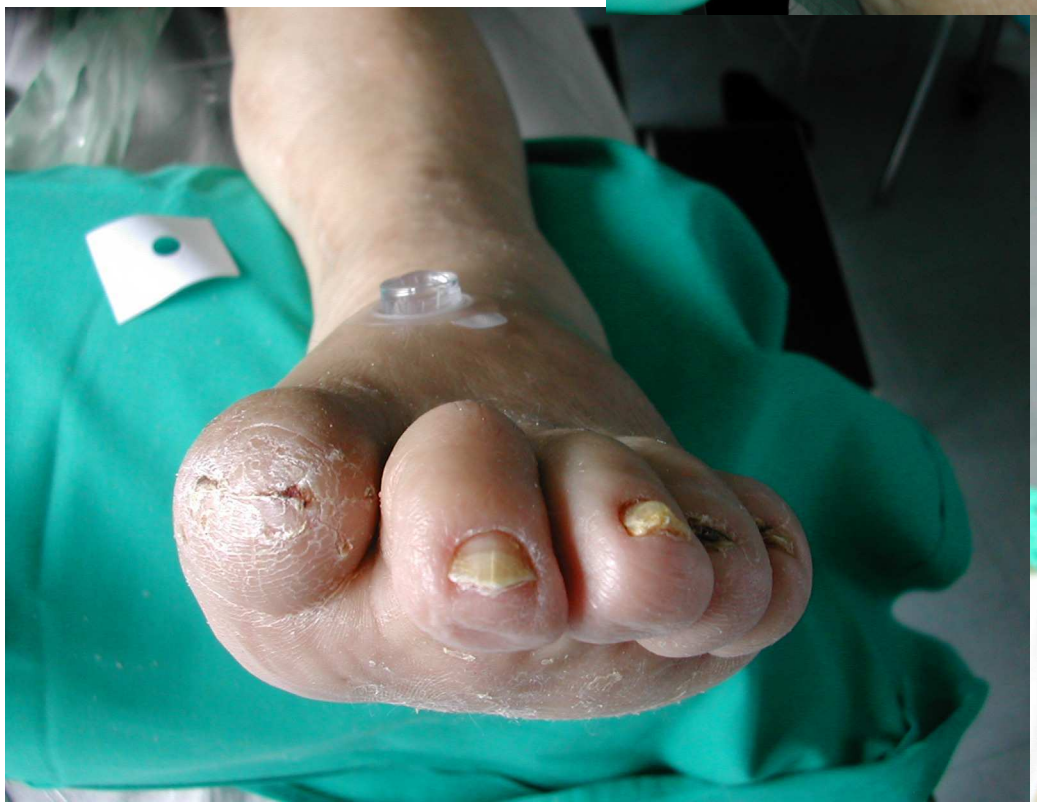
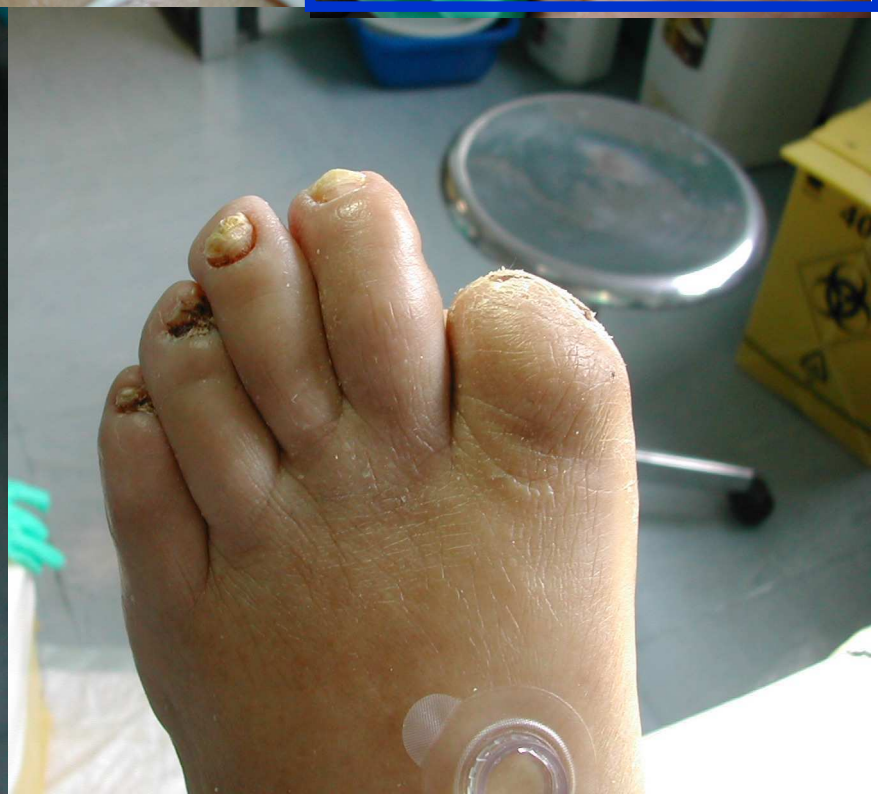
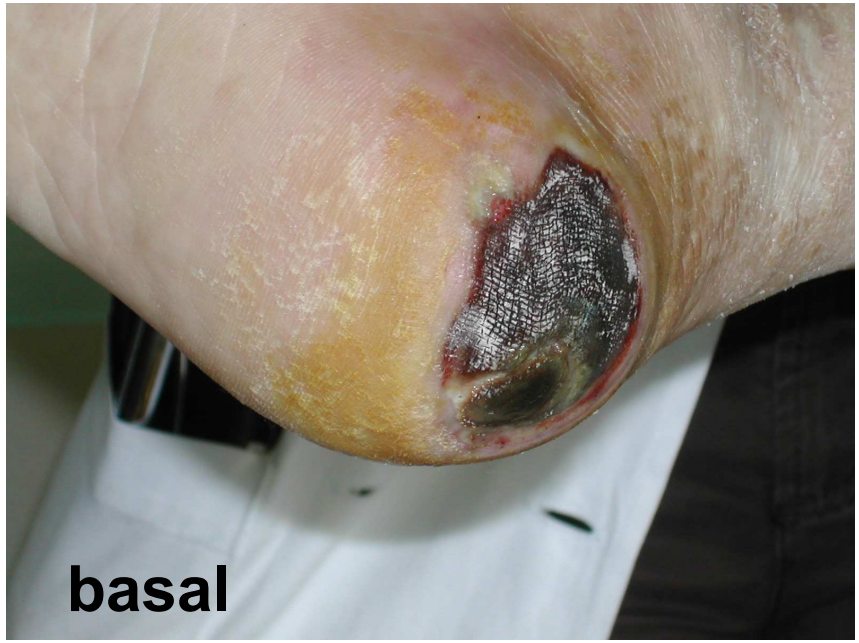
2nd month follow-up

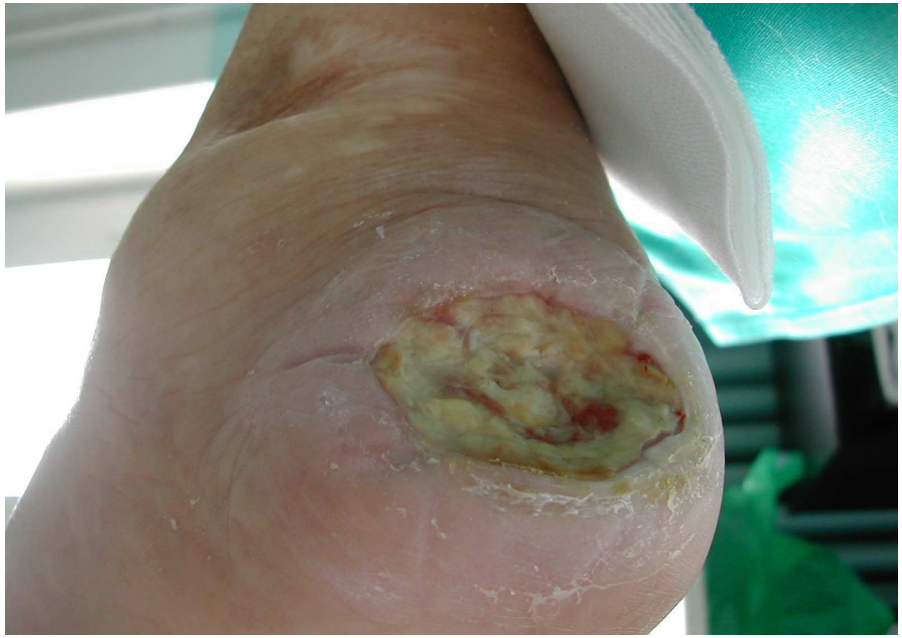






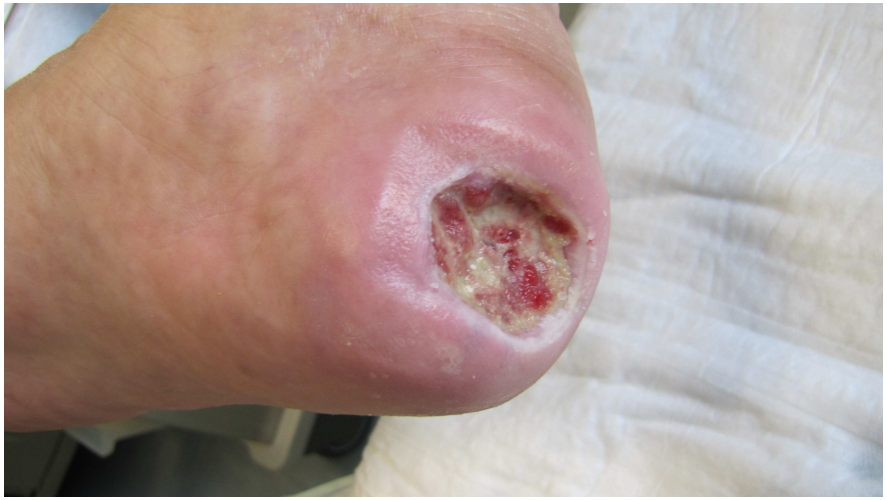




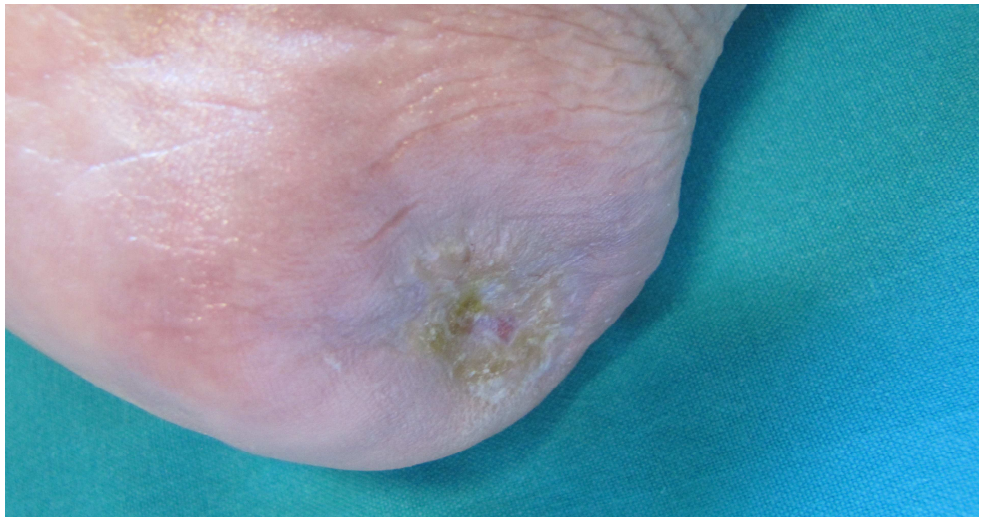


2nd month follow-up

right



3rd month follow-up

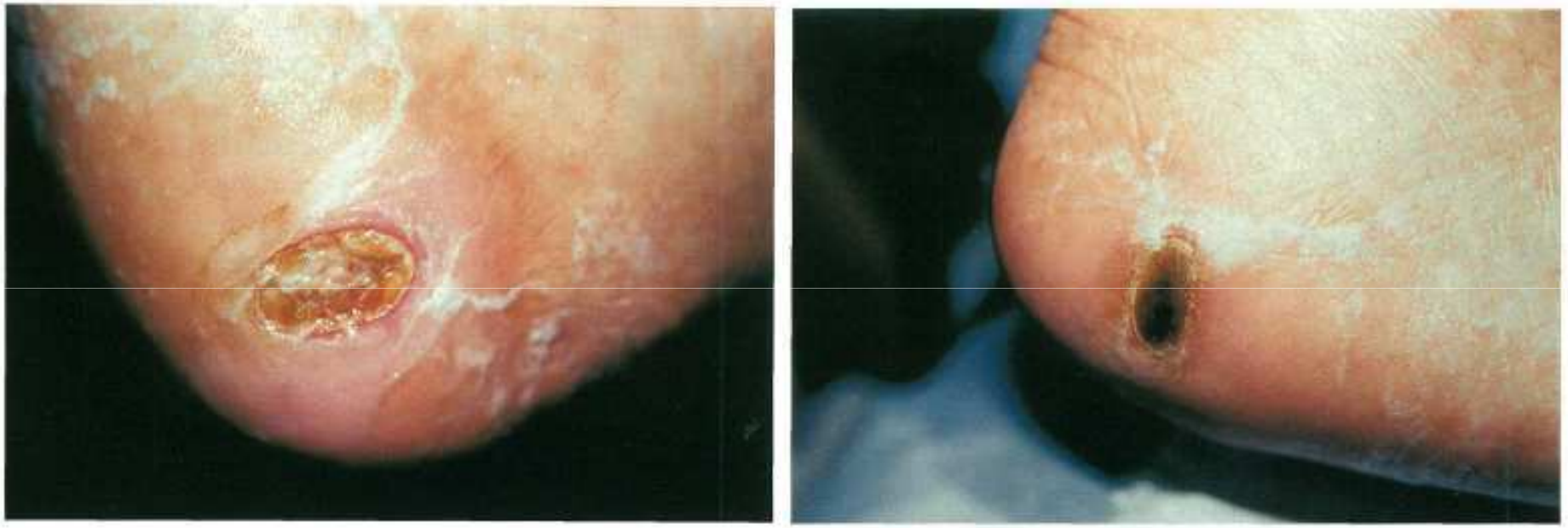


7 th month follow-up

LDL aferesi nel Paziente diabetico con Arteriopatia periferica e Piede diabetico

Clinical Trial of Low Density Lipoprotein-Apheresis for Treatment of Diabetic Gangrene

Takashi IIZUKA, Haruyo TAKEDA, Hiromi INOUE, Terukazu MIYAMOTO, Hiroko ITO, Masao OMURA, Hiroyuki TSUJI, Shyozo CHIBA and Tetsuo NISHIKAWA



A B

M 68 aa

10 trattamenti aferetici in 1 mese

Iizuka 1997

Therapeutic Apheresis and Dialysis
9(6):473–481, Blackwell Publishing Asia Pty Ltd

Rheopheresis in Patients with Critical Limb Ischemia—Results of an Open Label Prospective Pilot Trial

Reinhard Klingel,[1,2] Bernard Erdtracht,[3] Victor Gauss,[2] Andreas Piazolo,[4] Patrick Mausfeld-Lafdhiya,[1] and Curt Diehm[5]

[1]*Apheresis Research Institute, Cologne,* [2]*1st Department of Internal Medicine, University of Mainz, Mainz,* [3]*Rheopheresis Center Cologne, Cologne,* [4]*Center for Dialysis, and* [5]*Department of Internal Medicine, Clinic Karlsberg Langensteinbach, Langensteinbach, Germany*

8 patients with type 2 diabetes mellitus and non-healing foot ulcers caused by severe **ischemic diabetic foot syndrome**
7 rheopheresis session in a time span of **11 weeks**

TABLE 4. *Changes in wound healing as assessed using the diabetic wound classification system of Wagner*

	improved				unchanged		deteriorated	
Patient Number	1	2	4	6	5	8	3	7
WS Baseline (week 0)	2	2	2	2	2	2	5	4
WS Final (week 12)	0	1	0	1	2	2	5	5
WS Follow-up (week 24)	0	1	0	1	not done	2	not done	not done
Amputation	no	no	no	no	yes	yes	yes	yes
Level of amputation					minor	minor	major	major

WS, Wagner Stage.

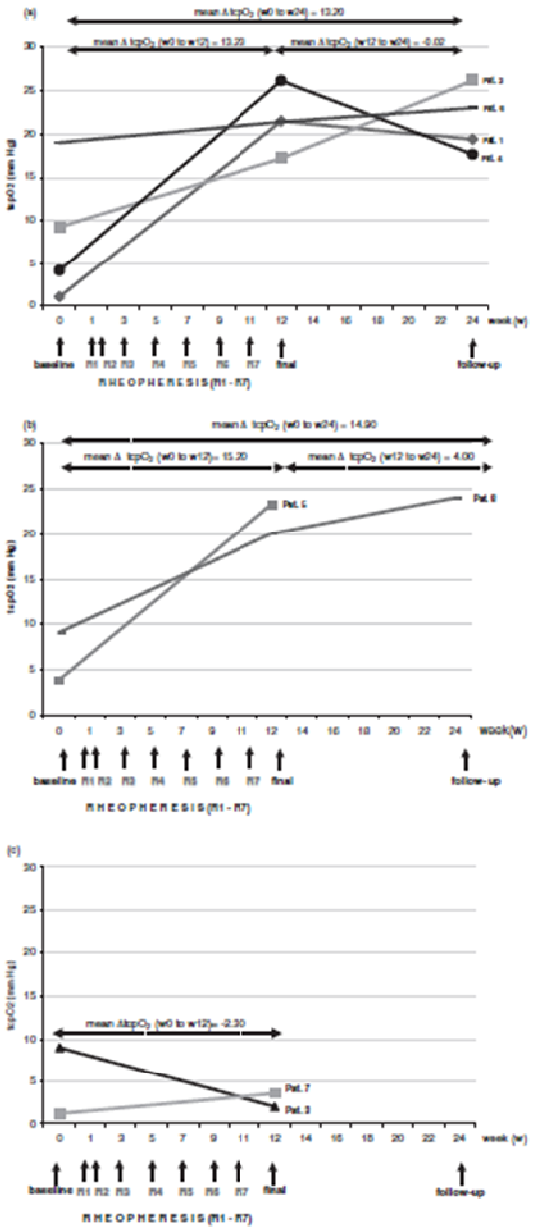


FIG. 3. (a) Change in $tcPO_2$ in four patients with *improvement* of wound healing as assessed by the Wagner criteria. (b) Change in $tcPO_2$ in two patients with *no change* of wound healing as assessed by the Wagner criteria. (c) Change in $tcPO_2$ in two patients with *deterioration* of wound healing as assessed by the Wagner criteria.

a) Change in tcPO2 in 4 patients with ***improvement*** of wound healing as assessed by the Wagner criteria

b) Change in tcPO2 in 2patients with ***no change*** of wound healing as assessed by the Wagner criteria

c) Change in tcPO2 in 2 patients with ***deteroration*** of wound healing as assessed by the Wagner criteria

R klingel TAD 2003

Therapeutic Apheresis
5(5):335–339, Blackwell Science, Inc.

Fibrinogen Adsorption in the Diabetic Foot Syndrome and Peripheral Arterial Occlusive Disease: First Clinical Experience

*Werner O. Richter, †Peter Jahn, ‡Norbert Jung, §Erika Nielebock, and ‖Hauke Tachezy

Institute for Lipid Metabolism and Hemorheology, Windach; †Dialysis Center, Elmshorn; ‡Dialysis Center, Mühlhausen; §Dialysis Center, Magdeburg; and ‖Dialysis Center, Hamburg, Germany

treatment were scheduled on Days 1,2,4,6,8,10,13,16,19,22, 25,28

TABLE 1. *Patients treated by fibrinogen adsorption: baseline characteristics*

Patient Number	Initials	Sex	Age (years)	Body weight (kg)	Body size (cm)	Diagnosis
1	SU	Male	67	111	180	2 ulcers right foot for 2 years. Diabetes mellitus since 1982.
2	HS	Male	61	88	179	Several ulcers left and right foot due to angiographically proven macroangiopathy. No tendency of healing for several months. Diabetes mellitus for 20 years, hemodialysis for 2 years.
3	HK	Male	68	75	170	Partial amputation of the left first toe 4 weeks ago, insufficient wound healing, pain. Amputation of the right forefoot 17 months ago. Diabetes mellitus for 50 years, hemodialysis for 2 years.
4	WO	Male	48	116	186	Amputation of the right forefoot 6 weeks ago, insufficient wound healing, pain. Diabetes mellitus for 15 years, hemodialysis for 3 years.
5	WH	Male	51	78	180	Peripheral arterial occlusive disease, amputation of the left fifth toe, 3 ulcers left shank, hemodialysis for 10 years.
6	ES	Female	67	94	169	Partial gangrene right fourth toe, 1 ulcer right shank. Diabetes mellitus for 10 years.
7	FW	Male	75	85	176	Necroses on several right and left toes. Diabetes mellitus for 25 years.
8	SK	Male	71	80	181	Gangrene of the complete right forefoot. Diabetes mellitus for 30 years.
9	GR	Female	59	45	154	Amputation of right fourth toe 3 weeks ago, insufficient wound healing. Renal transplantation 27 months ago.
10	RM	Female	61	81	158	Nonhealing ulcers left and right foot and shank. Diabetes mellitus for 20 years, hemodialysis for 6 years. Replacement of mitral valve 4 years ago. Anticoagulation by phenprocoumon.

Wound healing in 8 of the 10 patients

TABLE 3. *Patients treated by fibrinogen adsorption: number and efficacy of treatments*

Number	Initials	Number of treatments	Amount of plasma treated[a] (ml)	Initial fibrinogen concentration (mg/dl)	Fibrinogen concentration after adsorption[a] (mg/dl)	Clinical outcome
1	SU	22	5,930 ± 1,110	478	106.0 ± 20.7	Wound healing.
2	HS	26	4,720 ± 1,280	629	122.0 ± 24.1	Amputation of two gangrenous toes left (second and fourth toe) at the tenth day of treatment. Antibiotics had been withdrawn by the patient at the first day of treatment. After twenty-sixth therapy: Right foot: Granulation covering 80% of wound ground. Left foot: 90% decrease of wound area.
3	HK	14	3,670 ± 320	493	119.0 ± 19.7	Wound healing. Pain relief after first treatment.
4	WO	12	4,400 ± 750	534	177.0 ± 46.2	Wound occlusion, pain relief.
5	WH	12	5,920 ± 910	675	184.0 ± 79.6	Wound healing.
6	ES	12	1,825 ± 460	426	123.0 ± 43.0	Wound occlusion.
7	FW	12	1,960 ± 270	262	79.0 ± 9.9	Wound occlusion.
8	SK	6	2,960 ± 290	240	81.0 ± 20.4	As after sixth treatment, signs of inflammation persisted; amputation of the forefoot was performed.
9	GR	13	1,440 ± 550	243	81.0 ± 17.4	Wound healing.
10	RM	15	4,530 ± 1,290	757	133.0 ± 53.0	Wound healing. Demarcation of a necrotic areal (∅ 4 cm), left heel.

[a] Mean values ± SD (first treatment was not included because the aim was to lower fibrinogen to <250 mg/dl).

Richter 2001

Heparin-induced Extracorporal LDL Precipitation (H.E.L.P) in Diabetic Foot Syndrome – Preventive and Regenerative Potential?

Authors: H. Rietzsch[1], I. Panzner[2], T. Selisko[1], U. Julius[1], N. Jabs[1], M. Reimann[1], E. Bonifacio[3], M. Bornhäuser[4], S. R. Bornstein[1]

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[2] Technical University of Dresden, Department of Orthopedics
[3] Technical University of Dresden, Center for Regenerative Therapies
[4] Technical University of Dresden, Department of Medicine I, Dresden, Germany

HMR/531-1r/9.6.2008/Macmillan

17 diabetic patients with septic foot lesions (Wagner III-V)

Severe angiopathy which did not qualify them for revascularization

Systemic infection (leucocytosis, lymphadenitis)

High risk for amputation

Plasma fibrinogen > 6g/L

Number HELP treatment 1-7 (→fibrinogen <3 g/L)

Follow up for 2 to 73 months

Table 1 Baseline characteristics of patients before H.E.L.P. apheresis and outcome after conclusion of in patient treatment

Patient no.	Before heparin-induced extracorporal LDL precipitation				After heparin-induced extracorporal LDL precipitation			No of H.E.L.P. apheresis
	Sex/age (year)	HbA1c (%)	Fibrinogen (g/l)	Plasma viscosity (mPas)	Plasma viscosity (mPas)	Operation	Result	
1	M/68	9.6	8.0	n.m.	0.36	Amputation D5R	complete healing	2
2	M/68	9.1	8.3	1.73	2.60	1. Amputation D2D3L 2. Necrectomy planta	complete healing	3
3	M/47	8.2	10.0	1.71	2.10	1. Amputation D4R 2. Necrectomy	complete healing	3
4	M/65	10.5	8.9	1.34	1.99	Amputation D4L	complete healing	5
5	M/66	11.6	7.6	1.60	3.20	Amputation D4L	complete healing	1
6	M/75	12.3	8.4	n.m.	4.40	Amputation LL R	complete healing	1
7	M/76	8.4	7.7	n.m.	2.10	Amputation D1L (hallux)	complete healing	3
8	M/67	8.5	8.1	n.m.	2.50	1. Amputation D1R 2. Amputation LL R	complete healing	3
9	M/76	11.0	7.1	1.42	2.20	1. Amputation FF Lisfranc 2. Amputation FF Chopart	complete healing	4
10	F/76	7.6	10.4	1.56	3.20	1. Amputation FF Lisfranc 2. Amputation FF Chopart	complete healing	4
11	M/59	10.3	9.4	1.80	4.02	1. Amputation FF Lisfranc 2. Amputation FF Chopart	complete healing	7
12	M/53	anemia	13.4	1.98	5.30	Follow up resection Metatarsus	death after amputation	5
13	M/65	12.2	6.2	1.55	2.00	Amputation D1-D3R	complete healing	2
14	M/56	11.7	10.8	1.66	2.60	Necrectomy heel	remaining ulcer	6
15	M/55	10.6	6.9	1.68	2.60	Amputation FF L	complete healing	2
16	M/63	8.3	10.5	1.74	2.90	1. Necrectomy 2. Skin grafting	death (cardiac infarction)	2
17	M/54	7.1	6.4	1.60	2.80	1. Necrectomy 2. Joint resection D3R	complete healing	3

Abbreviations: D: distal; FF: forefoot; L: left; LL: lower-leg; n.m.: not measured; R: right

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Therapeutic Apheresis and Dialysis
9(6):473–481, Blackwell Publishing Asia Pty Ltd

Rheopheresis in Patients with Critical Limb Ischemia—Results of an Open Label Prospective Pilot Trial

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Fibrinogen Adsorption in the Diabetic Foot Syndrome and Peripheral Arterial Occlusive Disease: First Clinical Experience

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Case Report

Efficacy of Low-Density Lipoprotein Apheresis in Arteriosclerosis Obliterans of the Lower Extremities: Two Cases With Marked Alleviation of Clinical Symptoms

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Heparin-induced Extracorporal LDL Precipitation (H.E.L.P) in Diabetic Foot Syndrome – Preventive and Regenerative Potential?

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- **Casistiche piccole e non confrontabili (**case report, studi pilota**)**
- **Diversa patologia di pazienti:** diabetici vasculopatici, diabetici emodializzati, piede infetto**.**
- **Diversa gravità delle lesioni, diversa classificazione delle lesioni (**Wagner, Texas, Fontaine**)**
- **Diversi schemi di trattamento aferetico, con diversi tipi di aferesi (**fibrinogeno-aferesi, HELP, filtrazione a cascata) schemi di trattamento2 →12 trattamenti

- **Mancano studi randomizzati controllati.**

Azienda Ospedaliera Universitaria Integrata di Verona,
Comitato Etico per le Sperimentazioni

Codice studio 1953 del 25/05/2011

La LDL-aferesi nel trattamento del piede diabetico ischemico

Studio clinico **randomizzato, multicentrico, prospettico**, per verificare l'effetto del trattamento con LDL-aferesi in aggiunta alla terapia tradizionale sulla guarigione delle ulcere in pazienti con piede diabetico ischemico e vasculopatia periferica non rivascolarizzabile

HELP-Apheresis in the treatment of Diabetic Ischemic Foot (H.A.D.I.F.): A Randomized Controlled Trial

ClinicalTrials.gov Identifier: NCT01518205

Inclusion criteria:

- diabetic patients,
- M and F,
- age ≤ 80 years,
- ischemic diabetic ulcers (class I-II-III Texas wound classification System)
- vasculopathy with at least a previous event of failed revascularization (no ulcer healing).

HELP-Apheresis in the treatment of Diabetic Ischemic Foot (H.A.D.I.F.): A Randomized Controlled Trial

ClinicalTrials.gov Identifier: NCT01518205

Exclusion criteria:

- BMI > 35 kg/m2,
- malignant tumour,
- heart failure level not allowing the extracorporeal technique
- Haemodialysis

Texas Wound Classification System

	0	I	II	III
Stadio A	Lesione pre o post-ulcerativa completamente epitelizzata	Ulcera superficiale che non coinvolge tendini, capsula articolare,ossa	Ulcera profonda che interessa i tendini o la capsula articolare	Ulcera profonda che interessa l'osso o l'articolazione
Stadio B	Con infezione	Con infezione	Con infezione	Con infezione
Stadio C	Con ischemia	Con ischemia	Con ischemia	Con ischemia
Stadio D	Con infezione ed ischemia	Con infezione ed ischemia	Con infezione ed ischemia	Con infezione ed ischemia

HELP-Apheresis in the treatment of Diabetic Ischemic Foot (H.A.D.I.F.)

CONTROL ARM: Traditional Treatment

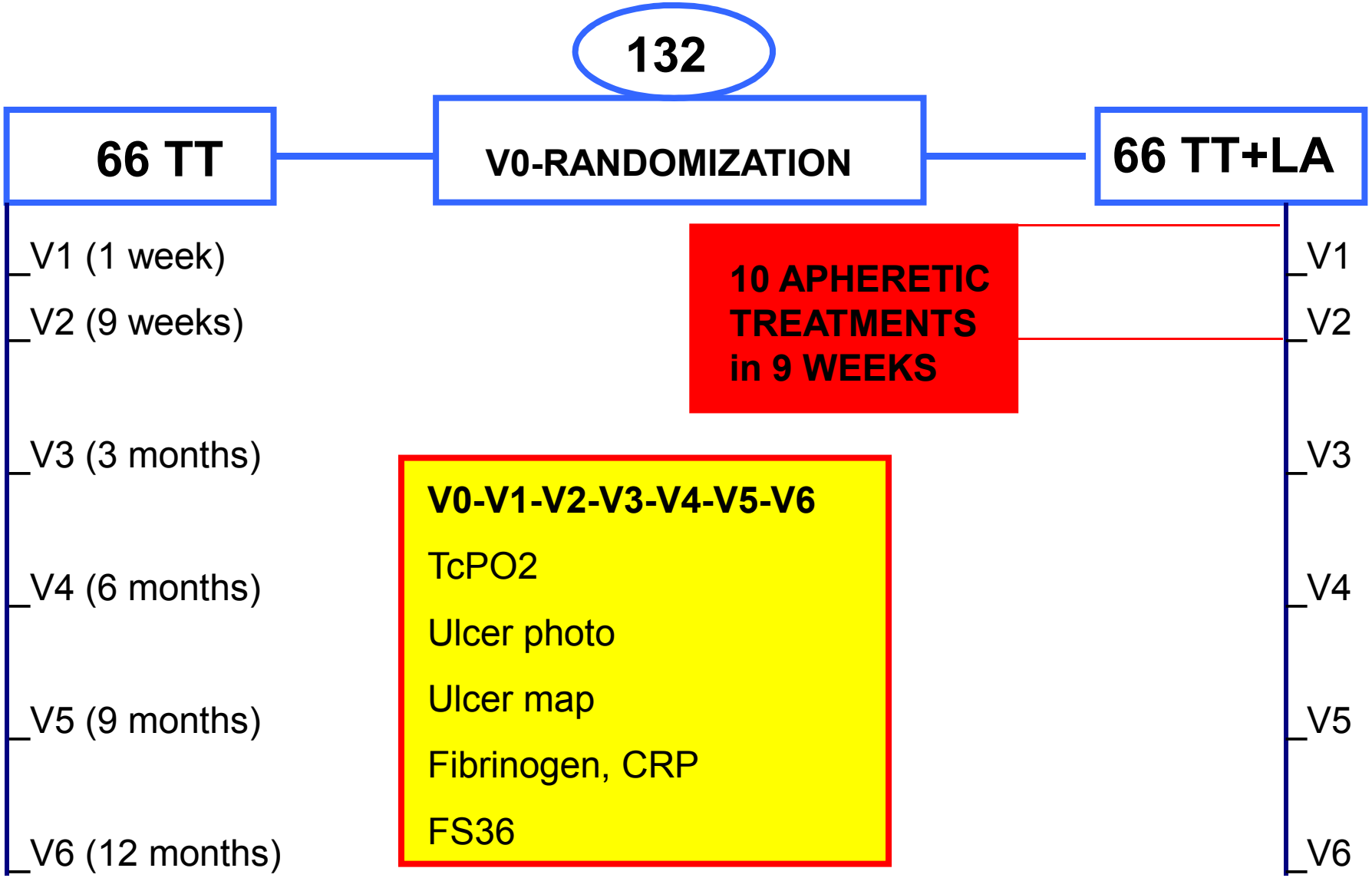
- standard medication of ulcers
- antibiotics therapy
- antiaggregant therapy
- statins

EXPERIMENTAL ARM:

Traditional Treatment + LDL-apheresis (HELP)

- 10 apheretic sessions in 9 weeks: first and second apheresis with a 3 days interval (i.e. 2 treatment in one week), then one session per week (every 7 days).

HADIF FLOW CHART



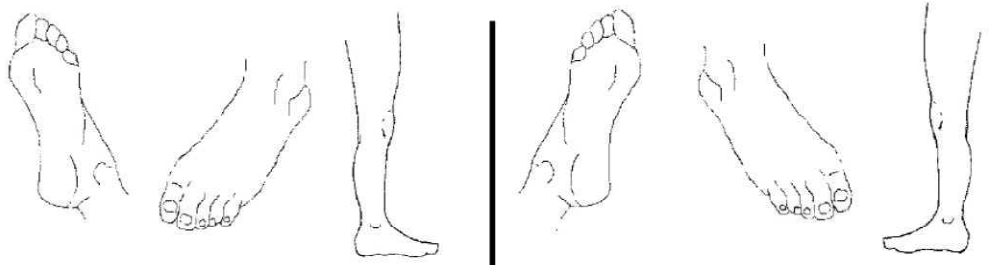
LDL-aferesi nel trattamento del piede diabetico ischemico

Scheda di valutazione delle lesioni del piede diabetico

Centro _____ visita _____ Data ____/____/_____

Paziente (iniziali) _____ sesso _____ Data di nascita ____/____/_____

SX SEDE DELLA LESIONE DX



Stadiazione (classificazione Texas University)

lesione	Grado 0 Pre/post ulcerativa	Grado 1 superficiale	Grado 2 Tendini + capsule	Grado 3 Osso + articolazioni
Stadio A integra				
Stadio B infezione				
Stadio C ischemia				
Stadio D Infezione + ischemia				

Descrizione della lesione

CONDIZIONE: - detersa/granuleggiante
- Fibrinosa - essudante -necrotica -infetta

DIMENSIONI: Larghezza _____ Lunghezza_____
Profondità _____

BORDI: -lineari - frastagliati - ipercheratosici
-infetti -macerati - necrotici

CUTE PERILESIONALE:
-Integra - arrossata - macerata - edema

TcPO2 piede dx _____ **TcPO2 piede sx**_____

SCALA DEL DOLORE (NRS)

HELP-Apheresis in the treatment of Diabetic Ischemic Foot (H.A.D.I.F.)

♥ **Primary end-point:** ulcer healing

♥ **Secondary end-points**

- improvements of peripheral oxygenation,
- resolution of pain,
- reduction of circulating inflammatory markers,
- cardiovascular events during one year's follow-up.

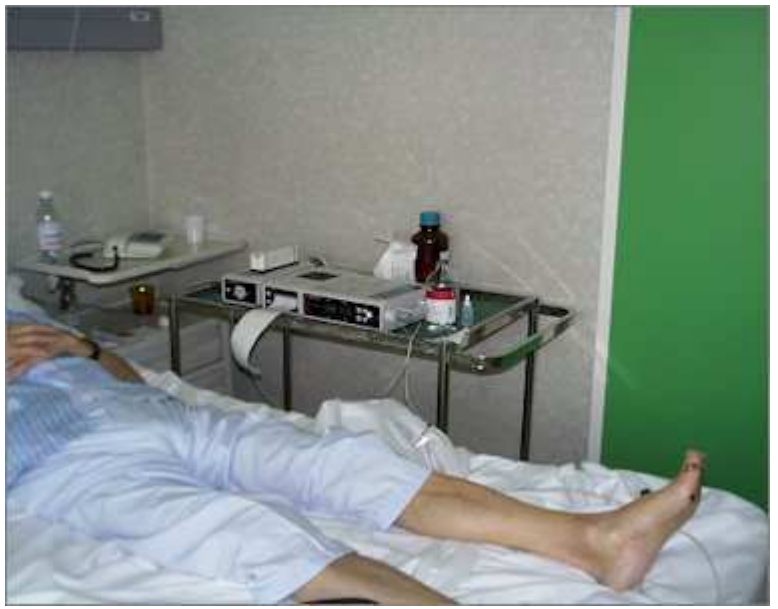
Grazie per l'attenzione!

Transcutaneous oximetry

- TcPO2 is a non invasive method for measuring oxygen diffusing to the surface of the skin from dermal capillaries.
- The values obtained represent a complex function of cutaneous blood flow, metabolic activity, oxyhemoglobin dissociation and oxygen perfusion through tissue
- Values of TcPO2 is determined to assess the severity and clinical progression and to evaluate cutaneous ischemia

Transcutaneous oximetry

- An oxygen tension of 30 mmHg suggests ischemia and non-healing but a range of ± 10 mmHg must be considered.
- Thus, it might be predicted that healing will not occur a $TcPO_2$ under 20 mmHg and will occur a $TcPO_2$ over 40 mmHg



Classificazione di Wagner

- **Classe 0 = Non ulcerazioni, presenza di eventuali deformità, edema, cellulite etc.**
- **Classe 1 = Ulcera superficiale**
- **Classe 2 = Ulcera profonda fino al tendine , alla capsula articolare, all'osso, senza infezione**
- **Classe 3 = Ulcera profonda con ascesso, osteomielite, artrite settica**
- **Classe 4 = Gangrena localizzata alle dita o al tallone**
- **Classe 5 = Gangrena di tutto il piede o di una porzione significativa**

The Fontaine Classification for chronic ischaemia

- **Stage 1 = No symptoms**
- **Stage 2 = intermittent caludication subvided into**
- **2a = without pain on resting, but with claudication at a distance of greater than 200 metres**
- **2b = without pain on resting, but with claudication distance of less than 200 metres**
- **Stage 3 = nocturnal and/or resting pain**
- **Stage 4 = necrosis and/or gangrene in the limb**