

# **Zinc hyaluronate effects on ulcers in diabetic patients**

By

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## SUMMARY

**Context:** The diabetic foot ulcer is one of the main complications of diabetes in the lower extremities. From 50 to 70% of lower extremity amputations are made to diabetic patients. The zinc hyaluronate has been proven in treatment of diabetic ulcers of the foot with promising results.

**Overall objective:** To determine the degree of efficacy of zinc hyaluronate in the cure of diabetic foot ulcers.

**Design:** Random open therapeutic test. Patients were followed for twelve weeks from June to December 2004.

**Location:** Tertiary care centre. Diabetic Foot Clinic.

**Patients:** Fifty patients with diabetes type 2 with foot ulcer were selected by consecutive sampling; both sexes were represented with ages between 40 and 80 years old and without a lower ischemia of the extremity. Twenty five of them were randomly assigned to the zinc hyaluronate group and the rest to the control group (conventional treatment). The distribution by gender (?) was similar in both groups, eleven females (44%) and 14 males (56%). The average age in the combination group of hyaluronic acid and zinc was  $56,76 \pm 8,78$  and in the conventional  $60,12 \pm 8,42$ , NS. No patient from the zinc hyaluronate group abandoned or was removed during the period of the study. A patient from the control group died.

**Intervention:** The zinc hyaluronate was applied once per day on the surface of the ulcer after cleaning it with the saline physiologic solution.

**Main measurement of the result:** The efficacy of the zinc hyaluronate was determined by the number of weeks that were required to obtain the complete closure of the ulcer with the epithelial fine tissue (average curative time).

**Material and methods:** Controlled clinical trial. Patients with diabetic foot ulcers. July 1<sup>st</sup>. through September 30<sup>th</sup>. 1004, 25 patients per group.

**Results:** The average glycaemia when entering the study was  $163,64 \pm 86,4$  mg/dl in the zinc hyaluronate group, and  $182,4 \pm 68,3$  mg/dl in the other group, NS. The area of the ulcer at the start of the study was  $13,28 \pm 11,8$  cm<sup>2</sup> in patients treated with zinc hyaluronate, and  $7 \pm 5,3$  cm<sup>2</sup> in those managed conventionally,  $p= 0,01$ . The time for closure of the ulcerous lesion was on average  $7,80 \pm 3,49$  weeks in the 25 patients of the zinc hyaluronate group, while only in two cases in the conventional treatment group the closure time for the ulcerous lesion was 12 weeks (one case seven and the other, nine weeks).

**Conclusions:** Zinc hyaluronate represents the first therapeutic option in the treatment of diabetic patient ulcers.

**Key terminology:** Diabetic foot ulcers, zinc hyaluronate, cicatrisation.

## INTRODUCTION

The diabetes *mellitus* and its complications represent the second cause of disability with a consequent high cost for society, healthcare institutions and social security and for the country's harmonious development (1).

The diabetic foot is one of the main complications of diabetes *mellitus* —50 to 70% of amputations of lower limbs are performed on diabetes mellitus patients — cause for 20 to 30% of hospital admissions, with a associated mortality of 3 to 7% per year and 50% the three following years. The recurrence of amputations for five years is 40% (1, 2).

Half of amputations in diabetic patients can be prevented with an early detection and timely treatment of the clinical manifestations (1).

Recently, hyaluronic (hyaluronan) acid ester has been used for curing skin lesions. This treatment is commonly applied to the wound by means of a gauze that is changed daily. The hyaluronate provides structural support, regulates the development and assists the receptor of the expression of the mediator gene. As a major molecule in the extracellular matrix, the hyaluronate has regulatory effects on the inflammation, angiogenesis, granulation and re-epithelisation in diabetic foot

lesions, for which it represents a solid alternative in the reduction of the amputation of lower limbs in the diabetic population (3).

## **SCIENTIFIC ANTECEDENTS**

### **Diabetic foot. Hyaluronic acid**

The subjacent lesions of the foot, that usually cause chronic ulceration and amputation, are known as “diabetic foot”. Infection, ulceration and destruction of deep tissue associated with neurologic abnormalities (loss of sensation of pain), and various degrees of peripheral vascular disease in lower extremities (4), are also defined as diabetic foot.

The diabetic foot lesions are the most common precursors for amputation of the lower extremity and have been identified as the main component in nine out of every ten ablative ailments (5).

Esterified hyaluronic acid has recently been used for curing skin lesions with very promising results (3).

### **Hyaluronic acid. Curing process**

Hyaluronic acid is one of the natural polymers that belong to the class of sulphated glycosaminoglycans and represents the main component of the extracellular matrix of the dermis, where besides having important structural and mechanical functions, it also plays a fundamental role in the curing process. Hyaluronic acid stimulates the development of fibrin, phagocytic activity, neutrophil and macrophage mobility, and the liberation of chemotactic factors for fibroblasts. Besides, it induces proliferation of fibroblasts and stimulates their metabolism during the granulation phase of the cicatrisation process, with a consequent increase in collagen fibres and in the deposit of ground substance (6, 7).

### **Hyaluronic acid. It establishes barriers**

Hyaluronic acid is a linear polysaccharide formed by alternating residues of N-acetyl-glucosamine and glucuronic acid that interact with other proteoglycans in order to provide stability and elasticity to the extracellular matrix of all tissues. Glucuronic acid forms the ground substance of conjunctive tissue and especially in the vitreous and aqueous humours, synovial fluid, umbilical cord and the pleural fluid. Hyaluronic acid in solution is very viscous. It is also known as a cement that establishes tissular barriers with properties that allow the passage of metabolically active substances and opposes the passage of bacteria (8).

This macromolecule network regulates cell hydration and the movement of substances within the

interstitial compartment (9).

### **Hyaluronic acid and tissular lesion**

The bulk of hyaluronic acid is cross-bonded with collagen and other high molecular weight substances, thus the concentration of free hyaluronic acid is low. However, the levels of hyaluronic acid rise dramatically immediately after the onset of the tissular lesion (10). Hyaluronic acid can be linked to receptors that are preferentially located in regions of active cell growth (11). The receptor is associated with the process of division (12, 13) and seems to be totally absent in cells without mitosis (11).

### **Hyaluronic acid. Neovascularisation**

In general, a sudden increase of Hyaluronic acid synthesis precedes mitosis and dissociates the cell by division of its substrate, which allows cell motion (14). The receptor of hyaluronic acid is gradually lost as the epithelial cell matures and migrates (11).

In an animal model, hyaluronic acid improves the microcirculatory perfusion at the tissue-reparation site, reduces the extravasation of fluorescein isocyanate dextran and speeds up the closure of the lesion (7).

A higher blood flow toward the lesion being cured suggests that the hyaluronic acid promotes neovascularisation and reduces the vascular tissular resistance. With respect to neovascularisation, the lesion's fluid contains promoting and inhibiting substances of vascular growth and the degradation products of hyaluronic acid are angiogenic in animal models.

### **Hyaluronic acid. The degradation**

The synthesis of hyaluronic acid is related to the expression of various hormones (insulin, prostaglandin, interleukin and somatomedin) and the majority of growth factors (platelet-derived growth factor, epidermal growth factor, basic fibroblast growth factor and transforming growth factor), including those hormones secreted by foetal and cancerous cells (8, 15-16). On the contrary, the inhibition of hyaluronic acid synthesis in mesenchymatous and epithelial cells stops the mitosis *in vitro* even in the presence of growth factors (8, 17-18). Consequently, the inhibition of the synthesis of hyaluronic acid can have an obligated role in the expression of growth promoting substances. In adults, free hyaluronic decreases gradually during reparation (19, 20) and is degraded by hyaluronidase and O<sub>2</sub> radicals, liberated from infiltrating neutrophils (21, 22) into

fragments of lower molecular weight (23, 24). Hyaluronic acid can also reduce the formation of granulation tissue (25, 26).

Table 1 A. Results ZINC HYALURONATE GROUP								
Name	Age	Gender	Years	Lesion	Left	Right	Retinopathy	Nephropathy
			Evolution	(Months)				
UAA	74	F	15	36	1		NO	NO
RFAM	62	F	20	2	1		YES	YES
GPS	55	M	19	18		1	YES	YES
HMJJ	51	M	15	13	1		YES	YES
DGA	54	F	12	4		1	YES	NO
PGM	54	M	1,6	1		1	NO	NO
GMR	58	M	23	7	1		YES	YES
BVA	58	M	25	2		1	NO	NO
ROB	50	M	10	2	1		NO	NO
RDS	58	F	10	1	1		NO	NO
ORC	58	F	8	8	1		YES	YES
AVJ	48	M	18	5	1		YES	YES
PPA	69	F	20	4	1		NO	YES
HCD	36	M	8	1		1	YES	NO
FUE	53	M	2	1	1		NO	NO
RPE	59	F	18	3	1		NO	NO
SHA	69	M	22	4		1	YES	YES
CFB	50	M	18	3	1		YES	YES
MOML	47	F	15	1		1	YES	YES
ULE	68	M	2	1	1		NO	NO
SCAF	47	M	13	6	1		NO	NO
GEAL	67	F	22	1	1		YES	YES
ROAM	53	F	16	12	1		YES	NO
GHH	67	F	22	1		1	YES	NO
ELF	54	M	14	2		1	NO	NO
Mean	56,76	F-11	14,74	5,56	16	9	NO= 11	NO= 14
Std. Dev.	8,78	M-14	6,72	7,70			YES= 14	YES= 11
Variance	77,02		45,12	59,34				

Table 1 B. Results zinc hyaluronate group									
Name	Neuropathy	Treatment	YAO	SO2%	Wagner	Glucose 1	Glucose 2	Cicatr. weeks	Area (cm)
UAA	YES	GBC	0,9	98	1	90	94	5	1,5
RFAM	YES	Glimetal	1	98	2	156	125	8	24
GPS	YES	Insulin	0,9	98	3	128	110	14	6
HMJJ	YES	Insulin	1	97	3	244	126	12	3,6
DGA	YES	GBC	1,3	97	2	232	146	8	8
PGM	YES	GBC	1,5	98	2	142	98	4	2
GMR	YES	Insulin	1	98	2	150	110	7	7
BVA	YES	GBC	1	98	2	234	148	6	16,5
ROB	YES	GBC	1,3	98	2	103	100	12	18,4
RDS	YES	GBC/M	0,9	98	2	211	134	9	36
ORC	YES	GBC	0,9	82	1	133	98	4	4,5
AVJ	YES	Tolbutamide	1,2	99	2	88	93	4	37,2
PPA	YES	Insulin	1	98	2	202	123	9	9
HCD	YES	GBC/M	1,2	99	3	245	125	7	10
FUE	YES	GBC	1	98	2	100	114	11	20
RPE	YES	GBC	1,1	98	3	78	86	12	15
SHA	YES	GBC	0,9	96	3	214	96	2	3

CFB	YES	Insulin	1,2	98	2	414	200	4	3,7
MOML	YES	GBC	0,9	100	2	54	100	3	5,7
ULE	YES	Diet	1	99	2	87	92	3	5,5
SCAF	YES	Insulin	0,9	97	2	321	168	11	36
GEAL	YES	Insulin	1	99	2	135	100	10	8
ROAM	YES	GBC	1,5	97	2	174	111	12	12
GHH	YES	Insulin	0,9	98	2	86	98	10	17,5
ELF	YES	GBC	1	99	2	70	86	8	2
Mean	NO= 0		1,06	97,40	W1= 2	163,64	115,24	7,80	12,48
Std. Dev.	YES= 25		0,18	3,32	W2= 18	86,40	27,34	3,49	10,92
Variance			0,03	11,00	W3= 5	7.464,16	747,27	12,17	119,36
Mean $\pm$ 1SD= 1,2 a 101.									
Healing speed= 1,60 cm <sup>2</sup> /week.									

### Hyaluronic acid. Feedback mechanism

In later stages of cure, macrophages are the dominant leucocytes in the lesion. These cells ingest hyaluronic acid (27, 28) and also produce angiogenic growth factors (29) and others that stimulate the fibroblasts to synthesise collagen and more hyaluronic acid (30).

It is unknown if these events are disconnected, but it is reasonable to propose that, in actively growing tissue like curing lesions, hyaluronic acid can be part of a feedback mechanism that promotes cell proliferation and migration but inhibits differentiation. Alternatively, its role in water homeostasis (8) can favour tissue hydration, that has a well known beneficial effect on curation.

### Zinc. Effects on ulcerous lesion

Zinc is a metallic salt with reported beneficial effects in dermatology, inflammation of the joint, ophthalmology and in the curing process of lesions, whose moderate deficiency in human beings is manifested as a delay in the cure of lesions (31-34).

The combination of hyaluronic acid with antibacterial effect of zinc sulphonamide has improved the curing process of surface lesions (35).

The anti-ulcerous activity of compounds that contain zinc shows that its presence is associated with the cure of the ulcerous lesion (36). The synergistic effect of hyaluronic acid is demonstrated with these results.

### Zinc hyaluronate

Currently there is a commercial product with the name Cicactiv® that contains hyaluronic acid and zinc and various authors have reported on the beneficial effects on the curing process of chronic lesions, in animal models as well as human beings (37, 38). However, due to methodological limitations like the size of the sample, a larger number of controlled and randomised (clinical trial) investigations are required to increase the knowledge of the effects of hyaluronic acid and zinc combination on diabetic foot ulcer cure (8).

## **STATEMENT OF THE PROBLEM**

Diabetes mellitus and its complications represent the second cause of disability with its consequent high cost for society, healthcare institutions and social security, and for the harmonious development of the country.

The diabetic foot is one of the main chronic complications of diabetes mellitus. Half of amputations in diabetic patients can be prevented with an early detection and timely treatment of clinical manifestations.

Recently, hyaluronic acid (hyaluronate) ester has been used for curing skin lesions.

Hyaluronate has regulatory effects on the inflammation, angiogenesis, granulation and re-epithelisation in diabetic foot lesions, for which it represents a solid alternative for the reduction of amputation of lower limbs in the diabetic population.

Overall objective

Determine the degree of efficacy of zinc hyaluronate (Cicactiv®) in the cure of diabetic foot ulcer cure.

Specific objectives

Classify diabetic foot ulcers by evolution time and site of the lesion.

Quantify the size of the lesion in square centimetres (area = side times side times over depth).

Measure the duration time to reach closure of the lesion with and without zinc hyaluronate.

Determine the characteristics of the neo-formation tissue by means of a histopathology study with biweekly periodicity.

Identify the adverse effects during the application of zinc hyaluronate to the lesion.

Material and methods

Design of the study: Controlled clinical trial.

Population of the Study: Patients with diabetic foot ulcers.

Unit of the study: Ulcers of the diabetic foot.

Place of the study: Diabetic Foot Clinic of The Speciality Hospital of Adolfo Ruiz Cortines Medical Centre.

Period of the study: July 1st. to September 30th. 2004.

Sample size: 50 patients per group.

**Table 1 B. Results zinc hyaluronate group**

Name	Neuropathy	Treatment	YAO	SO2%	Wagner	Glucose 1	Glucose 2	Cicatrix. weeks	Area (cm)
UAA	YES	GBC	0,9	98	1	90	94	5	1,5
RFAM	YES	Glimetal	1	98	2	156	125	8	24
GPS	YES	Insulin	0,9	98	3	128	110	14	6
HMJJ	YES	Insulin	1	97	3	244	126	12	3,6
DGA	YES	GBC	1,3	97	2	232	146	8	8
PGM	YES	GBC	1,5	98	2	142	98	4	2
GMR	YES	Insulin	1	98	2	150	110	7	7
BVA	YES	GBC	1	98	2	234	148	6	16,5
ROB	YES	GBC	1,3	98	2	103	100	12	18,4
RDS	YES	GBC/M	0,9	98	2	211	134	9	36
ORC	YES	GBC	0,9	82	1	133	98	4	4,5
AVJ	YES	Tolbutamide	1,2	99	2	88	93	4	37,2
PPA	YES	Insulin	1	98	2	202	123	9	9
HCD	YES	GBC/M	1,2	99	3	245	125	7	10
FUE	YES	GBC	1	98	2	100	114	11	20
RPE	YES	GBC	1,1	98	3	78	86	12	15
SHA	YES	GBC	0,9	96	3	214	96	2	3
CFB	YES	Insulin	1,2	98	2	414	200	4	3,7
MOML	YES	GBC	0,9	100	2	54	100	3	5,7
ULE	YES	Diet	1	99	2	87	92	3	5,5
SCAF	YES	Insulin	0,9	97	2	321	168	11	36
GEAL	YES	Insulin	1	99	2	135	100	10	8
ROAM	YES	GBC	1,5	97	2	174	111	12	12
GHH	YES	Insulin	0,9	98	2	86	98	10	17,5
ELF	YES	GBC	1	99	2	70	86	8	2
Mean	NO= 0		1,06	97,40	W1= 2	163,64	115,24	7,80	12,48
Std. Dev.	YES= 25		0,18	3,32	W2= 18	86,40	27,34	3,49	10,92
Variance			0,03	11,00	W3= 5	7.464,16	747,27	12,17	119,36
Mean ± 1SD= 1,2 a 101.									
Healing speed= 1,60 cm <sup>2</sup> /week.									

## GENERAL DESCRIPTION OF THE STUDY

A sample of 100 selected patients of the Diabetic Foot Clinic were invited to participate in the study, through an informative talk about its purpose. After their acceptance and signing of a letter of consent, they were randomised in two groups: A) treatment with zinc hyaluronic acid, application once a day, previous cure at home and follow-up for 20 weeks; and B) conventional treatment with daily cure at the assigned clinic and/or the patient's home.

All patients were given weekly appointments for control at the Diabetic Foot Clinic and administered zinc hyaluronate and cure materials during the study's period. Data were registered about the site and state of the ulcer's base, its width and depth (cm<sup>2</sup>) in a specially designed format; sample of capillary glycaemia for determination of metabolic control.

Adverse effects reported by patients were also recorded during the period of application of the treatment.

Samples were taken of the neoformation tissue for blinded histopathologic study with bi-weekly periodicity by anatomo-pathology physician.

#### Ethical aspects

All patients were informed about potential risks and benefits of the medications being studied and were in complete freedom of withdrawing from it, at the moment they were requested, without detriment to the received medical assistance.

This study abided by the Rules of Investigation of the General Healthcare Law valid in the country, and the Declaration of Helsinki, for investigation in human beings with the Tokyo and Venice modifications.

## **RESULTS**

Fifty diabetic patients were studied, 25 were randomised for the group to be treated with zinc hyaluronate and the remaining 25 for conventional treatment. The distribution by gender sex was similar in both groups, eleven feminine and 14 masculine. The average age in the zinc hyaluronate group was  $56,76 \pm 8,78$ , and in the conventional  $60,12 \pm 8,42$ , NS. The years of evolution of diabetes type 2 were an average of  $14,74 \pm 6,72$  among the patients treated with zinc hyaluronate, versus  $16,40 \pm 5,84$ , in those of the conventional treatment, NS.

In the zinc hyaluronate group, 16 cases consumed oral hypoglycemiants, eight insulin and one diet, while in the other grou 15 patients had been prescribed oral hypoglycemiants, nine insulin and one diet, NS.

Table 1 B. Results zinc hyaluronate group									
Name	Neuropathy	Treatment	YAO	SO2%	Wagner	Glucose 1	Glucose 2	Cicatrix. weeks	Area (cm)
UAA	YES	GBC	0,9	98	1	90	94	5	1,5
RFAM	YES	Glimetal	1	98	2	156	125	8	24
GPS	YES	Insulin	0,9	98	3	128	110	14	6
HMJJ	YES	Insulin	1	97	3	244	126	12	3,6
DGA	YES	GBC	1,3	97	2	232	146	8	8
PGM	YES	GBC	1,5	98	2	142	98	4	2
GMR	YES	Insulin	1	98	2	150	110	7	7
BVA	YES	GBC	1	98	2	234	148	6	16,5
ROB	YES	GBC	1,3	98	2	103	100	12	18,4
RDS	YES	GBC/M	0,9	98	2	211	134	9	36
ORC	YES	GBC	0,9	82	1	133	98	4	4,5
AVJ	YES	Tolbutamide	1,2	99	2	88	93	4	37,2
PPA	YES	Insulin	1	98	2	202	123	9	9
HCD	YES	GBC/M	1,2	99	3	245	125	7	10
FUE	YES	GBC	1	98	2	100	114	11	20
RPE	YES	GBC	1,1	98	3	78	86	12	15
SHA	YES	GBC	0,9	96	3	214	96	2	3
CFB	YES	Insulin	1,2	98	2	414	200	4	3,7
MOML	YES	GBC	0,9	100	2	54	100	3	5,7
ULE	YES	Diet	1	99	2	87	92	3	5,5
SCAF	YES	Insulin	0,9	97	2	321	168	11	36
GEAL	YES	Insulin	1	99	2	135	100	10	8
ROAM	YES	GBC	1,5	97	2	174	111	12	12
GHH	YES	Insulin	0,9	98	2	86	98	10	17,5
ELF	YES	GBC	1	99	2	70	86	8	2
Mean	NO= 0		1,06	97,40	W1= 2	163,64	115,24	7,80	12,48
Std. Dev.	YES= 25		0,18	3,32	W2= 18	86,40	27,34	3,49	10,92
Variance			0,03	11,00	W3= 5	7.464,16	747,27	12,17	119,36
Mean ± 1SD= 1,2 a 101.									
Healing speed= 1,60 cm <sup>2</sup> /week.									

The average glycemia when entering the study was  $163,64 \pm 86,4$  mg/dl in the zinc hyaluronate group, and  $182,4 \pm 68,3$  mg/dl in the other group, NS.

All patients (100%) in the zinc hyaluronate had a peripheral neuropathy diagnosis, as had 96% of the members of the group with conventional treatment.

The average ankle/arm ratio in the zinc hyaluronate group was  $1,06 \pm 0,18$  mm Hg, and  $0,96 \pm 0,15$  mm Hg in the conventional treatment group,  $p < 0,05$ .

Oxygen saturation was recorded between 82 and 100% in the zinc hyaluronate group, and between 92 and 99% among patients with conventional treatment.

According to the Wagner classification, 18 patients fit in grades, and the two remaining patients to grade 1 in the zinc hyaluronate group, while 20 cases classified as grade 2 and the remaining five to grade 3 in the group with conventional management.

The ulcer affected more the left foot in both groups: zinc hyaluronate with 16 cases (64%), conventional treatment 15 cases (60%), NS. The average time of ulcer evolution, measured in months,

was  $5,56 \pm 7,70$  in the zinc hyaluronate group, and

$6,76 \pm 9,35$  in the group with conventional treatment, NS.

The average area of the ulcer at the start of the study was  $12,48 \pm 10,92$  cm<sup>2</sup> in the patients treated with zinc hyaluronate, and  $7,00 \pm 5,3$  cm<sup>2</sup> in those managed conventionally,  $p=0,01$ .

The average closure time of the ulcerous lesion was  $7,80 \pm 3,49$  weeks, in the 25 patients with zinc hyaluronate, while in only two cases of the group with conventional treatment the closure was observed after twelve weeks of follow-up (one seven and the other nine weeks).

With respect to the morphologic assessment of ulcer cytology, the histopathology report indicates the presence of abundant grouped fibroblasts and endothelial cells, macrophages, lymphocytes present and few nuclear polymorphs in the zinc hyaluronate group, compared to few scattered fibroblasts and endothelial cells, few macrophages, absent lymphocytes and abundant nuclear polymorphs.

The correlation between the area of the ulcer at the beginning of the study and the closure time of the lesion measured in number of weeks was low,  $r=0,11$ .

## **DISCUSSION**

The surgical treatment has reigned as the main alternative for diabetic patient ulcers in our midst, together with the high hospitalisation costs and on occasions even a pension, with the consequent decrease in the productive capacity of the person, his family and society at large.

The combination of hyaluronic acid + zinc (Cicactiv®) has demonstrated its efficacy as a therapeutic option for diabetic patient ulcers with the results obtained in this study. The benefits from its application are a shorter ulcerous lesion closure time, minimum risk of added infection by stimulation of macrophages and lymphocytes in the area of the ulcer, stimulation of cicatrisation tissue conformed by fibroblasts and endothelial cells, decrease of disability costs, reinstatement of the individual to his daily activities and recovery of his quality of life.

Undoubtedly, the main advantage of zinc hyaluronate consists in dealing with a medication for topical and ambulatory application, with minimum averse effects.

Zinc hyaluronate represents the first therapeutic option for the treatment of diabetic patient ulcers.



Fig. 1. UAA 74 years old. Diabetes for 15 years. Lesion 3 years. Multiple treatments. Left foot. Start of treatment: June 7th. 2004. Cicatrization: July 10th. 2004. Total 5 weeks.



Fig. 2. FRAM 62 years old. Diabetes for 20 years. Lesion 5 weeks after fasciotomy. Left foot. Start of treatment: June 22nd. 2004. Cicatrization: August 2004. Total 8 weeks.



Fig. 3. GPS 55 years old. Diabetes for 19 years. Evolution of lesion: 18 months. Start of treatment: July 22nd. 2004. Cicatrization in 14 weeks.



Fig. 4. DGA 54 years old. Diabetes for 14 years. Lesion 4 months. Cicatrisation: 8 weeks.



Fig. 5. DGA 58 years old. Diabetes for 25 years. Start of lesion: June 4th. 2004. Right foot. Start of treatment: July 11th. 2004. 6 weeks for cicatrisation.



Fig. 6. HMJJ 51 years old. Diabetes for 15 years. Lesion 13 months. Wagner 3. Osteomyelitis. Start of treatment: June 24th. 2004. Duration: 12 weeks. Reduction of 90%. Left foot.



Fig. 7. PMG 62 years old. Diabetes for 18 months. Transmetatarsal amputation 2nd. toe. Start of lesion evolution: 15 days. Start of treatment: June 16th. 2004. Cicatrisation: July 15th. 2004. 4 weeks.



Fig. 8. CMR. Diabetes for 23 years. Lesion 7 months. Left foot. Start of treatment: July 29th. 2004. 7 weeks.



Fig. 9. ROB 50 years old. Evolution of diabetes: 10 years. Lesion: May 4th. 2004. Left foot. Start of treatment: June 22nd. 2004. Cicatrisation of 95%.



Fig. 10. RDS 58 years old. Diabetes for 10 years. Lesion evolution 1 month. Left foot. Start of treatment: June 30th. 2004. Cicatrisation: August 23rd. 2004. 9 weeks.



Fig. 11. ORC 58 years old. Diabetes for 8 years. SDstart of lesion: 8 weeks. Left foot. Start of treatment: June 21st. 2004. Cicatrisation: July 12th. 2004. Nephropathy. 4 weeks.



Fig. 12. AVJ 48 years old. Diabetes for 18 years. Evolution of lesion: 5 months. Initially treated with OH. Left foot. Start of treatment: June 29th. 2004. Charcot arthropathy. Cicatrisation: July 27th. 2004. 4 weeks.

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