Evaluation of Hyperbaric Oxygen Therapy in the treatment of diabetic foot lesion.

A randomised controlled prospective study.

→ Action COST B 14

This protocol has been designed by the Working group 4 of the COST action B14

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1. Rationale

Diabetic foot ulceration (DFU) is a major complication wich affects 4 to 10 p.cent of the diabetic population (1-2). As such, foot problems represent one of the most common reasons for hospital admission among diabetic patients. Despite numerous prevention and treatment protocols in the last two decades, the rate of lower extremity amputation is 15 times greater in diabetic patients than compared with non diabetic patients (3). More over, 50 p. cent of the diabetic amputees may require an amputation of the contra lateral limb during the first four years after an amputation of the first limb (4). Beside the human cost, economic cost is also very high. Hospitalisation for amputation in a diabetic patient has been estimated to a mean direct cost of 18 000 Euros and a mean duration of 41.8 days (5).

1.1. Pathophysiology

Sensory neuropathy, ischemia and infection are the principal pathogenic factors in DFU (6).

Peripheral neuropathy has a central role and is present in over than 80 p. cent of diabetic patients with foot lesions (7). In most cases, ulceration is a consequence of the loss of protective sensation allowing small injuries to often go unnoticed (8-9). However, the most common mechanism appears to be unperceived, excessive and repetitive pressure on plantar bony prominences, like metatarsal heads (10). That explains why non-weight bearing measures are mandatory in the overall treatment of DFU.

Ischemia is the other major factor contributing to DFU. Peripheral vascular disease has a high incidence in diabetic patients and has been shown to be a pathogenic factor in 60 p. cent of diabetic patients with non healing ulcers and 46 p. cent of those undergoing major amputation (11). Ischemia weakens local defences against infection because of reduced blood flow and tissue supply in oxygen, essential nutrients and growth factors. Transcutaneous oxygen measurement ($TcPO_2$), but not a reduced ankle-arm blood pressure index, has been shown to be an independent predictor of lesion and a level of 30 mmHg in ambient air is critical in predicting DFU healing (12). Evaluation of revascularisation possibility is therefore mandatory in the overall treatment of DFU.

Infection is a frequent complication favored by neuropathy and ischemia. Its severity may range from a mild, localised infection to a limb-threatening necrotizing process with fasciitis (6). Beside these devastating infections leading often to amputation, bone and joint involvement has been shown to be a factor of delayed healing and subsequent amputation even when ischemia has been relieved by a revascularisation procedure (13).

1.2. Rationale for hyperbaric oxygen therapy

The critical and fundamental role of oxygen in the physiology of wound healing is well documented (14-15). A review of the wound healing effects of oxygen is given by Brakora and Sheffield (16). Hypoxia not only may impair or halt wound healing but can also seriously impair leucocyte bacterial killing function (17-18).

Many factors cause an impaired oxygenation in the diabetic foot (19-20). Measurements of tissue oxygen tensions ($TcPO_2$) in non-healing diabetic wounds showed values far below those where wound healing could be expected. Even breathing 100 % O_2 did not raise the $TcPO_2$ enough. Hyperbaric oxygen therapy has been shown to be able to increase tissue O_2 tension in some diabetic patients with chronic wounds. A direct response and a response over time were demonstrated. This HBO induced increase in $TcPO_2$ has been shown to be predictive for healing success even in the presence of a low $TcPO_2$ in ambient air and a lack of increase in normobaric oxygen (21-23).

The rationale for using HBO in diabetic nonhealing wounds can be summarized as follows :

- Diabetic wounds are polymicrobial with a high incidence of anaerobic organisms. HBO increases the killing ability of leucocytes (24-26), is lethal to certain anaerobic bacteria and inhibits toxin formation by certain anaerobes (27-29).
- HBO increases the flexibility of red blood cells and acts synergistically on blood flow with pentoxifylline (30-32).
- HBO reduces tissue edema (33).
- HBO preserves intracellular adenosine triphosphate (34).
- HBO maintains tissue oxygenation in the absence of hemoglobin (35).
- HBO stimulates fibroblast proliferation, increases collagen formation and deposition, promotes more rapid growth of capillaries (17-18, 36-37).
- HBO terminates lipid peroxidation (38-39).

HBO can not substitute for surgical revascularization in advanced arterial insufficiency and cannot reverse an inadequate microvascular circulation. Thus, any clinical trial protocol must state that vascular reconstruction possibility has been properly evaluated and done if possible.

The first study on HBO in DFU treatment was done by Hart et al in 1979 (40) and was followed by several other anecdotal or retrospective studies. Prospective trials were reported by Doctor (41), Zamboni (42) but the largest prospective, randomised study so far was published by Faglia et al.(43). A total of 70 patients with Wagner grades 2, 3 and 4 were treated ; 35 with HBO and 33 without HBO. Variables in patients did not differ significantly in any item of clinical characteristics. The presence of neuropathy and vasculopathy did not differ significantly in both groups. As to the results, in the HBO group there were 3 major amputations (1 AKA and 2 BKA) which is 8.6 %, and in the non-HBO group 11 (4 AKA and 7 BKA) which is 33.3 %.

The reduction of the amputation relative risk (RR = 0.25) was statistically significant. The significance was highest in the group of patients with a Wagner classification of 4 (2/22 HBO, 11/20 non-HBO).

Considering these evidences, the Jury of the ECHM Consensus Conference on hyperbaric oxygen in the treatment of foot lesion in diabetic patients, held in London, the 4-5th of December, 1998, states (44) :
"There is some evidence from a number of trials, each of which suffers from methodological problems, to support the use of HBO in ischaemic limb-threatening problems in diabetic patients. This is Level 2 evidence.
A result of the meeting is the recognition of urgent need for a collaborative international trial for the application of HBO in diabetic foot lesions. Patients with diabetic foot problems warrant treatment by foot care teams with careful evaluation of metabolic, neuropthic and vascular factors. Potential candidates for HBO may include those with Wagner grade 3 to 5 lesions treated unsuccessfully by standard methods when amputation seems a possibility.
Pre-treatment evaluation should include an assessment of the probability of its success which might include : TcPO2 & O2 challenge at pressure, assessment of peripheral circulation by invasive / non invasive methods".

2. Protocol.

2.1. Objective :

To evaluate the efficacy of HBO in the healing of foot ulceration in diabetic patients.

2.2. Design :

Prospective randomised controlled study.

N.B : Double blinding has been thought not to be suitable because of technical difficulties in the HBO setting and possible interpretation bias.

2.3. Patients

The patients will be screened for eligibility to etablish that they meet the inclusion criteria and do not have any criterion for exclusion. Both written and verbal information will be given.

Each patient must sign and receive a dated copy of such an informed consent form and will be assured of his or her freedom to withdraw from participation in the study at any time. A baseline medical history is obtained, physical examination performed, and blood is drawn for laboratory tests. The patient should have been examined for vascular reconstruction possibility which has to be ruled out. The eyes should have been examined within the last year with visus and fundus photography.

2.3.1. Inclusion criteria :

2.3.1.1. Pre inclusion phase :

Patients will be enrolled in the pre inclusion phase if they fulfil the following criteria :

- Type I or II diabetes mellitus, diagnosed more than 2 years earlier
- Foot lesion, Wagner grade 2 - 4 (Annex 1), present for more than 12 weeks
- Ulcer area 0.25 - 25 cm^2. If more than one ulcer is present on the foot, only the largest is considered in the study.
- Proper evaluation of revascularisation possibility has been done and no (further) possibility of invasive procedures (angioplasty, bypass...) is present.

Only one foot lesion will be considered by patient.

2.3.1.2. Inclusion phase.

**** Patient will be definitively enrolled in the study if :***

- Foot lesion persists 3 weeks after pre inclusion
- Conventional treatment correctly followed.

2.3.2. Exclusion criteria

- Secondary diabetes
- Planned revascularization procedure
- Vascular reconstruction has been performed less than 12 weeks ago
- Urgent amputation needed
- Contra indication to HBO :
  - Acute respiratory disease
  - History of spontaneous pneumothorax
  - Acute ENT infection
  - Nonstabilized epilepsy

Nonstabilized HTA
Nonstabilized heart failure

- Associated therapy by steroids or chemotherapy
- Renal failure (creatinine > 250 µmol/L [2.8 mg/dL]) or patients requiring dialysis
- Patient unable or not willing to be followed for 1 year at the foot clinic

- Ethic criteria
  (pregnancy, children under 18, end of life, etc)
- Patient participating in an other trial or having been enrolled in an other trial within less than 6 months.
- Informed consent not obtained

All patients screened for inclusion in the study and finally not included will be recorded with the reason of non inclusion (cf screening form). Criteria for screening are : Diabetes known for more than 2 years, Foot lesion Wagner 2-4 persisting for more 12 weeks , no obvious revascularisation possibility.

2.4. Patient evaluation

2.4.1. Assessment at each visit

Assessment at pre inclusion

Age, gender, height, weight
Medical history
Medical history of diabetes
Medical history of foot ulcer (including dressing), Peripheral Artery Occlusive Disease (PAOD), amputations
Physical investigation including blood pressure
Current medication and medication in the past 3 months
Laboratory tests (Fasting blood sugar, glycosylated hemoglobin A1c, White Blood Count, C Reactive Protein, BUN, Plasma and Urine creatinine, microalbuminuria),
Evaluation of peripheral neurologic and circulatory status
Measurements of ulcer area
Foot X Ray
Characterization of the ulcer
Documentation of the ulcer by digitalised colour photographs
Control of shoes, weight bearing, and orthopedic appliances
Ophtalmological examination if not done in the last 3 months

Assessment at inclusion

Physical investigation including blood pressure
Current medication and medication in the past 3 weeks
Evaluation of peripheral neurologic and circulatory status ($TcPO_2$)

Measurements of ulcer area
Characterization of the ulcer
Foot X Ray
Documentation of the ulcer by digitalised colour photographs
Documentation of minor amputations and revision of the ulcer
Control of shoes, weight bearing, and orthopedic appliances
Laboratory tests.

Assessment at each week during study

Physical examination including blood pressure
Current medication
Adverse events, major amputation, death of the patient, intercurrent diseases, adverse changes in pre-existing diseases
Control of compliance to HBO treatment
Evaluation of peripheral neurologic and circulatory status (optional : TcPO2 at week 2 and 4)
Measurements of ulcer area
Characterization of the ulcer
Documentation of the ulcer by digitalised colour photographs
Documentation of minor amputations and revision of the ulcer
Control of shoes, weight bearing, and orthopedic appliances

Assessment at final evaluation (6 weeks)

Physical investigation including blood pressure
Current medication and medication in the past months
Adverse events , major amputation, death of the patient, intercurrent diseases, adverse changes in pre-existing diseases
Evaluation of peripheral neurologic and circulatory status (including TcPO2)
Measurements of ulcer area
Characterization of the ulcer
Documentation of the ulcer by digitalised colour photographs
Control of shoes, weight bearing, and orthopedic appliances
Documentation of minor amputations and revisions of the ulcer
Ophtalmological examination
Laboratory tests

Assessment at 1, 3, 6, 9, 12 months during follow up.

Physical investigation including blood pressure
Current medication and medication in the past months
Adverse events , major amputation, death of the patient, intercurrent diseases, adverse changes in pre-existing diseases
Evaluation of peripheral neurologic and circulatory status
Measurements of ulcer area
Characterization of the ulcer
Documentation of the ulcer by digitalised colour photographs
Control of shoes, weight bearing, and orthopedic appliances
Documentation of minor amputations and revisions of the ulcer
Laboratory tests (at the 1 year follow up visit)

2.4.2. Evaluation

Patients are evaluated at 3 levels : general, foot and wound.

· ***General evaluation :***

- Diabetes : Type, duration, usual treatment, fasting blood sugar and glycosylated hemoglobin A_1c. Reference values for the center must be given.

- Other associated vascular risk factors :
  Smoking habit, hyperlipidemia, sedentarity, arterial hypertension.

· Diabetes complication :

Heart :	Coronary artery disease Heart failure (NYHA)
Eye :	Visual acuity, Diabetic retinopathy (DRSS) (Annex 2)
Kidney :	Micro albuminuria (g/L in morning urine), Creatinine clearance (estimated or calculated), Blood urea and creatinine.

· ***Foot evaluation :***

As only one foot lesion shall be considered by patient, evaluation of foot concerns only that where the lesion is present.

- Neuropathy : Neuropathy symptom score (Annex 3),
  Neuropathy disability score (Annex 4),
  Semmes Wenstein monofilament (Annex 5)

- Vascular insufficiency :
  - Ankle and toe pressure
  - Ankle / brachial and toe / brachial pressure index
  - Transcutaneous oxygen pressure.

$TcPO_2$ has to be measured in, at least, 2 points : subclavicular area for reference site and close to the wound [In case of plantar lesion, TcPO2 measurements have to be perform on the dorsum of the foot in the symetrical location]. $TcPO_2$ device has to be calibrated before the measurement. $TcPO_2$ electrode temperature is set at 44°C. Measurements have to be done in the morning, before HBO session, patient lying on his back in a confortable ambience. Measurements are done, the patient breathing first ambient air, second normobaric pure oxygen by facial mask or hood. Measures are taken after equilibrium (15-20 minutes) and before an eventual progressive decrease. For centers where the possibility

exists, measurements are made, patients breathing 2.5 ata (250 kPa) hyperbaric pure oxygen in the chamber.

- Infection :
  Peri wound infection :
    - Mild : Redness and Erythema (more than 1 cm around the wound)
    - Moderate : Redness between 1 and 5 cm around the wound and Swelling and Pain
    - Major : Wide spreading infection (Temperature over 38,5°C, redness more than 5 cm around the wound, cellulitis, ...)

  Bone or joint infection :
  diagnosis of osteomyelitis or arthritis based on :
    - Exposed bone at the bottom of the ulcer
    - Abnormal X-Ray
    - Abnormal bone scan
    - Abnormal MRI
    - Positive culture of bone biopsy
- Inflammatory components :
  Body temperature (inclusion visit)
  C Reactive Protein, white cell blood count

**** Wound evaluation*** : only one lesion may be considered for each patient.
- size (square millimeters) : the ulcer area is determined after adequate debridement by planimetry ; center of the ulcer is considered as the intersection of the longest measure of width and length, measured at approximately right angles to the ulcer edge.
- location (Annex 6) : ulcer has to be drawn on the location form.
- aspect
- depth (mm)

Wound is classified following the Wagner scale (48) and the University of Texas diabetic wound classification (49) (Annex 1).

Digital picture (at least 2 : full foot, focused on lesion) has to be taken in a standardised way with a centimeter scale included at the wound level for picture analysis. Protocol for picture analysis will be subsequently determined.

2.5. Randomisation

Patient will be randomised at the end of the Inclusion visit.

Randomisation is done by center with a re-equilibration by block of 9 patients. Randomisation is prepared from a random number list. Allocated treatment is noted in sealed envelopes, numbered in a successive manner and opened according to inclusion order.

Inclusion form has to be filled as soon as patient is included and sent (fax or E-mail) to the Monitoring Committee coordinator.

2.6. Treatment

2.6.1.Conventional treatment

Conventional treatment will be applied to all patients included. It includes :

- Diabetes equilibrium : diet measures, eventually switch to insulin.
- Treatment of associated vascular risk factors : hyperlipidemia, hypertension.
- Reduction of edema (if present) : low Na diet, diuretic.
- Weight bearing measures have to be applied and tested for efficacy.
- Systemic antibiotics must be reserved to cases where bone or joint infection or cellulitis exists No local antibiotic is permitted
- Wound dressing : - Surgical debridement when necessary
  - NaCl 0,9 % gauze moistened or placebo gel
  - Dressing change once dialy.

2.6.2. Treatment studied

Three arms are considered. Main reason to consider 3 arms is to evaluate a dose-response effect of oxygen treatment. These 3 arms are :

- control arm : no HBO. Conventional treatment is continued.

- 1 HBO arm : HBO [2.5 ata (250 kPa), 90 minutes on oxygen at pressure, one session a day] is added to unchanged conventional treatment, 5 days a week during 6 weeks. During HBO session, air breaks are free to do (but have to be added to the total length of time).

- 2 HBO arm : HBO [2.5 ata (250 kPa), 90 minutes at pressure, 2 sessions a day with a minimal 2 hours interval] is added to unchanged conventional treatment, 5 days a week, during 6 weeks. During HBO session, air breaks are free to do (but have to be added to the total length of time).

2.6.3. Interruption or premature discontinuation of study

Treatment with HBO may be interrupted if any condition develops or occurs (i.e. occurrence of HBO contra-indication, ENT barotrauma) that creates an unacceptable risk with continued treatment, as judged by the investigator.

If the unacceptable risk with treatment is no longer present within 2 weeks, study treatment can be re-instituted for the remaining number of HBO sessions.

Treatment with HBO will also be interrupted in the event of :

- Non-compliance (interruption of the HBO treatment for a total duration of more than two weeks)
- Ulcer area increase by > 50 %
- Need for urgent amputation
- Unwillingness of the patient

All patients who discontinue treatment prematurely, will be followed according to the study protocol until 1 year after randomization. The reason for discontinuation will be documented.

2.6.4. Treatment during the follow-up

During the follow-up period, treatment is left to the decision of the physician in charge of the patient. If specific therapy in addition to conventional treatment is applied, it has to be noted in the patient case report.

2.7. Evaluation criteria

Final evaluation is made after 6 weeks of treatment

Evaluation has to be done by a physician independent of the treatment team and unaware of the study arm. Efforts have to be made in order to leave this observer blinded for the treatment modality.

**** Major End Point :*** Success: complete or more than 50 % of the wound surface is epithelialized.
Failure : non healed (unchanged or covered by less than 50 % of the wound surface)

**** Secondary End Points :***
- Major amputation (above ankle)
- Healing rate
- Infection disappearance rate.
- Time for complete healing
- Disability scale.
- Length of hospitalisation time
- Recurence rate.

- Eventual adverse effects.

2.8. Data analysis

* Data will be analysed in an intention-to-treat basis.

* Homogeneity between the 3 studied groups regarding patients characteristics, vascular risk factors, diabetes, foot and wound pre inclusion evaluation criteria will be checked by Chi - 2 for qualitative variables and Anova for quantitative variables

* Efficacy will be estimated on major and secondary end points

* Post-Hoc analysis will be done on sub groups : infected / non infected; ischemic / non ischemic

2.9. Number of patients to be enrolled

Taken into account the positive effect shown in the Faglia's study (40), setting α at 0.05 and β at 0.20, the drop-out during treatment at 20 % approximately 30 patients will be needed in each sub groups.

Thus between 150 and 200 patients have to be enrolled.
Randomisation has to be done in order to allocate appropriate number in each sub groups.

3. Study monitoring

The Working Group "diabetic foot lesion" of the action COST B14 shall act as the Monitoring Committee.

All aspects of the study will be monitored by the Monitoring Committee who will review randomly sampled study documents and attention will be paid to protocol violations, missing or incomplete data, and occurrence of severe adverse events.

4. Safety

Frequency, severity and duration of adverse events will be registered during treatment and at each visit according to the flow chart along with all clinically significant event (cf adverse effect form).

Severe and unexpected adverse events will be reported to the Monitoring Committee. These events should be entered on the appropriate Adverse Event Report. Expected adverse events will not be reported.

5. Ethical consideration

All centers participating in this study have to follow the code of Good Clinical Practice and to perform the study in accordance to the declaration of Helsinski.

All centers have to comply with their own national regulation concerning clinical research. In particular, approval of this protocol by the appropriate organism ruling the ethical aspects of clinical research has to be obtained. It is of the responsability of each center to prepare required documents in their own language in order to obtain this approval.

6. Publication and authorship

The results of the study should be presented in one or more reports designed for publication in suitable medical journal(s) following agreement between investigators.

As author/co-author for such a publication the following persons will be considered :

- Person(s) responsible for the first draft of the manuscript
- Physician at the department responsible for recruitment and treatment of at least 10 % of the total number of enrolled patients in the study

- Other participants will be acknowlegded in a list at the end.
- COST Action B14 will be acknowlegded as having supported the study.

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8. Annexes

Annex 1

Wagner grading system for diabetic foot lesion

Grade	Lesion
Grade 0	No open lesions ; may have deformity or cellulitis
Grade 1	Superficial ulcer
Grade 2	Deep ulcer to tendon, capsule, or bone
Grade 3	Deep ulcer with abscess, osteomyelitis, or joint sepsis
Grade 4	Localized gangrene - forefoot or heel
Grade 5	Gangrene of entire foot

Ref : Wagner. The diabetic foot. Orthopedics. 1987 ; 10 : 163-172.

The University of Texas Diabetic Wound Classification System

STAGE	GRADE 0	GRADE I	GRADE II	GRADE III
A	Pre-or post-ulcerative lesion, completely epithelialized	Superficial wound, not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Pre-or post-ulcerative lesion, completely epithelialized **with infection**	Superficial wound, not involving tendon, capsule, or bone **with infection**	Wound penetrating to tendon or capsule **with infection**	Wound penetrating to bone or joint **with infection**
C	Pre-or post-ulcerative lesion, completely epithelialized **with ischemia**	Superficial wound, not involving tendon, capsule, or bone **with ischemia**	Wound penetrating to tendon or capsule **with ischemia**	Wound penetrating to bone or **joint with ischemia**
D	Pre-or post-ulcerative lesion, completely epithelialized **with infection and ischemia**	Superficial wound, not involving tendon, capsule, or bone **with infection and ischemia**	Wound penetrating to tendon or capsule **with infection and ischemia**	Wound penetrating to bone or joint **with infection and ischemia**

Ref : Lavery LA, Amstrong DG, Harkless LB. Classification of diabetic foot ulcerations J. Foot Ankle Surg. 1996 ; 35 : 528-31

Annex 2

Diabetic retinopathy severity scale for individuals eyes.

1. DR absent
2. Micro aneurysms only
3. Mild non proliferative DR
4. Moderately severe non proliferative DR
5. Severe non proliferative DR
6. Mild proliferative DR
7. Moderate proliferative DR
8. High risk proliferative DR
9. Cannot grade

Ref : Derived from : Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs-an extension of the modified Airlie House classification. ETDRS Report Number 10. Ophtalmology. 1991 ; 98 : 786-806.

ETDRS Final Retinopathy Severity Scale for individual Eyes

Level	Severity	Definition
10	**DR absent**	Microaneurysms and other characteristics absent
12	Non-DR Abnormalities	
14	DR questionable	14A HE definite; microaneurysms absent
		14B SE definite; microaneurysms absent
		14C IRMA definite; microaneurysms absent
15[a]	DR questionable	Hemorrhage(s) definite; microaneurysms absent
20	**Microaneurysms only**	Microaneurysms definite; other characteristics absent
35[b]	**Mild NPDR**	35A Venous loops ≥ D/1
		35 B SE, IRMA, or VB = Q
		35C Retinal Hemorrhages present
		35D HE ≥ D/1
		35E HE ≥ M/1
		35F SE ≥ D/1
43	**Moderate NPDR**	43A H/Ma = M/4-5 or S/1
		43B IRMA) D/1-3
47	**Moderately severe NPDR**	47A Both Level 43 characteristics
		47B IRMA = D/4-5
		47C H/Ma = S/2-3
		47D VB = D/1
53	**Severe NPDR**	53A ≥ 2 of the 3 Level 47 characterictics
		53B H/Ma ≥ S/4-5
		53C IRMA ≥ M/1
		53D VB ≥ D/2-3
	53E Very Severe NPDR	53E ≥ 2 of 53B, 53C, and 53D
61	**Mild PDR**	61A FPD and/or FPE only (regressed PDR)
		61B NVE < ½ disc area in ≥ 1 field
65	**Moderate PDR**	65A NVE ≥ M/1 (≥ ½ disc area in ≥ 1 field=
		65B NVD = D and VH or PRH = A or Q
		65C VH or PRH = D and NVE < M/1 and NVD absent
71	**High-risk PDR**	71A VH or PRH ≥ M/1 (M = about 1 disc area)
		71B NVE ≥ M/1 and VH or PRH ≥ D/1
		71C NVD = D and VH or PRH ≥ D/1
		71D NVD ≥ M
75	High-risk PDR	75 NVD ≥ M and VH or PRH ≥ D/1
81	Advanced PDR: Fundus partially obscured, center of macula attached	NVD = cannot grade, or NVD < D and NVE = cannot grade in ≥ 1 field and absent in all others; and retinal detachment at center of macula < D
85	Advanced PDR: Posterior fundus obscured, or center of macula detached	85A VH = VS in Field 1 or 2 85 B Retinal detachment at center of macula = D
90	Cannot grade, even sufficiently for level 81 or 85	

[a] Levels 12, 14 and 15 are not considered separate steps in the scale, but are pooled with level 10 or 20 (or excluded).

[b] NPDR levels 35 and above all require presence of microaneurysms.

Abbreviations: DR = diabetic retinopathy; NPDR = non proliferative DR; PDR = proliferative DR; HE = hard exudates; SE = soft exudates; IRMA = intraretinal microvascular abnormalities; VB = venous beading; H/Ma = hemorrhages/microaneurysms ; NVE = new vessels elsewhere ; NVD = new vessels on or adjacent to optic disc ; VH = vitreous hemorrhage; PRH = preretinal hemorrhage

Severity categories are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), Severe (S), or very severe (VS) and extent is the number of photographic fields at that severity level. For example, M/2-3 means there are two or three fields from fields 3 to 7 with moderate severity and none with higher severity.

Annex 3

Neuropathy Symptom Score

Symptoms	Absent	Present	Nocturnal exacerbation
Muscular cramp	0	1	2
Numbness	0	1	2
Pin and needles	0	1	2
Abnormal cold or hot sensations	0	1	2
Lancinating pain	0	1	2
Deep aching pain	0	1	2
Burning pain	0	1	2
Irritation caused by bed clothes at night	0	1	2

Total : |____|____|

Ref : A.G.M. Boulton, A. Dedes, E. Vecioli, C. Manes, Comparison of risk factors for problems in diabetic patients, attending teaching hospital outpatient clinics in four European states. Diabetic Medicine, 1994 (11), 709-11

Annex 4

Neuropathy disability score

	Sensation Normal		Sensation impaired up to									
			Base of the toe		Midfoot		Ankle		Midleg		Knee	
	R	L	R	L	R	L	R	L	R	L	R	L
Pin	0	0	1	1	2	2	3	3	4	4	5	5
Cotton wood	0	0	1	1	2	2	3	3	4	4	5	5
Tuning fork	0	0	1	1	2	2	3	3	4	4	5	5
Icy tuning fork	0	0	1	1	2	2	3	3	4	4	5	5

Sensory score (total / 2) : |___|___|

	Normal		Elicited with reinforcement		Absent	
Reflex	R	L	R	L	R	L
Patellar	0	0	1	1	2	2
Achilles	0	0	1	1	2	2

Reflex score (Total) : |___|___|

Neuropathy Disability score : |___|___|

Ref : M.J Young, A.G.M. Boulton, A.F. Macleud, D.R.R Williams, F.H. Fonksen, Multicenter study of the prevalence of diabetic peripheral neuropathyin the U.K. Hospital clinic population. Diabetologia, 1993 (36), 150-54.

Annex 5

Guidelines for S-W monofilament examination

* a 10 g monofilament (5.07 Semmes-Weinstein) is used
* Examination must be done in a quiet and relaxed supine patient's position, closed eyes.
* First apply the monofilament on the patient's hands to teach him/her what to feel. The patient must not be able to see if the filament is applied
* The three sites are tested on both feet : the big toe pulp, Ist an Vth metatarsus head.
* Apply the filament perpendicular to test skin surface by sufficient force to cause the filament bending for about 45°, the whole procedure should take approximately 2 seconds.
* Ask the patient IF and WHERE they have felt the pressure applied.
* Repeat the measurement TWICE at the same site in a RANDOM order.
* Express the result separately for each foot in a ratio : ig 4/6 means the patient has felt 4 touches from 6, 6/6 means the patient has felt everything.
* During whole procedure, test twice by a blind application the patient's drive to comply with you. If the patient's answer positively while no filament is applied, cancel everything, explain this to patient more and repeat whole prodecure.

Ref : Adapted under the "Practical Guidelines on the Management and the prevention of the Diabetic foot" edited by International Working group on the Diabetic Foot, Amsterdam.

Annex 6

LOCATION FORM