Low-Intensity Laser Irradiation Improves Skin Circulation in Patients With Diabetic Microangiopathy

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OBJECTIVE — Diabetic foot problems due to angiopathy and neuropathy account for 50% of all nontraumatic amputations and constitute a significant economic burden to society. Low-intensity laser irradiation has been shown to induce wound healing in conditions of reduced microcirculation. We investigated the influence of low-intensity laser irradiation by means of infrared thermography on skin blood circulation in diabetic patients with diabetic microangiopathy.

RESEARCH DESIGN AND METHODS — Thirty consecutive patients with diabetic ulcers or gangrenes and elevated levels of glycosylated hemoglobin were randomized by blocks of two to receive either a single low-intensity laser irradiation with an energy density of 30 J/cm^2 or a sham irradiation over both forefoot regions in a double-blind placebo-controlled clinical study. Skin blood circulation as indicated by temperature recordings over the forefoot region was detected by infrared thermography.

RESULTS — After a single transcutaneous low-intensity laser irradiation, a statistically significant rise in skin temperature was noted ($P < 0.001$ by ANOVA for repeated measurements), whereas in the sham-irradiated control group, a slight but significant drop in temperature ($P < 0.001$) was found. Subsequently performed contrasts for comparison of measurements before and after irradiation revealed significant temperature increases at 20 min of irradiation time ($P < 0.001$), at the end of the irradiation ($P < 0.001$), and 15 min after stopping the irradiation ($P < 0.001$). In the sham-irradiated feet, the drop in local skin temperature was not significant at 20 min ($P = 0.1$), but reached significance at the end of the sham-irradiation procedure ($P < 0.001$) and 15 min after the end of sham irradiation ($P < 0.001$).

CONCLUSIONS — The data from this first randomized double-blind placebo-controlled clinical trial demonstrate an increase in skin microcirculation due to athermic laser irradiation in patients with diabetic microangiopathy.

Reduced skin microcircualtion as a sign of diabetic microangiopathy is a common complication in diabetic patients (1,2). Recent research provides evidence that endothelial and smooth muscle dysfunction contribute to impaired microcirculation in patients with diabetes, the major functional abnormality being the marked limitation of microvascular vasodilation to varied stimuli (3,4). In association with the neuropathy, disturbed microcirculation is responsible for the development of diabetic gangrenes, ulcers, and infections of both skin and bone in long-term diabetic patients. The risk of diabetic microangiopathy has been shown to be correlated with the patient's glycemic control as measured by glycosylated hemoglobin (5–8). Among the various methods for investigating skin blood flow, infrared thermography is considered to be a valuable noninvasive tool (9–12).

Low-intensity laser irradiations have been reported to be of beneficial influence on processes of impaired microcirculation and delayed wound healing. The clinical use of this phototherapy is, however, still controversial (13). One of the major causes for this skepticism is the lack of properly controlled clinical studies. We, therefore, investigated the influence of a single low-intensity laser irradiation on skin microcirculation in patients with diabetic microangiopathy in a randomized double-blind placebo-controlled study.

RESEARCH DESIGN AND METHODS

Patients

Patients who were referred to the Department of Dermatology, University of Vienna, Vienna, Austria, between January 1996 and April 1997 because of diabetic ulcers or gangrenes were subjected to an initial infrared thermography to evaluate skin circulation. Of these, 30 patients showing a reduced temperature profile over their forefoot region (mean temperature <29°C) and levels of glycosylated hemoglobin >6% were included in the study. Clinical or blood-chemical signs of infection and medication with drugs that might influence platelet aggregation, vasodilatation, or both were exclusion criteria. The patients' baseline characteristics were as described in Table 1 and included the following: age, sex distribution, duration and type of diabetes, fasting serum glucose level, percentage of glycosylated hemoglobin, smoking habits, rate of diabetes-related complications, and baseline skin temperature over the forefoot regions (Table 1).

The protocol was approved by the University of Vienna ethics comittee, and after obtaining informed consent, the subjects were randomized by blocks of two into two groups: group 1 received a single session of simultaneous low-intensity laser irradiation over both forefoot regions, while both forefeet in group 2 were sham irradiated.

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Table 1—*Demographic and clinical baseline characteristics of patients with diabetic microangiopathy and elevated glycosylated hemoglobin*

	Sham-irradiated group	Laser-irradiated group
n	15	15
Age (years)	62 ± 16.1	61.8 ± 15.9
Sex (M/F)	7/8	9/6
IDDM	7	4
NIDDM	8	11
Duration of diabetes (years)	9.9 ± 7.9	13.5 ± 11.1
Fasting serum glucose level (mg/dl)	173.2 ± 74.1	171.7 ± 57.2
HbA_{1c} (mg %)	8.5 ± 1.2	8.7 ± 2.2
Smokers	3	3
Macroangiopathy	3	5
Gangrene	5	6
Ulcer (neuropathatic and ischemic)	10	9
History of previous amputation	3	5
Hypertension	12	11
Microalbuminuria	6	7
Neuropathy	5	4
Retinopathy	10	9
Baseline forefoot skin temperature (°C)	27.2 ± 2.7	26.7 ± 2.8

Data are *n* or means ± SD. Macroangiopathy was diagnosed by angiography. Ulcer diagnosis was adapted from Laing (39). Hypertension was defined as blood pressue >160/95 mmHg. Microalbuminura was defined as albumin excretion >30 mg/24 h (40). Neuropathy was diagnosed clinically as peripheral symmetric paresthesia, worsening at night (40). Retinopathy was diagnosed using fundus photography. Baseline forefoot skin temperature was calculated from the average for both feet.

Thermography unit and temperature recordings

A noncontact infrared thermography camera (Thermo Tracer TH1100; nbn electronics, Graz, Austria) coupled with a microcomputer was used for the temperature recordings. This instrument measures the infrared radiation emitted from the patient's skin with a sensitivity of 0.1°C. Analysis of the thermograms was performed with the PicWinIris software Version 2.22 (nbn electronics), which allows measurements over a defined region of interest. In our study, the area distal to a line drawn between the medial and lateral malleolus was defined as the forefoot region. Thermograms were taken at 0, 20, and 50 min after the start and 15 min after the end of the irradiation procedure. An examiner who was unaware of the study protocol analyzed the temperature recordings.

Laser device and irradiation protocol

Two helium-neon lasers (wavelength 632.8 nm, power output 30 mW) were used for the light irradiation. The beam (original spot diameter 5 mm) was diverged by the instrument's scanner, and the irradiation time was set to 50 min to receive an energy density of 30 J/cm² at the skin surface. Initial tests with these irradiation parameters (monitoring the temperature when irradiating a swab for a period of 50 min) revealed that the laser beam itself was athermic, i.e., it did not induce a rise in temperature. After a period of 30 min spent in a supine position to reach equilibrium with the room temperature, which was kept constant at 24°C during the intervention, the patient's eyes were covered with wavelength-selective eyewear, and the temperature recordings were started. For sham irradiation, the lasers were positioned in the same manner as for laser irradiation but were not turned on.

Statistical analysis

For statistical evaluation, the measurements for both feet of each patient were averaged. The temperature courses of both groups were analyzed by analysis of variance for repeated measurements, and because they were found to be significantly different, contrasts for comparisons of all timepoints to baseline values were performed. Statistical signifance was defined as $P < 0.05$. Results are presented as means ± SD.

RESULTS — The demographic and clinical baseline characteristics were similar in both groups (Table 1). After a single transcutaneous low-intensity laser irradiation, a statistically significant rise in skin temperature was noted ($P < 0.001$), whereas in the sham-irradiated control group, a slight but significant drop ($P < 0.001$) in temperature was found. Subsequently performed contrasts for comparison of measurements of all timepoints to baseline (Fig. 1) revealed a significant temperature increase of 0.58 ± 0.68°C at 20 min of irradiation time ($P < 0.001$), of 1.06 ± 1.03°C at the end of the irradiation ($P < 0.001$), and of 1.22 ± 1.01°C 15 min after stopping the irradiation ($P < 0.001$). In the sham-

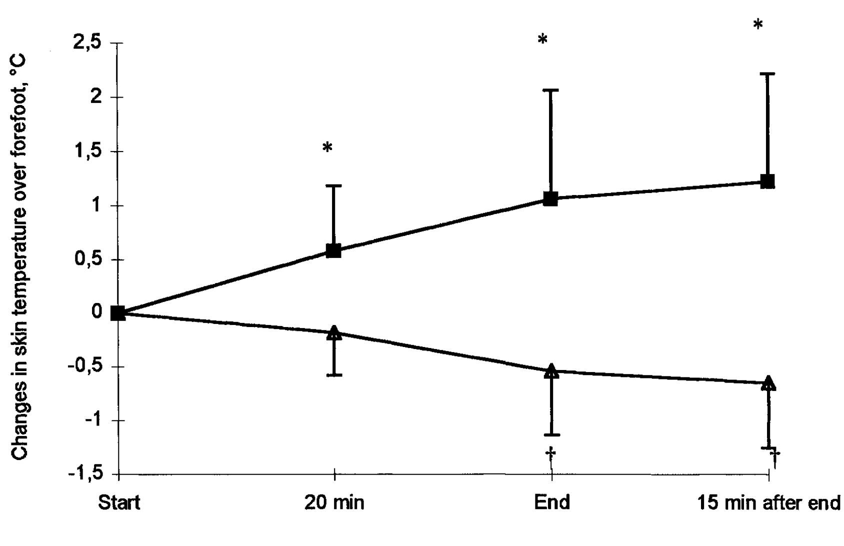

Figure 1—*Alterations in skin temperature (mean ± SD) over forefoot regions after laser (■) and sham irradiation (△) in patients with diabetic microangiopathy. Significant differences (P < 0.001) from baseline are indicated by (*) in the laser-treated group and by (†) in the sham-irradiated group.*

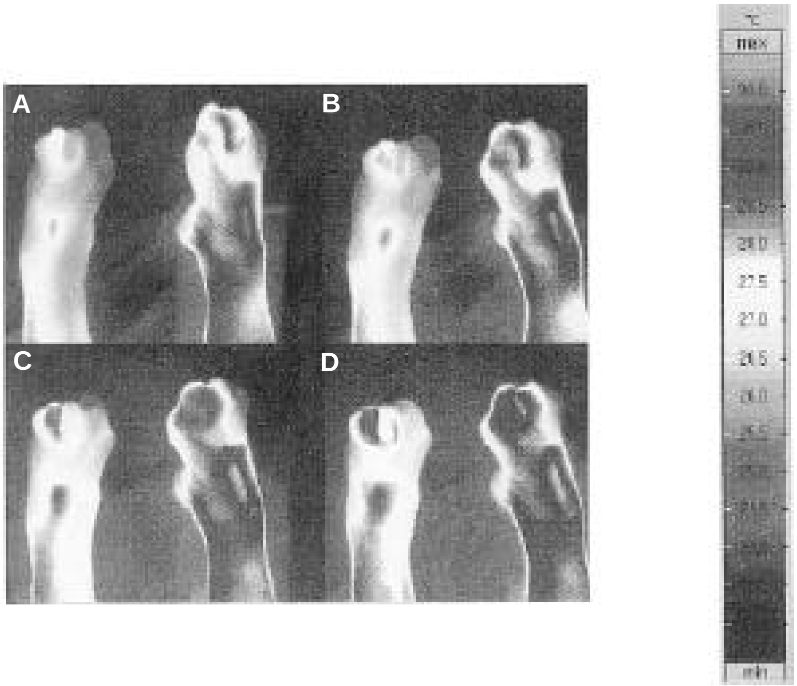

Figure 2—*Typical course of skin temperature in a patient with diabetic microangiopathy under laser irradiation. Temperature patterns at start of laser irradiation* (A)*, at 20 min of laser irradiation* (B)*, after 50 min of laser irradiation* (C)*, and 15 min after stopping laser irradiation* (D) *are shown.*

irradiated feet, the decrease in local skin temperature was 0.18 ± 0.41°C at 20 min ($P = 0.1$), 0.54 ± 0.62°C at the end of the sham-irradiation procedure ($P < 0.001$), and 0.65 ± 0.64°C at 15 min after the end of sham irradiation ($P < 0.001$). Representative temperature courses of the laser-treated and the sham-irradiated groups are shown in Figs. 2 and 3, respectively. None of the patients reported any side effects from the treatment.

CONCLUSIONS

— Diabetic foot problems due primarily to disturbed microcirculation cause considerable morbidity and costs, and their significance for the individual, as well as for the society, is evident from a variety of publications dealing with the socioeconomic aspects of these disorders (14–18).

Although the exact pathophysiological pathways leading to diabetic microangiopathy have not yet been fully elucidated, several hypotheses have been established in which the role of decreased reactivity of arterioles to various stimuli in association with increased capillary pressure and permeability are the most favored (3,4,19).

Since low-intensity lasers have been introduced as tools for stimulating wound healing, this form of phototherapy has been used successfully in various disorders leading to impairment of microcirculation and wound healing, especially in cases in which traditional treatments have previously failed (20–22). There are, however, also studies reporting conflicting results on the effects of lasers on wound healing and its constituents (13,23). The reason for these discrepancies might be found in the great variety of irradiation protocols and animal or culture models used. Moreover, there is evidence that the effects of low-intensity light irradiation also depend on the physiological state of the cell or tissue at the moment of exposure (24,25). Thus it is not surprising that only minor or no effects are observed under physiological conditions. Concerning the molecular mechanisms of action of low-intensity laser irradiation, photosensitized formation of reactive oxygen species (25), activation of previously partially inactivated enzymes (mainly ATPases [26]), stimulation of Ca-influx and mitosis rate (27), and augmented formation of mRNA and protein secretion (28,29) have been reported. Interestingly enough, reduced activity of Na^+-K^+-ATPase is suspected to be involved in the induction of diabetic neuropathy (30). At the cellular level, enhancement of cell proliferation and motility are frequently noted after laser irradiation (24,31,32), which are of significant importance for wound healing procedures.

Because reduced skin microcirculation was present bilaterally and to exclude a possible induction of systemic effects after topical laser irradiation (33), we irradiated both forefeet of our patients. The increase in skin microcirculation achieved after laser irradiation in the present study was found as early as 20 min after initiating light expo-

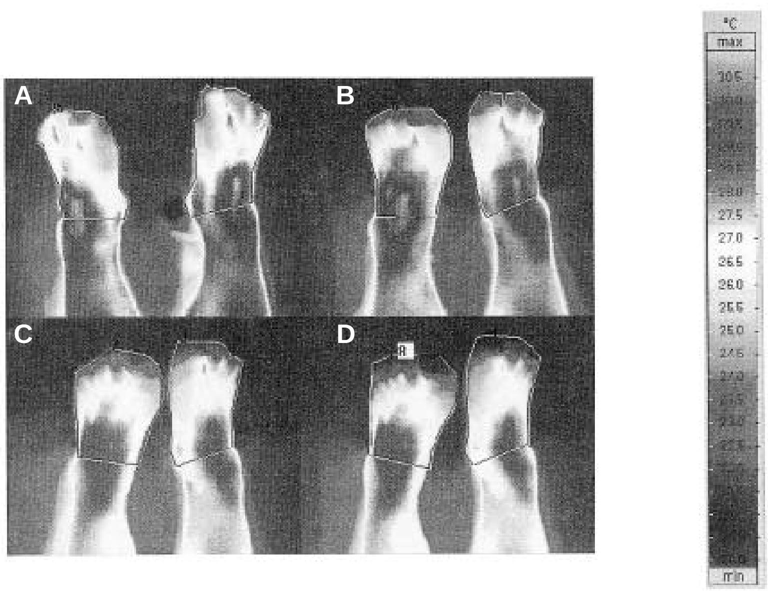

Figure 3—*Typical course of temperature in a patient with diabetic microangiopathy under sham irradiation. Temperature patterns at start of sham irradiation* (A)*, at 20 min of sham irradiation* (B)*, after 50 min of sham irradiation* (C)*, and 15 min after stopping sham irradiation* (D) *are shown.*

sure and persisted up to 15 min after stopping it. Because of this relatively short time within which the observed changes in blood flow occurred, one can postulate that in addition to the long-term effect of low-power lasers on the proliferation of endothelial cells during angiogenesis that has been demonstrated by our group and other researchers (34,35), a short-term reaction is induced. This reaction is presumably caused by the release of transmitter substances, which in turn are responsible for the opening of preexisting capillaries. Because of the variety of laser-induced biological effects mentioned earlier, the observed increase in skin temperature might also be regarded as secondary to enhancement of cell metabolism. The drop in skin temperature during the late phases of sham irradiation was unexpected, since a 30-min period for equilibrium with ambient temperature was allowed before treatment. This drop could be explained by an additional loss of warmth occurring after a plateau phase of steady state between skin temperature and room temperature.

The validity of our data is underlined by a recently published study by Yu et al. (36), who demonstrated the beneficial influence of laser light on wound healing in diabetic mice. Moreover, the improvement of skin microcirculation achieved in the present study is comparable with data previously published by our group (37) and with findings from studies dealing with the effects of other treatment modalities used to improve skin circulation in diabetic patients. Greenstein et al. (38) reported a mean temperature rise after chemical lumal sympathectomy of $<0.75°C$ in diabetic patients. The effect of the anti-platelet agent cilostazol on peripheral vascular disease in diabetic patients was investigated in another publication (11). The authors found a mean rise in skin temperature of 3.3°C after a 1-month administration of the drug. Intravenous administration of the prostacyclin analogon iloprost increased skin temperature by $\sim$2°C in patients with diabetic neuropathy but was associated with a 38% rate of adverse effects (12). In this context, the fact that low-intensity laser irradiation is free of side effects underlines the benefits of this phototherapy. Finally, it has to be stressed that the effects induced by the light source and irradiation parameters used in our study (i.e., athermic monochromatic red visible light) are, in contrast to other phototherapeutic modalities (such as thermotherapeutically applied lamps emitting nonmonochromatic red and infrared light at much higher outputs [$\leq$1,500 W]), nonthermic (i.e., the increase in skin temperature is not induced by the temperature of the beam but by reactions in the tissue).

The present study is, to our knowledge, the first randomized double-blind placebo-controlled clinical trial demonstrating the beneficial effect of low-intensity laser irradiation in patients suffering from diabetic microangiopathy. Although only a relatively short observation time was chosen in our experimental setting, one could, in light of the persistence of skin blood flow improvement even after stopping laser exposure, consider a possible induction of a long-term effect of low-intensity laser irradiation in this indication. Whether this phototherapy could be used prophylactically to reduce tissue damage resulting from diabetic microvascular disturbances, thus preventing long-term hospitalization and amputations in these patients, remains to be elucidated by further studies.

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References

1. Jorneskog G, Brismar K, Fagrell B: Skin capillary circulation severely impaired in toes of patients with IDDM, with and without late diabetic complications. *Diabetologia* 38:474–480, 1995
2. Jorneskog G, Brimar K, Fagrell B: Skin capillary circulation is more impaired in the toes of diabetic than non-diabetic patients with peripheral vascular diesease. *Diabet Med* 12:36–41, 1995
3. Morris SJ, Shore AC, Tooke JE: Responses of the skin microcirculation to acetylcholine and sodium nitroprusside in patients with NIDDM. *Diabetologia* 38:1337–1344, 1995
4. Jaap AJ, Pym CA, Seamark C, Shore AC, Tooke JE: Microvascular function in type 2 (non-insulin-dependent) diabetes: improved vasodilation after one year of good glycaemic control. *Diabet Med* 12:1086–1091, 1995
5. Royal College of General Practitioners: *Survey of Primary Care in London*. Occasional paper 16. London, Royal College of General Practitioners, 1981
6. Danne T, Weber B, Dinesen B, Mortensen HB: Threshold of HbA_{1c} for the effect of hyperglycemia on the risk of diabetic microangiopathy (Letter). *Diabetes Care* 19:183, 1996
7. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
8. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995
9. Di Carlo A: Thermography and the possibilities for its applications in clinical and experimental dermatology. *Clin Dermatol* 13:329–336, 1995
10. Seifalian AM, Stansby G, Jackson A, Howell K, Hamilton G: Comparison of laser Doppler perfusion imaging, laser Doppler flowmetry, and thermographic imaging for assessment of blood flow in human skin. *Eur J Vasc Surg* 8:65–69, 1994
11. Uchikawa T, Murakami T, Furukawa H: Effects of the anti-platelet agent cilostazol on peripheral vascular diease in patients with diabetes mellitus. *Drug Invest* 42:322–324, 1992
12. Shindo H, Tawata M, Aida K, Onaya T: Clinical efficacy of a stable prostacyclin analogon, iloprost, in diabetic neuropathy. *Prostaglandins* 41:85–96, 1991
13. Basford JR: Low energy laser treatment of pain and wounds: hype, hope, or hokum? *Mayo Clin Proc* 61:671–675, 1986
14. Laing P, Cogley D, Klenerman L: Economic aspects of diabetic foot. *Foot* 1:111–112, 1991
15. Trautner C, Haastert B, Giani G, Berger M: Incidence of lower limb amputations and diabetes. *Diabetes Care* 19:1006–1009, 1996
16. Ebskov B, Ebskov L: Major lower limb amputation in diabetic patients: development during 1982 to 1993. *Diabetologica* 39:1607–1610, 1996
17. Levin ME, O'Neal LW: Preface. In *The Diabetic Foot*. Levin ME, O'Neal LW, Eds. St. Louis, MO, CV Mosby, 1988, p. ix–x
18. The Diabetes Control and Complications Trial Research Group: Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. *JAMA* 276:1409–1415, 1996
19. Tooke JE. Peripheral microvascular disease in diabetes. *Diab Res Clin Pract* 30 (Suppl.): 61–65, 1996
20. Schindl L, Kainz A, Kern H: Effect of low power laser irradiation on indolent ulcers caused by Buerger's disease. *Laser Ther* 4:25–31, 1992
21. Schindl A, Schindl M, Schindl L: Successful treatment of persistent radiation ulcer by low power laser therapy. *J Am Acad Dermatol* 37:646–648, 1997
22. Schindl A, Schindl M, Schindl L: Successful phototherapy with low intensity laser irradiation of a chronic radiation ulcer in a patient with lupus erythematosus and dia-

betes mellitus. *Br J Dermatol* 137:840–841, 1997
23. Pogrel MA, Chen JW, Zhang K: Effects of low energy gallium-aluminium-arsenide laser irradiation on cultured fibroblasts and keratinocytes. *Lasers Surg Med* 20:426–432, 1997
24. Steinlechner CWB, Dyson M: The effects of low level laser therapy on the proliferation of keratinocytes. *Laser Ther* 5:65–73, 1993
25. Karu, T: Effects of visible radiation on cultured cells, yearly review. *Photochem Photobiol* 52:1089–1098, 1990
26. Passarella S, Casamassima E, Molinari S, Pastore D, Quagliariello E, Catalano IM, Cingolani A: Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett* 175:95–99, 1984
27. Lubart R, Malik Z, Rochkind S, Fisher T: A possible mechanism of low level laser–living cell interaction. *Laser Ther* 2:65–68, 1990
28. Funk JO, Kruse A, Neustock P, Kirchner H: Helium-neon laser irradiation induces effects on cytokine production at the protein and the mRNA level. *Exp Dermatol* 2:75–83, 1993
29. Funk JO, Kruse A, Kirchner H: Cytokine production after helium-neon laser irradiation in cultures of human peripheral blood mononuclear cells. *J Photochem Photobiol B Biol* 16:347–355, 1992
30. Zorilla-Harnandez E, Frati-Munari A, Lozano-Castaneda O, Villalpando-Hernandez S, Boulton AJ: Diabetic neuropathy: current concepts on etiopathogenesis, diagnosis, and treatment. *Gac Med Mex* 130:18–25, 1995
31. Lubart R, Friedmann H, Levinsthal T, Lavie R, Breitbart H. Effect of light on calcium transport in bull sperm cells. *J Photochem Photobiol B Biol* 15:337–341, 1992
32. Haas AF, Isseroff RR, Wheeland RG, Rood PA, Graves PJ. Low-energy helium-neon laser irradiation increases the motilitity of cultured keratinocytes. *J Invest Dermatol* 94:822–826, 1990
33. Rochkind S, Rousso M, Nissan M, Villarreal M, Barr-Nea L, Rees DG: Systemic effects of low-power laser irradiation on the peripheral and central nervous system, cutaneous wounds, and burns. *Lasers Surg Med* 9:174–182, 1989
34. Schindl L, von Baehr R, Krause A, Kern H, Schindl A, Schindl M: Influence of low incident energy laser irradiation on the Arthus phenomenon induced in rabbit´s cornea: a controlled study. *J Clin Laser Med Surg* 12:31–33, 1994
35. Ghali L, Dyson M. The direct effect of light therapy on endothelial cell proliferation in vitro. In *Angiogenesis Key Principles-Science-Technology-Medicine*. Steiner R, Weisz PB, Langer R, Eds. Basel, Birkhäuser, 1992, p. 411–414
36. Yu W, Naim JO, Lanzafame RJ: Effects of photostimulation on wound healing in diabetic mice. *Lasers Surg Med* 20:56–63, 1997
37. Schindl L, Kainz A, Kern H: Effect of low level laser irradiation on indolent ulcers caused by Buerger´s disease: literature review and preliminary report. *Laser Ther* 4:25–29, 1992
38. Greenstein D, Brown TF, Kester RC: Assessment of chemical lumbar sympathectomy in critical limb ischemia using thermal imaging. *Int J Clin Monit Comput* 11:31–34, 1994
39. Laing P: Diabetic foot ulcers. *Am J Surg* 167:31S–36S, 1994
40. Nathan DM: Long-term complications of diabetes mellitus. *N Engl J Med* 328:1676–1685, 1993