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

Andreas Schindl, MD  
Martin Schindl, MD  
Heidemarie Schön, MD  
Robert Knobler, MD  
Lisalette Havelec, PhD  
Liesbeth Schindl, MD

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 gangrene 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/cm² 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 microcirculation 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 gangrene, 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 patients' 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 gangrene 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 committee, 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.

From the Division of Special and Environmental Dermatology (A.S., R.K.) and the Division of Immunology, Allergy, and Infectious Diseases (H.S.), Department of Dermatology, University of Vienna Medical School; the Institute for Lasermedicine (M.S., L.S.); and the Department of Medical Statistics (L.H.), University of Vienna, Vienna, Austria.

Address correspondence and reprint requests to A. Schindl, MD, Department of Dermatology, Division of Special and Environmental Dermatology, University of Vienna Medical School, Waehringer Guertel 18–20, A-1090 Vienna, Austria. E-mail: andreas.schindl@akh-wien.ac.at.

Received for publication 30 September 1997 and accepted in revised form 19 December 1997.
Thermography unit and temperature recordings
A noncontact infrared thermography camera (Thermo Tracer TH 1100; 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 significance 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-

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<th>Table 1— Demographic and clinical baseline characteristics of patients with diabetic microangiopathy and elevated glycosylated hemoglobin</th>
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<td>Baseline forefoot skin temperature (°C)</td>
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Data are n or means ± SD. Macroangiopathy was diagnosed by angiography. Ulcer diagnosis was adapted from Laing (39). Hypertension was defined as blood pressure >160/95 mmHg. Microalbuminuria was defined as albumin excretion >30 mg/24 h (40). Neuropathy was diagnosed clinically as peripheral symmetric paresthesia, worsening at night (40). Retinopathy was defined using fundus photography. Baseline forefoot skin temperature was calculated from the average for both feet.

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 (†) in the sham-irradiated group.
Laser for improvement of diabetic microangiopathy

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 AT Pases [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 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.

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.
ure and persisted up to 15 min after stop-
ning 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 pre-
sumably caused by the release of transmit-
ter substances, which in turn are
responsible for the opening of perexisting
capillaries. Because of the variety of laser-
induced biological effects mentioned ear-
er, the observed increase in skin
temperature might also be regarded as sec-
ondary to enhancement of cell metabo-
ism. 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 pre-
viously 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-platlet 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. Intra-
venous administration of the prostacyclin
analogon iloprost increased skin tempera-
tureby ~2°C in patients with diabetic neu-
ropathy 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 ther-
motherapeutically applied lamps emitting
nonmonochromatic red and infrared light at
much higher outputs [<1,500 W>], non-
thermic (i.e., the increase in skin tempera-
ture is not induced by the temperature of
the beam but by reactions in the tissue).

The present study is, to our knowl-
edge, the first randomized double-blind
placebo-controlled clinical trial demon-
strating 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,
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 irra-
diation in this indication. Whether this
phototherapy could be used prophylacti-
cally 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.

Acknowledgments — The authors wish to
thank Herbert Hönigsmann, Department of
Dermatology Division of Special and Environ-
mental Dermatology, University of Vienna Med-
ical School, for encouragement and critical
review of the manuscript.

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Diabetes Care, volume 21, number 4, April 1998 583
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