Skin Reactive Hyperemia in Diabetic Patients
A Study by Laser Doppler Flowmetry

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Objective: To assess whether laser Doppler flowmetry could detect differences in the cutaneous response to postischemic reactive hyperemia between patients with non-insulin-dependent diabetes mellitus (NIDDM) and nondiabetic controls and among subgroups of NIDDM patients. Research Design and Methods: We measured the cutaneous blood flow on the forearms during the postischemic reactive hyperemia test in diabetic patients and nondiabetic controls. Subjects were 25 patients with NIDDM from the outpatient clinics of dermatology, ophthalmology, and endocrinology and 25 nondiabetic volunteers matched for sex and age. Of the patients with NIDDM, 14 had proliferative retinopathy, and 13 were obese. Cutaneous postischemic reactive hyperemia test monitored by measuring the cutaneous blood flow with laser Doppler flowmetry was used. Peak blood flow (P) after arterial occlusion, the time required to reach this peak (T_P) and the ratio (K) between these two quantities ($K = P/T_P$) were measured. Results: In diabetic patients, P was significantly lower ($P < 0.02$) than in nondiabetic control subjects. In diabetic patients with proliferative retinopathy, K was lower ($P < 0.05$) than in diabetic patients without retinopathy. Diabetic patients with a body mass index (BMI; wt/ht^2) <25 kg/m^2 had a longer T_P ($P < 0.002$), whereas the control group BMI did not affect this parameter. The combination of retinopathy and BMI <25 gave the longest T_p values ($P < 0.0001$). Conclusions: Postischemic hyperemia tests in diabetic patients reveal cutaneous microcirculatory changes in the forearm (lower P). Advanced retinopathy is associated with functional disturbances (lower K), especially when combined with a low BMI (<25; longer T_p). *Diabetes Care* 14:958–62, 1991

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There is a growing interest in microcirculatory changes in different organs of diabetic patients, and a common etiology is sought (1). Abnormalities of small-vessel blood flow in the hands of diabetic patients have been detected by various techniques; vital capillary microscopy (2), transcutaneous Po_2 measurements (3), intravital fluorescence videomicroscopy (4), and laser Doppler flowmetry (LDF; 5,6). LDF is a noninvasive technique in which the microcirculation of the superficial skin can be examined (7–10). The time course of the cutaneous response to postischemic reactive hyperemia (CPIRH) test, when studied by LDF, can provide accurate and detailed information about changes in microcirculation (8,10,11), because it reveals information about the hemodynamics of the limb, including the residual capability to respond to an arrest in circulation and to compensate for it. Provocative studies of this type have been conducted in patients with peripheral vascular disease to quantitatively assess arterial insufficiency of the limbs (8) and study other general characteristics of the skin blood flow (10).

Using LDF, we investigated the hypothesis that diabetes interferes with the cutaneous response to ischemia. This study compared CPIRH in the forearms of diabetic patients with that of nondiabetic control subjects and compared within the group of patients with diabetes those with known microvascular pathology, i.e., diabetic retinopathy, with those without retinopathy.

RESEARCH DESIGN AND METHODS

The subjects were 25 patients (12 men, 13 women; 33–80 yr of age, mean age 64.5 yr) with NIDDM >4 yr in duration and 25 healthy nondiabetic volunteers

matched for sex and age (35–80 yr of age, mean age 64.4 yr). The patients were referred from dermatology, ophthalmology, and diabetes outpatient clinics. The subjects gave informed consent for the study, the protocol of which was approved by the Israeli Ministry of Health Committee for the Conduct of Human Research. A thorough medical history was taken, and a physical examination was performed on all subjects. Sex, age, body mass index (BMI; wt/ht^2 in kg/m^2; 25 kg/m^2 was taken as the threshold for obesity), smoking habits, hypertension, and ischemic heart disease were recorded. None of the controls or diabetic subjects were taking drugs with a known action on the blood vessels at the time of investigation, apart from hypoglycemic agents in the diabetic group.

All the diabetic patients were checked for microvascular complications as follows: *1*) serum creatinine levels, *2*) gross proteinuria assessed by dipstick on single urine specimens (Multistix 10 SG with Clinitek 200 urine chemistry analyzer; Ames, Elkhart, IN), and *3*) fundoscopic eye examination with fluoresceine angiography. Macrovascular disease was assessed by peripheral pulse exam. In all patients, all pulses of the upper extremities were palpable. All but four (whose tibialis posterior and/or dorsalis pedis pulses were not palpable) also had normal lower extremity pulses. The neurological examination included the search for abnormal sweating history, bladder or bowel dysfunction, and postural hypotension as indications of autonomic neuropathy, and patients with neuropathy were excluded from the study. Blood glucose control was assessed by HbA_{1c} (Helena glyco-Tek affinity column method, Helena, Beaumont, TX). Normal range in our laboratory was 5.2–7.5% HbA_{1c}. The clinical characteristics of the diabetes patients and nondiabetic control patients are shown in Table 1.

TABLE 1
Clinical characteristics of diabetic patients and nondiabetic control subjects

	Diabetic	Control
n (M/F)	12/13	12/13
Age (yr)	64.5 ± 2.0	64.4 ± 2.18
Duration of diabetes (yr)	16.2 ± 2.3	
BMI (kg/m^2)	25.28 ± 0.80	25.00 ± 0.64
n	13	12
Mean ± SE BMI >25 kg/m^2	28.50 ± 0.67	27.70 ± 0.58
n	12	13
Mean ± SE BMI <25 kg/m^2	21.8 ± 0.6	22.4 ± 0.4
HbA_{1c}	10.3 ± 0.4	6.5 ± 0.2
Patients on diet (*n*)	2	
Patients on oral hypoglycemic drugs (*n*)	13	
Patients on insulin (*n*)	10	
Hypertension (*n*)	9	3
Smokers (*n*)	4	4
Ischemic heart disease (*n*)	6	2
Proliferative retinopathy (*n*)	14	
Nephropathy (*n*)	1	

Values are means ± SE. HbA_{1c} normal range 5.2–7.5%. BMI, body mass index.

Cutaneous postischemic reactive hyperemia test. Basic flow was recorded for 5 min in the middle of the flexor aspect of both forearms. The arm was then clamped in a pneumatic cuff and inflated to 300 mmHg for 4 min, during which blood-flow measurements were continuously recorded. The cuff was then instantaneously deflated, and recording was continued for an additional 4 min.

Cutaneous microvascular blood flow measurements. A laser Doppler flowmeter (Perimed, Stockholm) was used (7,9). Cutaneous flow was measured on the tracing of the time course of the response as the difference between the value recorded and the baseline flow. The following parameters were measured: P, peak flow above rest flow; T_P, time lapse required to reach P; and the metabolic quotient $K = P/T_P$ (12). All measurements were done in the same room at 21 ± 1.5°C after a 30-min acclimatization of the patient.

Student's *t* test for independent groups was used to compare the two groups (NIDDM vs. nondiabetic control patients). Three-way analysis of variance was used to compare the subgroups of diabetic patients.

RESULTS

Figure 1 illustrates the time course of the response, and Table 2 summarizes the results of the CPIRH test in diabetic patients compared with nondiabetic controls. The data was log transformed to stabilize the variance and achieve normality. Baseline flow differences were not significant. In the diabetic patients, mean ± SE P was significantly lower (9.42 ± 0.70) than in nondiabetic control patients (12.18 ± 0.90) ($P < 0.02$).

In diabetic patients with retinopathy (Table 3), the ratio K (31.41 ± 3.90) was lower than in those without retinopathy (50.87 ± 10.90) ($P < 0.05$). Diabetic patients with BMI <25 kg/m^2 (Table 3) had a significantly longer T_P (0.40 ± 0.06) than those with BMI >25 kg/m^2 (0.23 ± 0.02) ($P < 0.002$), whereas in the control group, no difference was found between subjects with BMI either above or below 25 kg/m^2. There was an interaction between the factors of retinopathy and BMI. Diabetic patients with retinopathy and BMI <25 kg/m^2 (0.59 ± 0.06) had a longer T_P than those with retinopathy and BMI >25 kg/m^2 (0.203 ± 0.016) ($P < 0.0001$). Hypertension did not affect the reactive hyperemia response. The subgroups did not differ in age, duration of disease, or HbA_{1c} levels.

CONCLUSIONS

A lower P of CPIRH, indicating impaired cutaneous vascular reactivity, was found in the forearms of diabetic

patients but not in nondiabetic control patients. Although Table 1 shows that high blood pressure was more frequent in diabetic patients, separate studies indicated that hypertension had no effect on CPIRH results. Indeed, when we compared 15 nondiabetic patients with high blood pressure to 15 nondiabetic control patients, no significant difference in their CPIRH response was detected. Similarly, Orlandi et al. (13) compared 20 patients with hypertension to 20 age- and sex-matched normotensive control subjects. Using LDF, they measured skin blood flow at the peak of CPIRH and found no significant differences. Hatanaka et al. (14), who observed decreased fingertip blood flow in diabetic patients with LDF, observed normal fingertip blood flow in individuals with hypertension. Finally, our subgroups of diabetic patients with or without hypertension did not differ statistically in any of the measured parameters (Table 3). Therefore, we believe our findings represent true differences influenced by diabetes rather than by hypertension.

This impaired CPIRH response may be explained by various mechanisms: *1*) failure of maximal vasodilatation at the precapillary sphincter muscle level (3,15); *2*) sympathetic denervation (16); *3*) impairment of nutritional cutaneous circulation (17); *4*) decreased ability of erythrocytes to change their shape, as a result of glycosylation of their membranes, thereby reducing the capillary blood flow (18); and *5*) a relative deficiency of vasodilator prostaglandins in the arterial wall of diabetic patients (19), because prostaglandin E–like substances are operative in the mechanism of reactive hyperemia in the human forearm (20).

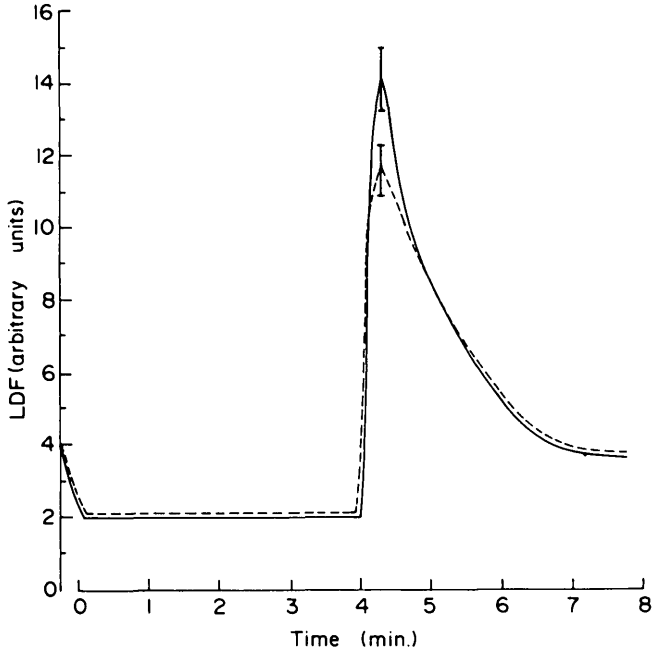

FIG. 1. Cutaneous response to postischemic reactive hyperemia (average of both forearms) as measured by laser Doppler flowmetry (LDF) in 25 subjects with diabetes (*dashed line*) and 25 matched control subjects (*solid line*). SE of peak is indicated.

TABLE 2
Cutaneous response to postischemic reactive hyperemia test as measured by laser Doppler flowmetry (LDF) in diabetic patients vs. nondiabetic control subjects

	n	Peak (P)	Time to peak (T_P; min)	*K* (P/T_P)
Diabetic	25	9.42 ± 0.70*	0.31 ± 0.04	40.0 ± 2.8
Control	25	12.2 ± 0.9	0.31 ± 0.02	43.4 ± 2.1

Values are means ± SE. Results are averages of both forearms. Peak LDF readings expressed in arbitrary units.
*$P < 0.02$ vs. control.

Regardless of the specific mechanism involved, our results indicate that there are functional microvascular disturbances in the forearms of diabetic patients. This observation adds to existing knowledge regarding functional microvascular disturbances in insulin-dependent diabetes mellitus (IDDM) and NIDDM. Katz et al. (21) showed an increased permeability to pentetic acid in the capillaries of the forearm of patients with NIDDM, indicating an abnormality, although these physiological changes were not correlated to the anatomic microvascular structure of the skin. Earlier studies showed an increased permeability of capillary walls in diabetic patients with long-term microvascular complications (4,17). Ajjam et al. (22) demonstrated a significant reduction in luminal area in dermal capillaries in the arms of diabetic patients (NIDDM and IDDM) with microvascular complications that correlated with the functional test of measuring skin finger temperature after an ischemia induced by 3 min of cuff occlusion, where a lower temperature was measured in diabetic patients. They also demonstrated a reduced wheal and flare response to intracutaneous histamine injection into the forearms of diabetic patients. Findings similar to ours were observed in IDDM patients, where transcutaneous P_{O_2} measurements gave a lower and slower forearm CPIRH response (3). An impaired skin microvascular vasodilator response to local trauma was demonstrated by Rayman et al. (23) in widely separated skin sites; peak response was lower in the IDDM group, but the time course was the same.

Within the diabetic group of patients, our study addressed the effects of retinopathy and/or obesity (BMI >25 kg/m^2). The subgroup of diabetic patients with retinopathy was characterized by a significantly lower K (P/T_P). A measure of the rate of ascent of blood flow toward its peak value, K determines the time required to supply a sudden needed increase of blood flow (12). Tooke et al. (24) demonstrated an impaired response to hyperemia in IDDM patients with microangiopathic complications. After a 1-min occlusion of the digital artery, the duration of the hyperemia, measured on the fingernail fold, was significantly longer only in those patients with microangiopathy. Concerning obe-

TABLE 3
Cutaneous response to postischemic reactive hyperemia test as measured by laser Doppler flowmetry (LDF) in diabetic patients

	n	Peak (P)	Time to peak (TP; min)	K (P/T_p)
Retinopathy	14	9.2 ± 0.7	0.37 ± 0.06	31.41 ± 3.90*
No retinopathy	11	9.6 ± 0.9	0.23 ± 0.04	50.87 ± 10.90
Body mass index (kg/m²)				
<25	12	10.42 ± 0.70	0.40 ± 0.06†	40.58 ± 9.60
>25	13	8.5 ± 1.1	0.23 ± 0.02	39.46 ± 6.10
Hypertensive	9	9.33 ± 1.60	0.30 ± 0.07	39.48 ± 9.10
Normotensive	16	9.46 ± 0.74	0.30 ± 0.04	40.0 ± 7.1

Values are means ± SE. Results are averages of both forearms. Peak LDF readings expressed in arbitrary units.
*$P < 0.05$ vs. no retinopathy.
†$P < 0.002$ vs. body mass index >25 kg/m².

sity, although BMI had no influence on the results of nondiabetic controls, diabetic patients with BMI <25 kg/m² had a significantly longer T_p. Therefore, BMI has an influence on the blood flow of diabetic patients. Moreover, this prolongation of time required to reach the peak response was much more pronounced when the diabetic patients had both retinopathy and BMI <25 kg/m².

Although the findings of this study are statistically significant, they cannot be of clinical value when applied to a diabetic individual. Further improvements in LDF techniques and instrumentation and a better understanding of the involved pathophysiological mechanisms may eventually bring the cutaneous postischemic reactive hyperemia test to diabetes clinics.

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