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Influence of metabolic control and duration of disease on microvascular dysfunction in diabetes assessed by laser Doppler anemometry

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Key words: Diabetes mellitus, laser Doppler anemometry, capillary blood cell velocity, metabolic control, disease duration

Summary: A reduced and delayed postocclusive reactive hyperaemia has been demonstrated in diabetic patients using videophotometric capillaroscopy and laser Doppler fluxmetry. The aim of the present study was to examine by means of the new technique of laser Doppler anemometry whether impairment of skin microcirculation differs between type 1 and type 2 diabetic patients especially with regard to metabolic control and duration of diabetes. Sixteen type 1 and 19 type 2 diabetic patients were investigated and subdivided in patients with "good" (HbA_{1c} < 7.5%) or "bad" (HbA_{1c} > 7.5%) metabolic control and in patients with a diabetes duration of less or more than 10 years. Two age- and sex-matched groups comprising 16 and 19 non-diabetic subjects served as controls. The capillary blood cell velocity (CBV) was measured in the dorsal middle phalangeal area during rest and after 3-min arterial occlusion. In type 1 diabetic patients we found a reduced peak CBV (0.69 ± 0.08 mm/s vs. 0.96 ± 0.07 mm/s, $p < 0.05$) and a prolonged time to peak CBV (33.8 ± 4.8s vs. 13.6 ± 1.9 s, $p < 0.001$). The delay of the postocclusive reactive hyperaemia was shown not only in patients with a diabetes duration of more than 10 years and HbA1c values above 7.5% but also in patients with a shorter disease duration and better metabolic control. In type 2 diabetes time to peak CBV (46.8 ± 8.5 s vs. 16.4 ± 2.2 s, $p < 0.001$) was also prolonged already in the first 10 years of the disease. However with regard to metabolic control a reduced peak CBV (0.54 ± 0.04 mm/s vs. 0.70 ± 0.04 mm/s, $p < 0.05$) and a prolonged time to peak CBV (56.6 ± 14.8 s vs. 13.7 ± 2.7 s, $p < 0.01$) was found in type 2 diabetes only in the group of patients with HbA_{1c} > 7.5%. The results indicate that in type 2 diabetes actual metabolic control might be of greater importance for the microvascular dysfunction than in type 1 diabetes and that the skin capillary circulation is impaired already in the first 10 years of both diabetes types.

Introduction

Microcirculation is known to be disturbed in many organs of diabetic patients (Pfeiffer and Schatz, 1995). Beside retinopathy and nephropathy diabetic cardiopathy (Yarom et al., 1992), neuropathy (Malik et al., 1989) and skin lesions are considered as possible sequelae of functional and morphologic abnormalities at the microvascular level. A reduction of capillary skin blood flow during reactive hyperaemia may cause a regional ischaemia and an impaired tissue exchange during stress situations like walking and increased pressure from shoes (Jörneskog et al., 1995a). The reduced and delayed maximal vasodilatation during hyperaemic response could increase the risk for development of chronic foot ulcers in diabetic patients.

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Several noninvasive techniques have been developed to investigate the microcirculation of the skin. The laser Doppler fluxmetry (LDF) measures erythrocyte volume and velocity in the skin capillaries and in the subpapillary vascular bed comprising terminal arterioles and postcapillary venules. The laser Doppler output signal is generated to more than 90% by flow in subpapillary vessels (Fagrell, 1994). The capillary loops subserving skin nutrition carry much less blood than either the deep subpapillary plexus or arteriovenous anastomoses, whose main role is that of thermoregulation. The videophotometric capillaroscopy allows to determine the capillary blood cell velocity (CBV) in the nailfold, where the capillary loops run parallel to the skin surface. In most areas of the human body, except the nailfold, the lips and the nipples, the skin capillaries are located in a 90° angle to the skin surface, and only the tip of the capillary loops can be visualized. By means of a new laser Doppler anemometer it is now possible to measure CBV in capillaries orientated perpendicular to the

Table 1 Clinical details of the diabetic patients and the non-diabetic control subjects

	Type 1 diabetes (n=16)	Control group 1 (n=16)	Type 2 diabetes (n=19)	Control group 2 (n=19)
Sex: male /female (n)	8/8	8/8	12/7	12/7
Age (years)	36 ± 3	37 ± 3	61 ± 3	60 ± 3
BMI (kg/m^2)	24.9 ± 1.3	26.7 ± 1.8	28.4 ± 1.6	28.4 ± 2.7
Systolic blood pressure (mmHg)	112 ± 5	122 ± 5	131 ± 7	136 ± 4
Diastolic blood pressure (mmHg)	64 ± 2	75 ± 2	71 ± 3	75 ± 2
Skin temperature (°C)	30.5 ± 0.6	30.6 ± 0.6	31.2 ± 0.4	30.7 ± 0.4
Essential hypertension (n)	3	4	13	12
Peripheral vascular disease (n)	1	0	3	1
Coronary artery disease (n)	1	2	6	5

Results expressed as number (n) or mean ± SEM

skin surface and thus examine such skin areas where diabetic ulcers may develop.

Under resting conditions various alterations of capillary and total skin microcirculation were observed in diabetic patients. A reduced resting capillary circulation was found in diabetic patients with severe late complications awaiting pancreas transplantation (Jörneskog et al., 1990), in patients with "bad" (HbA_{1c} 8.7 ± 0.8%) metabolic control (Jörneskog et al., 1998) and even in patients without late complications (Jörneskog et al., 1995b). Some studies showed no significant differences of resting CBV in diabetic patients as compared to controls (Jörneskog et al., 1995a; Fagrell et al., 1984; Tooke et al., 1985b; Pazos-Moura et al., 1990). An increase of resting capillary blood flow and total skin microcirculation has been demonstrated especially in patients with peripheral neuropathy (Flynn et al., 1988; Netten et al., 1996). Resting total skin microcirculation measured by laser Doppler fluxmetry was similar in diabetic patients and control subjects although there was a tendency towards higher LDF values in diabetic patients with microangiopathic complications (Jörneskog et al., 1995b; Netten et al., 1996). In general the usefulness of measurements of the cutaneous microcirculation under resting conditions is limited by great intra- and interindividual variability (Fagrell et al., 1977; Bollinger et al., 1974).

Measurements during postocclusive reactive hyperaemia are more reproducible than investigations under resting conditions. Peak CBV following release of a 1-min arterial occlusion of the proximal phalanx of a finger or a toe is often impaired in diabetes (Jörneskog et al., 1995a; Jörneskog et al., 1990; Jörneskog et al., 1995b; Pazos-Moura et al., 1990) and time to peak CBV is significantly prolonged (Jörneskog et al., 1990; Fagrell et al., 1984; Tooke et al., 1985b; Pazos-Moura et al., 1990; Jörneskog et al., 1991; Haak et al., 1998).

The aim of the present study was to examine by means of the new technique of laser Doppler anemometry whether impairment of skin microcirculation differs between type 1 and type 2 diabetic patients especially with regard to metabolic control and duration of diabetes.

Material and methods

Subjects. Sixteen type 1 and 19 type 2 diabetic patients as well as one age- and sex-matched non-diabetic control group for each diabetes type were investigated. Clinical characteristics are presented in Table 1 and 2.

Type 1 diabetic patients. This group consisted of 16 patients (8 men, 8 women) with a mean age of 36 (range 20–60) years and a mean diabetes duration of 12.6 (range 0–40) years. Four patients had been admitted to the hospital because of an onset of diabetes mellitus. Duration of disease was less than 10 years (3.8 ± 1.3 years) in nine patients and more than 10 years (23.8 ± 3.4 years) in seven patients. One patient suffered from neuropathic foot ulcers. Eleven were treated with intensified conventional insulin therapy and five with continuous subcutaneous insulin infusion. Seven patients were smokers. A "good" metabolic control with HbA_{1c} < 7.5% (7.0 ± 0.8%) was found in nine patients and a "bad" one with HbA_{1c} > 7.5% (9.2 ± 0.6%) in seven patients.

Type 2 diabetic patients. This group comprised 19 patients (12 men, 7 women) with a mean age of 61 (range 42–79) years and a mean diabetes duration of 13.1 (range 0–28) years. Two patients were studied at clinical manifestation of diabetes mellitus. Duration of disease was less than 10 years (5.1 ± 2.7 years) in nine patients and more than 10 years (20.3 ± 2.0 years) in 10 patients. Two patients had previous and three actual foot ulcers. 15 patients were treated with insulin (three with conventional insulin therapy and 12 with intensified conventional insulin therapy), two with oral hypoglycaemic medication and two with diet only. One patient was smoker. A "good" metabolic control with HbA_{1c} < 7.5% (6.5 ± 0.3%) was found in nine patients and a "bad" one with HbA_{1c} > 7.5% (8.9 ± 0.3%) in 10 patients.

Table 2 Clinical details of the diabetic patients

	Type 1 diabetes	Type 2 diabetes
Peripheral neuropathy (n)	6	10
Autonomic neuropathy (n)	2	1
Retinopathy (n)	4	2
Nephropathy (n)	5	7
Foot ulcers (n)	1	5
Duration of diabetes (years)	12.6 ± 3.0	13.1 ± 2.4

Results expressed as number (n) or mean ± SEM

Control subjects. Two age- and sex-matched control groups were studied. Control group 1 for the type 1 diabetic patients comprised 16 non-diabetic individuals and control group 2 for the type 2 diabetic patients 19 non-diabetic persons. In control group 1 six persons had a family history of diabetes and five were smokers. In control group 2 six had a family history of diabetes and four were smokers.

Subjects suffering from diseases affecting microcirculation of the skin such as Raynaud's syndrome, collagen vascular diseases, psoriasis and atopic dermatitis were excluded.

Methods. All subjects were acclimatized for at least 20 min before the investigations started, and the room temperature was kept between 21–23 °C. All participants were asked to refrain from smoking, drinking coffee and taking drugs affecting blood pressure the day of the study. The subjects were examined in a sitting position with the hand at heart level. The skin capillary circulation was investigated at the fourth finger of the left hand, which was stabilized by a special finger holder. The finger was illuminated by a 100 W halogen cold light source with a fibre-optic light guide (Euromex EK 1, Arnhem, Holland). The light passed through a green filter to enhance the visualization of the capillaries. A drop of paraffin oil was placed onto the finger to make the skin transparent and to further reduce surface reflections. CBV in single capillaries was measured at the dorsal middle phalangeal area using the laser Doppler anemometer CAM 1 (KK Technology, Braeside, Axminster, Devon, England; Lawrenz Medizinelektronik, Sulzbach, Germany). A cuff was applied at the upper arm of each subject to perform suprasystolic arterial occlusion for investigation of the postocclusive reactive hyperaemia. At the beginning of the procedure resting CBV was recorded for 2 min. The cuff was then inflated for 3 min with a pressure of at least 50 mmHg above the systolic blood pressure. After release of the arterial occlusion peak CBV and time to peak CBV were measured. Percentage increase of CBV (CBV%) after arterial occlusion was calculated. A previous investigation by means of laser Doppler anemometry found a better reproducibility for time to peak CBV ($r = 0.97$; $p \leq 0.0001$) compared to peak CBV ($r = 0.67$; $p \leq 0.002$) (Stücker et al., 1996).

Laser Doppler anemometer. The capillaroscopy system CAM1 (KK Technology, England) includes a microscope objective lens and a CCD camera (Model XC-75CE, Sony, Japan) providing an approximately 220× magnified image of the column of red blood cells within the capillary on a monitor. CAM1 uses a 780 nm 7 mW near infra-red laser diode with a total laser output <1.5 mW. The laser beam is focussed by the microscope objective lens to a spot size of approximately 10 μm diameter. This results in a very small probe volume so that the velocity in a single capillary can be measured. Actual sample depth depends on the tissue but is typically less than 100 μm. A CCD camera (Model XC-75CE, Sony, Japan) is focussed so that the object plane and the laser focal point are the same. The output from the camera is used to identify the location of capillaries within the field of view. The operator then adjusts and maintains the position of the CAM1 with three micromanipulators so that the laser beam is positioned on a suitable capillary. The positioning of the laser beam on the arterial side of the apex of a capillary is achieved using both the capillary microscope and the audible Doppler signal, which is amplified through a loudspeaker. The laser beam is positioned so that the maximal strength of the signal is obtained. If a blood cell is moving with a velocity component perpendicular to the object plane the laser radiation will be reflected with a Doppler shift, which is proportional to the velocity of the blood cell. The Doppler shifted light is collected by the objective lens. Some laser light will also be backscattered by the vessel wall and the surrounding tissue without being Doppler shifted and is collected by the objective lens, too. A wavelength-dependent beamsplitter separates the collected laser radiation from the CCD image and routes it via two mirrors and another beamsplitter to the photodetector, which detects the mixing or heterodyning of the two optical signals. The mixing produces a signal containing the sum and difference frequencies. The difference frequency, or actual Doppler shift, generates an electrical current in the photodetector which is then amplified and filtered, and the Doppler shift frequency is detected. As the Doppler shift is proportional to the velocity of the reflecting blood cells, the velocity can be calculated. The values of CBV are expressed as millimetres per second, assuming that the signal arose from a vessel perpendicular to the skin surface. Variations of capillary angle influence the recorded CBV value but the error is small (e.g. the CBV value would be reduced by 5% at an angle of 18 degrees from the perpendicular). The CAM1 can be used to measure velocities between 0.02 and 14.6 mm/s. A personal computer fitted with a CAM1

Table 3 Microcirculatory data in the diabetic patients and control subjects

	Resting CBV (mm/s)	Peak CBV (mm/s)	Time to peak CBV (s)	CBV%
Type 1 diabetes	0.33 ± 0.04	0.69 ± 0.08[a]	33.8 ± 4.8[c]	113 ± 16
Duration of diabetes:				
<10 years (n = 9)	0.34 ± 0.04	0.72 ± 0.09	25.9 ± 4.6[a]	115 ± 16
>10 years (n = 7)	0.32 ± 0.08	0.64 ± 0.14	43.9 ± 8.0[a]	109 ± 31
Metabolic control:				
HbA_{1c} < 7.5% (n = 9)	0.33 ± 0.06	0.63 ± 0.10	39.6 ± 7.2[a]	103 ± 21
HbA_{1c} > 7.5% (n = 7)	0.34 ± 0.06	0.76 ± 0.13	26.4 ± 5.1[a]	125 ± 25
Control group 1	0.43 ± 0.04	0.96 ± 0.07	13.6 ± 1.9	143 ± 22
Type 2 diabetes	0.34 ± 0.03	0.61 ± 0.06	46.8 ± 8.5[c]	104 ± 26
Duration of diabetes:				
<10 years (n = 9)	0.30 ± 0.03	0.61 ± 0.08	41.3 ± 7.1[a]	100 ± 22
>10 years (n = 10)	0.37 ± 0.05	0.62 ± 0.08	51.8 ± 15.1[a]	107 ± 47
Metabolic control:				
HbA_{1c} < 7.5% (n = 9)	0.32 ± 0.04	0.69 ± 0.10	35.9 ± 6.4	136 ± 48
HbA_{1c} > 7.5% (n = 10)	0.36 ± 0.05	0.54 ± 0.04[a]	56.6 ± 14.8[b]	75 ± 24
Control group 2	0.34 ± 0.03	0.69 ± 0.05	16.4 ± 2.2	124 ± 19

Results expressed as mean ± SEM
[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ as compared to non-diabetic control subjects. Subgroups of diabetic patients are compared to their age- and sex-matched subgroups of the control groups. CBV (capillary blood cell velocity) was measured by laser Doppler anemometry

interface card digitally processes the signals and provides the user display, control and data storage.

Assessment of neuropathy. Autonomic cardiac neuropathy was assessed by measuring the heart rate variation during rest and its responses to deep breathing and Valsalva manoeuvre (Pro Sci Card, Pro Science, Germany). Peripheral neuropathy was investigated by measuring pain, vibration and thermal sensory thresholds (Path-Tester MPI 100, PHYWE, Germany). Seven determinations were made at the dorsum of the left foot to test the warm and 7 to test the cold thresholds. The mean values were calculated. The measurements of the thermal sensory thresholds started at a temperature of 32.0 °C, which was increased respectively decreased by 0.7 °C/s. The pain thresholds were taken as a mean of eight recordings measured on the dorsum of the left foot. The test temperature started at 40.0 °C with an increase of 0.7 °C/s. Vibratory perception thresholds were measured at the external malleolus of the left foot using a vibration frequence of 100 Hz. The intensity of the vibration was three times increased in the first part of the measurement and in the second part three times decreased by 0.50 µm/s.

Assessment of retinopathy. The eyes were examined in mydriasis by an ophthalmologist with ophthalmoscopy and also by non-mydriatic retinal camera (CR4-45NM, Canon, Japan).

Assessment of nephropathy. Urinary albumin concentration was measured and albumin excretion rate was determined from 24 h urine collections.

Skin temperature. The skin temperature was measured in the dorsal middle phalangeal area of the fourth finger of the left hand by medical precision thermometry (CTD85-M Universal Precision Thermometer, Ellab Instruments, Denmark).

Blood tests. Venous blood was taken for determination of haemoglobin, haematocrit, blood glucose, glycated haemoglobin (HbA_{1c}, normal 4.0–6.0%, IM_xSystem, Abbott) serum cholesterol, serum triglyceride, serum creatinine and plasma fibrinogen.

Statistical analysis

All results are expressed as mean ± SEM. The results obtained from measurements of CBV were not normally distributed. Differences between the groups were tested by Mann-Whitney U test. A value of $p < 0.05$ was considered statistically significant. Subgroups were compared to their age- and sex-matched non-diabetic controls.

Results

Capillary circulation (Table 3). No significant differences of resting CBV were found in type 1 and type 2 diabetic patients as compared to their controls. Peak CBV was reduced in type 1 diabetes ($p < 0.05$) as compared to the control subjects, whereas peak CBV in type 2 diabetes mellitus was reduced only in the group of patients with HbA_{1c} > 7.5% ($p < 0.05$) (Fig. 1). Time to peak CBV was markedly prolonged both in type 1 ($p < 0.001$) and type 2 diabetic patients ($p < 0.001$) as compared to the controls. With regard

to metabolic control time to peak CBV was prolonged in type 2 diabetes only in the group of patients with HbA_{1c} > 7.5% (Fig. 2). In type 1 and in type 2 diabetes time to peak CBV was prolonged in patients with a disease duration of both less and more than ten years (Figs. 3 and 4). Mean values of time to peak CBV were higher in type 1 and in type 2 diabetic patients with a duration of disease of more than 10 years as compared to patients with a diabetes duration of less than 10 years, but no statistical significant differences were found. No significant differences of the percentage increases of CBV before and after arterial occlusion were calculated in type 1 and type 2 diabetic patients as compared to control groups.

Skin temperature was similar in type 1 and 2 diabetic patients as compared to contol groups 1 and 2.

Blood tests (Table 4). Blood glucose and HbA_{1c} did not differ comparing both patient groups but were significantly higher as compared to the control subjects. Haemoglobin, haematocrit, plasma fibrinogen, serum creatinine, serum cholesterol and serum triglyceride were similar in patients and control subjects.

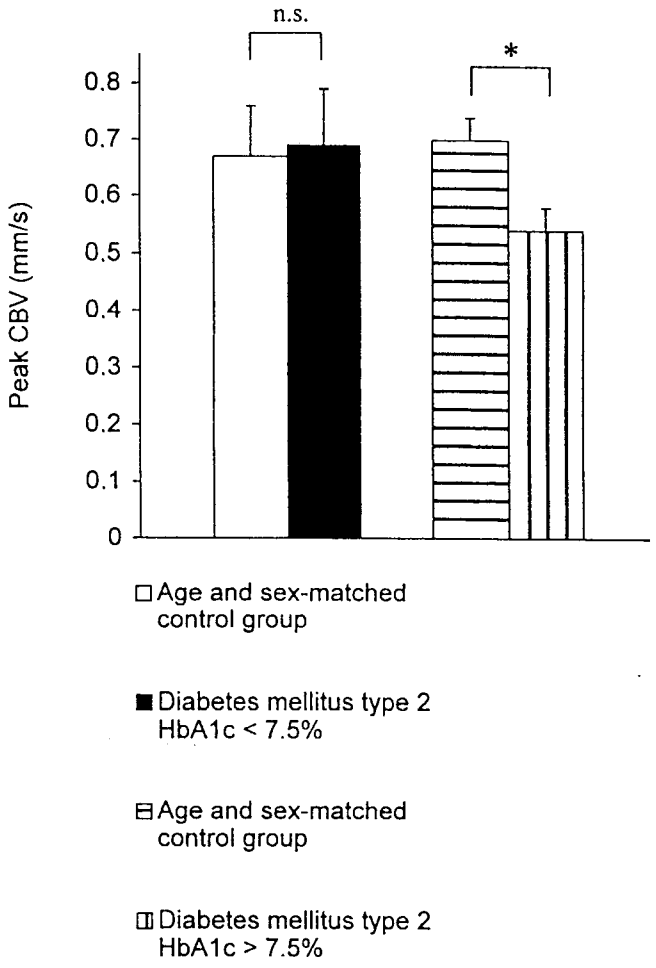

Fig. 1 Peak capillary blood cell velocity (CBV) in type 2 diabetic patients with HbA_{1c} < 7.5% (n = 9) and HbA_{1c} > 7.5% (n = 10) and in age- and sex-matched control groups. Bars represent mean ± SEM. *p < 0.05

Discussion

The present study demonstrates a disturbed cutaneous capillary circulation in type 1 and 2 diabetes by means of laser Doppler anemometry. In type 1 diabetic patients a reduced and delayed postocclusive reactive hyperaemia was found. The delay of the reactive hyperaemia was measured not only in patients with a diabetes duration of more than 10 years and HbA_{1c} values above 7.5% but also in patients with a shorter duration of the disease and a better metabolic control. In type 2 diabetes on the other hand a marked reduction and delay of the reactive hyperaemia response was found only in the group of patients with "bad" metabolic control, defined as HbA_{1c} > 7.5%. As in type 1 diabetes this delay was demonstrable already in the first 10 years of the disease.

In contrast to previous studies on cutaneous capillary circulation in diabetes mellitus by means of videophotometric capillaroscopy we used laser Doppler anemometry. Videophotometric capillaroscopy allows to determine blood cell velocities only in capillaries running parallel to the skin surface. Thus, examinations using this technique are restricted to the nailfold and suppose that nailfold capillaries are representative of the remainder of the skin. The fact that capillaries of the nailfold and of the adjacent skin are perfused from underneath by the same arterioles supports this assumption. However, only in the nailfold capillaries come of metarterioles without ramification. Furthermore, being located in a thin layer of skin, the nailfold capillaries have unique thermal and nutritional conditions differing from the rest of the skin. Laser Doppler anemometry enables to measure blood flow in capillaries orientated perpendicular to the skin surface and thus examine skin areas developing diabetic ulcers. Further advantages of laser Doppler anemometry are that the measurements are performed online and not only in capillaries with good optical signals, i.e. with visible erythrocyte aggregates and plasma gaps. Thus, no patient has to be excluded from measurement because of a restricted capillary visibleness.

Reasons for disturbances of the cutaneous microcirculation may change during the course of diabetes. At the onset of the disease abnormalities of the microvascular haemodynamics are reversible and may be due to alterations in smooth muscle cell function (McVeigh et al., 1992), probably partly caused by altered endothelial cell function resulting in increased endothelium-derived relaxing factor (Graier et al., 1993) and decreased prostacyclin production (John-

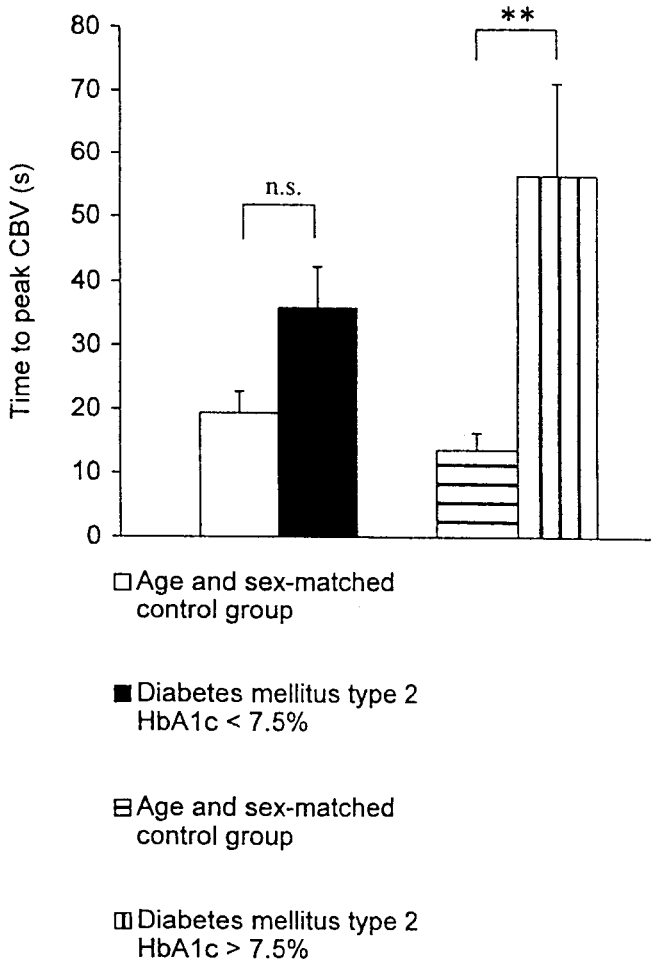

Fig. 2 Time to peak capillary blood cell velocity (CBV) in type 2 diabetic patients with HbA_{1c} < 7.5% (n = 9) and HbA_{1c} > 7.5% (n=10) and in age- and sex-matched control groups. Bars represent mean ± SEM. ** p < 0.01

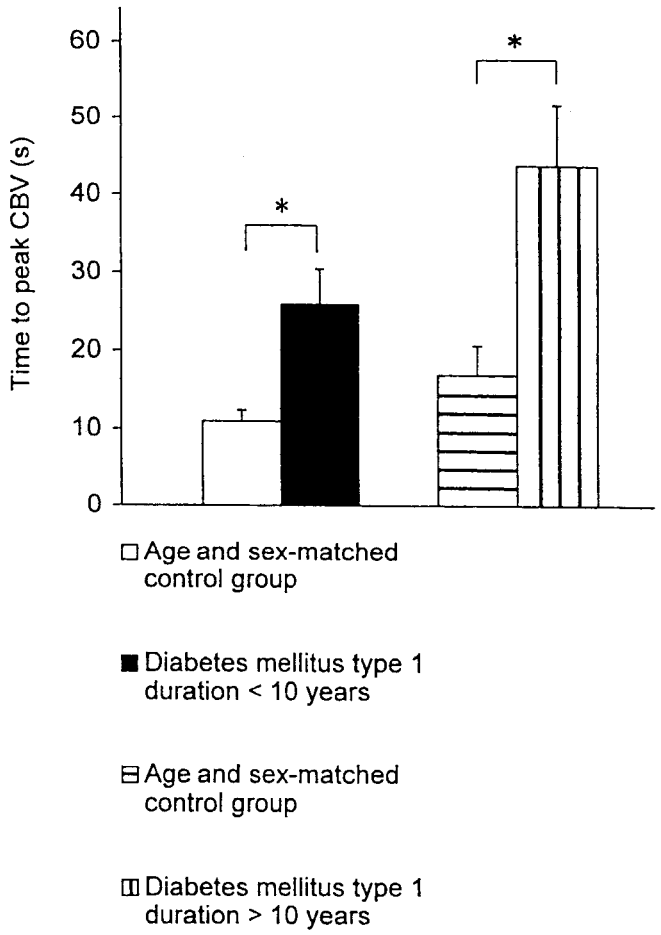

Fig. 3 Time to peak capillary blood cell velocity (CBV) in type 1 diabetic patients with a disease duration of less (n = 9) and more (n = 7) than 10 years and in age- and sex-matched control groups. Bars represent mean ± SEM. * p < 0.05

son et al., 1979; Silberbauer et al., 1979). Haemorheological abnormalities, such as reduced erythrocyte deformability (McMillan et al., 1978), hyperfibrinogenaemia (Ganda et Arkin, 1992) and increased blood viscosity (Lowe et al., 1980) may further enhance disturbances of microcirculation. Hyperglycaemia stimulates the activity of the polyol pathway. Consequences are a decreased sodium-potassium-ATPase activity due to depleted pools of myo-inositol and a pseudohypoxia caused by redox imbalance impairing contractile properties of vascular smooth muscles (Greene et al., 1987; Williamson et al., 1993).

In accordance with this concept of microvascular dysfunction at initial stages of diabetes an impairment of the maximum hyperaemic response to local heating was found in the feet of newly diagnosed non-insulin dependent diabetic patients (Sandeman et al., 1991). Skin microvascular autoregulatory responses assessed by measurement of postocclusive reactive hyperaemia and veno-arteriolar reflex were found to be disturbed in type 1 diabetes with a disease duration of less than one year (Tooke et al., 1985b). An impaired cutaneous postocclusive reactive hyperaemia was described in insulin-dependent diabetic patients without late complications and with a mean diabetes duration of 4.8 years (Jörneskog et al., 1995b). In the present study a delayed postocclusive reactive hyperaemia was demonstrated in type 1 and 2 diabetic patients with a disease duration of less than 10 years.

Another hint for the reversibility of disturbed skin capillary dynamics in diabetes is that insulin was found to increase postocclusive reactive hyperaemia and total capillary blood flow in type 1 diabetic patients perhaps by inducing a redistribution of total skin microcirculation in favour of the nutritive capillary circulation (Tooke et al., 1985a).

Long-term morphologic microvascular changes resulting in an impaired autoregulatory capacity are considered as possible sequelae of accumulation of

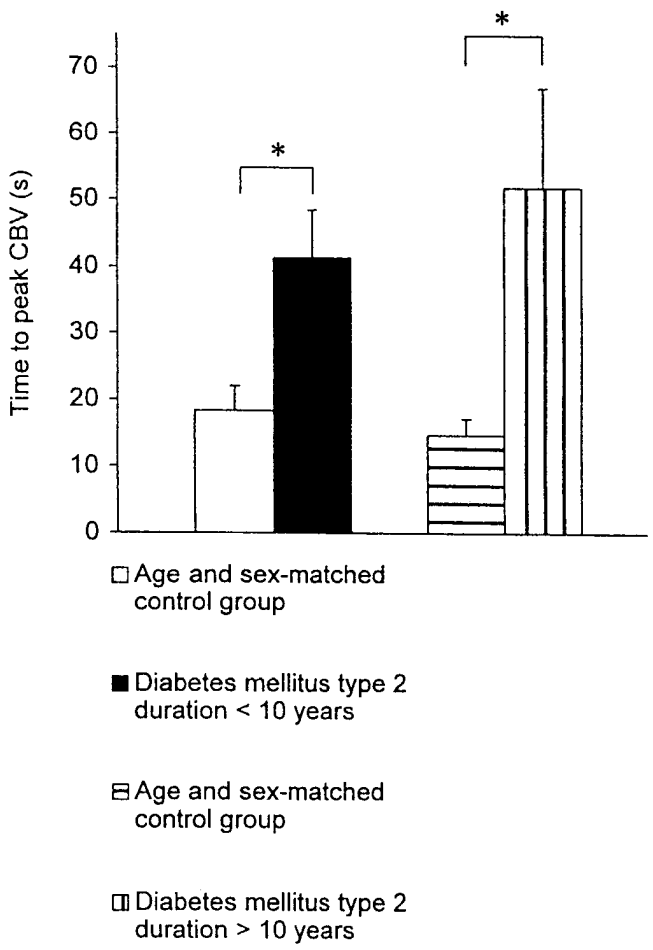

Fig. 4 Time to peak capillary blood cell velocity (CBV) in type 2 diabetic patients with a disease duration of less (n = 9) and more (n = 10) than 10 years and in age- and sex-matched control groups. Bars represent mean ± SEM. * $p < 0.05$

advanced glycosylation end products (Brownlee et al., 1988) and, according to the haemodynamic hypothesis of diabetic microangiopathy, of an increased microvascular flow and intracapillary pressure in early diabetes (Zatz and Brenner, 1986; Tooke, 1986; Rayman et al., 1985; Parving et al., 1983). Another explanation for the observed impairment of reactive hyperaemia is the concept of capillary steal phenomenon which assumes that sympathetic denervation causes opening of arterio-venous anastomoses and therefore a maldistribution of blood between nutritional capillary and deeper, thermoregulatory skin circulation (Watkins and Edmonds, 1983; Boulton et al., 1982; Tesfaye et al., 1993). Some investigations of patients with diabetic neuropathy, however, could not support this hypothesis (Flynn et al., 1988; Netten et al., 1996).

Although the mentioned disturbances in long-term diabetes are only partly or not reversible, no delay of postocclusive reactive hyperaemia was demonstrated in type 1 diabetes with a disease duration of more than ten years and "good" metabolic control (Jörneskog et al., 1998; Tooke et al., 1985b). The problem of studies on the influence of metabolic control on microcirculatory disturbances is that they are often not of a longitudinal design. A normal microvascular function in patients with satisfactory HbA_{1c} values may be, on the one hand, caused by an improvement of a former impaired microcirculation and thereby a hint to reversible alterations and, on the other hand, the result of a continuous good metabolic control since onset of the disease and thus expression of missing morphologic changes. The same problem exists with the interpretation of the data of the present study. In type 2 diabetes we found a reduction and delay of the postocclusive reactive hyperaemia only in the group of patients with $HbA_{1c} > 7.5\%$ not knowing whether metabolic control was "bad" during the preceding weeks only or also during longer periods before. Supporting the concept of regression of microvascular disturbances after normalization of blood glucose a normal microvascular reactivity or an increase of basal capillary blood cell velocity was demonstrated after combined pancreas and kidney transplantation in patients with diabetes (Jörneskog et al., 1990; Jörneskog et al., 1987).

Table 4 Blood tests in diabetic patients and non-diabetic control subjects

	Type 1 diabetes (n = 16)	Control group 1 (n = 16)	Type 2 diabetes (n = 19)	Control group 2 (n = 19)
Haemoglobin (g/dl)	13.8 ± 0.5	14.5 ± 0.4	14.6 ± 0.4	14.3 ± 0.4
Haematocrit (%)	40 ± 1	42 ± 1	43 ± 1	41 ± 1
Plasma fibrinogen (mg/dl)	357 ± 44	301 ± 24	395 ± 31	358 ± 24
Serum creatinine (mg/dl)	1.0 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
Serum cholesterol (mg/dl)	200 ± 13	217 ± 11	247 ± 13	224 ± 10
Triglyceride (mg/dl)	124 ± 20	143 ± 19	194 ± 24	155 ± 21
Blood glucose (mg/dl)	186 ± 19	94 ± 2	144 ± 12	98 ± 4
HbA_{1c} (%)	8.0 ± 0.6	5.0 ± 0.2	7.8 ± 0.4	5.1 ± 0.1

Results expressed as mean ± SEM

In conclusion, early disturbances of the cutaneous microcirculation in diabetes appear to be of functional nature as indicated by an impaired postocclusive reactive hyperaemia already in the first ten years of both type 1 and type 2 diabetes. The hypothesis that metabolic control is of importance for microvascular reactivity was supported, however, only in type 2 diabetes where an impaired postocclusive reactive hyperaemia was observed only in patients with "bad" metabolic control. Reversibility of functional microvascular disorders during short-term improvement of glycaemic control as well as a lack of morphologic changes due to an acceptable long-term metabolic control may be the reasons. Laser Doppler anemometry enables to indicate diabetic microvascular dysfunction in single capillaries orientated perpendicular to the skin surface and thus to examine skin areas developing diabetic ulcers.

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