Early Detection of Microcirculatory Impairment in Diabetic Patients With Foot at Risk

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OBJECTIVE — To assess microcirculatory impairment and alterations of the skin oxygen supply in diabetic patients with foot at risk.

RESEARCH DESIGN AND METHODS — This study evaluated skin blood flow in 21 type 2 diabetic patients with a foot at risk (defined as a foot with neuropathy but without ulceration or previous ulcerations), 20 type 2 diabetic patients without foot lesions or neuropathy, and 21 normal subjects as a control group. The skin blood flow was determined by measuring the transcutaneous oxygen pressure (TcPO₂) at the dorsum of the foot in supine and sitting position. The clinical assessment included standard measures of peripheral and autonomic neuropathy, but peripheral vascular disease was excluded by Doppler ultrasound.

RESULTS — In supine position, TcPO₂ was significantly reduced (means ± SE) in diabetic patients with foot at risk (6.04 ± 0.52 kPa) compared with diabetic (7.14 ± 0.43 kPa, P = 0.035) and nondiabetic (8.10 ± 0.44 kPa, P = 0.01) control subjects. The sitting/supine TcPO₂ difference was higher in diabetic subjects with foot at risk (3.13 ± 0.27 kPa) compared with both diabetic (2.00 ± 0.18, P = 0.004) and nondiabetic (1.77 ± 0.15 kPa, P = 0.0003) control subjects. The mean sitting/supine ratio was 1.70 ± 0.12 in diabetic patients with foot at risk, 1.32 ± 0.04 in diabetic control subjects, and 1.25 ± 0.03 in nondiabetic control subjects (P = 0.007). The sitting/supine TcPO₂ ratio was negatively correlated with the heart rate variation coefficient at rest (r = −0.32, P = 0.044) and at deep respiration (r = −0.31, P = 0.046).

CONCLUSIONS — Our data indicate that skin oxygen supply is reduced in type 2 diabetic patients with foot at risk. This is probably due to an impaired neurogenic blood flow regulation and may contribute to capillary hypertension, followed by disturbed endothelial function leading to edema and skin damage of the foot. The determination of TcPO₂ appears to be a useful tool in screening type 2 diabetic patients for foot at risk.


Foot ulcerations in diabetic patients are a major health problem, often leading to lower-limb amputations and an increased death rate (1,2). The management of diabetic foot ulcers creates considerable costs, estimated at about $1.5 billion in the U.S. Medicare system in 1995 (3). Diabetic neuropathy, mechanical stress, and blood flow alterations are involved in the pathogenesis of diabetic foot ulceration (4,5). These factors interact with the microcirculation, resulting in the failure of skin capillary blood flow (5–9). Besides other factors, reduced skin oxygenation and both sensory and autonomic neuropathy increase the risk of foot ulceration, and screening for and detection of these factors may be useful (5,10). The autonomic nervous system, which supplies sympathetic adrenergic fibers to the arterioles and arteriovenous shunts, directly influences peripheral circulation (8,11). As shown in several studies, transcutaneous oxygen pressure (TcPO₂) measurement provides useful information about microcirculation in diabetic patients without clinical signs of tissue hypoxia (12–14). However, the interactions between autonomic neuropathy and skin blood flow and TcPO₂ in diabetic foot syndrome are not well characterized, and the role of TcPO₂ measurement for detecting impaired microcirculation in the early stages of diabetic foot syndrome is unclear (15). The aim of this study was to assess the skin oxygen supply in type 2 diabetic patients with foot at risk but without previous ulcerations and to determine whether alterations of TcPO₂ in these patients are related to variables of peripheral or autonomic neuropathy.

RESEARCH DESIGN AND METHODS — From September 1998 to April 2000, we enrolled 41 type 2 diabetic patients without previous or current foot ulcerations or peripheral occlusive vascular disease in the study. As a control group, 21 nondiabetic subjects were included. Using a comprehensive interview, patients or control subjects with cardiovascular disease or with any potentially interfering neurological conditions or drug therapies were detected and excluded from the study. Further evaluation of patients and normal subjects considered age, sex, height, weight, BMI, type of diabetes, and diabetes duration. HbA₁c was measured to assess the quality of blood glucose control during the months before the study. According to the results of the neurological examination (described below), diabetic patients were either grouped as patients with peripheral diabetic neuropathy, and therefore foot at risk, (n = 21) or as diabetic patients without signs of neuropathy and without foot
Table 1—Characteristics of 21 diabetic patients with neuropathic foot at risk, 20 patients with diabetes without foot lesions, and 21 control subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neurogenic foot at risk group</th>
<th>Diabetic group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.8 ± 11.2</td>
<td>63.4 ± 17.5</td>
<td>59.9 ± 15.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 5.1</td>
<td>26.1 ± 3.5</td>
<td>25.1 ± 4.5</td>
</tr>
<tr>
<td>Male/female</td>
<td>11/10</td>
<td>9/11</td>
<td>9/12</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>12.0 ± 9.7</td>
<td>10.1 ± 8.5</td>
<td>—</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 1.0*</td>
<td>7.1 ± 1.1</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.2 ± 0.0</td>
</tr>
</tbody>
</table>

Data are n or means ± SD. Age, BMI, sex, HbA1c, diabetes duration, and ankle brachial index did not differ among the groups. For HbA1c, between diabetic patients with or without foot at risk and the control group, *P < 0.001.

at risk (n = 20). Detailed characteristics of type 2 diabetic patients and nondiabetic control subjects are shown in Table 1. The study was approved by the ethical committee of the medical faculty, and informed consent was obtained from patients and control subjects.

**Skin blood flow determination**

Skin blood flow was determined by measuring TcPo₂ with the TCM 30 (Radiometer, Copenhagen) and use of a heated Clark O₂ electrode that was fixed to the skin with an adhesive ring, at a temperature of 45°C. The contact liquid was supplied by the manufacturer. The measuring site was carefully cleaned before the probe was fixed. The average calibration period was 10 min. TcPo₂ measurements were performed at the dorsum of the foot, with the patients initially in a supine and then in a sitting position with their legs hanging down for postural provocation. The reference value was determined by placing the probe on the right side of the chest in the sclavonic region and calculating the regional perfusion index (16). To further exclude peripheral vascular disease or mediasclerosis as potential sources of error, the ankle pressures were measured with a 10-cm-wide pneumatic cuff and a Doppler flow probe (Huntleigh Diagnostics, Cardiff, U.K.). Multiple readings, usually three, were always obtained, and the average pressure was recorded. Ankle brachial indexes were calculated by dividing the pressure at the ankle by the brachial pressure. The highest arm pressure was used as denominator.

**Evaluation of peripheral and autonomic diabetic neuropathy**

Peripheral diabetic neuropathy was evaluated by the vibration perception threshold with the calibrated Rydell-Seiffer tuning fork and the Phywe Vibratester (Phywe System, Hochstberg, Germany) at the dorsal surface of the great toe and the external malleolus of both sides. Three determinations of each method were made, and the mean values were calculated. Autonomic neuropathy was assessed by recording heart rate variation at rest, deep respiration, and Valsalva maneuver (ProSciCard, Linden, Germany). Autonomic neuropathy was confirmed by at least two positive tests of the assessment (17). All tests were performed in the morning, after patients and control subjects had rested for 10–15 min, in a room in which the temperature was maintained between 21 and 25°C.

**Statistical analysis**

Statistical analyses included descriptive statistics; the means, the standard deviation, and the standard error of the mean were calculated. Differences in continuous variables between the groups were compared by analysis of variance, and nominal variables were compared using Fisher’s exact test. Correlations between TcPo₂ and the variables of peripheral or autonomic neuropathy were calculated with linear regression analysis. Statistical analyses were performed using JMP version 4.0 for Windows (SAS Institute, Cary, NC). P < 0.05 was considered statistically significant.

**RESULTS** — A total of 21 diabetic patients (11 males and 10 females, aged 65.8 ± 11.2 years), without previous or existing foot ulcers but with neuropathy, were included in the foot at risk group. A total of 20 patients (9 males and 11 females, aged 63.4 ± 17.5 years), with diabetes but without foot lesions and neuropathy, comprised the diabetic control group. A total of 21 normal subjects (9 males and 12 females, aged 59.9 ± 15.9 years) were included in the control group (Table 1). There was no significant difference in age, sex, BMI, duration of diabetes, HbA1c, or ankle brachial index between the foot at risk group and the diabetic patients without neuropathy or a history of foot lesions (Table 1). As expected, HbA1c differed significantly between the two diabetic groups and the control group of normal subjects (Table 1).

At rest (supine position), TcPo₂ was significantly reduced (mean ± SE) in diabetic patients with foot at risk (6.04 ± 0.52 kPa) compared with diabetic patients without neuropathy or a history of foot lesions (7.14 ± 0.43 kPa) and the control group (8.10 ± 0.44 kPa) (P = 0.035 and P = 0.01, respectively). In contrast, TcPo₂ in the sitting position did not differ among the three groups (foot at risk group: 9.17 ± 0.38 kPa; diabetic patients without neuropathy: 9.14 ± 0.31 kPa; nondiabetic control subjects: 9.87 ± 0.34 kPa; P = NS) (Fig. 1). The difference between sitting and supine TcPo₂ was significantly higher in the diabetic group with foot at risk (3.13 ± 0.27 kPa) compared with the diabetic control group (2.0 ± 0.18 kPa) and the control group (1.77 ± 0.15 kPa) (P = 0.004 and P = 0.0003, respectively). Correspondingly, the mean sitting/supine ratio was 1.70 ± 0.12 in diabetic patients with foot at risk, 1.32 ± 0.04 in the diabetic group, and 1.25 ± 0.03 in the control group (P = 0.007). As expected, there was no significant difference in regard to the TcPo₂ difference and the sitting/supine ratio between the diabetic group without neuropathy and foot lesions and the control group (Fig. 1).

In the foot at risk group, the vibration perception threshold, the heart rate variation coefficient at rest, and deep respiration differed significantly compared with the diabetic control group and the control group of normal subjects (P < 0.0001). As expected, there was no significant difference between the diabetic group without neuropathy or a history of foot ulcers and normal subjects, except for a signifi-
cant difference in the heart rate variation coefficient at deep respiration ($P = 0.036$). The Valsalva test did not differ significantly among the three groups.

In patients with neuropathic foot at risk, the sitting/supine ratio of TcPO$_2$ was inversely correlated (Fig. 2) with the heart rate variation coefficient at rest ($r = -0.32, P = 0.044$) and deep respiration ($r = -0.31, P = 0.046$). There was no significant correlation between the vibration perception threshold or the Valsalva maneuver and the TcPO$_2$ ratio ($P = 0.15$ and $P = 0.34$, respectively).

**CONCLUSIONS** — In addition to peripheral neuropathy and occlusive vascular disease, an impaired microcirculation appears to play an important role in the development of the diabetic foot syndrome, which is defined as any acute or chronic lesion of the foot in diabetic patients. The interaction between neuropathy and abnormalities in the microcirculation is complex, and a disturbed microcirculation is already present in clinically mild neuropathy. Our aim was to assess the skin oxygen supply, determined as TcPO$_2$, in type 2 diabetic patients with foot at risk and to determine whether alterations in skin oxygen supply are related predominantly to peripheral or to autonomic neuropathy.

The main finding of our study was that TcPO$_2$ is significantly reduced in type 2 diabetic patients with foot at risk but without peripheral occlusive vascular disease compared with both diabetic patients without diabetic foot syndrome risk factors and nondiabetic subjects. Considering the overshooting increase in TcPO$_2$ in the sitting position, these findings are compatible with an impaired vessel autoregulation in patients with foot at risk. It has previously been shown that such an impaired autoregulation can be found in diabetic patients with a history of foot ulcers (5,10). We extended these findings to the observation that the altered skin oxygen supply may precede the development of diabetic foot ulcers. Therefore, it is conceivable that impaired vessel autoregulation is a major factor in the pathogenesis of diabetic foot ulcers. Interestingly, the altered skin oxygen supply in type 2 diabetic patients is not related to the extent of peripheral neuropathy, as assessed by the Phywe Vibratexeter (Phywe System). In contrast, we have demonstrated a clear inverse correlation between the TcPO$_2$ sitting/supine ratio and heart rate variation at rest and during deep respiration. This indicates that the disturbed vessel autoregulation may be regarded as a consequence of diabetic autonomic neuropathy. This observation is in concordance with some (8,11) but not all (15,18) previous studies. The most prob-
able mechanism by which impaired vessel autoregulation is involved in the development of diabetic foot ulcers is an increase in anastomotic blood flow through the arteriovenous shunts, which is thought to be caused by peripheral autonomic neuropathy. This leads to higher tissue temperature and metabolic demand and has been suggested to predispose to edema formation with a subsequent increase in tissue pressure, resulting in impaired capillary flow (8) and, as a consequence, diminished TcPO₂ in the supine position. The overshooting increase in TcPO₂ may be explained by an impaired postural vasoconstriction in diabetic patients with autonomic neuropathy, which, in contrast to normal subjects (19), causes an increased hydrostatic pressure in dependency, followed by edema formation.

Our data indicate that, in type 2 diabetic patients with foot at risk, the skin oxygen supply is reduced and vessel autoregulation is clearly impaired. Because reduced skin oxygen supply has been shown to be an independent risk factor for diabetic foot ulcers (10), measurement of TcPO₂ appears to be a useful tool for identifying diabetic patients with foot at risk.

References

Figure 1: A: The correlation of the sitting/supine ratio of TcPO₂ and the heart rate variation coefficient at rest. *R = −0.32 and P = 0.044. B: The correlation between the sitting/supine ratio of TcPO₂ and the heart rate variation coefficient at deep respiration. †R = −0.31 and P = 0.046. C: The correlation of the sitting/supine ratio of TcPO₂ and the Valsalva maneuver. ‡R = −0.15 and P = 0.34.
Early detection of microcirculatory impairment


