Transcutaneous oximetry but not arterial toe blood pressure or ankle-brachial index is related to macular thickness in patients with chronic diabetic foot ulcers

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Abstract

Objectives: Diabetes related vascular complications of the lower extremity could be classified as micro- and macrovascular. Ankle-brachial index (ABI) and toe blood pressure (TBP) measurements evaluate macro-circulation, whereas transcutaneous oximetry (TcPO₂) is considered to be a composite measure of vascular function, thereby also reflecting microcirculation. Microvascular disease in the eye involves abnormal capillary permeability and possibly thereby increased macular thickness. The aim of the present clinical study was to evaluate if microvascular disease in the eye was related to measures of foot ischemia in patients with diabetes mellitus.

Methods: Twenty consecutive patients with diabetes and chronic full-thickness foot ulcers were included. Peripheral ischemia was diagnosed using TcPO₂, TBP and ABI. Macular thickness was measured with optical coherence tomography technique.

Results: Based on TcPO₂, TBP and ABI measurements 14, 13 and 13 patients, respectively, were classified as ischemic. Patients with ischemic TcPO₂ levels at the dorsum of the foot had significantly higher macular thicknesses. This was not the case in patients with ischemic TBP or ABI levels.

Conclusion: TcPO₂, unlike TBP and ABI, seems to be a clinically relevant measure of peripheral microvascular disease in patients with diabetes mellitus and may, if low, indicate an increased risk of macular edema.

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INTRODUCTION

Chronic foot ulcers as well as glomerulopathy and retinopathy are severe long-term complications of diabetes mellitus [1-3]. Diabetic retinopathy (DRP) is a progressive disease predominantly affecting the integrity of the microscopic vessels in the retina and its earliest visible sign is microaneurysms [4, 5]. In many cases the permeability of the blood-retina barrier is compromised by yet not fully understood mechanisms resulting in leakage of fluid from the capillaries to the surrounding tissue [6]. This leads to an increase of volume and consequently to increased retinal thickness, measurable with ocular coherence tomography (OCT) technique [7, 8]. When this increased retinal thickness involves the macula, it is referred to as diabetic macular edema (DME), a condition linked to visual impairment [9-11]. The prevalence of DME in the Wisconsin Epidemiologic Study of Diabetic Retinopathy was 11.1% [12]. Similarly, diabetic nephropathy mirrors microvascular disease, and a firm link has been demonstrated between nephropathy and retinopathy in diabetic patients [2, 13].

Chronic foot ulcers in diabetic patients have a multifactorial etiology including neuropathy, infection and macro- as well as microvascular disease, where ankle-brachial index (ABI) and arterial toe blood
pressure (TBP) are used to estimate macrovascular function [3,14]. Lately transcutaneous oximetry (TcPO₂) has been used as a composite measure of vascular function in evaluating oxygen tissue delivery, thereby also reflecting microcirculatory factors involved in ulcer etiology and healing [14,15].

The aim of the present study was to evaluate if macular thickness was related to ischemia in patients with diabetes and impaired peripheral blood flow, i.e. in patients with chronic foot ulcers.

**METHODS**

Twenty consecutive patients with diabetes and chronic full-thickness foot ulcers below the ankle were included in this study. All participants provided written informed consent. The protocol was approved by the Ethics Committee at the University of Lund, Sweden. The study is registered as NCT00953186 at ClinicalTrials.gov.

**Macular thickness measurements**

Macular thickness was measured using OCT technique (OCT 2000, Zeiss-Humphrey, Dublin, CA, USA; application version A2). OCT is a standard method giving images of the retinal structures, and retinal thickness is defined as the distance between the surface of the inner retina and the outer layer of the photoreceptors [7,16,17] (Fig.1). Using the fast macular protocol of the OCT-instrument, six consecutive radial macular scans of 6 mm length and equally spaced orientation were centered on the foveola by the patients’ fixing their gaze at the fixation light of the instrument [7].

The mean foveal thickness is defined as the calculated mean thickness of the central 1000 μm diameter area of the macula. Minimum thickness of the six radial scans was determined manually and the lowest value was taken as central macular thickness [7,18]. In healthy non-diabetic eyes central macular-thickness, as measured with the OCT2000 instrument, is between 140 and 200 μm [17].

**TcPO₂ measurements**

TcPO₂ measurements were obtained with a radiometer device (TCM-2 Radiometer, Copenhagen, Denmark). After calibration all measurements were performed in supine position after 20 min of rest. Room temperature was kept between 21 and 24°C. Patients were asked to avoid smoking or coffee for at least two hours before investigations.

According to our protocol TcPO₂ was measured on the dorsum of the foot, 2 cm proximal to the base of the third toe or as close to this location as possible. Areas directly overlying bone or superficial veins were avoided. The measuring site was carefully cleansed, before the electrochemical transducer was applied to the skin using adhesive rings and contact liquid supplied by the manufacturer. To increase skin oxygen permeability the transducer was heated to 42°C. After baseline equilibration, TcPO₂ values were recorded once every minute while the patient was breathing air for six minutes. The highest TcPO₂ value during this period was chosen.

**Arterial toe blood pressure measurements**

A small cuff was applied around the first toe, or, if not applicable, the second toe. Return of pulsatile blood flow, i.e. TBP, was detected by pulse oximetry [19, 20]. All measurements were performed in supine position after 20 minutes of rest. TBP was measured on both legs, and the lowest value was used in calculations.

**Ankle-brachial index measurements**

Systolic arm blood pressure was measured in supine position. Systolic ankle pressure was measured with a pen Doppler over the dorsal pedal and posterior tibial arteries, if these values differed the highest was used. Ankle blood pressure was measured on both legs, and the lowest value was used in calculations of ABI.

**Patient classification**

Patients were classified according to TcPO₂, TBP and ABI. Predefined cutoff levels for ischemia were: TcPO₂ ≤ 55 mmHg, TBP ≤ 60 mmHg and ABI ≤ 0.9 or ≥ 1.4 [21-23].

**Statistics**

Frequencies are given in percent and continuous data as median and min-max. Mann-Whitney U-test was used for comparison between groups, and differences in frequencies were analyzed with Fisher’s exact test. Relations between parameters were evaluated using Spearman Rank-correlation test. A two-sided P-value below 0.05 was considered as statistically significant. Statistical analysis was performed with the use of Statistica software, version 10.0 (Statsoft Inc, Tulsa, OK, USA).

**Figure 1.** An OCT-image of the macula, showing the vitreoretinal interface, the reflective layer adjacent to the retinal pigment epithelium and the foveolar depression.
RESULTS

Twenty patients (40 eyes) with median diabetes duration of 22 (16-35) years were included. Patient characteristics are given in Table 1. Median TcPO$_2$ was 48 (21-89) mmHg, median TBP 55 (14-140) mmHg and median ABI 0.77 (0.36-1.74). Based on TcPO$_2$, TBP and ABI measurements 14, 13 and 13 patients, respectively, were classified as ischemic (Fig.2).

Mean foveal thickness was significantly related to central foveal thickness ($r^2 = 0.805$, $P < 0.001$) (Fig.3). A significant relation was present between TcPO$_2$ and central foveal thickness ($r = -0.329$, $P = 0.04$, $r^2 = 0.109$). This relation was statistically insignificant for TcPO$_2$ and mean foveal thickness ($r = -0.309$, $P = 0.052$, $r^2 = 0.096$). Central foveal thickness was neither significantly related to TBP ($r = -0.014$, $P = 0.93$, $r^2 = 0.000$) nor to ABI ($r = -0.209$, $P = 0.195$, $r^2 = 0.044$). Also, neither TBP ($r = -0.036$, $P = 0.833$, $r^2 = 0.001$) nor ABI ($r = -0.074$, $P = 0.65$, $r^2 = 0.006$) were significantly related to mean foveal thickness.

Patients with ischemic TcPO$_2$ levels at the dorsum of the foot had significantly higher mean foveal and central foveal thicknesses in the eye (Fig.4). Central foveal thickness was 230 (159-354) µm in patients with ischemic and 204 (164-283) µm in patients with normal TcPO$_2$ levels ($P = 0.03$). Similar differences were seen for mean foveal thicknesses (200 (140-330) µm vs 165 (130-250) µm, $P = 0.03$). This was not seen using TBP or ABI as circulatory measures (Fig.4). Mean foveal thickness was 229 (159-354) µm in patients with low and 215 (164-329) µm in patients with normal ABI ($P = 0.24$), and 215 (159-329) µm vs 230 (164-354) µm in patients with low or normal TBP, respectively ($P = 0.2$). Corresponding figures for central foveal thickness were 178 (140-300) and 188 (130-300) µm (ABI, $P = 0.62$) and 200 (140-300) µm vs 175 (130-330) µm (TBP, $P = 0.16$).

![Figure 2. Numbers of diabetic patients with chronic foot ulcers (total n=20) with ischemia according to TcPO$_2$-levels, ankle-brachial index (ABI) and toe blood pressure (TBP). Predefined cutoff levels for foot ischemia were: TcPO$_2$ ≤ 55 mmHg, TBP ≤ 60 mmHg and ABI ≤ 0.9 or ≥ 1.4.](http://www.jeim.org)

![Figure 3. Relation between central foveal thickness and mean foveal thickness in patients with diabetes and chronic foot ulcers.](http://www.jeim.org)

Table 1. Patient’s baseline characteristics

<table>
<thead>
<tr>
<th>Type of diabetes (type 1/type 2)</th>
<th>25%/75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>80%/20%</td>
</tr>
<tr>
<td>Age</td>
<td>73 (45-85) years</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12 (9.5-15.1) g/dl</td>
</tr>
<tr>
<td>Hemoglobin A$_{1c}$</td>
<td>6.3 (5.3-10.9) %</td>
</tr>
<tr>
<td>Creatinine</td>
<td>103 (63-339) µmol/l</td>
</tr>
<tr>
<td>Present smokers</td>
<td>25%</td>
</tr>
<tr>
<td>Previous smokers</td>
<td>50%</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>40%</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>20%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>35%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>25%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>85%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>90%</td>
</tr>
<tr>
<td>Dialysis or renal transplantation</td>
<td>15%</td>
</tr>
<tr>
<td>Major amputation</td>
<td>15%</td>
</tr>
<tr>
<td>History of Charcot foot arthropathy</td>
<td>10%</td>
</tr>
<tr>
<td>Previous vascular surgical intervention in the lower limb</td>
<td>70%</td>
</tr>
</tbody>
</table>

Pharmacological treatment

| Insulin                     | 90% |
| Metformin                  | 25% |
| Sulfonylurea                | 20% |
| ACE-inhibitor / angiotensin receptor blocker | 90% |
| Diuretics                  | 55% |
| Beta-blockers              | 35% |
| Aspirin or clopidogrel      | 70% |
| Warfarin                   | 25% |
| Statins                    | 85% |
DISCUSSION

Diabetes related long-term peripheral vascular complications in the lower extremity could be classified as micro- and macrovascular. Macrovascular complications mainly include atherosclerosis and peripheral large artery disease, in clinical routine often evaluated using ABI and TBP as objective measures. In patients with diabetes mellitus, TBP might thereby be considered as the better method, since ankle blood pressure may be falsely elevated in patients with media sclerosis [24]. TcPO$_2$, in clinical routine a more seldom used circulatory measure, is influenced by arterial oxygen supply as well as local factors such as oxygen consumption and capillary density and function [25, 26]. Thus, while TBP predominately mirrors macrocirculation, TcPO$_2$ elucidates a composite measure of micro- as well as macrocirculation. Accordingly, this composite circulatory measure has previously been shown to be a clinically valuable tool in different settings, including selection of patients for hyperbaric oxygen therapy in terms of improved ulcer healing of chronic foot ulcers. In concert with these findings hyperbaric oxygen therapy has been shown to improve microcirculation in these patients [15, 27, 28].

Diabetic microvascular complications also involve retina, kidney and nerve function. The blood-retina barrier (BRB) prevents fluid leakage through the retinal capillary walls. The function of this barrier is complex and yet not fully understood. It involves endothelial cells, pericytes, astrocytes, Muller cells and several proteins establishing tight junctions [6]. Diabetes might lead to dysfunction of pericytes, endothelial cells and some of the involved proteins. Fluid leakage - further amplified by the onkotic action of extravasated solutes - might be a consequence, and the process is further augmented by inflammatory leukokines, cytokines and growth factors [6]. Accordingly, microvascular disease in the eye involves abnormal capillary permeability and thereby increased macular thickness [6, 29].

In the present study OCT technique was used to evaluate macular thickness. Thereby accurate and reproducible measures were accessed. As this procedure is time-consuming and expensive we decided to limit our explorative study to include 20 patients with diabetes mellitus and known peripheral vascular disease.

In the present study we found that eye macula thickness was significantly increased in patients with ischemic foot TcPO$_2$. This was not the case in patients with ischemic TBP or ABI levels. Hyperbaric oxygen (HBO) therapy has been shown to improve TcPO$_2$ levels in the foot and to enhance diabetic foot ulcer healing [27, 30]. Accordingly, it might be appropriate to evaluate the effect of HBO on macular thickness.

Our findings support the concept of foot TcPO$_2$, unlike TBP and ABI, as a clinically relevant measure of peripheral microvascular disease in patients with diabetes mellitus.

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COMPETING INTERESTS

None to declare.
REFERENCES
