Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes

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WHAT THIS PAPER ADDS
This is, to the author’s knowledge, the first study that examines the influence of time to revascularization on outcome of ischemic foot ulcers in patients with diabetes. This study observed consecutively presenting and prospectively followed patients with diabetes, foot ulcers, and severe PAD, treated and followed by a multidisciplinary foot team. Shorter time to revascularization and less tissue destruction positively affects the probability of healing over time of ischemic foot ulcer in patients with diabetes. The present study highlights the need to prioritize investigation and revascularization in patients with diabetes and peripheral ischemia to improve the outcome of foot ulcer.

Objectives: There is limited information about whether time from recognition of decreased perfusion to revascularization affects the probability of healing in a patient with a diabetic foot ulcer. The aim of the present study was to examine whether time to revascularization after referral to a multidisciplinary foot center was related to the outcome of foot ulcers in patients with diabetes and severe peripheral arterial disease (PAD).

Methods: Patients with diabetes, a foot ulcer, and a systolic toe pressure <45 mmHg or an ankle pressure <80 mmHg were prospectively included at the foot center, and considered for revascularization according to a preset protocol. All patients underwent invasive revascularization, either percutaneous transluminal angioplasty (PTA) or reconstructive vascular surgery. All patients had continuous follow-up until healing or death irrespective of the type of revascularization.

Results: A total of 478 patients were included (age 74 [range 66–80] years, 60% males), of whom 315 patients (66%) had PTA, and 163 (34%) had reconstructive surgery. Of the 478 patients, 217 (45%) healed primarily, 88 (19%) healed after a minor amputation, 76 (16%) healed after a major amputation and 92 patients (19%) died unhealed. The median time from inclusion in the study to revascularization was 8 weeks (3–18 weeks). Time to vascular intervention within 8 weeks (p < .001), maximum Wagner grade reached <3 (p < .001), absence of peripheral edema (p = .033), and presence of intermittent claudication (p = .001) were related to a higher probability of healing.

Conclusions: Time to revascularization and extent of tissue damage were related to the probability of healing of ischemic foot ulcer in patients with diabetes over time. In the presence of a decreased perfusion in a patient with diabetes and a foot ulcer not only revascularization per se but also timing of revascularization is important for the possibility of healing without a major amputation.

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INTRODUCTION

Foot ulcer is a major complication among patients with diabetes, with a lifetime risk for developing foot ulcer as high as 25%.1,2 Foot ulcer in patients with diabetes is associated with an increased risk of lower limb amputation, and thus the primary aim of treatment for ischemic foot ulcer is limb preservation.3 A coordinated healthcare system with a multidisciplinary approach is essential to reduce the number of amputations.4 Development of diabetic foot ulcer (DFU) is attributed to many interacting factors, the most common ones being peripheral neuropathy and peripheral arterial disease (PAD).5 PAD is an important precipitating factor in the outcome of diabetic foot ulcer, as 50% of
diabetic patients with foot ulcer have PAD.\textsuperscript{5,6} PAD is also considered as the most important factor related to the outcome of diabetic foot ulcer.\textsuperscript{7}–\textsuperscript{9}

Invasive revascularization, including open reconstructive surgery and/or endovascular intervention, is the most effective treatment that may improve peripheral circulation and remedy symptoms.\textsuperscript{8} The majority of studies on revascularization in ischemic conditions include both patients with and without diabetes and examines the rate of limb salvage improvement, rather than ulcer healing as an outcome after a specific intervention.\textsuperscript{10}–\textsuperscript{12}

We have previously shown that invasive revascularization positively affects the probability of healing of ischemic foot ulcer in patients with diabetes.\textsuperscript{13} It is suggested that vascular imaging and subsequent revascularization be considered in patients with diabetes and ischemic foot ulcer if no healing has occurred within 6 weeks of appropriate non-invasive treatment irrespective of non-invasive vascular test results.\textsuperscript{14} However, there is very limited information regarding effect of waiting time to revascularization on the outcome of diabetic foot ulcer. The aim of this study was to examine the relationship between time to revascularization and the probability of healing without major amputation in consecutively presenting patients with diabetes and ischemic foot ulcer, referred to a diabetic foot center.

**MATERIAL AND METHODS**

**Study population**

A total of 1,151 consecutively presenting patients with diabetes and ischemic foot ulcer were admitted to a multidisciplinary foot center during the years 1984–2006. Out of these patients, 478 had either percutaneous transluminal angioplasty (PTA) or reconstructive surgery, and were included in the present study. The patients’ data were prospectively recorded. Patients who did not have an invasive revascularization were excluded. The reasons why no invasive revascularization was done in excluded patients have been described previously.\textsuperscript{13} The study was approved by the local ethics committee.

**Inclusion criteria**

Patients with diabetes mellitus, foot ulcer (Wagner grade 1–5, at or below the ankle) and a systolic toe pressure <45 mmHg and/or systolic ankle pressure <80 mmHg were included. When pressures could not be recorded, patients with non-palpable foot pulses with an ulcer Wagner grade 4–5 or pain at rest were included. Rest pain was defined as severe persistent pain localized to the foot and relieved by dependency. All patients were Fontaine grade 4.\textsuperscript{16}

**Study design**

Patients were followed and treated according to a preset standardized protocol by a multidisciplinary team both in and out of hospital until healing, with or without amputation, was achieved, or until the patient died with an unhealed ulcer.\textsuperscript{13,15} A more detailed description of management protocols during study period including protocols on local wound treatment is available in the Supplementary Information (online only). All lesions were assessed and documented by the same team. Outpatient treatment was carried out in collaboration with primary healthcare and home nursing services. Physical examination of the foot was performed at inclusion and regularly during the study by the multidisciplinary team.

The core team consisted of a diabetologist, an orthopedic surgeon, an orthotist, a podiatrist, and a registered nurse educated in diabetes. Systolic toe and ankle blood pressure was measured using strain gauge and Doppler techniques at the vascular laboratory.\textsuperscript{17} Radiological arterial investigation was carried out according to a prescheduled program by a vascular surgeon integrated in the team on a regular basis. Specially trained casting technicians provided a continuous service for total contact casting. A specialist in infectious diseases was available for consultations when required.

At entry to the study data were collected on previous management, referral, patient characteristics, co-morbidities, ulcer characteristics and laboratory investigations.\textsuperscript{13}

Each patient was represented by one lesion below the ankle. Patients with two or more concurrent lesions were represented by the one with the worst outcome. Patients with three or more ulcers on the same foot were classified as having multiple ulcers. The most superficial ulcer included was a full thickness skin ulcer penetrating into the subcutaneous layer. The Wagner grade at inclusion and the maximal Wagner grade reached were recorded. Minor amputation is defined as amputation through or below the ankle joint; and major amputation is defined as amputation above the ankle joint.\textsuperscript{18}

**Vascular intervention**

Angiography was performed at the discretion of a vascular surgeon according to a written program that was jointly agreed upon. A retrograde aorto-femoral angiogram, routinely visualizing the distal vessels including the pedal arch, was performed if the medical condition allowed and subject to informed consent. The catheter was placed as distal as possible and delayed and magnified lateral foot views were routinely obtained. The popliteal and crural arteries were selectively catheterized when possible. All patients undergoing angiography were treated according to a program prior to and after intervention with respect to hydration and choice of pharmaceutical drugs to avoid renal failure.\textsuperscript{19} The decision for revascularization was taken by the vascular surgeon at the weekly interdisciplinary diabetic foot round, mainly based on the ulcer characteristics, findings of peripheral pressure measurements, and the response to the given conservative management.\textsuperscript{20}

Simultaneous PTA was performed when possible. In case of stenoses or occlusions of more than one crural artery, revascularization of all stenosed or occluded crural arteries was attempted. The decision and performance of
revascularization by vascular surgeon was based on its technical availability and thus not necessarily directed to the artery/arteries supplying the angiosome or ulcer area. After PTA patients were put on low molecular weight heparin for a minimum of three months. All patients were treated with acetylsalicylic acid (ASA) or clopidogrel if no contraindication was present.

In patients where PTA was not possible or not successful, reconstructive surgery was considered and performed at the discretion of the vascular surgeon, provided the patient’s medical condition allowed surgery and subject to informed consent. Distal reconstructive surgery was defined as bypass to or distal to the tibioperoneal trunk. Post-operative care and follow up were performed in cooperation with and under the supervision of the team according to program. Time to revascularization was calculated from first presentation at the diabetic foot center, since the time from onset of ulcer was often unknown.

**Statistical analysis**

Values are given as median and interquartile range (IQR, 25th to 75th). Comparisons between groups were made using the Mann–Whitney or chi-square test. Statistical significance was defined as $p < .05$. Cox proportional hazard regression (backward stepwise, lr, method) was used to estimate the independent effect of waiting time to invasive vascular intervention on time to ulcer healing. Time to revascularization from arrival to the clinic was entered as a vascular intervention on time to ulcer healing. Time to estimate the independent effect of waiting time to invasive vascular intervention (backward stepwise, lr, method) was used to analyze the independent effect of waiting time to invasive vascular intervention. The analysis was adjusted for the type of invasive vascular intervention and for the study inclusion period (1, 1984–1989; 2, 1990–1999; 3, 2000–2006). Patients in the reconstruction surgery group ($n = 15$) who had exploration only were excluded from this analysis.

Univariate survival analysis of the statistically significant variables in the previous model was done using Kaplan–Meier analysis where statistical significance was determined by log-rank test. Statistical analysis was performed using SPSS statistics 21.0 (IBM corporation, New York, NY, USA).

**RESULTS**

**General characteristics**

Four hundred and seventy-eight patients were included. Three patients dropped out following the revascularization, and 475 continued follow up in the study. The median age was 74 years (66–80 years); 60% were men, with a median time of known diabetes of 15 years (10–24 years) (Table 1). Intermittent claudication was present in 34% of patients, rest pain in 63%, and peripheral edema in 57%. A systolic toe pressure $<45$ mmHg and an ankle pressure $<80$ mmHg were seen in 78% and 43% of patients respectively. At inclusion, 21% of the patients had deep ulcer of Wagner grade $\geq 3$, but 50% of the patients showed ulcer progression during follow up and 55% had reached a maximum Wagner grade of $\geq 3$ at some stage during the study period. Median follow up time until outcome was 10 months (5–16 months).

**Table 1.** Clinical characteristics at inclusion.

<table>
<thead>
<tr>
<th></th>
<th>All ($n = 475$)</th>
<th>Patients healed without major amputation ($n = 305$)</th>
<th>Patients healed after major amputation or deceased unhealed ($n = 170$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>60% (284)</td>
<td>60% (184)</td>
<td>59% (101)</td>
<td>.846</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>74 (66–80)</td>
<td>72 (65–79)</td>
<td>76 (70–80)</td>
<td>.007</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>58 (44–67)</td>
<td>57 (43–67)</td>
<td>60 (49–68)</td>
<td>.119</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>15 (10–24)</td>
<td>15 (9–25)</td>
<td>15 (10–23)</td>
<td>.929</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.8 (6.2–9.0)</td>
<td>7.8 (6.1–9.0)</td>
<td>7.9 (6.4–9.0)</td>
<td>.879</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>92 (75–127)</td>
<td>90 (74–120)</td>
<td>95 (78–148)</td>
<td>.016</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>160 (140–170)</td>
<td>160 (140–175)</td>
<td>160 (140–170)</td>
<td>.548</td>
</tr>
<tr>
<td>Ankle pressure (mmHg)</td>
<td>80 (60–110)</td>
<td>80 (60–110)</td>
<td>80 (60–111)</td>
<td>.968</td>
</tr>
<tr>
<td>Toe pressure (mmHg)</td>
<td>30 (20–40)</td>
<td>30 (20–40)</td>
<td>30 (20–40)</td>
<td>.821</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>51% (242)</td>
<td>52% (159)</td>
<td>49% (83)</td>
<td>.502</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>38% (180)</td>
<td>35% (108)</td>
<td>42% (72)</td>
<td>.200</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>34% (162)</td>
<td>39% (120)</td>
<td>25% (42)</td>
<td>.001</td>
</tr>
<tr>
<td>Rest pain</td>
<td>63% (299)</td>
<td>61% (187)</td>
<td>66% (113)</td>
<td>.319</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>57% (270)</td>
<td>54% (164)</td>
<td>63% (107)</td>
<td>.080</td>
</tr>
<tr>
<td>IHD</td>
<td>41% (196)</td>
<td>38% (117)</td>
<td>47% (80)</td>
<td>.081</td>
</tr>
<tr>
<td>CHF</td>
<td>27% (127)</td>
<td>22% (66)</td>
<td>36% (62)</td>
<td>.001</td>
</tr>
<tr>
<td>CVD</td>
<td>28% (131)</td>
<td>27% (82)</td>
<td>29% (50)</td>
<td>.595</td>
</tr>
<tr>
<td>Wagner grade $\geq 3$</td>
<td>21% (98)</td>
<td>22% (68)</td>
<td>18% (30)</td>
<td>.239</td>
</tr>
<tr>
<td>Max. Wagner grade $\geq 3$</td>
<td>55% (262)</td>
<td>48% (146)</td>
<td>68% (116)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Note.** Data are % ($n$), or median (interquartile range). IHD = ischemic heart disease; CHF = congestive heart failure; CVD = cerebrovascular disease.

a Three drop-out patients are not included.

b Patients with primary healing of ulcer or healing after a minor amputation.

c Ulcer Wagner grade at inclusion.

d Maximal ulcer Wagner grade reached during the study period.
**Revascularization**

PTA was performed in 315 patients (66%). The levels of interventions were at the iliac artery (10%), femoral artery (53%), popliteal artery (35%), and at the crural arteries in 46% of cases, with an average of 1.5 procedures per extremity. Reconstructive vascular surgery was attempted in 163 patients (34%). In 15 (9%) an exploration revealed that no reconstruction was possible. In the remaining 148 patients, 62% (n = 92) had distal procedures, tibioperoneal trunk or below (Supplemental Table). No difference was found between patients who had PTA or reconstructive surgery regarding ulcer progression (data not shown).

**Time to revascularization**

Median time from first presentation at the diabetic foot center to revascularization was 8 weeks (3–18 weeks). Patients who had shorter time to revascularization (≤8 weeks) than those with longer time to revascularization (>8 weeks) had more often peripheral edema (62% vs. 50%, p = .025) and more often rest pain (69% vs. 56%, p = .005). Median time between diagnostic angiography and PTA was 0 week (0–0.1 week), while median time between diagnostic angiography and reconstructive surgery was 4 weeks (2–10 weeks).

**Outcome**

Of the 475 patients, 305 (64%) healed without major amputation, 217 (45%) healed primarily, and 88 (19%) healed after a minor amputation. Sixteen percent of the patients healed after a major amputation (n = 76) and 19% (n = 92) died unhealed. Two patients had an ongoing ulcer at the end of follow up. Thus 80% of the surviving patients healed without major amputation. The median healing time irrespective of intervention was 10 (5–16) months. Median healing time for primary healing was 8 (4–15) months, and for healing after minor amputation was 14 (9–20) months.

Patients who healed without major amputation were younger (p = .007), had lower serum creatinine (p = .016), congestive heart failure less frequently (p = .001), signs of ulcer progression less often (p < .001), and intermittent claudication more often (p = .001) (Table 1).

**Factors affecting probability of healing over time**

Shorter time to revascularization (Fig. 1), Wagner grade <3 reached during follow-up period (Fig. 2), and presence of intermittent claudication were significantly related to higher probability of healing without major amputation over time. The presence of peripheral edema was significantly related to a lower probability of healing (Table 2). No statistical differences were seen between patients with and without intermittent claudication regarding toe pressure or ankle pressure. However, patients with intermittent claudication less often had peripheral edema compared with those without intermittent claudication (49% vs. 62%, p = .008).

Univariate survival analysis of each of these factors was done using Kaplan–Meier analysis. Each factor, time to vascular intervention (p < .001), maximal Wagner grade <3 (p < .001), absence of peripheral edema (p = .013), and intermittent claudication (p < .001), showed significant relation to healing without major amputation over time. Kaplan–Meier analysis was done for time to revascularization in patients who had reconstructive vascular surgery or PTA separately. Both groups showed significant relation to healing without major amputation over time (Fig. 3A,B). A similar analysis was done separately for time to revascularization for patients who healed primarily and for those...
who healed after minor amputation. Time to revascularization showed a statistically significant relation to both healing primarily ($p = .006$), and to healing after minor amputation ($p < .001$). Kaplan–Meier analysis was done for maximal Wagner grade in patients who had reconstructive vascular surgery or PTA separately. Both groups showed significant relation to healing without major amputation over time (Supplementary Fig. A,B).

**DISCUSSION**

In this study of consecutively presenting and prospectively followed patients with diabetes, foot ulcers and severe PAD, treated and followed by a multidisciplinary foot team, time to revascularization, extent of tissue destruction, peripheral edema, and intermittent claudication were related to the probability of healing without major amputation.

This is, to the author’s knowledge, the first study that examines the influence of time to revascularization on outcome of ischemic foot ulcer in patients with diabetes. No difference was seen between patients who had endovascular or open revascularization with regard to time to revascularization after first visit to the diabetic foot team.

In the present study, a shorter time from first presentation at the foot team to revascularization, predicted a better healing probability without major amputation. The finding was the same for PTA and for reconstructive surgery. Currently, an observation time of 4–6 weeks is recommended by the International Working Group on the diabetic foot before revascularization is considered in patients with diabetes and ischemic foot ulcer, irrespective of the results of the non-invasive vascular tests. The European Society for Vascular Surgery recommends local debridement in the situation of deep foot infection, before considering revascularization in the same patient group. Similarly, in the Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II), revascularization should be considered if clear signs of critical limb ischemia are present or if healing does not occur despite optimal non-invasive treatment.

There is limited information regarding the outcome of revascularization in patients with diabetes, severe PAD, and a foot ulcer. Most studies include patients with and without diabetes and also report on outcome in term of limb salvage rather than ulcer healing. In one study by Faglia E et al., regarding early debridement and revascularization in patients with diabetes and an acute deep foot infection, the authors concluded that immediate revascularization allows for an outcome similar to patients without PAD. All patients in that study had a deep foot infection, which was the primary reason for the admission. It was concluded that early surgery with regard to foot infection had a better outcome than clinical observation using systemic antibiotics. The average time difference to revascularization for the immediate versus later revascularization groups was only 6 days.

In the present study, the extent of tissue destruction reached during follow up predicts worse healing over time. Similar findings have recently been shown among patients with diabetes and ischemic foot ulcer not available for revascularization. This is in agreement with previous observations. This result per se, in addition to the finding that time to revascularization affects outcome, may reflect the need to consider invasive revascularization as early as possible in patients with diabetes and ischemic foot ulcer irrespective of the presence of pain or the extent of wound and tissue destruction.

The presence of peripheral edema in this study was significantly related to a lower probability of healing. Peripheral edema has previously been shown to be related to diabetes.

**Table 2.** Survival analysis for factors affecting healing probability.

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent claudication</td>
<td>1.64 (1.26–2.13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0.76 (0.58–0.98)</td>
<td>.033</td>
</tr>
<tr>
<td>Max. Wagner grades &lt;3 reached</td>
<td>1.92 (1.50–2.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time to intervention &lt;8 weeks</td>
<td>1.96 (1.52–2.52)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Note.* Healing is primary healing or healing after a minor amputation. HR = hazard ratio; CI = confidence interval.

A Time between first presentation at diabetic centre and revascularization.

**Figure 3.** Probability of ulcer healing without major amputation in relation to time to revascularization in patients who had (A) reconstructive vascular surgery or (B) percutaneous transluminal angioplasty.
foot ulcer healing in patients with diabetes. Peripheral edema was also found to be more common in patients with diabetes and foot ulcer who required amputation or died unhealed than in those with primary healing. Edema is often multifactorial in origin, and its treatment should also focus on the predisposing cause.

Assessment of the need for revascularization in patients with ischemic diabetic foot ulcers has frequently been based on the presence of persisting ischemic pain, or when healing probability is low by conservative treatment only. The fact that almost all patients in the present study underwent revascularization, except for the 15 patients who only had exploration, bias the results toward the high prevalence of ischemic pain (97%), which indicates the importance of ischemic symptoms in decision-making by the vascular surgeon regarding revascularization and time for intervention. Intermittent claudication, as a sign of peripheral ischemia, is known to be generally less frequent in patients with diabetes than in those without it.

Time to revascularization in this study was calculated from first visit to the foot team, since time from foot ulcer onset is usually unknown or not confirmed. Delay between the onset of a foot lesion and first treatment is common. Almost 40% of foot lesions are not detected by the patient him/herself but by relatives or healthcare staff. Furthermore, patients with diabetes who believe that pain is a reliable symptom of foot ulceration are less likely to seek medical advice early for foot care. The delay between initial treatment of foot ulcer and referral to a foot clinic is also common, where the main reasons are underestimation of the severity of foot lesions or lack of recognition of ischemia. There is still limited information regarding factors influencing the patient’s willingness to attend medical care and regarding time delay in referral patterns and pathways to intervention, particularly in patients with diabetes and ischemic foot ulcers. In the Eudros study, an ulcer duration of 1 week to 3 months was reported in 57% of the patients and >3 months in 27%. Long ulcer duration was associated with the risk of non-healing. However, ulcer duration was reported as at entry into the study. In a large Swedish study, Gershater et al. reported an estimation of ulcer duration of 11 weeks (range 0–350 weeks), which had no significant effect on ulcer outcome.

Some methodological issues need to be considered when evaluating the present cohort study. A potential negative selection bias has to be taken into account, because the patients were admitted to a university-based foot center, and no exceptions were made with regard to age, comorbidity, or expected survival, and it cannot be excluded that a few patients with foot ulcer were treated in other healthcare units without the foot team’s knowledge. The present study is based on a pre-defined protocol regarding inclusion, evaluation, and follow up. However, the decision for vascular intervention was at the discretion of the vascular surgeon. In the present study, the outcome after PTA was not compared with that of vascular surgery, since according to the design of the study, PTA was performed as an initial choice of treatment, and vascular surgery was performed in patients not considered suitable for PTA. It should also be recognized that recruitment to the present study was stopped when magnetic resonance angiography and computed tomography angiography became routine procedures and even more extensive endovascular techniques were introduced.

In conclusion, shorter time to revascularization and less tissue destruction positively affects the probability of healing of ischemic foot ulcer in patients with diabetes over time. The present study highlights the need to prioritize investigation and revascularization in patients with diabetes and severe peripheral ischemia to improve the outcome of foot ulcer.

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY INFORMATION

Supplementary information related to this article can be found online at http://dx.doi.org/10.1016/j.ejvs.2014.06.041.

REFERENCES
