Local signs and symptoms in relation to final amputation level in diabetic patients

A prospective study of 187 patients with foot ulcers

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Local signs and symptoms were evaluated in 187 consecutively presenting diabetic patients undergoing amputation for foot ulcers. From admission until final outcome the patients were treated by the same multidisciplinary team both as in- and outpatients. At the time of amputation, the types of lesions were superficial/deep ulcer (n 17), ulcer with deep infection, but without gangrene (n 40), and gangrene with or without infection (n 130). Healing after a minor amputation (below the ankle) occurred in 74 patients, while 88 patients healed after a major amputation (above the ankle), and 25 patients died before healing had occurred. Deep infection and presence of popliteal or pedal pulses were associated with healing after minor amputation and so were ulcers on the small toes, metatarsal head area and midfoot. Pain, progressive gangrene, intermittent claudication, and decubital and multiple ulcers were related to healing after major amputation. In a logistic regression analysis, pain, progressive gangrene and intermittent claudication remained. However, none of these factors excluded healing of a minor amputation and thus selection of amputation level in diabetic patients with foot ulcers cannot be based upon these factors exclusively.

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More than 80 percent of amputations in diabetic patients are precipitated by a foot ulcer (Pecoraro et al. 1990). Several different clinical and laboratory parameters have been suggested as guidelines for the selection of amputation level in diabetic patients. So far, no test, non-invasive or otherwise, has proved to be fully reliable. The decision whether to amputate, and at what level, still ultimately rests upon clinical judgement (O'Neal 1988). Most studies are retrospective and are usually concerned with below-knee amputation as compared to through-knee or above-knee amputation, while others deal with mixed cohorts. The aim of this prospective study was to describe local clinical signs and symptoms and their relation to the ultimate outcome of amputation (healing below ankle, healing above ankle or death before healing had occurred) in a large consecutive series of diabetic patients with foot ulcer undergoing amputation.

Patients and methods

In a prospective study running from July 1, 1983 until December 31, 1991, 188 of 720 consecutively presenting patients with diabetes mellitus, referred to a foot-care team at the University Hospital, Lund because of foot ulcers, required an amputation during the observation period. In 1 patient, the wound had not yet healed, leaving 187 patients for the study. There were 105 men and 82 women with a median age of 72 (32–94) years and with a median duration of diabetes of 16 (1–59) years. Metabolic control was maintained by diet alone in 18 patients, by oral agents in 40 and by insulin in 129 patients. In 9 patients, previous amputations had been performed and healed at toe or forefoot level in the same leg. On the contralateral side, 9 amputations below the ankle, 1 Syme amputation and 18 amputations above the ankle had been done. All patients had clinical signs of polyneuropathy (biothesiometer value > 30 and/or atrophy of the extensor digitorum brevis muscle in 179 and absent Achilles reflex in the remaining 8 patients). In 110 patients, ischemia was present, as defined by an ankle pressure < 80 or a toe pressure < 45 mmHg (Apelqvist et al. 1992). Of the remaining 77 patients, 61 had clinical signs of peripheral vascular disease, as expressed by an ankle index < 0.8, absence of both pedal pulses, claudication, or rest pain.

Clinical characteristics and definitions

Each patient was represented by the first amputation occurring after enrolment in the study and was evaluated with regard to the final level of amputation. All lesions were documented by color photography. In 4 patients with simultaneous bilateral amputation, the leg with the most severe lesion was chosen. Lesions were classified according to Wagner (1981). Gangrene was defined as a continuous necrosis of the skin and underlying structures (muscle, tendon, joint, or bone), indicating an irreversible damage where healing cannot be anticipated without loss of some part of the extremity. Gangrene, whether wet or dry, was classified as minor when it involved some portion of a toe, toes and/or the forefoot and as major gangrene when it involved so much of the foot that no local revision or amputation was sufficient and an amputation above ankle level was required. Amputation below the ankle is referred to as minor and above the ankle as major. All local signs presented refer to the affected leg only. Edema was defined as swelling of the foot so pronounced as to leave a clear imprint after pressure by a finger. Peripheral pulses of the lower extremity (dorsalis pedis, posterior tibial, popliteal and femoral arteries) were examined by palpation and recorded as present or absent. Rest pain was defined as severe and persistent pain localized to the foot and relieved by lowering of the foot. Deep infection was defined as evidence of abscess, osteitis or septic tenovaginitis. For site description, the following areas were used: great toe, small toes, metatarsal head area, mid-foot, heel, and multiple ulcers (≥ 3). Cause of the ulcer was established by questioning the patient and/or relatives or nursing staff and also by inspecting stockings and footwear. Healing was defined as intact skin for at least 6 months or, if the patient died within that period, as intact skin at the time of death. Examination of muscular and sensory functions were performed at the patient's first visit. The vibration perception threshold (VPT) was measured with a biothesiometer; values exceeding 30 arbitrary units (scale 1–50) were considered indicative of sensory neuropathy (Boulton et al. 1986). Muscle-wasting and weakness and the Achilles reflexes were tested as previously described (Lithner et al. 1991). In 12 patients, the presence of muscle weakness and/or atrophy could not be evaluated due to the condition of the patient.

Distal blood pressure measurements were performed with strain gauge or Doppler techniques as previously described (Apelqvist et al. 1989a).

Treatment

The general treatment policy was to avoid any unnecessary amputation, and, when necessary, to amputate as distally as possible and to maintain ambulation. As a consequence, most amputations were done as emergency procedures.

All patients were treated by a foot-care team (diabetologist, orthopedic surgeon, diabetes nurse, podiatrist and orthotist) both as in- and out-patients and followed-up by the same team until final outcome in order to ensure a comprehensive medical approach and to eliminate differences in strategy between individual physicians and surgeons. In-patient treatment was used only when surgery was required, in septic conditions or because of intercurrent disease.

Medical and surgical treatment prior to amputation

The medical treatment has been previously described (Larsson et al. 1993). Dry and inactive necrosis or minor gangrene was, in most cases, left to undergo mummification and auto-amputation as long as pain, progression of gangrene and infection would allow. In the event of active, deep infection, particularly abscess formation, extensive debridement under general or regional anesthesia was carried out. Minor debridements were done in the consulting room as required, care being taken to avoid interfering with barely viable tissue.

A vascular surgeon was consulted regarding 103 patients. Revascularization (n 26) or angioplastic procedures (n 10) were performed in 36 patients at a median time of 2 (1–38) months prior to amputation. 2 patients with minor amputations had a revascularization and 1 had an angioplastic procedure after the amputation, but before healing had occurred. Arteriography without intervention was done in another 50 patients, while 14 patients were assessed by the vascular surgeon and found not to qualify for further investigations due to the local situation or the general condition of the patient.

Amputation

The decision to amputate was taken by the orthopedic surgeon and the diabetologist on clinical grounds, the criteria being progressive gangrene, intolerable pain, in spite of adequate analgesic medication, and septic and/or toxic conditions not responding to medical treatment. A non-healing ulcer per se was not an indication for amputation. The level of amputation was also chosen on clinical grounds as the most distal level possible where healing could be anticipated, minimal requirements being intact skin and no local

Table 1. Primary amputation levels in relation to final outcome in 187 diabetic patients

Primary amputation level		Final amputation level: Below ankle, Healed	Below ankle, Dead	Above ankle, Healed	Above ankle, Dead
Below ankle	112	74	11	24	3
Above ankle	75	–	–	64	11
Total	187	74	11	88	14

Table 2. Patient characteristics. Number of patients or median (range)

	Healed below ankle (n 74)	Healed above ankle (n 88)	Dead not healed (n 25)
Men/women	47/27	47/41	11/14
Age (yr)	65 (32–94)	74 (42–91)***	82 (41–93)***
Duration of diabetes (yr)	20 (1–59)	14 (1–55)**	11(3–30)*

**$P < 0.01$, ***$P < 0.001$, vs. healed below ankle.

signs of infection or severe ischemia. No tourniquet was used at amputation. The lowest level of amputation was at the interphalangeal joint of the big toe. 73 percent of amputations below the ankle were left open for secondary healing. Skin grafts were done in 24 patients during the healing stage. In all amputations above the ankle, the skin was closed primarily. The criteria for reamputation were pain, progression of gangrene, infection at the amputation site not responding to local revision and/or antibiotics and progressive breakdown of the wound.

Weight bearing

Bed-rest for more than 72 hours was avoided except in patients with septic conditions or severe intercurrent diseases. Following debridement or minor amputation in ambulatory patients, weight-bearing was resumed as soon as pain and local circumstances permitted, with the aid of individually fitted orthoplast footwear or a total-contact walking cast. An individually fitted orthopedic shoe was provided when healing was complete.

Statistics

Values are given as median and range. Fischer's exact test and the Mann-Whitney U-test were used to evaluate potential prognostic factors univariately. Multiple logistic regression was used to investigate the simultaneous influence of prognostic factors. The regression analyses were performed in a stepwise manner, using the significance levels as inclusion criteria. All tests were two-sided and had a significance level of 5 percent.

Results

Amputation level and outcome

Primary amputation level was below the ankle in 60 percent of the patients (Table 1). Reamputation from minor to major level was done in 27 patients after a median time interval of 36 (4–177) days. The most common indication for reamputation was progressive gangrene (n 21). The final amputation level was below the ankle in 45 percent of the patients (14 toe amputations, 29 single ray and 19 multiple ray resections, 16 complete transmetatarsal and 7 atypical mid-foot amputations). The final level was below the knee in 78 patients, through the knee in 4 and above the knee in 20 patients. There was no amputation through the ankle. Unless otherwise stated, those who healed below ankle are compared with those who healed above ankle and those who died; subdivision of those who healed above ankle with regard to primary amputation level is made under a separate heading.

25 patients died unhealed. As a group, they were older than those who healed and had a median survival time of 2 (1–8) months after amputation (Table 2).

Cause, type, and site of ulcer

A distinct precipitating cause of the ulcer could be demonstrated in 119 patients, the most common being faulty shoes or socks (n 40). No major differences with regard to outcome could be demonstrated between the causes, with the exception that decubital ulcers (n 8), which were all in the ischemic group, resulted in major amputations (data not shown).

Most patients had minor or major gangrene (Table 3). No relation to outcome could be demonstrated with regard to minor gangrene; one third of the patients who had such a lesion healed after a minor amputation. Deep infection was related to healing after a minor amputation.

Ulcers located in the small toes, the metatarsal heads or the mid-foot area were related to healing after minor amputation (Table 3). Multiple ulcers were more common in patients with major amputations compared to all other sites.

Indication for amputation

In 63 percent of the patients more than one indication was given for the amputation, most commonly

Table 3. Type and site of ulcer in relation to outcome of amputation

	Healed below ankle (n 74)	Healed above ankle (n 88)	Dead not healed (n 25)
Type of ulcer			
Superficial ulcer	0	4*	0
Deep ulcer	5	5	3
Deep infection	31	6***	3**
Minor gangrene	38	54	14
Major gangrene	–	19	5
Site of ulcer			
Big toe	21	21	6
Small toes	29	14**	5
Metatarsal head area and mid-foot	17	4***	4
Heel	–	16	3
Multiple (≥ 3)	7	33***	7*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. healed below ankle.

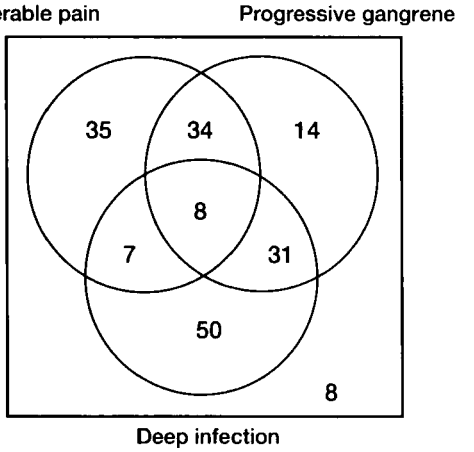

Figure 1. The interrelationship between major causes for amputation. The figures indicate number of patients.

Table 4. Indications for amputation in relation to type of ulcer

Type of ulcer	n	Indications				
		Pain	Progr. gangr.	Deep inf.	Septic/ toxic c.	Misc.
Superficial or deep ulcer	17	13	–	–	–	14
Deep inf.	40	5	–	38	0	8
Minor gangr.	106	54	69	50	12	15
Major gangr.	24	12	18	8	5	3
Total	187	84	87	96	17	40

Table 5. Indications for amputation in relation to final outcome

Indication	Healed below ankle (n 74)	Healed above ankle (n 88)	Dead not healed (n 25)
Pain	11	57***	16***
Progressive gangrene	21	53***	13*
Infection	54	28***	14
Septic/toxic conditions	2	9	6**
Miscellaneous	14	20	6

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. healed below ankle.

infection, progressive gangrene and pain. At least one of these 3 indications were present in all but 8 patients (Figure 1).

Pain was the main cause of most amputations with a superficial or deep ulcer, only rarely in cases of deep infection and in 52 percent of patients with gangrene (Table 4). Deep infection was a major or contributory cause of amputation in 45 percent of patients with gangrene. In 1 patient, an acute vascular occlusion was the single reason for amputation. In 39 patients, other miscellaneous indications, such as massive or progressive ulceration, mechanical factors or proximal complications to vascular surgery were noted as contributory causes.

Infection as an indication for amputation was most common in patients who healed after minor amputation (Table 5). Progressive gangrene and pain were more common in patients who healed after major amputation but 21 and 11 patients, respectively, with these conditions healed after a minor amputation. No relation to amputation level was seen with regard to septic and/or toxic conditions, but 6 of 15 patients in this group died unhealed.

Peripheral pulses, intermittent claudication, and rest pain

One or more signs of peripheral neuropathy were present in all the patients.

A palpable pulse in the popliteal or any one of the pedal arteries was related to healing after a minor amputation (Table 6). However, healing after minor amputation occurred in 44 of 148 patients with no palpable pedal pulses.

A history of intermittent claudication was present in 24 percent of the patients and was related to major amputation.

Rest pain at the time of enrolment was present in 46 percent of the patients and was related to healing after major amputation. In this group, healing after minor amputation was seen in 27 percent of the patients or in half of those in whom a primary minor amputation was done.

Table 6. Peripheral pulses, intermittent claudication, rest pain and edema in relation to final outcome

	Healed below ankle (n 74)	Healed above ankle (n 88)	Dead not healed (n 25)
Femoral pulse present	72 (1)	85	25
Popliteal pulse present	56 (1)	40***	14
Pedal pulse present	29 (1)	5***	4*
History of claudication	9	32***	3
Rest pain at enrolment	23	49**	14*
Edema present	38	48	12

Figures within parentheses indicate results not available.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. healed below ankle.

Table 7. Outcome after primary vs. secondary major amputation

	Healed below ankle	Healed above ankle with primary amputation	
	(n 74)	below ankle (n 24)	above ankle (n 64)
Type of ulcer			
Superficial ulcer	0	0	4
Deep infection	31	1***	5
Minor gangrene	38	22***	32(***)
Site of ulcer			
Small toes	29	10	4(***)
Metatarsal head area and mid foot	17	1	3
Multiple (≥ 3)	7	5	28(*)
Indication			
Infection	54	12*	16(*)
Progressive gangrene	21	17***	36
Pain	11	13***	44
Signs of vascular disease			
Popliteal pulse present	56 (1)	10**	30
Pedal pulse present	29 (1)	1***	4
History of claudication	9	8*	24
Rest pain at enrolment	23	13	36

Figures within parentheses indicate results not available.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. healed below ankle.
(*)$P < 0.05$, (***)$P < 0.001$, vs. primary amp. below ankle.

Outcome in relation to primary vs. secondary major amputation

Of 88 patients who healed after a major amputation, 24 had had a primary below-ankle amputation and a subsequent reamputation to major level, while in 64 the major amputation was primary (Table 7). Deep infection and the presence of popliteal or pedal pulse were more common among patients who healed after a minor amputation than among those who required a reamputation to major level. Presence of minor gangrene and progressive gangrene or pain as an indication for amputation were more common in the latter group.

Table 8. Summary of results of logistic regression analysis with regard to risk for major amputation

Factor	RR[a]	*P*-value
Intermittent claudication	6.3 (1.6–24.3)	0.007
Progressive gangrene	13.6 (3.7–50.0)	<0.001
Pain as an indication	12.9 (3.7–44.5)	<0.001

[a] Relative risk (factor present vs. absent) of a major amputation with multivariate adjustments for age, gender, and smoking habits (95 percent confidence intervals).

Simultaneous analysis of risk factors for major amputation

To investigate the simultaneous influence of potential risk factors for major amputation, a logistic regression analysis was performed concerning those who healed after a minor or a major amputation. Progressive gangrene or pain as an indication for amputation and intermittent claudication remained significant risk factors for major amputation (Table 8).

Discussion

This is the first prospective study of diabetic patients with foot ulcers where the relation between local signs and symptoms and the final amputation level has been studied. A history of intermittent claudication and pain or progressive gangrene as an indication for the amputation were found to be the most important factors.

Final amputation level was below the ankle in 76 percent of the patients where such an attempt was made. Comparisons in this respect to other reports are very difficult due to differences concerning patient selection, type of lesions included, policies and decision-making regarding indications and level selection for amputation. Moreover, patients who die unhealed are often excluded from the evaluation (O'Neal 1988, Fylling and Knighton 1989).

Type of ulcer was found to be an important factor related to the ultimate amputation level. All patients who had had an amputation with a superficial ulcer (n 4) healed after a primary major amputation performed because of severe pain. This finding indicates that a non-healing ulcer was not per se considered an indication for amputation in this study, which is contrary to most other studies, where non-healing is commonly used as an indication for amputation (Fylling and Knighton 1989). In 52 percent of all patients, a deep infection was present, concomitant with (n 58) or without (n 40) gangrene. This

illustrates the close interrelationship between the two, i.e., a deep infection often escalates to gangrene, or gangrene can become infected as a complication. However, 73 of 130 patients with gangrene did not show any clear evidence of infection. Healing with a minor amputation was seen in a large proportion of patients with deep infection which shows that early and aggressive treatment of this condition has a high rate of success. As expected, the presence of gangrene was associated with a high probability of a major amputation (Wagner 1981, Levin 1988). However, 38 of 60 patients with minor gangrene healed at that level, indicating that healing below the ankle is not uncommon in the presence of minor gangrene. This might reflect the multifactorial background of gangrene, some cases being due to gradually developing ischemia, some developing suddenly because of embolic disease and some being due to local factors, such as infection (Apelqvist et al. 1989b). The possible influence of local circulatory disturbances and hemorheologic changes has not been evaluated.

Multiple ulcers were commoner in patients with major amputation than in those amputated at all other sites, which indicates that such patients probably have a more severe peripheral vascular disease (Apelqvist et al. 1989b).

The indication for amputation was often multifactorial. Pain and progressive gangrene were strongly related to major amputation or death, in agreement with previous observations (O'Neal 1988, Borssén and Lithner 1989, Fylling and Knighton 1989, Apelqvist et al. 1992). However, even the combination of gangrene and pain as an indication for amputation was consistent with healing after a minor amputation in 9 of 66 patients. Ideally, ischemic pain should be distinguished from pain due to other causes, such as neuropathy, infection or local ulcer pain. With an open foot lesion requiring amputation, with or without gangrene or infection, it is often not possible to make a correct distinction in this regard.

A pedal pulse was present in 20 percent of the patients and was related to the possibility of healing below the ankle which is in agreement with previous observations (Dwars et al. 1992) although theirs was a mixed cohort. However, healing below the ankle occurred in 44 patients in spite of absent pedal pulses. Thus, the presence of a pedal pulse indicates a high probability for healing below the ankle, whereas healing is not uncommon in the absence of pedal pulses.

Only 24 percent of the patients had intermittent claudication. This finding has to be considered with caution, since a clinical history of claudication is an insensitive and non-specific indicator of impaired circulation in diabetic patients (Palumbo and Melton 1985). Despite this fact, the present study suggests that a combination of claudication and foot ulcer is unfavorable, since it was more common in patients who healed after a major amputation or died before healing had occurred.

Pain is a frequent indication for amputation (O'Neal 1988, Borssén and Lithner 1989, Fylling and Knighton 1989). In the present study, pain was strongly related to healing after a major amputation or death. However, in 23 patients with rest pain at enrolment and in 11 patients with pain as an indication for amputation, healing after a minor amputation was achieved. Only half of the patients with gangrene had pain as an indication for amputation. These findings are in agreement with other reports (Apelqvist et al. 1990, 1992) where a lower incidence of rest pain in diabetic patients was found than in non-diabetic patients with threatening limb loss (Thomas et al. 1988). Several authors have suggested that this is because the majority of those patients have extensive peripheral neuropathy (Edmonds et al. 1986, Boulton 1988, Sicard et al. 1988), which is in agreement with the present findings where all patients tested had at least one sign and two thirds had 3 or 4 signs of peripheral neuropathy.

As a group, the patients who died unhealed show a marked resemblance to those who healed after a major amputation. However, in the former group both minor and major amputations were represented, and the numbers are too small to allow further analysis within the group.

One major concern in clinical studies when evaluating the importance of different patient characteristics in relation to the final result is the potential influence of these factors being known to the investigator when making his decisions. We have endeavored to minimize such influence by applying strict amputation criteria and having the patients treated by the same physicians both as in- and out-patients and followed to a final outcome. Our claim of unbiased decisions with regard to choice of primary amputation level is supported by the similarity between those with a primary and those with a secondary major amputation and the dissimilarity between patients healed after a minor amputation and those reamputated from a minor to a major level.

In conclusion, pain, progressive gangrene and intermittent claudication were the most important factors related to major amputation in diabetic patients with foot ulcers. However, none of these factors excluded the healing of a minor amputation

and consequently the selection of amputation level in diabetic patients with foot ulcers cannot be based upon these factors exclusively.

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