

RESEARCH ARTICLE

Minor amputation does not negatively affect health-related quality of life as compared with conservative treatment in patients with a diabetic foot ulcer: An observational study

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Abstract

Background Health-related quality of life (HRQoL) is poor in patients with persistent diabetic foot ulcers and poor HRQoL predicts worse outcomes in these patients. Amputation is often considered a treatment failure, which is why conservative treatment is generally preferred over amputation. However, it is unclear whether minor amputation negatively affects HRQoL compared with conservative treatment in patients with diabetic foot ulcers.

Methods In the cohort of the multicenter, prospective, observational Eurodiale study, we determined difference in change of HRQoL measured by EQ-5D between patients with a diabetic foot ulcers that healed after conservative treatment (n = 676) and after minor amputation (n = 145). Propensity score was used to adjust for known confounders, attempting to overcome lack of randomization.

Results Baseline HRQoL was not significantly different between patients treated conservatively and undergoing minor amputation. In addition, there was no difference in the change of HRQoL between these groups. In patients who healed 6 to 12 months after the first visit, HRQoL on the anxiety/depression subscale even appeared to improve more in those who underwent minor amputation.

Conclusions Minor amputation was not associated with a negative impact on HRQoL in patients with a diabetic foot ulcers. It may therefore not be considered treatment failure in terms of HRQoL but rather a viable treatment option. A randomized controlled trial is warranted to further examine the influence of minor amputations on health-related quality of life.

KEYWORDS

diabetic foot ulcer, Euroqol 5D, health-related quality of life, minor amputation

1 | INTRODUCTION

Health-related quality of life (HRQoL) is poor in patients with a diabetic foot ulcer (DFU),^{1–6} and a low HRQoL predicts major amputation and death in these patients.⁷ Amputation is often considered treatment failure, as it may negatively affect a patient's mobility and (mental) well-being. On the other hand, in the presence of extensive tissue loss, amputation could be considered part of treatment. Although a major amputation has an evident negative effect on HRQoL,³ the effect of a minor amputation—performed in up to 20% of patients with DFUs during treatment^{8–10}—is less clear. Three studies have longitudinally assessed HRQoL in patients with DFUs^{2,11,12}; these studies have primarily focused on the difference in HRQoL between persistent and healed ulcers but have not directly studied the effect of minor amputation on HRQoL. In cross-sectional studies, HRQoL was found to be worse in patients with a persisting DFU than in those who had healed primarily or after minor amputation.^{3,11–14}

To our knowledge, there are no prospective data on the impact of a minor amputation on HRQoL. We therefore determined the impact of a minor amputation on HRQoL in the Eurodiale study by comparing the change in HRQoL of patients who healed after a minor amputation with that of those who healed primarily. The Eurodiale study included patients with a new DFU presenting to 1 of 14 specialized foot clinics and prospectively followed them until death, healing, major amputation, or up to 1 year; data on HRQoL were gathered at study inclusion and at the last study visit. We used propensity score weighting to adjust for known confounders attempting to overcome lack of randomization.

2 | MATERIALS AND METHODS

Between September 1, 2003, and October 1, 2004, all patients with diabetes mellitus presenting with a new foot ulcer to any of 14 diabetic foot centers in 10 European countries were included. Both in- and outpatients were included. The design and rationale of this multicenter, observational, prospective Eurodiale study have been described in detail elsewhere.¹⁵ We excluded patients treated in the participating centers for an ulcer of the ipsilateral foot during the previous 12 months and those with a life expectancy of less than 1 year. All patients were treated according to protocols based on the International Consensus on the Diabetic Foot.¹⁶ Dedicated investigators gathered the data; the ethics committees relevant to the 14 participating centers approved the study protocol and all included patients gave written informed consent. Patients were followed monthly until healing of the foot ulcer(s), major amputation, or death or up to a maximum of 1 year. The aim of the present study was to determine if change in HRQoL was different for patients who healed after minor amputation compared with those who healed primarily. Data on treatment, including minor amputation, were gathered at each monthly visit. Minor amputation was defined as any amputation distal to and including the midfoot. Healing was defined as complete epithelialization of the whole foot at 2 consecutive visits. In patients with minor amputation, healing could occur by primary or secondary intention.

HRQoL, one of the main predefined outcome measures of the Eurodiale study, was assessed with the EQ-5D-3L from the Euroqol

group.¹⁷ Patients completed the EQ-5D-3L at study inclusion and at the last study visit, which took place at the time of healing, after major amputation or 1 year after study inclusion, whichever took place first.

EQ-5D-3L is a generic HRQoL tool, consisting of the following 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain corresponds to a single, simple question with the following 3 response options: no problems (score = 1), some problems (score = 2), and severe problems (score = 3). The 5 domains can be aggregated into an index score that represents the value society attaches to the EQ-5D responses. This EQ-5D index ranges from -0.594 to 1: an index below zero indicates a state valued lower than death, an index of 0 is equivalent to death, and an index of 1 is equivalent to full health. Higher scores in the domains indicate more problems in the specific domain, whereas a higher EQ-5D index (eg, closer to 1) indicates better HRQoL.

The EQ-5D is translated into the 10 languages relevant for this study. Permission to use EQ-5D in the Eurodiale study was obtained from the EuroQol group. For the current report, we analyzed patients whose ulcer healed with conservative treatment and patients who healed after minor amputation. Patients who underwent major amputation were excluded. The main outcome measure was the difference in the score of each of the 5 EQ-5D domains at study conclusion between patients who healed after minor amputation and those who healed with conservative treatment, beyond any difference that was already present at baseline (Figure 1).

Analyses were stratified for time to ulcer healing (0–6 months and 6–12 months), as ulcers that healed within 6 months were less severe than those that healed between 6 to 12 months (data not shown), which may have influenced HRQoL accordingly. An additional consideration for this stratification was that the time between 2 HRQoL measurements influences the difference between the measurements: a small difference with a large correlation is expected with a short interval and a large difference with a smaller correlation is expected with a long interval. Analyses were corrected for the following covariates that were likely to affect outcome¹⁸: sex, age, diabetes duration, ulcer depth, ulcer size, ulcer duration, ulcer location, presence of periwound edema, infection, peripheral arterial disease, heart failure, neurological disorder, inability to stand or walk without help, visual impairment, end-stage renal disease, and diabetic polyneuropathy.

3 | STATISTICAL ANALYSIS

The mean change of HRQoL with 95% confidence interval was stratified for ulcers not healed, ulcers healed within 6 months, and ulcers healed in 6 to 12 months.

The difference in the incidence of minor amputation and the distribution of covariates measured at presentation between those patients whose ulcer healed within 6 months and those whose ulcer healed in 6 to 12 months was tested by chi-squared tests (categorical variables) and *t* tests (continuous variables).

The association between a minor amputation and a change of HRQoL in the patients with a healed ulcer at follow up was analyzed in linear regression models. The longitudinal nature of the data—up to 2 HRQoL recordings per patient—was adjusted for by generalized

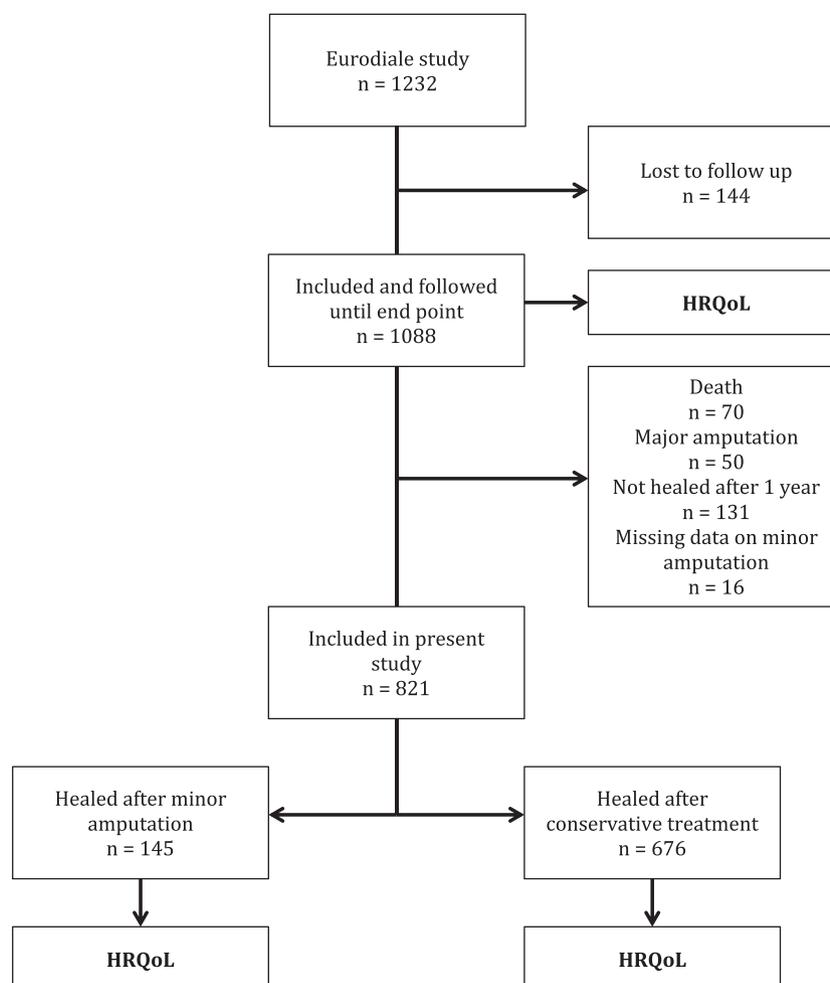


FIGURE 1 Flow chart of the present study

estimating equations. Propensity score was used to adjust for known confounders, attempting to overcome lack of randomization.¹⁹ This propensity score—the probability for minor amputation as estimated from the available data—was calculated from a multivariable logistic regression including all the previously mentioned covariates and center. The weights used in the linear regression are the inverse of the estimated probability of the observed occurrence of minor amputation: the propensity score for patients that had amputation, and 1 minus the propensity score for patients that did not have an amputation.

All analyses were done using SAS 9.4; the significance level was set at 5%.

4 | RESULTS

Of the 1 088 patients who concluded the Eurodiale study, 70 (6%) died and 50 (5%) underwent major amputation, and therefore 968 patients were available for analysis. Of these, 837 (86%) healed during follow up and 131 (14%) were not healed at 12 months. Of the ulcers healed, 543 (66%) healed within 6 months and 278 (36%) after 6, but before 12 months. Of the patients that healed, 145 (18%) underwent minor amputation. Baseline characteristics of the patients that healed are depicted in Table 1. Ulcer healing took longer in patients who underwent minor amputation compared with those who healed with conservative treatment ($P < .01$). Compared with patients who healed with

conservative treatment, those who healed after minor amputation had deeper and larger ulcers that were more frequently infected and located on the toes; periwound edema and peripheral arterial disease were also more often present (all $P < .01$). Sex, age, HbA1c, duration of diabetes, ulcer duration, and comorbidities were comparable between the groups.

In the patients whose ulcer did not heal, HRQoL did not significantly change, except for an improvement of pain ($P < .01$). In all patients whose ulcer healed, HRQoL improved significantly over the treatment period irrespective of treatment modality. In the analyses stratified for time to healing, minor amputation was not associated with a significant change in HRQoL compared with conservative treatment, neither in the 5 EQ-5D domains nor in the EQ-5D index. In patients who healed after 6 months, the anxiety/depression score improved ($P < .01$) in those who underwent minor amputation in comparison to those who were treated conservatively. The score on the other EQ-5D domains and the EQ-5D index showed more improvement in patients undergoing minor amputation compared with those treated conservatively, but this improvement did not reach statistical significance (Figure 2).

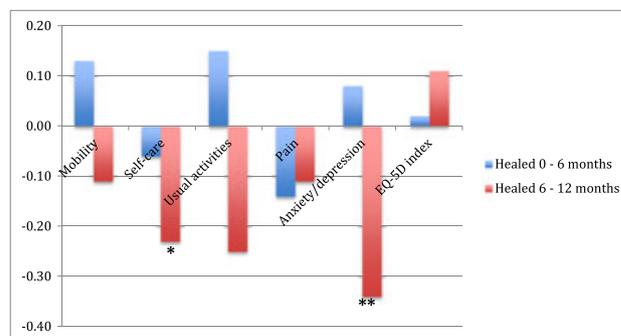
5 | DISCUSSION

Estimating the healing potential of a DFU is a clinical challenge. The cause of a poorly healing ulcer is frequently multifactorial, making it

TABLE 1 Baseline patient characteristics

	Conservative treatment	Minor amputation	P
Healing, n (%)			<.01
0–6 months	478 (61.2)	65 (38.0)	
6–12 months	198 (25.4)	80 (46.8)	
Not healed at 12 months	105 (13.4)	26 (15.2)	
Covariates			
Sex, n (%)			.12
Male	490 (62.7)	118 (69.0)	
Female	291 (37.3)	53 (31.0)	
Age, mean (SD)	64.3 (12.8)	64.5 (11.5)	.83
HbA1c, n (%)			.26
< 7.5%	237 (30.5)	49 (28.7)	
7.5–8.4%	150 (19.3)	40 (23.4)	
8.5–10%	163 (21.0)	35 (20.5)	
> 10%	35 (20.5)	25 (14.6)	
Not measured	141 (18.2)	22 (12.8)	
Diabetes duration, n (%)			.14
< 5 years	106 (14.1)	22 (13.2)	
5–10 years	130 (17.3)	19 (11.4)	
> 10 years	516 (68.6)	126 (75.4)	
Ulcer depth, n (%)			< .01
Superficial	519 (66.5)	30 (17.5)	
Deep	262 (33.5)	141 (82.5)	
Ulcer size, n (%)			< .01
< 1 cm ²	329 (42.3)	40 (23.5)	
1–5 cm ²	390 (50.1)	101 (59.4)	
> 5 cm ²	59 (7.6)	29 (17.1)	
Ulcer duration, n (%)			.10
< 1 week	143 (18.5)	23 (13.5)	
1 week–3 months	456 (58.9)	98 (57.3)	
> 3 months	175 (22.6)	50 (29.2)	
Ulcer location, n (%)			< .01
Toes	395 (54.0)	106 (65.4)	
Midfoot	248 (33.9)	48 (29.6)	
Heel	88 (12.1)	8 (4.9)	
Periwound edema, n (%)	244 (31.4)	97 (56.7)	< .01
Infection, n (%)	383 (51.6)	118 (72.8)	< .01
Peripheral arterial disease, n (%)	307 (40.2)	104 (61.5)	< .01
Heart failure (NYHA III–IV), n (%)	75 (9.7)	12 (7.0)	.31
Neurological disorder, n (%)	51 (6.6)	8 (4.7)	.48
Inability to stand or walk without help, n (%)	63 (8.1)	14 (8.2)	.97
Visual impairment, n (%)	106 (13.7)	24 (14.2)	.90
End-stage renal disease, n (%)	36 (4.6)	10 (5.9)	.55
Diabetic polyneuropathy, n (%)	661 (86.2)	150 (88.2)	.54

difficult to assess the need for and timing of a minor amputation. For instance, in the case of severe infection of the ulcer, the choice between either removal of the infected tissue by minor amputation and a conservative approach to prevent a minor amputation can be difficult.



* $p < 0.05$; ** $p < 0.01$

FIGURE 2 Change in EQ-5D scores for minor amputation relative to conservative treatment stratified for time to ulcer healing and corrected for propensity score. Negative values for mobility, self-care, usual activities, pain, and anxiety/depression indicate decreased problems in the specific domain and therefore better quality of life for minor amputation compared with conservative treatment; a negative value for the EQ-5D index indicates decreased quality of life for minor amputation compared with conservative treatment

This study longitudinally examined the effect of a minor amputation on HRQoL measured by EQ-5D-3L in patients with a DFU whose ulcer healed within 1 year. HRQoL in diabetic foot disease has primarily been measured using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), a generic HRQoL tool,²⁰ which consists of 36 items concerning physical, mental, and social well-being. It correlates well with disease-specific tools such as the Diabetic Foot Ulcer Scale (DFS)²¹ and the Cardiff Wound Index Scale (CWIS),^{22,23} and healing of the foot ulcer is associated with improved HRQoL as measured by the SF-36.^{2,11} The EQ-5D has been shown to perform at least as well as the SF-36 in patients with diabetes²⁴ and is easier to use because of its limited size.²⁵ It has also shown to be responsive to changes in health status in patients after podiatric surgery²⁶ and in patients with rheumatoid arthritis^{27–29} and venous leg ulcers,³⁰ conditions that may be considered comparable with DFUs regarding HRQoL issues. In our study, nonhealing was associated with no change in HRQoL as measured by EQ-5D, whereas healing of the ulcer was associated with an improvement of HRQoL. These data suggest that the EQ-5D is indeed responsive to changes in health status in patients with diabetic foot disease.

As reported previously, toe amputations were performed most frequently (55% of minor amputations) in the Eurodiale cohort and only a small proportion of patients underwent a midfoot amputation (11%).³¹ The major finding of our study was that these minor amputations were not associated with a negative impact on HRQoL. When the duration of the ulcer was taken into account, we observed improved anxiety/depression scores in patients with an ulcer persisting longer than 6 months who healed after minor amputation compared with those who healed after conservative treatment. Although statistically not significant, the same pattern was observed in the other EQ-5D domains. On the basis of the present data, we conclude that a minor amputation was not associated with a major negative impact on HRQoL as measured by a generic instrument such as the EuroQoL 5D. We cannot exclude that the number of events may have been too small to detect a negative effect of minor amputation on HRQoL. However, it is in our opinion unlikely that with increasing numbers

the results (numerically) favoring amputation would reverse into statistically significant results favoring conservative treatment. As reported previously, patients that undergo a minor amputation have more severe ulcers than patients treated conservatively.³¹ It is possible that these patients with more severe foot disease anticipate a poorer outcome, such as major amputation, and that healing after minor amputation diminishes their anxiety.

Our study has several limitations. First, the EQ-5D is a generic and rather crude HRQoL tool, which is not specific for diabetic foot disease. However, it has proven to be useful in patients with diabetes,²⁴ has been used in patients with DFUs before,³ and was responsive to change in health status in our cohort: HRQoL improved in those whose ulcer healed, and it did not in those whose ulcer did not heal. Second, final measurement of HRQoL was obtained immediately after healing of the ulcer: it is unclear if the change of HRQoL is equally sustained in both groups for a longer period after ulcer healing. Third, our study was not a randomized trial and selection bias may have been present: patients with more severe ulcers and worse HRQoL—and therefore the potential for more improvement of HRQoL—may have been more likely to be selected for amputation. We adjusted for this by propensity score weighting, which is a method that mimics randomization by giving weights to each patient relative to the likelihood of the treatment—minor amputation or no amputation—they actually received; this likelihood was determined through a collection of baseline covariates. In the propensity analyses, these covariates are balanced between the treatment groups; a limitation of this approach is that only known covariates can be included. In a proper randomized study, unknown confounders can also be accounted for, but for practical reasons, a study on the effect of amputation on HRQoL is difficult to conduct. It should be noted that none of the HRQoL outcomes was significantly different at baseline between persons with and without minor amputation later in the treatment course, which is an indication that the propensity score weighting, ie, pseudo-randomization, was probably successful. Fourth, the calculation of detectable differences demonstrated that our study might not have been sufficiently powered to detect all differences in change in HRQoL, as some of the measured differences were smaller than the detectable difference. If the measured difference is smaller than the detectable difference, there are 2 options: (1) there is no difference or (2) the study was unable to detect the difference. As nearly all results are in favor of minor amputation, we believe that, although it may not be better, minor amputation is unlikely to be worse than conservative treatment from a QoL-perspective and that our conclusions are valid.

Hence, our study showed that minor amputation was not associated with a negative impact on HRQoL in patients with a DFU. Therefore, minor amputation should probably not be considered treatment failure but can instead be considered a viable treatment option in patients with DFUs. Future studies are necessary to validate our findings, and to ascertain if the equal improvement of HRQoL, we found in patients treated conservatively and with minor amputation is consistent over time.

CONFLICT OF INTEREST

None.

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