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Diabetic complications do not hamper improvement of health-related quality of life over the course of treatment of diabetic foot ulcers – the Eurodiale study

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ABSTRACT

Aims: Diabetic complications, and in particular diabetic foot ulcers (DFUs), are associated with low health-related quality of life (HRQoL). We evaluated whether the presence of diabetic complications also influenced the improvement of HRQoL during DFU treatment.
Methods: 1088 patients presenting for DFU treatment at the centers participating in the Eurodiale study were followed prospectively up to one year. HRQoL was measured both at presentation and after healing or at end of follow up, using EQ-5D: a standardized instrument consisting of five domains and a summary index. The influence of diabetic comorbidity on the course of HRQoL was evaluated for each of the EQ-5D outcomes in multi-level linear regression analyses, adjusting for baseline characteristics.
Results: HRQoL improved in all EQ-5D outcomes over the course of treatment for those DFUs that healed. The few significant differences in the development of HRQoL between patients with and without comorbidity showed a more beneficial development for patients with comorbidity in DFUs that did not heal or healed slowly.
Conclusions: Comorbidity does not hamper improvement of HRQoL in DFU treatment. On the contrary, HRQoL improved sometimes more in patients with certain comorbidity with hard-to-heal ulcers.

1. Introduction

The number of people with diabetes mellitus is increasing worldwide, in Europe to an estimated prevalence of 10% among people aged 20–79 years by 2030.[1] Consequently, the incidence of chronic complications of diabetes is rising, with an increase in costs related to their hospitalization and management.[2] The chronic complications of diabetes are now considered an 'emerging

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pandemic'[3] with diabetic foot ulcers (DFUs) as one of the most feared complications. Moreover, DFUs are associated with high morbidity and mortality. The survival rate of a patient with a DFU is shorter than for those patients suffering from prostate or breast cancer and similar to that of colon or lung cancer patients.[4,5]

Several cross-sectional studies documented severely decreased health-related quality of life (HRQoL) and depression in people with DFU[6–10] and a lower HRQoL after referral to specialized foot centers was associated with higher mortality and risk of major amputation during follow-up.[11] Longitudinal studies showed that ulcer healing is associated with an increase in HRQoL and non-healing often with a further decrease.[7,12–14] Patients with DFUs are frequently frail elderly patients with multiple comorbidities that also affect HRQoL[9,15,16] as well as DFU healing[17,18] and mortality.[19] Given this high rate of co-morbidity it is the aim of this paper to determine whether improvement in HRQoL during the healing period is hampered by the presence of these comorbidities in order to take supportive initiatives for improving the quality of life for these patients. The present analysis was performed using data from the Eurodiale study, a large prospective study in patients presenting with a new DFU.

2. Material and methods

2.1. Study design and population

The Eurodiale study was an observational, prospective cohort study with the aim of investigating the factors that determine clinical and HRQoL outcomes as well as healthcare consumption in patients with a new DFU. The Eurodiale consortium comprised of 14 centers with longstanding expertise in the field of diabetic foot disease in 10 European countries. The design and rationale of the study has been described in detail elsewhere.[20,21] The ethical committees relevant to the 14 study centers all approved the study protocol.

In summary, all patients with diabetes presenting for the first time with a new foot ulcer in one of the Eurodiale Study Group centers between 1 September 2003 and 1 October 2004 were included in the study. Patients treated for an ulcer on the ipsilateral foot during the preceding 12 months and patients with a life expectancy shorter than one year were excluded. All patients gave prior written consent.

2.2. Data collection and definitions

All patients were treated according to protocols based on the International Consensus on the Diabetic Foot, which include off-loading, regular wound debridement, diagnosis and treatment of infection, critical ischaemia and foot deformities. Furthermore, included patients were monitored on a monthly basis until healing of the foot, major amputation or death, up to a maximum of one year. An ulcer was considered healed if the skin was intact on the whole of the foot at two consecutive visits. If more than one ulcer was present, the foot was defined as healed once all ulcers were healed. Major amputation was defined as an amputation through the ankle or above.

At presentation, data on socio-demographics (age, sex, current employment, partner involved in care, center), life-style characteristics (smoking, chronic alcohol use, BMI), disease characteristics (diabetes duration, insulin use, hemoglobin A1c (HbA1c), serum creatinine), ulcer characteristics (ulcer duration, size, depth and location, infection, CRP, peripheral artery disease (PAD), polyneuropathy, osteomyelitis, limb threatening ischemia) and comorbidities (heart failure, neurological disorder, inability to stand or walk without help, visual impairment, end-stage renal disease (ESRD)) were recorded on standardized case record forms. Additionally, on a separate form, HRQoL data were collected. HRQoL data were again collected at the time the ulcer had healed during the one year observation period or when it remained unhealed after one year. No follow-up HRQoL data were collected for patients who experienced a major amputation within one year after presentation and these data could also not be collected in patients with an active ulcer who died during follow-up. All information was recorded by dedicated investigators in each centre who were trained during plenary meetings and on-site visits that took place prior to and during the study. The methods and definitions used during collection and analysis of the data from the standardized case record forms have been described in detail previously.[21]

Comorbidities were defined on the standardized case record form. Heart failure: Chronic heart failure and/or angina pectoris New York Heart Association Class 3 or 4. Neurological disorder: Any neurological disorder (diabetic neuropathy excluded) resulting in loss of motor or sensory function (e.g. stroke). Inability to stand or walk without help: Any disorder (except PAD) resulting in inability to stand without help or inability to walk. Visual impairment: Severe visual impairment of any cause resulting in the inability to read a newspaper after correction. ESRD: End stage renal disease (hemodialysis, peritoneal dialysis or renal transplant).

HRQoL was measured by EQ-5D which is a standardized generic instrument for use as a measure of health outcome (www.euroqol.org). EQ-5D consists of five domains – Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression – corresponding to five simple questions, which easily can be used as part of a clinical interview, with each question having three response scores: 1 - no problems, 2 - some problems, and 3 - severe problems. Additionally, these domains are aggregated into an EQ-5D index, representing the value society gives to the responses, scoring −0.594 (lowest value) to 1 (highest value).[22] EQ-5D is translated into many languages and was available for all the languages relevant for the present study. Permission to use EQ-5D in the Eurodiale study was obtained from the EuroQol group. The Eurodiale study was performed according the Declaration of Helsinki and medical ethical approval was obtained in all participating centers.

2.3. Statistical analysis

The main analyses in this paper were done separately in three subgroups of the data: patients with ulcers that healed in less than 6 months, ulcers that healed after more than six months but less than a year, and ulcers that did not heal in one year. Differences in socio-demographic, life-style, disease and ulcer characteristics and HRQoL at presentation between the three subgroups defined by ulcer healing were tested with chi-squared tests (categorical characteristics) and t-tests (continuous characteristics).

The development from the first recording at presentation to the second recording at end of treatment of each of the HRQoL outcomes were analyzed in linear regression models; a random patient effect was included in the models to account for repeated recordings of HRQoL for each patient. Moreover, the use of mixed models accounted for attrition bias. Analyses were performed unadjusted and adjusted for socio-demographic (age as linear effect), life-style, disease, and ulcer characteristics.

A first set of analyses investigated the general development of HRQoL during the ulcer treatment period. Thereafter, a second set of analyses investigated the influence of the presence at presentation of selected comorbidities on the development of HRQoL. For better overview, this second set is represented as a series of figures, one for each EQ-5D domain, where the change in HRQoL from presentation to follow-up when one of the comorbidities is present is juxtaposed with the change when the corresponding comorbidity is absent. Hence, the distance in the figures between these two assessments shows whether the presence of the comorbidity affects the effect of treatment on HRQoL; significant ($p < 0.05$) differences are denoted by a star in the right margin.

3. Results

Of the 1232 patients initially enrolled, 144 (12%) were lost to follow-up. At presentation, these patients were slightly older and had higher prevalence of heart failure, deeper ulcers and ulcers of longer duration than those included.[20] During the one-year follow-up 70 (6.4%) patients died and 50 (4.6%) patients had a major amputation and these were omitted from the analyses. Of the 968 patients in the analyses no baseline HRQoL data were collected for 64 (6.6%) and no follow-up HRQoL data were collected for 166 (17.2%) (Fig. 1).

Baseline HRQoL was not significantly different between the patients with ulcers that healed within 0–6 months, within 6–12 months or that did not heal during 12 months (Table 1). Over the course of treatment HRQoL showed statistically significant improvements in most EQ-5D domains and in the EQ-5D index for the patients with a healed ulcer without much difference between ulcers that healed fast or healed slowly. Conversely, for the patients for whom the ulcer did not heal within the year, there was no evidence for improvement; notably a significant decline was observed in the domain Self-care and a non-significant decline in Usual activities (Table 2).

When the effect of comorbidities was studied, baseline HRQoL levels were in general worse in the presence of comorbidities in patients for whom the ulcer healed in 7–12 months and for whom the ulcer did not heal within a year, compared to patients in whom the ulcer healed within 6 months. No effect of the different comorbidities was found on the improvement of HRQol in the patients in whom the ulcer healed in the first 6 months (Figs. 2–3).

In the patients with a healed ulcer in 7–12 months, Anxiety/Depression improved during treatment more in the presence than in the absence of ESRD (from mean 1.71 → to mean 1.36 for patients with ESRD versus mean 1.44 → 1.33 without ESRD, Figs. 2 and 3). In the patients with an unhealed ulcer after 12 months, Usual activities improved during treatment more in the presence than the absence of heart failure (1.79 → 1.50 vs. 1.56 → 1.68), and the same pattern was observed for Pain/Discomfort (2.14 → 1.70 vs. 1.71 → 1.50) and the

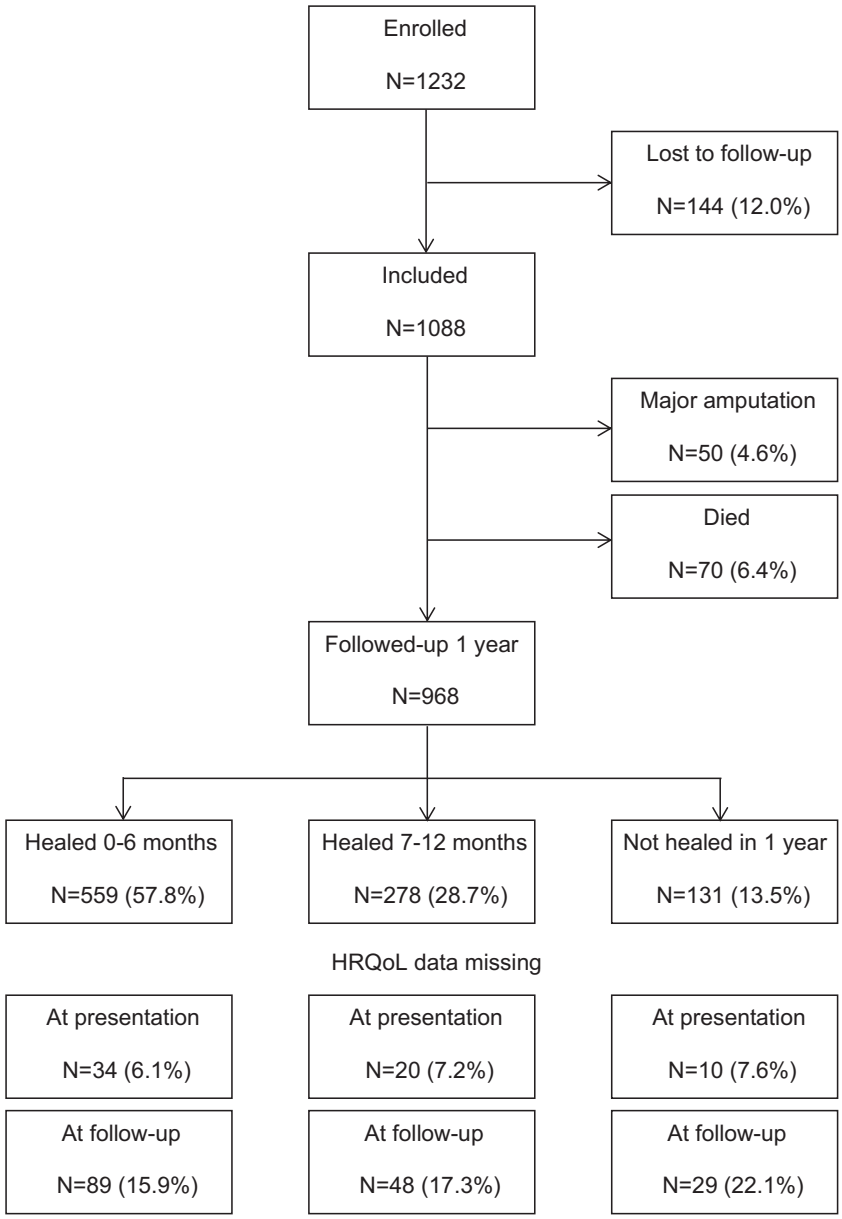

Fig. 1. Flowchart of inclusion and exclusion from the analyses in this paper.

Table 1
Patient and ulcer characteristics and health-related quality of life at presentation.

	Healed 0–6 months n = 559 (57.8%)	Healed 7–12 months n = 278 (28.7%)	Not healed after 1 year n = 131 (13.5%)	p-value
Patient and ulcer characteristics				
Age (years), *mean ± SD*	64.3 ± 12.1	64.2 ± 12.8	65.1 ± 13.7	0.5642
Male sex, *n (%)*	348 (62.3)	117 (63.7)	94 (71.8)	0.1244
Employment, *n (%)*				
Currently employed	125 (22.6)	58 (21.1)	20 (15.3)	
Currently unemployed	101 (18.3)	50 (18.2)	19 (14.5)	
Retired	327 (59.1)	167 (60.7)	92 (70.2)	0.2204
Partner involved in care, *n (%)*	341 (61.1)	154 (56.2)	73 (56.6)	0.3295
Chronic alcohol use, *n (%)*	117 (32.1)	63 (23.0)	43 (32.8)	0.0182
Currently smoking, *n (%)*	86 (15.4)	40 (14.4)	20 (15.3)	0.9254
Body-Mass Index, *n (%)*				
Less than 20 kg/m2	6 (1.1)	9 (3.2)	6 (4.6)	
Between 20 and 27 kg/m2	188 (33.6)	100 (35.0)	43 (32.8)	
Between 27 and 35 kg/m2	279 (49.9)	118 (42.4)	55 (42.0)	
Over 35 kg/m2	44 (7.9)	25 (9.0)	17 (13.0)	
Not measured	42 (7.5)	26 (9.4)	10 (7.6)	0.0533
Hemoglobin A1c, *n (%)*				
<7.5% (<58 mmol/mol)	166 (29.9)	87 (31.5)	36 (27.5)	
7.5–8.4% (58–68 mmol/mol)	108 (19.4)	57 (20.6)	29 (22.1)	
8.5–10% (69–85 mmol/mol)	108 (19.4)	61 (22.1)	32 (24.4)	
>10% (>85 mmol/mol)	66 (11.9)	30 (10.9)	14 (10.7)	
Measurement not done	108 (19.4)	41 (14.9)	20 (15.3)	0.7185
Serum creatinine, *n (%)*				
<120 μmol/l	289 (51.9)	147 (53.3)	69 (52.7)	
120–200 μmol/l	71 (12.7)	40 (14.5)	17 (13.0)	
200–300 μmol/l	12 (2.2)	13 (4.7)	0 (0.0)	
>300 μmol/l	13 (2.3)	10 (3.6)	6 (4.6)	
Measurement not done	172 (30.9)	66 (23.9)	39 (29.7)	0.0691
Duration of diabetes, *n (%)*				
<5 years	81 (15.1)	34 (12.6)	14 (11.1)	
5–10 years	101 (18.7)	31 (11.5)	20 (15.9)	
>10 years	357 (66.2)	204 (75.8)	92 (73.0)	0.0434
Insulin treatment, *n (%)*	384 (69.1)	192 (69.6)	88 (67.7)	0.9296
Deep ulcer, *n (%)*	190 (34.0)	152 (54.7)	69 (52.7)	<0.0001
Size of ulcer, *n (%)*				
<1 cm^2	268 (48.2)	80 (28.9)	32 (24.4)	
1–5 cm^2	255 (45.9)	160 (57.8)	78 (59.5)	
>5 cm^2	33 (5.9)	37 (13.4)	21 (16.0)	<0.0001
Duration of ulcer, *n (%)*				
<1 week	119 (21.5)	39 (14.1)	12 (9.2)	
1 week – 3 months	320 (58.0)	163 (58.8)	76 (58.0)	
>3 months	113 (20.5)	75 (27.1)	43 (32.8)	0.0004
Location of ulcer, *n (%)*				
Toes	323 (62.1)	134 (51.9)	52 (40.3)	
Midfoot	157 (30.2)	89 (34.5)	56 (43.4)	
Heel	40 (7.7)	35 (13.6)	21 (16.3)	<0.0001
CRP, *n (%)*				
Normal	169 (31.2)	55 (20.5)	34 (26.2)	
Less than 3× upper limit of normal	66 (12.2)	45 (16.8)	8 (6.1)	
More than 3× upper limit of normal	72 (13.3)	66 (24.6)	36 (27.7)	
Measurement not done	235 (43.3)	102 (38.1)	52 (40.0)	<0.0001
Infection, *n (%)*	278 (52.5)	161 (60.1)	70 (57.9)	0.1040
PAD, *n (%)*	214 (38.8)	136 (50.6)	69 (54.3)	0.0003
Diabetic polyneuropathy, n (%)	474 (86.5)	240 (87.0)	110 (85.3)	0.8983
Osteomyelitis, n (%)	161 (29.2)	108 (40.2)	44 (33.9)	0.0073
Limb threatening ischemia, n (%)	42 (7.8)	41 (15.2)	26 (20.5)	<0.0001
Comorbidities				
Heart failure (NYHA III–IV), *n (%)*	46 (8.3)	29 (10.5)	15 (11.5)	0.4099
Neurological disorder, *n (%)*	28 (5.1)	21 (7.6)	10 (7.7)	0.2552
Inability to stand or walk without help, *n (%)*	39 (7.0)	25 (9.1)	14 (10.8)	0.2848
Visual impairment, *n (%)*	75 (13.5)	44 (16.4)	15 (11.5)	0.3534
End-stage renal disease, *n (%)*	21 (3.8)	18 (6.5)	7 (5.3)	0.2099
EQ-5D				
Mobility, *n (%)*				
No problems	203 (39.0)	84 (33.2)	33 (27.3)	
Some problems	295 (56.7)	158 (62.5)	81 (66.9)	
Severe problems	22 (4.2)	11 (4.3)	7 (5.8)	0.1281
Self-care, *n (%)*				
No problems	399 (77.5)	194 (77.3)	84 (69.4)	
Some problems	100 (19.4)	48 (19.1)	31 (25.6)	
Severe problems	16 (3.1)	9 (3.6)	6 (5.0)	0.4188
Usual activities, *n (%)*				
No problems	283 (54.7)	132 (52.4)	63 (52.5)	
Some problems	188 (36.4)	93 (36.9)	44 (36.7)	

Table 1 (*continued*)

	Healed 0–6 months n = 559 (57.8%)	Healed 7–12 months n = 278 (28.7%)	Not healed after 1 year n = 131 (13.5%)	p-value
Severe problems	46 (8.9)	27 (10.7)	13 (10.8)	0.9096
Pain/Discomfort, *n (%)*				
None	200 (38.8)	96 (37.9)	42 (35.0)	
Moderate	263 (51.0)	125 (49.4)	65 (54.2)	
Extreme	53 (10.2)	32 (12.7)	13 (10.8)	0.8090
Anxiety/Depression, *n (%)*				
None	304 (58.9)	154 (60.9)	74 (61.1)	
Moderate	185 (35.9)	83 (32.8)	44 (36.4)	
Extreme	27 (5.2)	16 (6.3)	3 (2.5)	0.5542
Index, *mean ± SD*	0.64 ± 0.32	0.61 ± 0.33	0.60 ± 0.31	0.2449

EQ-5D index (0.41 → 0.58 vs. 0.62 → 0.65). In these patients also a greater improvement in Usual activities and the EQ-5D index was observed in the presence of visual impairment (2.07 → 1.67 vs. 1.52 → 1.67; 0.29 → 0.53 vs. 0.64 → 0.66, respectively). In these patients with an unhealed ulcer also the EQ-5D index improved more in the presence of neurological disorder (0.33 → 0.67 vs. 0.62 → 0.64). No other effects of the various comorbidities on the change in HRQol during treatment were observed.

4. Discussion

The present communication is to the best of our knowledge the first study into the role of comorbidity on the course of HRQoL during treatment of DFUs. We show, in accordance with previous investigations,[7,12,13] that HRQoL improved in all domains in patients with a DFU in whom the ulcer healed, but also that non-healing was not associated with a further decline of the already poor HRQoL. The data indicate that, although the presence of comorbidity is associated with a poor HRQoL at baseline, these comorbidities did not influence negatively the course of HRQoL. In contrast, the presence of certain comorbidities was actually associated with a larger improvement in HRQoL during the treatment period, notably in ulcers that took longer time to heal or did not heal within the one-year follow-up.

The presence of comorbidity was associated with worse HRQoL at initial presentation with a new DFU, in accordance with previous investigations.[16] This low HRQoL at baseline implies a greater improvement potential during follow-up, which may in part be the explanation for the larger improvement of HRQoL in the presence of comorbidity, as seen in some of the results. This is reinforced by the fact that these larger improvements were predominantly seen in the ulcers that did not heal, which are tentatively the ulcers that – untreated – affect HRQoL most. Low HRQoL at presentation may be a consequence of the comorbidity or the ulcer per se as well as lack of adequate treatment prior to presentation and late referral to the diabetic foot clinic.[23]

When both DFU and comorbidity are present, quality, quantity and variety of care may be improved through the larger number of specialties involved. This has been documented in other studies on comorbidity[24] although the relationship may be inconsistent depending on the disorders and situation.[25] Care improvement with various case management systems has gained much attention in recent years.[26,27] Structured management of type 2 diabetes with comorbidity has been successful regarding HRQoL.[28] The prevailing modern paradigm for the care of patients with DFU, i.e. multifactorial treatment by a multidisciplinary team, has elements similar to case management systems, e.g. universal coverage, information based on consensus, education in self-care involving family and relatives, coordination between services and providers with access to immediate help at adequate level.[29] Hence, although there are several deficiencies in care delivery for patients with DFU,[23] even in specialized centers, it seems likely that our results may partly be explained by improved care.

It is indeed surprising that improvements primarily took place in patients not only suffering comorbidities, but also had slow or non-healing ulcers. In addition to the longer exposure to improved care as elaborated on in the previous paragraph, this chronic situation with multiple complications, however, could also create an adaptation to and acceptance of the role of being a patient with considerable need

Table 2
The development of health-related quality of life over the course of treatment for diabetic foot ulcer.

		Presentation	Follow-up	Adjusted analyses			
		Mean ± SD	Mean ± SD	d[1]	95% confidence interval for d		p-value
Mobility	Healed in 0–6 months	1.65 ± 0.56	1.51 ± 0.51	−0.145	−0.211	−0.079	0.0000
	Healed in 7–12 months	1.71 ± 0.54	1.55 ± 0.55	−0.162	−0.259	−0.065	0.0014
	Not healed within 1 year	1.79 ± 0.54	1.71 ± 0.54	−0.087	−0.226	0.051	0.2197
Self-care	Healed in 0–6 months	1.26 ± 0.50	1.20 ± 0.45	−0.051	−0.097	−0.005	0.0295
	Healed in 7–12 months	1.26 ± 0.52	1.25 ± 0.51	−0.004	−0.089	0.080	0.9189
	Not healed within 1 year	1.36 ± 0.58	1.41 ± 059	0.143	0.033	0.253	0.0130
Usual activities	Healed in 0–6 months	1.54 ± 0.65	1.42 ± 0.63	−0.129	−0.197	−0.061	0.0002
	Healed in 7–12 months	1.58 ± 0.68	1.47 ± 0.65	−0.098	−0.211	0.016	0.0945
	Not healed within 1 year	1.58 ± 0.68	1.67 ± 0.67	0.078	−0.050	0.207	0.2339
Pain/Discomfort	Healed in 0–6 months	1.72 ± 0.64	1.48 ± 0.60	−0.224	−0.295	−0.153	0.0000
	Healed in 7–12 months	1.75 ± 0.67	1.52 ± 0.60	−0.219	−0.347	−0.092	0.0010
	Not healed within 1 year	1.76 ± 0.64	1.52 ± 0.64	−0.156	−0.313	0.002	0.0568
Anxiety/Depression	Healed in 0–6 months	1.46 ± 0.59	1.33 ± 0.54	−0.134	−0.198	−0.070	0.0000
	Healed in 7–12 months	1.45 ± 0.61	1.33 ± 0.53	−0.061	−0.162	0.039	0.2341
	Not healed within 1 year	1.41 ± 0.54	1.43 ± 0.55	0.086	−0.048	0.219	0.2117
Index	Healed in 0–6 months	0.637 ± 0.320	0.742 ± 0.283	0.104	0.073	0.135	0.0000
	Healed in 7–12 months	0.611 ± 0.330	0.722 ± 0.299	0.090	0.029	0.150	0.0040
	Not healed within 1 year	0.599 ± 0.314	0.645 ± 0.308	0.020	−0.051	0.092	0.5776

[1] Difference in the corresponding HRQoL score between baseline and final follow-up.

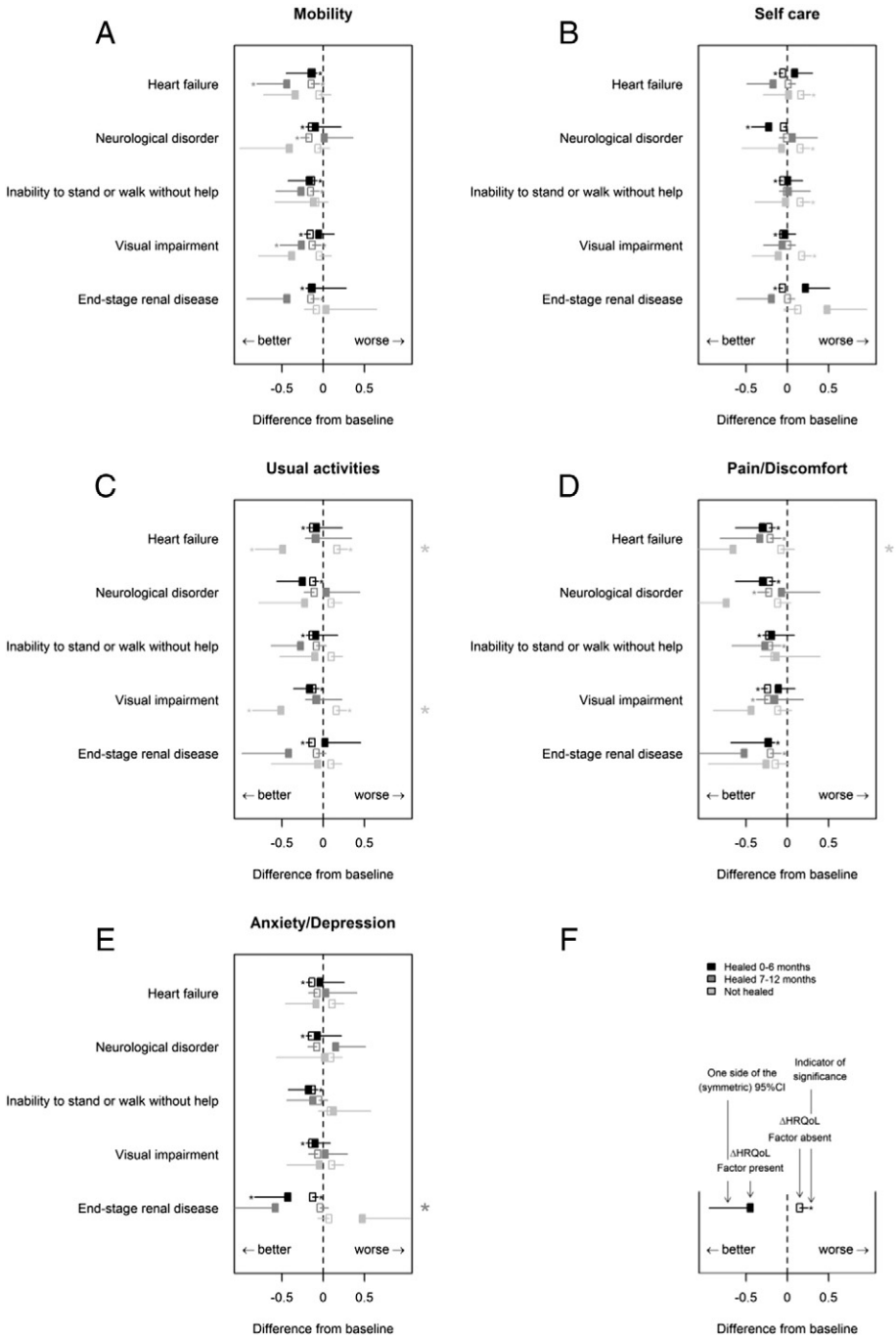

Fig. 2. The mean development of the five EQ-5D domains for patients with and without specific diabetic comorbidity.

of care. Despite the pervasive negative of impact of a DFU, positive consequences have also been noted in focus groups in early investigations[30] including feeling closer to spouse or partner, a greater appreciation of the need for foot care and the development of patience in order to deal with the frustration of daily life. Such positive effects of disease in HRQoL studies deserve more attention, not least in association with the possible role of the multidisciplinary team.

Comorbidity and decreased HRQoL at presentation were associated with higher mortality and higher rates of major amputation in earlier analyses.[11,19,31] Since we could not include in our analyses patients who died or had their leg amputated in the treatment period, the patients with comorbidity as included in the current analyses may be artificially more healthy and with better HRQoL. However, this does not affect the estimates of change in HRQoL from initial presentation to follow-up. Hence, we do not think that differential attrition may explain the effect of comorbidity on the course of HRQoL during treatment.

The strength of the present study is the large population of consecutively included and prospectively followed patients, who have been treated within a limited time-frame, and thereby are suitable for analyses of the many factors involved in DFU disease. A limitation is that our results pertain to a limited number of comorbidities, and analyses of more than one comorbidity, or of other comorbidities such as chronic pain disorders or airway obstruction, might show different results. In addition, the EQ-5D instrument is a generic and not a disease specific measure and thereby not particularly sensitive. It is,

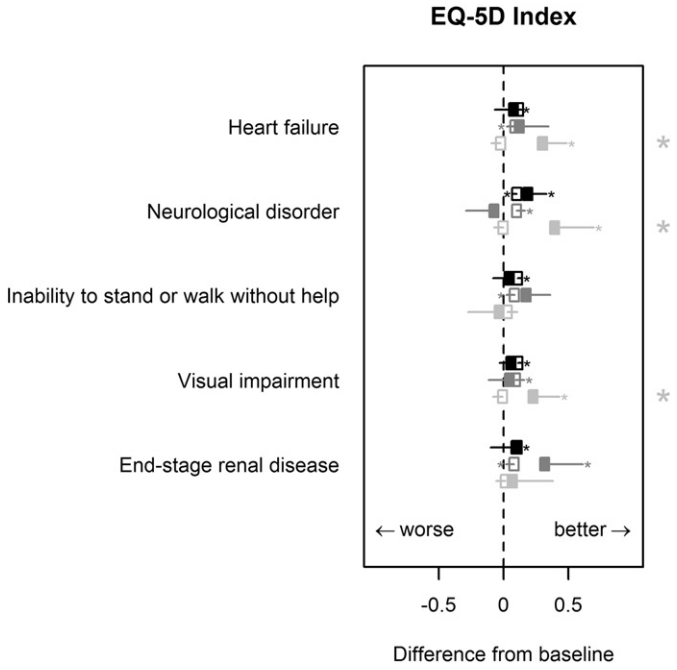

Fig. 3. The mean development of the EQ-5D index for patients with and without specific diabetic comorbidity.

however, easy and fast to perform and has been found suitable for studies that include a large number of patients so that missing data are widely avoided and consistent results are obtained.[8]

In conclusion the study confirms other studies: that healing of DFUs is associated with improvement in HRQoL; this was seen in fast- and slow-healing ulcers, non-healing was not associated with deterioration. Patients with a DFU and one or more comorbidities had a poorer HRQoL at presentation but comorbidity did not hamper improvement of HRQoL during healing of the ulcer. In contrast, in a small group the presence of comorbidity was associated with an improvement in some domains of HRQoL in patients with slow and non-healing DFUs treated in specialized diabetic foot centers. Beyond the higher potential for improvement in these patients, these findings might be the result of intensified care of these complex patients by the multidisciplinary teams in these centers and perhaps patients' adaptation and acceptance of the situation requiring multifactorial care. These results emphasize the value of a holistic approach in the treatment of patients with a DFU.

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