

# The Diabetic Person Beyond a Foot Ulcer

## Healing, Recurrence, and Depressive Symptoms

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**Background:** Several studies have shown a significant relationship between depressive symptoms and wound healing, but these studies have not assessed the effects of depressive symptoms on diabetic foot prognosis. We specifically designed our study to assess the role of depressive symptoms in healing and recurrence of diabetic foot ulcers.

**Methods:** A consecutive series of 80 type 2 diabetic patients aged 60 years and older with foot ulcers was enrolled in a cohort observational study with a 6-month follow-up. Patients who healed within 6 months of enrollment were included in a 12-month follow-up study for assessment of ulcer recurrence. Depressive symptoms were assessed with the geriatric depression scale.

**Results:** Healing was associated with a smaller ulcer area, shorter delay between ulcer onset and treatment, lower glycosylated hemoglobin, and higher ankle-brachial index. Both smoking status and Texas and Wagner scores also had a significant impact on healing. Patients who healed had significantly lower scores on the geriatric depression scale, and those with scores  $\geq 10$  had a significantly higher risk of not healing at 6 months (relative risk, 3.57; 95% confidence interval, 1.05–12.2). Patients with a recurrent ulcer (59.3%) showed significantly higher total cholesterol levels, higher scores on the Greenfield index of disease severity and geriatric depression scale, and a higher prevalence of cerebrovascular disease. Depressive symptoms maintained a significant association with persistence and recurrence of ulcer even after adjustment for confounders.

**Conclusions:** Depressive symptoms are associated with impaired healing and recurrence of ulcers in elderly type 2 diabetic patients. (J Am Podiatr Med Assoc 98(2): 130-136, 2008)

Predictors of negative outcome of diabetic foot ulcers include peripheral artery disease<sup>1</sup>; wound size, duration, and grade<sup>2</sup>; and low serum albumin.<sup>3</sup> Depressive symptoms have been reported to be associated with increased mortality in the general population and with increased morbidity and mortality in cardiovascular diseases such as stroke<sup>4</sup> as well as in malignancies and other conditions.

Diabetic foot ulcers are associated with impairment of quality of life and depressed mood,<sup>5-8</sup> particularly when healing does not occur after prolonged

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treatment.<sup>8</sup> Although several experimental<sup>9, 10</sup> and clinical studies<sup>11-14</sup> have shown a significant relationship between psychological factors and wound healing, they have not assessed the effects of depressive symptoms on diabetic foot healing.

### Materials and Methods

A prospective cohort study, with a 6-month follow-up, was conducted on a consecutive series of 80 type 2 diabetic patients 60 years and older with chronic foot ulcers (duration > 3 months) who were free of major cognitive impairment (Mini-Mental State Examination score > 18)<sup>15</sup> and had provided written, informed consent. Table 1 summarizes the characteristics of the subjects enrolled. All patients referred to

**Table 1. Characteristics of the 80 Study Participants**

	Total Sample	GDS Score < 10	GDS Score ≥ 10
No.	80	39	41
Female (%)	56.3	43.2	67.4 <sup>a</sup>
Age (mean ± SD) (years)	74.4 ± 8.3	72.1 ± 6.8	76.4 ± 8.9 <sup>a</sup>
Body mass index, (mean ± SD) (kg/m <sup>2</sup> )	28.4 ± 5.0	28.7 ± 5.8	28.2 ± 4.2
Waist circumference (mean ± SD) (cm)	100.6 ± 15.9	101.8 ± 18.2	99.6 ± 13.7
Diabetes duration (mean ± SD) (years)	23.0 ± 13.9	18.5 ± 12.8	26.9 ± 13.9 <sup>b</sup>
HbA1c level <sup>c</sup> (mean ± SD) (%)	8.0 ± 1.4	7.9 ± 1.5	8.1 ± 1.3
Total cholesterol (mean ± SD) (mg/dL)	198.5 ± 40.0	187.7 ± 38.5	206.9 ± 36.4 <sup>a</sup>
Triglycerides <sup>d</sup> (median [interquartile range]) (mg/dL)	128 (95–182)	128 (92–156)	158 (109–205) <sup>a</sup>
Current smoker (%)	21.3	21.6	20.9
Former smoker (%)	28.8	35.1	23.3 <sup>a</sup>
GDS score (mean ± SD)	12.4 ± 8.5	4.8 ± 2.9	18.9 ± 5.7 <sup>b</sup>
Greenfield index of disease severity (mean ± SD)	11.6 ± 4.0	10.6 ± 3.4	12.6 ± 4.2
Ankle-brachial index < 0.8 (%)	52.5	56.8	48.8
Vibration perception threshold > 25 volts (%)	82.5	86.5	79.1
Duration of ulcer <sup>d</sup> (median [interquartile range]) (days)	53 (30–120.7)	59 (29.5–120)	47 (30–121)
Location of ulcer (no.)			
Plantar	22	9	13
Dorsal	3	2	1
Toes	34	19	15
Other	21	11	10
Ulcer area <sup>d</sup> (median [interquartile range]) (cm <sup>2</sup> )	2 (0.5–7)	2 (0.5–7.2)	2 (0.9–7)
Wagner grade (%)			
1 or 2	83.9	85.1	80.2
≥ 3	16.1	14.9	19.8
University of Texas score, %			
1A–1D	20.1	22.7	18.4
2A–2D	64.8	68.2	61.7
3A–3D	15.1	9.1	19.9 <sup>a</sup>
Medical history, %			
Hypertension	72.5	62.8	83.8 <sup>a</sup>
Cardiac disease <sup>e</sup>	37.5	29.7	44.2 <sup>a</sup>
Cerebrovascular disease <sup>f</sup>	15.0	5.4	23.3 <sup>a</sup>
Chronic renal failure <sup>g</sup>	16.3	18.9	14.0
Retinopathy	45.0	40.5	48.8
Previous foot ulcer	54.6	50.8	58.1
Previous amputation	16.1	14.0	18.1
Previous depressive disorders	38.8	32.4	44.2 <sup>a</sup>
Current diabetes treatment (%)			
Insulin	48.3	43.2	53.5
Oral hypoglycemic drugs	56.3	59.1	53.5

Abbreviation: GDS, geriatric depression scale.

<sup>a</sup>*P* < .05 versus the GDS < 10 group.

<sup>b</sup>*P* < .01 versus the GDS < 10 group.

<sup>c</sup>The HbA1c test measures glycosylated hemoglobin.

<sup>d</sup>Values are expressed as median (25<sup>th</sup>–75<sup>th</sup> percentile).

<sup>e</sup>Previous myocardial infarction, angina pectoris, or congestive heart failure.

<sup>f</sup>Previous stroke or transient ischemic attack.

<sup>g</sup>Creatinine > 1.5 mg/dL.

the Geriatric Unit, University of Florence, Florence, Italy, between June 1, 2002, and May 31, 2003, and meeting all inclusion criteria were enrolled in the study. The foot care unit is an outpatient clinic within a

diabetes and metabolism unit of a university hospital; patients are referred either by their primary-care physicians or by other specialists within the hospital.

To investigate possible determinants of ulcer heal-

ing, parameters related to ulcer size and pathogenesis and to the patients' metabolic status were studied. The following were carried out at enrollment: a complete medical history, physical examination, standard electrocardiogram, routine blood tests (including glycosylated hemoglobin [HbA1c] [HPLC, Menarini Diagnostici, Florence, Italy; upper normal limit, 6.2%]), and a 24-hour microalbuminuria test.

Lower-limb blood flow was assessed through the ankle-brachial index as previously described<sup>16</sup> with a handheld 10 MHz Doppler (Huntleigh Diagnostics, Ltd, Eatontown, New Jersey); echo-color Doppler examination of lower-limb arteries was also performed. Vibration perception threshold was measured with a biothesiometer (Medical Diagnostic Instruments, Newbury, Ohio) at the tip of the first toe and on the lateral malleoli bilaterally.

Ulcers were classified according to Wagner<sup>17</sup> and the University of Texas.<sup>18</sup> The ulcer area in each patient was traced on a transparent plastic grid (Op-Site; Smith & Nephew Endoscopy, Andover, Massachusetts), and a photograph of the wound was recorded. The wound area was later calculated by computerized morphometric measurement and expressed in centimeters squared; changes in size were assessed monthly for 6 months or until complete healing, defined as full epithelialization of the wound with the absence of drainage. When more than one lesion was present, only the largest ulcer was taken into account.

All patients received oral acetyl salicylic acid 100 mg/day for the duration of the study, and local medications were administered following the practical guidelines on the management of foot ulceration.<sup>19</sup> This process included debriding all callus, necrotic, and fibrotic tissue; to detect underlying abscesses or sinuses, debridement was performed until bleeding tissue was exposed. A swab for bacteriological analysis was taken every month to detect infection, as recommended,<sup>19</sup> and the microbiological results were recorded. Appropriate systemic antibiotic treatment was prescribed in all patients with local signs of infection (eg, cellulitis, purulence, exposed bone) or positive bacterial cultures (a high number of colonies). Therapeutic shoes (with pressure-relieving insoles) were prescribed to patients with plantar ulcers (n = 10, 12.5%) for pressure relief.

Depressive symptoms were assessed with the 30-item geriatric depression scale (GDS), a tool specifically designed to rate depression in the elderly. Of the many instruments used to identify depression in the elderly, the GDS is probably the most widely used in research settings. Its items require a yes or no response, and a score of  $\geq 10$  is considered positive for a depressive condition.<sup>20</sup> The Greenfield index of dis-

ease severity was used to assess comorbidity<sup>21</sup> and is considered a marker of global severity possibly affecting clinical outcome; this scale has the advantage of being simple to use and more informative than disease count.

Patients who healed within 6 months of enrollment were included in the follow-up study for assessment of ulcer recurrence. All patients received a prescription for therapeutic footwear after ulcer healing. Incidence of recurrent ulcers was assessed after 12 months; investigators contacted the patients and invited them to a follow-up visit. Those who refused were asked by phone if new foot ulcers had occurred.

Continuous variables were compared between groups with the Student *t* test and Mann-Whitney *U* test whenever appropriate. The  $\chi^2$  test was used for between-group comparisons of categorical variables. Relative risk of not healing (with 95% confidence interval) was calculated in different groups, and a Cox regression was performed for multivariate analysis. For statistical analysis, the University of Texas score was converted into a numerical variable, with 1A = 1, 1B = 2, 1C = 3, 1D = 4, 2A = 5, 2B = 6, etc.

## Results

Forty-four patients (55%) had a GDS score at enrollment of  $\geq 10$  (five of these patients were treated with selective serotonin reuptake inhibitors during the follow-up); these patients were older than the rest of the sample and showed longer duration of diabetes and higher comorbidity than the rest of the sample. Patients with depressive symptoms also showed a higher prevalence of hypertension, cerebrovascular disease, and cardiovascular disease. A greater proportion of patients with GDS scores  $\geq 10$  reported a previous diagnosis of depressive disorders than in patients with GDS scores  $< 10$ . A greater proportion of women was found among those with GDS scores  $\geq 10$  than among those with scores  $< 10$  (Table 1), reflecting significantly higher mean GDS scores in the female sex (mean  $\pm$  SD,  $14.4 \pm 8.6$  versus  $9.8 \pm 7.7$ ;  $P = .016$ ).

Infection was detected in 60 (75.0%) cases. Culture examination revealed the presence of *Enterobacteriaceae* (79.5%), *Staphylococcus aureus* (52.3%), and anaerobic bacteria (13.6%); other germs detected in a smaller proportion of patients included *Pseudomonas aeruginosa* (11.4%), *Streptococcus pyogenes* (6.8%), and *Enterococcus* (6.8%).

## Ulcer Healing

No patients dropped out during the study. Of the 80 patients enrolled, 8 (10.0%) had undergone surgical revas-

cularization of lower limbs, 63 (78.8%) healed within 6 months, and 6 patients (7.5%) underwent amputations (5 minor and 1 major amputation). Healing was associated with smaller ulcer area (median [interquartile range], 2.0 [0.5–4.4] cm<sup>2</sup> versus 10.5 [2.3–28.0] cm<sup>2</sup>;  $P = .001$ ), shorter delay between ulcer onset and treatment (48 [25–100] days versus 92 [47–174] days;  $P = .009$ ), lower HbA1c ( $7.9 \pm 1.4\%$  versus  $8.4 \pm 1.0\%$ ;  $P = .048$ ), lower Greenfield index of disease severity (11 [9–15] versus 14 [10–16];  $P = .05$ ), and higher ankle-brachial index ( $0.92 \pm 0.21$  versus  $0.81 \pm 0.25$ ;  $P = .043$ ). Healing rate at 6 months (ie, proportion of patients with complete healing) was significantly lower in current smokers than in the rest of the sample (64.7% versus 82.5%;  $P = .045$ ). Wagner grade and University of Texas scores also had a significant impact on healing (data not shown).

Patients who healed within 6 months had significantly lower GDS scores than those who did not heal within 6 months ( $6.0 \pm 4.2$  versus  $16.1 \pm 6.1$ ;  $P = .005$ ), and those with GDS scores  $\geq 10$  had a significantly higher risk of not healing within 6 months than those with GDS scores  $< 10$  (30.2% versus 10.8%,  $P = .034$ ; relative risk, 3.57; 95% confidence interval, 1.05–12.2; Fig. 1A). When excluding patients who underwent revascularization ( $n = 3$ , 3.8%), the proportion of patients who did not heal remained significantly higher in patients with GDS  $\geq 10$  than in the rest of the sample (11.4% versus 32.5%,  $P = .022$ ; relative risk, 3.97; 95% confidence interval, 1.16–13.60).

With the Cox regression analysis, after adjusting for age and sex, only GDS scores  $\geq 10$  were significantly associated with a lower healing rate (Table 2). These results were confirmed when patients who underwent revascularization procedures were excluded from the analysis (data not shown).

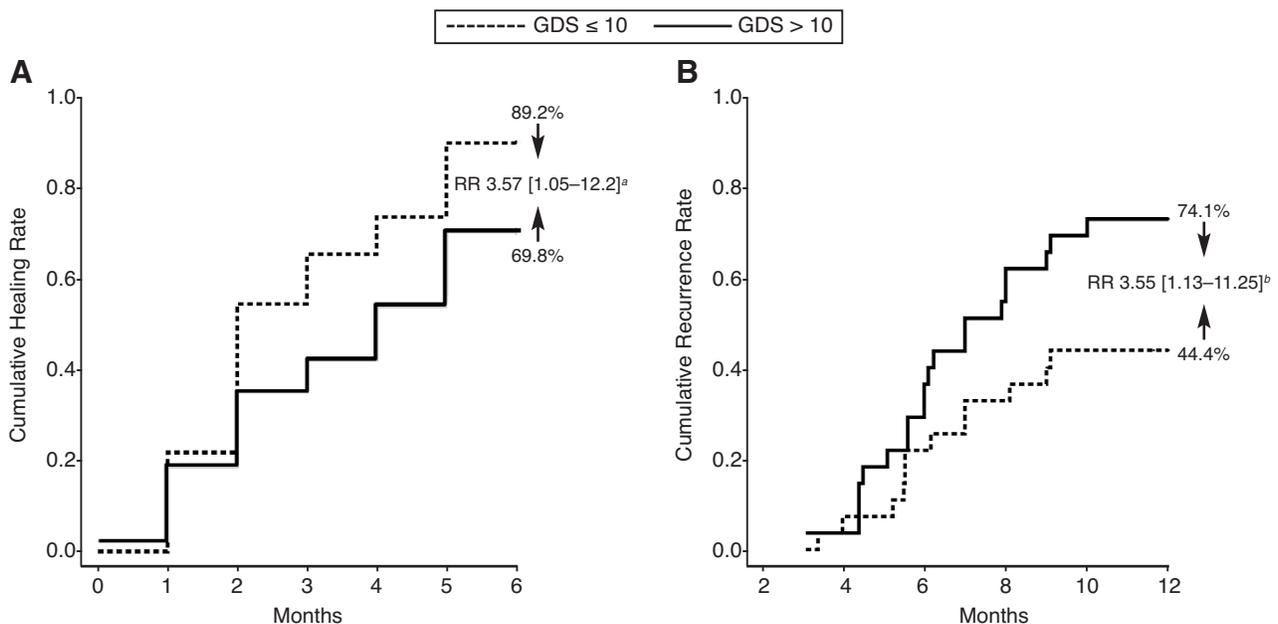
### Ulcer Recurrences

Of the 63 patients who had healed within 6 months, four (6.3%) died during the 12-month follow-up study, and five refused to participate in the follow-up study; these nine patients were excluded from the recurrence analysis. Mean follow-up time was  $8.5 \pm 3.1$  months.

Foot ulcers recurred in 32 (59.3%) patients. At the follow-up visit, 20 patients (31.7%) still used therapeutic footwear; the proportion of patients wearing therapeutic footwear at follow-up was significantly lower among those with GDS scores  $\geq 10$  than among those with GDS scores  $< 10$  (21.4% versus 53.8%;  $P < .05$ ).

When compared with the rest of the sample, patients with a recurrent ulcer showed significantly ( $P < .05$ ) higher total cholesterol, Greenfield index of disease severity and GDS scores, and prevalence of cerebrovascular disease (data not shown).

Those with GDS scores  $\geq 10$  (28, 51.9%) showed a significantly higher incidence of foot ulcers than the rest of the sample (74.1% versus 44.4%;  $P = .027$ ; relative risk, 3.55; 95% confidence interval, 1.13–11.25; Fig. 1B). With the Cox regression, after adjusting for



**Figure 1.** Differences in healing (A) and recurrence (B) rates by geriatric depression scale (GDS) score. RR, relative risk. <sup>a</sup> $P = .034$ ; <sup>b</sup> $P = .027$ .

**Table 2. Age- and Sex-Adjusted Hazard Ratios for Ulcer Not Healing**

Risk Factors	Exp(B) <sup>a</sup>	95% Confidence Interval	P
Greenfield index of disease severity	1.052	0.972–1.139	.201
Ankle-brachial index	1.160	0.453–2.971	.758
Current smoker	1.017	0.979–1.057	.397
Duration of ulcer	1.002	0.997–1.004	.181
Area of ulcer	1.016	0.933–1.035	.072
University of Texas score <sup>a</sup>	1.017	0.999–1.034	.059
Geriatric depression scale score $\geq 10$	2.004	1.131–3.542	.017
HbA1c	1.172	1.960–1.428	.098

Abbreviation: HbA1c, glycosylated hemoglobin level.

<sup>a</sup>For continuous variable, risk is expressed as additional risk for each unit of increment.

age and sex, recurrence of ulcers was significantly associated with depression and increased vibration perception threshold (Table 3).

## Discussion

Treatment of diabetic foot ulcers usually focuses on interventions for local pathogenetic factors, including debridement, pressure relief, antibiotic treatment for infection, and revascularization. Epidemiological studies confirm that local factors are relevant predictors of outcome; in fact, impaired blood flow is associated with delayed healing,<sup>1</sup> and diabetic neuropathy is a predictor of recurrence of ulcers.<sup>22</sup> This study confirmed the association of lower-limb arteriopathy and polyneuropathy with ulcer outcome. In fact, beyond ulcer area, healing of ulcers was delayed in patients with higher scores on the University of Texas scale, which takes into account ulcer depth, infection, and ischemia. On the other hand, recurrence of ulcers was predicted by reduced vibratory perception, which is an index of diabetic polyneuropathy, but not by lower-limb arteriopathy.

Available evidence suggests that general metabolic parameters could also play a role in ulcer healing. In fact, some studies showed a significant association of persistence of ulcers with elevated (> 6.2%) HbA1c level, after adjustment for local factors.<sup>23</sup> We found a significant delay of healing in patients with elevated HbA1c levels, which suggests that accurate glycemic control could be useful not only in the prevention but also in the treatment of foot ulcers. However, cross-

**Table 3. Age- and Sex-Adjusted Hazard Ratios for Ulcer Recurrence**

Risk Factors	Exp(B) <sup>a</sup>	95% Confidence Interval	P
Greenfield index of disease severity <sup>a</sup>	1.011	0.912–1.159	.804
Ankle-brachial index < 0.8	1.659	0.731–4.451	.345
Vibration perception threshold > 25 volts	12.050	2.103–79.898	.012
Geriatric depression scale score $\geq 10$ ]	4.995	3.015–13.987	.001
HbA1c	1.051	0.890–1.502	.678

Abbreviation: HbA1c, glycosylated hemoglobin level.

<sup>a</sup>For continuous variable, risk is expressed as additional risk for each unit of increment.

sectional studies, such as those currently available, do not allow the inference of causal relationships; therefore, the effect of intensive blood glucose control on ulcer healing should be confirmed through intervention studies. Unexpectedly, elevated HbA1c was not associated, in this series of patients, with a higher recurrence rate. This result could be because of an insufficient sample size; alternatively, the relatively good glycemic control in this sample could have prevented the detection of the expected effect of frank hyperglycemia on recurrence of ulcers.

Several studies have shown that diabetic foot ulcers are associated with impaired quality of life and depression.<sup>5-8</sup> It has also been reported that a progressive impairment of mood occurs when ulcers do not heal despite prolonged treatment.<sup>8</sup> Studies have investigated the relationship of foot ulcers with depressive symptoms, either cross-sectionally or by exploring the effect of healing on subsequent modifications of mood. Ours is the first report of depression being associated with subsequent impaired healing of diabetic ulcers. Interestingly, the presence and the degree of depressive symptoms as assessed by a specific scale validated for older persons was a better predictor of ulcer outcome than a previous formal diagnosis of a depressive disorder. Previous diagnosis of a depressive disorder might have been a less sensitive method to detect mood disturbances because it might have missed the mild alterations of mood, or because cases of depressive disorders were not referred to a physician. Furthermore, some patients could have failed to report a previously diagnosed depressive disorder. Depressed mood could be the consequence of greater disease severity or comorbidity; if this was the

case, a higher GDS score could be an index of severity of overall health impairment.

However, the effect of GDS on healing was retained after adjusting for indices of ulcer severity and comorbidity, which suggests a direct, independent effect of mood on the healing process. Depressive disorders are common in diabetic patients,<sup>24</sup> and disease complications, such as foot ulcers, may have a further negative emotional impact. In fact, foot complications can impair quality of life considerably, which can lead to significantly depressed mood. On the other hand, depressed mood could reduce adherence to prescribed diabetes care and impair metabolic control.<sup>25</sup> Furthermore, depressed mood could be associated with lower compliance to prescribed foot care (wound dressing, hygiene, systemic medication, etc), possibly interfering with healing. Other possibilities are a possible direct effect of mood on regulation of blood pressure, catecholamine secretion,<sup>26</sup> platelet function,<sup>26</sup> and immune status.<sup>27</sup>

Similar considerations could be made for the relationship between depressed mood and recurrence of ulcers. In fact, mood depression could be the marker of higher comorbidity, leading to a higher recurrence rate. It is also conceivable that depressed mood could be associated with impaired foot care, which could facilitate the onset of new ulcers. The possibility of other pathogenetic mechanisms directly linking depression with ulcer recurrence<sup>26, 27</sup> cannot be excluded.

## Conclusion

The present study was targeted at type 2 diabetic patients 60 years and older. Mood depression is more frequent in older individuals.<sup>20</sup> It should also be considered that the majority of foot problems in diabetic patients occur at or after age 60. However, our results need to be confirmed in a sample of younger subjects before they can be extended to diabetic patients with foot ulcers in general.

The results of this study suggest that mood depression is a risk marker—and could be a pathogenetic factor—for delayed healing and recurrence of foot ulcers in elderly type 2 diabetic patients. Adequate screening for mood disorders could have a relevant prognostic value in those patients. The possible beneficial effect of antidepressant therapy in depressed diabetic patients with lower-limb lesions deserves further investigation.

Although treatments targeting local pathogenetic factors have a crucial role in the management of diabetic foot ulcers, the patient with foot problems should be considered as a whole. Despite common acceptance of the fact that general metabolic parameters

deserve appropriate therapy, psychological screening and treatment are often neglected. In fact, the proportion of patients at enrollment in this study with depressive symptoms who were receiving specific pharmacological treatment was negligible (11%).

The management of diabetic foot ulcers should include (along with an appropriate therapy for local and metabolic factors) adequate consideration of emotional aspects, which could play a relevant role in the outcome of local lesions.

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## References

1. MOULIK PK, MTONGA R, GILL GV: Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care* **26**: 491, 2003.
2. MARGOLIS DJ, ALLEN-TAYLOR L, HOFFSTAD O, ET AL: Diabetic neuropathic foot ulcers: predicting which ones will not heal. *Am J Med* **115**: 627, 2003.
3. LEHTO S, RONNEMAA T, PYORALA K, ET AL: Risk factors predicting lower extremity amputations in patients with NIDDM. *Diabetes Care* **19**: 607, 1996.
4. EVERSON SA, ROBERTS RE, GOLDBERG DE, ET AL: Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Arch Intern Med* **158**: 1133, 1998.
5. RAGNARSON TG, APELQVIST J: Health-related quality of life in patients with diabetes mellitus and foot ulcers. *J Diabetes Complications* **14**: 235, 2000.
6. CARRINGTON AL, MAWDSLEY SK, MORLEY M, ET AL: Psychological status of diabetic people with or without lower limb disability. *Diabetes Res Clin Pract* **32**: 19, 1996.
7. ECKMAN MH, GREENFIELD S, MACKAY WC, ET AL: Foot infections in diabetic patients: decision and cost-effectiveness analyses. *JAMA* **273**: 712, 1995.
8. NABUURS-FRANSEN MH, HULBERTS MS, NIEUWENHUIZEN KRUSEMAN AC, ET AL: Health-related quality of life of diabetic foot ulcer patients and their caregivers. *Diabetologia* **48**: 1906, 2005.
9. KIECOLT-GLASER JK, MARUCHA PT, MALARKEY WB, ET AL: Slowing of wound healing by psychological stress. *Lancet* **346**: 1194, 1995.
10. MARUCHA PT, KIECOLT-GLASER JK, FAVAGEHI M: Mucosal wound healing is impaired by examination stress. *Psychosom Med* **60**: 362, 1998.
11. ANDERSON TP, ANDBERG MM: Psychosocial factors associated with pressure sores. *Arch Phys Med Rehabil* **60**: 341, 1979.
12. COLE-KING A, HARDING KG: Psychological factors and delayed healing in chronic wounds. *Psychosom Med* **63**: 216, 2001.
13. KIECOLT-GLASER JK, GLASER R, GRAVENSTEIN S, ET AL: Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci U S A* **93**: 3043, 1996.
14. OLSHANSKY K: Psychological factors in recurrent pressure sores. *Plast Reconstr Surg* **90**: 930, 1992.
15. FOLSTEIN MF, ROBINS LN, HELZER JE: The Mini-Mental State Examination. *Arch Gen Psychiatry* **40**: 812, 1983.
16. WINSOR T, SIMMONS EM, BORHANI N, ET AL: A diagnostic

- aid for determining peripheral arteriosclerosis obliterans. *Dis Chest* **52**: 451, 1967.
17. WAGNER FW JR: The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle* **2**: 64, 1981.
  18. ARMSTRONG DG, LAVERY LA, HARKLESS LB: Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* **21**: 855, 1998.
  19. APELQVIST J, BAKKER K, VAN HOUTUM WH, ET AL: International consensus and practical guidelines on the management and the prevention of the diabetic foot. International Working Group on the Diabetic Foot. *Diabetes Metab Res Rev* **16** (suppl 1): S84, 2000.
  20. YESAVAGE JA, BRINK TL, ROSE TL, ET AL: Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17**: 37, 1982.
  21. GREENFIELD S, BLANCO DM, ELASHOFF RM, ET AL: Patterns of care related to age of breast cancer patients. *JAMA* **257**: 2766, 1987.
  22. MANTEY I, FOSTER AV, SPENCER S, ET AL: Why do foot ulcers recur in diabetic patients? *Diabet Med* **16**: 245, 1999.
  23. MARSTON WA: Risk factors associated with healing chronic diabetic foot ulcers: the importance of hyperglycemia. *Ostomy Wound Manage* **52**: 26, 2006.
  24. PEYROT M, RUBIN RR: Persistence of depressive symptoms in diabetic adults. *Diabetes Care* **22**: 448, 1999.
  25. MAZZE RS, LUCIDO D, SHAMOON H: Psychological and social correlates of glycemic control. *Diabetes Care* **7**: 360, 1984.
  26. NEMEROFF CB, MUSSELMAN DL, EVANS DL: Depression and cardiac disease. *Depress Anxiety* **8** (suppl 1): S71, 1998.
  27. ADER R, COHEN N, FELTEN D: Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet* **345**: 99, 1995.