Diabetic Peripheral Neuropathy and Depressive Symptoms

The association revisited

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OBJECTIVE — We examined the association between severity of diabetic peripheral neuropathy and depressive symptoms and investigated the potential mediators of this association.

RESEARCH DESIGN AND METHODS — The Hospital Anxiety and Depression Scale (HADS) was used to assess depressive symptoms in 494 patients (mean age 62 years; 70% male; 72% type 2 diabetic) with diabetic neuropathy diagnosed by the Neuropathy Disability Score (NDS) and the Vibration Perception Threshold (VPT). Diabetic neuropathy symptoms, activities of daily living (ADLs), and social self-perception were measured by the neuropathy and foot ulcer–specific quality-of-life instrument, NeuroQoL; perceptions of diabetic neuropathy symptom unpredictability and the lack of effective treatment were assessed by the revised Illness Perception Questionnaire.

RESULTS — Both the NDS and VPT were significantly associated with the HADS after controlling for demographic and disease variables. Although diabetic neuropathy symptoms mediated this association, with unsteadiness being most strongly associated with HADS, the relationship between foot ulceration and depression was nonsignificant. The association between diabetic neuropathy symptoms and HADS was partially mediated by two sets of psychosocial variables: *1*) perceptions of diabetic neuropathy symptom unpredictability and the lack of treatment control and *2*) restrictions in ADLs and changes in social self-perception.

CONCLUSIONS — These findings establish the association between diabetic neuropathy and depressive symptoms and identify potential targets for interventions to alleviate depressive symptoms in persons affected by diabetic peripheral neuropathy.

Diabetes Care 28:2378–2383, 2005

Diabetic peripheral neuropathy is common, affecting up to 50% of patients (1), and predisposes patients to severe functional limitations through symptoms of unremitting pain and unsteadiness. Its end-stage complications such as foot ulceration and amputation (2,3) are associated with substantial health care costs, socioeconomic consequences including loss of work time (4), and reduced quality of life (5).

Although evidence suggests that long-term complications of diabetes are associated with depressive symptoms (6,7), the relationship between diabetic neuropathy specifically and depressive symptoms is less clear. Although individual studies examining the association between diabetic neuropathy and depression have produced conflicting results, a recent meta-analysis suggests that the balance of evidence supports the relationship (6). The conflicting findings and heterogeneity of explained variance among the studies examined in this meta-analysis may be due partly to differences in the procedures used to diagnose neuropathy, because most of these investigations were conducted before standardized diagnostic criteria for neuropathy had been established (1,8), resulting in the inclusion of different patient populations, some of whom may not have had neuropathy. For example, with two exceptions (9,10), all previous studies used either a single test of neurological dysfunction or symptoms alone to define neuropathy. Because different types of nerve fibers are affected by neuropathy in different individuals, it is now well established that diagnosis of neuropathy requires more than one test of neurological deficits (1). Moreover, because the severity of neuropathy defined by objective tests correlates poorly with subjective severity, e.g., patients experiencing neuropathic pain often have remarkably preserved nerve function on clinical examination (11), symptoms alone cannot be relied upon to diagnose neuropathy. An additional limitation of the earlier reports is that predominantly painful symptoms were assessed in studies that found a significant association between depression and neuropathy. The results of these studies have limited generalizability, however, because <10% of patients with neuropathy experience severely painful symptoms (12), and many experience no symptoms (13). Furthermore, pain is only one neuropathic symptom, and the possible relationship between depression and other somatic experiences of diabetic neuropathy such as unsteadiness and foot ulcers has not been addressed. Finally, no re-

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Received for publication 11 April 2005 and accepted in revised form 26 June 2005.

Abbreviations: ADL, activity of daily living; HADS, Hospital Anxiety and Depression Scale; IPQ-R, revised Illness Perception Questionnaire; NDS, Neuropathy Disability Score; VPT, Vibration Perception Threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ports have examined the potential psychosocial mediators of the association between patients' somatic experience of neuropathy and depressive symptoms. Thus, identification of a link and the ways by which diabetic neuropathy relates to depressive symptoms would facilitate the development of effective interventions for the alleviation of depression and the improvement of physical and psychological functioning of individuals affected by diabetic neuropathy.

Our main objective was, therefore, to investigate the association between diabetic neuropathy severity and depressive symptoms in a sample of patients whose neuropathy was diagnosed by well-established, objective tests of neurologic dysfunction. Our primary hypothesis was that diabetic neuropathy severity as measured by objective tests would be significantly associated with depressive symptoms and that this relationship would be due to, i.e., mediated by, patients' subjective experiences of neuropathic pain, reduced feeling in the feet and unsteadiness, and the presence of a neuropathic foot ulcer.

The second set of hypotheses addressed the psychosocial factors expected to link patients' somatic experience of neuropathy to depressive symptoms. In keeping with theoretical models of chronic illness and depressive symptoms, we anticipated that two sets of psychosocial variables would link the somatic experience of diabetic neuropathy to depressive symptoms: *1*) patients' interpretation of neuropathic symptoms as episodic and unpredictable and the treatment as ineffective (14) and *2*) diabetic neuropathy–related restrictions in activities of daily living (ADLs) and the perceptions of diminished value of the self due to inability to perform social-family roles (15,16).

RESEARCH DESIGN AND METHODS

— A consecutive sample of 522 patients with peripheral neuropathy and either type 1 or type 2 diabetes who met the inclusion criteria was approached from three sites: Manchester, U.K.; Baltimore, Maryland; and State College, Pennsylvania. Of these, 494 agreed to participate, giving a 5% refusal rate. Permission to conduct this study was granted by institutional review boards at all three sites.

In accordance with international guidelines (6) two clinical tests were used to diagnose neurological dysfunction: the Neuropathy Disability Score (NDS) and the Vibration Perception Threshold (VPT), as previously described (17). Neuropathy was diagnosed if subjects had an NDS ≥3 and a mean VPT of ≥25 V (18); both these tests have been shown to predict outcomes, e.g., foot ulceration (19,20). Patients were excluded if they had peripheral vascular disease (defined as <1 palpable foot pulse or previous bypass surgery/angioplasty), a history of major amputation (any lower-limb amputation proximal to the midfoot), or other severe chronic medical diseases or complications of diabetes precluding participation (such as renal failure/dialysis, stroke, or widespread malignant disease). Patients were also excluded if they were unable to understand English sufficiently well to complete the self-report psychological measures or had insufficient (corrected) vision to complete the questionnaires. After explanation of the study details and an initial examination for suitability, written consent was obtained.

Measures

Three scales from a neuropathy-specific quality-of-life instrument, NeuroQoL, were used to assess the frequency of neuropathic symptoms (17). The basic format asked, "In the past 4 weeks how often have you experienced the following symptoms?": *1*) neuropathic pain and/or paresthesia (seven items, e.g., burning or throbbing sensation in the feet, excessive heat or cold, shooting or stabbing pain; Cronbach's $\alpha = 0.88$), *2*) symptoms of reduced feeling in the feet (three items, including numbness, inability to feel objects and/or temperature with the feet; $\alpha = 0.90$), and *3*) unsteadiness (two items, including problems with balance while walking and problems with balance while standing; $\alpha = 0.86$). All items were rated on a 5-point Likert scale (1 = never and 5 = all the time).

A foot ulcer history was obtained by asking each subject "Have you ever had a foot ulcer (an open sore on your foot)?" The presence of foot ulcers defined as a full-thickness skin break below the malleoli was determined by examination at the time of the baseline assessment.

Cognitive representation of diabetic neuropathy and its treatment was assessed using two theoretically relevant scales from the revised Illness Perception Questionnaire (IPQ-R), measuring the patients' perceptions of diabetic neuropathy and its symptoms as episodic-unpredictable and lacking treatment control (21). Following recommendations of the authors of the IPQ-R, this instrument was adapted to diabetic neuropathy by replacing the generic "illness" with neuropathy, referring to it as "reduced feeling in the feet." The participants were asked to indicate on a 5-point Likert response scale how much they agreed or disagreed with a series of statements (scale ranging from 1 = strongly disagree to 5 = strongly agree), with higher scores reflecting more perceived treatment control and less symptom predictability. The treatment control scale consists of five items capturing the patients' belief as to whether treatment would be effective in controlling diabetic neuropathy and its symptoms (e.g., "There is very little that can be done to improve symptoms of reduced feeling in my feet"; $\alpha = 0.75$). The four-item episodic-unpredictable timeline scale assesses the perceptions of neuropathic symptoms as episodic and unpredictable (e.g., "The symptoms of reduced feeling in my feet change a great deal from day to day," "Symptoms of reduced feeling in my feet are very unpredictable"; $\alpha = 0.86$).

Neuropathy-related restrictions in activities of daily living (ADLs) were assessed using a three-item NeuroQoL scale (17) asking: "In the past 4 weeks how often have your foot problems interfered with your ability to perform your paid work or tasks around the house and to take part in leisure activities?" ($\alpha = 0.95$). The response scale was from 1 = never to 5 = all the time.

Neuropathy-related changes in social self-perception (the self perceived as social-family burden) were measured by a three-item interpersonal-emotional burden scale from the NeuroQoL (17). Respondents used a 5-point scale (from 1 = not at all to 5 = very much) to rate their status relevant to each of the following statements: "In the past 4 weeks how much have your foot problems interfered with your relationships with people close to you?" "Have you felt more physically dependent than you would like to be on people close to you?" "Has your role in the family changed as a result of your foot problems?" ($\alpha = 0.91$).

Depressive symptoms were assessed with the seven-item subscale from the Hospital Anxiety and Depression Scale (HADS), measuring the absence of both positive affect and pleasure from everyday tasks (22). The HADS was designed to

avoid the confounding of somatic symptoms of concurrent physical disorders such as sleep problems and/or pain, with the assessment of anxious and depressive symptoms in medically ill persons. Items are scored so that a higher score indicates greater severity of symptoms; for example, "I feel as if I am slowed down" or "I can laugh and see the funny side of things": nearly all the time = 3, very often = 2, sometimes = 1, or not at all = 0. The HADS subscale measuring depressive symptoms had $\alpha = 0.84$.

Control variables were selected to rule out potential confounding results and included sex, age, education, marital status, type and duration of diabetes, number of diabetes complications other than neuropathy, and number of comorbid disorders. Comorbid disorders included all self-reported medical conditions other than diabetes and its complications. Complications of diabetes, including retinopathy, nephropathy, and cardiovascular disease, were recorded by patients' self-report.

Additionally, because significant differences existed between the U.K. and U.S. participants (Table 1), all analyses controlled for the study site. Information regarding the use of antidepressant medication (tricyclic antidepressants, selective serotonin reuptake inhibitors, and other antidepressants) was obtained from a patient self-report. To account for the potential confounding effects of antidepressants, two parallel analyses were conducted, one of which controlled for whether patients took antidepressant medication and the other excluded all subjects taking any antidepressant medication.

Statistical methods

All data were analyzed using SPSS 11.0. To maximize the number of subjects to be included in the regression analyses, missing data for all continuous/ordinal independent variables were replaced by the overall mean for that variable. The maximum number of participants failing to respond for any single variable was 11 (for years of education), and the average across variables was 3. For categorical variables with missing data (e.g., diabetes type and marital status), a dummy variable was created for which missing data were coded as 1 on the dummy variable and 0 on the original variable. The dummy variables were not significant in any regression and are not presented below. Patients with missing data for the dependent variable were dropped from the analysis (10 patients). This resulted in an n of 484 of the total N of 494 for the regression analyses as opposed to an n of 431 if listwise deletion was used. Analysis using listwise deletion produced essentially the same findings.

Hypotheses were tested using hierarchical stepwise linear regression. Hierarchical entry was performed by entering variables in blocks: first the control variables, then objective indicators of diabetic neuropathy severity, followed by symptoms and measures of cognition, and finally by diabetic neuropathy–related restrictions in ADLs and changes in social self-perception. Some blocks contained subblocks representing conceptual distinctions. Control variables were forced into the model. For all other blocks, variables within a given block were allowed to enter in a stepwise manner, based on the lowest P value to enter. Procedures recommended by Baron and Kenny (23) were used to evaluate potential mediators. A variable can be considered a mediator if it meets the following four conditions: *1*) the independent variable significantly predicts the mediator, *2*) the independent variable significantly predicts the dependent variable in the absence of the mediator, *3*) the mediator has a significant unique effect on the dependent variable, and *4*) the relationship of the independent variable to the dependent variable is attenuated upon the addition of the mediator to the model. Sobel's variance estimate (24) was used as the test of whether the indirect effect of the independent variable on the dependent variable via the mediator is significantly different from zero.

RESULTS — The patient characteristics are presented in Table 1. Subjects were recruited to have moderate to severe neuropathy on objective testing, and 16% of them had active foot ulcers at the time of the interview, the majority of which (96%) were recurrent.

Six hierarchical linear regression models were tested to predict the HADS score (Table 2). Demographic and disease variables accounted for ~6% of the total variance in depression scores. More educated respondents reported fewer depressive symptoms. Patients with type 2 diabetes and with more long-term complications of diabetes and concomitant medical disorders reported significantly more depressive symptoms (model I in Table 2).

Association between objective and subjective severity of neuropathy and depressive symptoms

When objective indicators of diabetic neuropathy severity were added to the model (model II in Table 2), they accounted for an additional 5% of variance in depression scores. Both the NDS ($\beta = 0.13$) and VPT ($\beta = 0.15$) were significantly associated with higher depression scores. Because neither having an active ulcer nor having had an ulcer in the past was related to depression scores at the bivariate level, ulcer status was not included in this model.

When diabetic neuropathy symptoms were added to the model (model III in Table 2), they accounted for an additional 28% of the variance in depression scores. Higher levels of symptoms of reduced feeling in the feet ($\beta = 0.18$), pain ($\beta = 0.27$), and unsteadiness ($\beta = 0.30$) were significantly related to higher levels of depression scores.

Using the procedures described above, we found that the relationship between NDS and depressive symptoms was significantly mediated by all three diabetic neuropathy symptoms. The relationship between VPT and depression scores was mediated by two sets of neuropathic symptoms: reduced feeling in the feet and unsteadiness.

Illness cognition as a mediating path between somatic experience of diabetic neuropathy and depressive symptoms

Two scales from the IPQ-R (treatment control and episodic-unpredictable timeline) were entered next (model IV in Table 2). Greater perceived treatment control was associated with fewer depressive symptoms ($\beta = -0.12$), and the episodic-unpredictable timeline was associated with higher depression scores ($\beta = 0.16$). Together they accounted for an additional 3% of the variance. The indirect path of pain to depressive symptoms through episodic-unpredictable timeline beliefs was significant. The episodic-unpredictable timeline did not mediate the relationships of depression with unsteadiness or reduced feeling in the feet. Perceptions that treatment was effective in controlling neuropathy did not mediate relationships between somatic experience of neuropathy and depressive symptoms.

Table 1 —*Characteristics of the study population*

	U.K.	U.S.	Total
n	316	168	484
Male sex (%)	72.2	66.7	70.2
Age (years)	61.50 ± 11.54	62.56 ± 9.82	61.86 ± 10.98
Education (%)*			
Primary	4.1	1.8	3.4
Secondary	58.5	41.7	54.0
Some college	23.1	11.9	19.7
College graduate	7.3	25.6	14.0
Postgraduate	4.4	19.5	8.9
Marital status (has partner)	64.9	73.2	67.8
Diabetes type (type 1)*	34.5	16.7	28.3
Diabetes duration	17.45 ± 11.62	16.95 ± 10.83	17.18 ± 11.19
Number of diabetes complications	1.57 ± 1.06	1.54 ± 1.18	1.56 ± 1.10
Number of concomitant disorders*	0.74 ± 0.89	1.43 ± 1.24	0.98 ± 1.07
NDS	7.33 ± 2.17	7.63 ± 2.12	7.43 ± 2.17
VPT*	39.30 ± 9.33	44.39 ± 9.33	41.06 ± 9.63
Active foot ulcers (%)	16.4	14.9	15.9
NeuroQoL symptom scores:			
Pain	1.94 ± 0.91	2.00 ± 0.75	1.96 ± 0.86
Unsteadiness†	2.26 ± 1.32	2.60 ± 1.24	2.38 ± 1.30
Reduced feeling*	2.55 ± 1.48	3.40 ± 1.31	2.85 ± 1.48
IPQ-R Episodic-unpredictable timeline	2.91 ± 0.88	2.81 ± 0.89	2.88 ± 0.93
IPQ-R Treatment control	3.12 ± 0.71	2.99 ± 0.73	3.07 ± 0.72
NeuroQoL Restrictions in ADL†	2.39 ± 1.41	2.75 ± 1.28	2.51 ± 1.37
NeuroQoL Changes in social self-perception	2.04 ± 1.35	2.31 ± 1.25	2.14 ± 1.32
HADS	5.41 ± 4.26	4.83 ± 3.65	5.20 ± 4.06
Antidepressant medications (%)			
Tricyclic antidepressants only	11.6	10.7	11.3
Selective serotonin reuptake inhibitors only‡	4.3	10.7	6.5
Both	0.9	1.2	1.0

Data are % or means ± SD. χ^2 tests were used to evaluate categorical variables, and independent samples *t* tests were used to evaluate continuous variables. Significant differences between study sites: *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

Diabetic neuropathy–related restrictions in ADLs and changes in social self-perception as a mediating path between somatic experience of neuropathy and depressive symptoms

Finally, restrictions in ADLs and changes in social self-perception were examined in relation to depression scores, each entering the equation on a separate step (models V and VI in Table 2). Restrictions in ADLs accounted for an additional 2% of the variance in depression scores, and changes in social self-perception accounted for another 2% of the variance. To test for possible mediation we again followed the procedures of Baron and Kenny (23). Results showed that self-perception was a significant mediator of the relationship between activity restriction and depression scores. The relationship between reduced feeling in the feet and depressive symptoms was mediated by social self-perception. In addition, while retaining their significant direct paths to depressive symptoms (model VI), both pain and unsteadiness also had significant indirect paths through changes in the social self-perception.

The final model accounted for 46% of the variance in depression scores. Neuropathy-related factors accounted for 40% of the variance in depressive symptoms. Residual plots were approximately normal (skew = 0.46 and kurtosis = 0.66), with little evidence of heteroscedasticity. Parallel analyses controlling for antidepressant medication and excluding subjects taking antidepressant medication ($n = 84$) showed virtually identical results (results not shown).

CONCLUSIONS — This study of diabetic patients with moderate to severe peripheral neuropathy provides evidence that severity of neuropathy is associated with depressive symptoms in such patients, with neuropathy-related factors accounting for nearly half of the variance in depression scores. The results supported our expectations that the association between the clinical tests of neuropathic severity (NDS and VPT) and depressive symptoms would be mediated by neuropathic symptoms. Each symptom set (pain, unsteadiness, and symptoms of reduced feeling in the feet) was independently associated with depressive symptoms and together accounted for the relationship between objective indicators of diabetic neuropathy severity and depression scores. The observation that only symptoms of unsteadiness and reduced feeling in the feet (not pain) accounted for the association between VPT and depression scores, whereas each of the three symptom sets mediated the association between NDS and depression, is entirely consistent with the underlying pathology of neuropathy. Whereas symptoms of unsteadiness and reduced feeling in the feet and the sensory modality of vibration, VPT, represent dysfunction in large myelinated nerve fibers, pain is a small fiber–related symptom and is captured by the NDS, which is a composite measure of both small and large fiber dysfunction (18).

Although the association between the neuropathic pain and depression in diabetes has been previously documented (10,25), the emergence of unsteadiness as the symptom that was most strongly associated with depressive symptoms warrants further attention. In an early report linking postural instability to neuropathy, Cavanagh et al. (26) described the frequent patient report of unsteadiness, which was ascribed to an impaired afferent large fiber input from the lower extremities, resulting in reduced proprioception. More recently, these findings have been replicated and have demonstrated that, in some populations, diabetic neuropathy fully accounts for diabetes-related physical limitations (27). Our results confirm that unsteadiness is common and distressing for patients (23% reporting balance problems either most or all of the time). One possible explanation as to why unsteadiness is largely overlooked by practitioners is that postural instability is likely to be perceived by patients as an indicator of di-

Table 2 —*Hierarchical stepwise linear regression: predictors of depression in patients with diabetic peripheral neuropathy*

	Model I	Model II	Model III	Model IV	Model V	Model VI
R^2	0.06	0.11	0.39	0.42	0.44	0.46
Demographic/disease variables						
Sex	0.04	0.08	0.03	0.03	0.02	0.03
Education	−0.12*	−0.11*	−0.07	−0.05	−0.04	−0.05
Type 2 diabetes	0.13*	0.12*	0.03	0.03	0.04	0.04
Diabetes duration	0.03	−0.01	0.01	−0.00	−0.01	0.00
Has partner	0.01	0.01	0.01	0.03	0.03	0.01
Age	−0.07	−0.07	0.01	0.01	0.02	0.03
U.S. study site	−0.08	−0.13†	−0.16‡	−0.15‡	−0.16‡	−0.16‡
Number of diabetes complications	0.11*	0.09*	0.03	0.04	0.04	0.02
Number of comorbidities	0.12*	0.12*	0.02	0.02	0.02	0.02
Objective diabetic neuropathy severity						
NDS		0.13†	−0.04	−0.05	−0.04	−0.05
VPT		0.15†	0.04	0.05	0.05	0.05
Diabetic neuropathy symptoms:						
NeuroQoL Reduced feeling in feet			0.18†	0.16†	0.11*	0.08
NeuroQoL Pain			0.27‡	0.21‡	0.19‡	0.16†
NeuroQoL Unsteadiness			0.30‡	0.28‡	0.23‡	0.18†
Perceptions of diabetic neuropathy and its treatment						
IPQ-R Treatment control				−0.12†	−0.13‡	−0.14‡
IPQ-R Episodic-unpredictable timeline				0.16‡	0.14‡	0.13‡
NeuroQoL Restrictions in ADLs					0.18‡	0.08
NeuroQoL Changes in social self-perception						0.23‡

Data are standardized regression coefficients (β). *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

minishing self-resources, a sign of premature aging rather than an illness-related disability, and thus is not reported during a medical consultation (5). Although there are nonneuropathic causes of unsteadiness, such as a history of stroke, marked visual impairment, or side effects of medications (e.g., antidepressants), patients with significant cerebrovascular disease (e.g., stroke) or severely impaired vision were excluded, and we conducted a parallel analysis that excluded subjects taking antidepressant medication. The analysis produced essentially identical results with unsteadiness being the symptom most strongly associated with depression, and in light of previous studies (26,27), diabetic neuropathy seemed to be the most likely cause of unsteadiness in these diabetic subjects with moderate to severe neuropathy.

Our results did not demonstrate a significant association between neuropathic foot ulcers and depressive symptoms. This finding is somewhat counterintuitive, in view of the evidence that foot ulcers are associated with severe restrictions in mobility, loss of work time, and other disruptions in ADLs (28). A possible explanation for why symptoms are and foot ulcers are not associated with depression could be that neuropathic foot ulcers are typically painless, thereby intruding little on an individual's consciousness and causing minimal emotional distress.

Several interesting findings emerged about the role of illness cognition. The episodic-unpredictable timeline partly mediated the association between neuropathic pain and depressive symptoms and had a direct effect on depression. This suggests that one of the characteristic features of neuropathic pain, its tendency to unpredictable periodicity, has a significant relationship with depressive symptoms in patients suffering from neuropathic pain. Second, the relationship between the cognitive appraisals of diabetic neuropathy and depressive symptoms remained largely unchanged after restrictions in ADLs, and changes in self-perception were entered into the model. This result indicates that the perceptions of diabetic neuropathy symptoms as unpredictable and uncontrollable are directly associated with depressive symptoms, independent of functional disability, thereby supporting the hypothesis of two separate pathways from chronic illness to depressive symptoms (14).

Our results indicate that restrictions in ADLs partly mediate the association between neuropathic symptoms and depression and explain the additional variance in depression scores beyond that explained by neuropathic severity. These findings provide further support for studies demonstrating that depressed affect is at least in part a function of restricted activities (15). Diabetic neuropathy–related changes in social self-perception also were associated with depressive symptoms and in turn reduced the effects of restrictions in ADLs on depression to nonsignificance, suggesting that restrictions in ADLs are associated with depression primarily because they affect social and family role performance. The findings are consistent with those of studies reporting the perceived changes in the social self-concept as a mediator of the relationship between illness severity and depression (16,29).

The limitations of our study are that the observations presented are cross-sectional and cannot resolve issues of causality. For example, it has been shown that depression can have a negative impact on social relationships over time (30), implying that we should regard social relationships as an outcome rather than as a predictor. Similarly, depression may influence the perception and report of diabetic neuropathy symptoms: depressed patients may have more negative evaluations. Both descriptive longitudinal and experimental studies are needed to determine the causal relationships. Additionally, it is important to note that other physiological factors, not assessed in this study, such as interleukin-6, a proinflammatory cytokine, known to be elevated in more severe illness, appear to induce "sickness behavior" and might have therefore accounted for some of the relationship between neuropathic symptoms and depression (31).

Our study has several practical implications. First, it establishes that persons suffering from diabetic peripheral neuropathy have an increased risk for depressive symptoms. Second, this report identifies a symptom, unsteadiness, that may represent an important path linking neuropathy to depressive symptoms. Practitioners should

therefore actively inquire about unsteadiness when assessing diabetic neuropathy in their patients, especially because there is preliminary evidence that physiotherapy and gait training may help patients to cope with this distressing disability (32). Consideration should also be given to providing such patients with mobility aids to provide increased confidence that they will not fall while walking. Finally, this study defines two possible psychosocial routes linking neuropathy to depressive symptoms (cognitive representation of diabetic neuropathy and diabetic neuropathy–related disruptions in functioning and changes in social-family roles). Thus, it identifies potential targets for interventions to alleviate depressive symptoms in subjects affected by diabetic peripheral neuropathy.

Acknowledgments— This work was supported by Diabetes UK and American Diabetes Association grants.

We also acknowledge the contributions of Andrew Findlow in Manchester, U.K., Mary Becker, Ronda Renosky, and Josy Mauger at State College, Pennsylvania, and Neill Scheffler in Baltimore, Maryland.

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