Cognitive Function Is Not Associated With Recurrent Foot Ulcers in Patients With Diabetes and Neuropathy

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OBJECTIVE — To study whether there is an association between cognitive impairment and the relapse rate of foot ulcers in diabetic patients and those with previous foot ulcers.

RESEARCH DESIGN AND METHODS — This single-center prospective study assessed the association of cognitive function and risk for ulcer relapse in 59 patients with diabetes (mean age 65.1 years, diabetes duration 16.5 years, and A1C 7.4%), peripheral neuropathy, and a history of foot ulceration. Premorbid and current cognitive functions were measured (multiple-choice vocabulary test [Lehrl], number-symbol test, mosaic test [HAWIE-R], and trail-making tests A and B [Reitan]). Prevalence of depression was evaluated retrospectively (diagnoses in patient files or use of antidepressive medication). Patients were re-examined after 1 year.

RESULTS — Three patients (5%) died during follow-up (one of sepsis and two of heart problems). The remaining 56 patients (48%) developed 27 new foot ulcerations (78% superficial ulcerations [Wagner stage 1]). Characteristics of patients with and without ulcer relapse were not different. In a binary logistic regression analysis, cognitive function is not predictive of foot reulceration.

CONCLUSIONS — Cognitive function is not an important determinant of foot reulceration.

Diabetes Care 32:894–896, 2009

Diabetic patients and those with a history of foot ulcers are at risk for foot reulceration (1,2). Although cognitive function is known to be impaired in patients with diabetes compared with that in nondiabetic control subjects (3), no studies have examined the potential role of cognitive impairment, an important factor for educational success (4), in the development or recurrence of diabetic foot ulcers. Our hypothesis is that cognitive function is associated with the relapse rate of foot ulcers in patients with diabetes and previous foot ulcers.

RESEARCH DESIGN AND METHODS

— This single-center prospective study was performed at a tertiary care center for diabetes (university hospital) and approved by the local ethics committee. Between October 2003 and June 2004, 69 patients with type 2 diabetes and previous foot ulcers were included. All gave written informed consent. Of these, 68% participated in a structured patient education program at our clinic. At baseline, a single investigator performed the neuropsychological testing, and all patients were examined for new ulcers 12 months later. Ten patients were excluded because testing was impossible (impaired vision [$n = 7$] or Parkinson's disease and debility [$n = 3$]). Testing assessed premorbid cognitive function (PCF) using a questionnaire by Wolfram and Wieczorek (5). Current cognitive function (CCF) was assessed using the multiple-choice vocabulary test by Lehrl (6); the number-symbol test and mosaic test, which are both part of the Hamburg-Wechsler Adult Intelligence Scale (HAWIE-R) (7); and the trail-making test parts A and B by Reitan (8), an indicator for cognitive impairment due to brain damage. Loss of cognitive function was calculated by subtracting CCF from PCF. All test results were transferred into intelligence quotient (IQ) points according to age-related scales (100 IQ points reflect normal intelligence compared with the general population).

Prevalence of depression was estimated retrospectively by searching for a diagnosis of depression or use of antidepressive drugs in the patient files. Peripheral diabetic neuropathy was diagnosed using the neuropathy symptom score and neuropathy disability score by Young et al. (9). The number of previous foot ulcerations was drawn from patient files, wound stages classified according to the Wagner wound classification system (six stages from no lesion to total necrosis) (10), retinopathy graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria, and nephropathy with creatinine clearance and microalbuminuria. A1C was measured using high-performance liquid chromatography (TOSOH-HLC-723-GHbV; Tosoh, Tokyo, Japan) (range 4.5–5.9; mean ± SD 5.2 ± 0.33%). Blood pressure was measured with patient seated using an oscillometric sphygmomanometer (OMRON).

SPSS (version 14; Chicago, IL) was used for statistical analyses, with $P < 0.05$ regarded as significant. A χ^2 test was performed for categorical data and ordinal data with less than four categories, the Mann-Whitney U test for non-normally distributed data, and the Student's t test for normally distributed data. A binary logistic regression analysis was performed.

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Received 9 March 2008 and accepted 4 February 2009.
Published ahead of print at http://care.diabetesjournals.org on 24 February 2009. DOI: 10.2337/dc08-0490.

RESULTS — Characteristics of the study patients (39 male, 17 female, all Caucasian) were as follows: age 65.1 ± 8.9 years, diabetes duration 16.5 ± 9.1 years, A1C 7.38 ± 1.30%, blood pressure 149.5 ± 25.3/77.5 ± 13.0 mmHg, number of antihypertensive drugs 2.5 ± 1.1 (span 0–6), BMI 31.6 ± 4.9 kg/m^2, and number of previous ulcers 2.9 ± 2.4 (median 2.0; span 1–9). Prevalence of severe neuropathy (neuropathy disability score >7) was present in 75% of patients (n = 44), and 15% (n = 9) suffered from diabetic osteoarthropathy. Orthopedic footwear was used by 78% (n = 46), and specialized foot care by 80% (n = 47). Peripheral artery disease was present in 53% (n = 31), and other macrovascular problems (past myocardial infarct, cardiovascular disease, or stroke) in 58% (n = 34). Insulin therapy was used by 90% (n = 47), and statins by 49% (n = 29). Low social status (without professional education and jobless) was recorded for 4% (n = 2), retirement for 76% (n = 45), and living with relatives for 81% (n = 48). Smoker or ex-smoker was recorded for 64% (n = 38), and drinking two or more alcohol equivalents per day was 15% (n = 9). Those suffering from nephropathy were 71% (n = 42), from retinopathy 51% (n = 30), and from both microvascular complications 39% (n = 23). A diagnosis of depression and/or antidepressive drugs was prevalent in 14% (n = 8).

The results of neuropsychological testing are as follows: (results in IQ points) PCF, 102.0 ± 8.7; CCF, 89.7 ± 11.1; number-symbol test, 95.3 ± 12.3; mosaic test, 94.6 ± 14.1; and trail-making test, 67.5 ± 13.5. After 12 months, three patients had died (sepsis, heart insufficiency, or sudden cardiac death). New foot lesions occurred in 27 patients (48%); 3 (5%) underwent a minor amputation (two toes and one forefoot).

The remaining 56 patients with and without ulcer relapse were not different for neuropsychological testing or other characteristics (results in Table 1). Cognitive function was not predictive for ulcer relapse in the binary logistic regression analysis using ulcer relapse as a dependent variable (odds ratio [95% CI] PCF 0.99 [0.94–1.06], CCF 0.99 [0.04–1.04], loss of cognitive function 1.01 [0.96–1.06], multiple-choice vocabulary test 0.99 [0.96–1.02], number-symbol test 0.98 [0.94–1.02], mosaic test 0.99 [0.96–1.04], trail-making test 1.0 [0.97–1.05]). Adjusting for age, diabetes duration, and depression did not alter the results.

Table 1—*Characteristics of patients with and without ulcer relapse*

	No ulcer relapse	Ulcer relapse	*P*
n	29 (52)	27 (48)	
Sex (male/female)	20 (70)/9 (31)	19 (70)/8 (30)	1.0
Age (years)	65.3 ± 7.9	63.8 ± 9.6	0.52
Diabetes duration (years)	14.9 ± 6.6	18.2 ± 10.9	0.18
Weight (kg)	90.5 ± 15.6	97.9 ± 18.6	0.11
BMI (kg/m^2)	31.4 ± 4.7	32.4 ± 5.0	0.44
A1C (%)	7.6 ± 1.5	7.1 ± 0.8	0.16
Systolic blood pressure (mmHg)	144.6 ± 28.2	155.41 ± 21.4	0.11
Diastolic blood pressure (mmHg)	75.7 ± 13.6	80.1 ± 12.7	0.21
Severe neuropathy	22 (76)	20 (74)	0.88
Number of previous foot ulcers	2.5 ± 2.0	3.0 ± 2.6	0.34
Prior amputation	10 (35)	8 (30)	0.78
Osteoarthropathy (Charcot foot)	4 (14)	4 (15)	1.0
Use of orthopedic footwear	23 (79)	21 (78)	1.0
No podiatric care	9 (31)	3 (11)	0.07
Received structured patient education	19 (66)	19 (70)	0.7
Diagnosis of depression or use of antidepressive drugs	5 (17)	3 (11)	0.5
Retinopathy	12 (41)	15 (56)	0.42
Nephropathy	18 (62)	21 (78)	0.54
Dialysis	1 (4)	1 (4)	1.0
Microvascular complications*	8 (28)	12 (44)	0.19
Peripheral vascular disease	17 (59)	12 (44)	0.42
Use of statins	16 (55)	12 (44)	0.30
Use of insulin	26 (90)	22 (82)	0.46
Low social status**	2 (7)	0 (0)	0.49
Alcohol >2 drinks/day	4 (14)	5 (19)	0.73
Current smoker or ex-smoker	19 (66)	18 (67)	1.0
Cognitive function in IQ points			
PCF	102.1 ± 8.92	102.0 ± 8.88	0.98
CCF	91.8 ± 12.3	90.6 ± 9.8	0.67
Loss of cognitive function	10.3 ± 10.3	11.5 ± 11.4	0.67
Multiple-choice vocabulary test	107.0 ± 18.0	103.8 ± 14.2	0.47
Number-symbol test	97.2 ± 13.7	94.3 ± 10.7	0.37
Mosaic test	95.7 ± 15.9	95.4 ± 11.3	0.93
Trail-making test A	67.4 ± 13.2	68.3 ± 15.3	0.80
Trail-making test B	67.5 ± 15.5	69.4 ± 15.9	0.64

Data are means ± SD or *n* (%). Values for cognitive function represent IQ points. *Patients with retinopathy and nephropathy. **Patients without professional education and jobless. NDS, neuropathy disability score.

CONCLUSIONS — In this study, no difference of cognitive function was found in patients with and without ulcer relapse. Therefore, a failure of patient education to prevent recurrent foot ulcers cannot be attributed to reduced cognitive function.

Patient characteristics were not different for ulcer relapse and nonrelapse patients. This is important because numerous confounders (e.g., age, A1C, diabetes duration, blood pressure, smoking, and alcohol intake) are reported to be associated with decreased cognitive function (11) and foot problems (3). For the study, 48% of patients developed a new ulceration, which is in keeping with other reported rates (2,12).

Depression is a major differential diagnosis for cognitive dysfunction (13) and has been shown to have a 30% prevalence among diabetic patients with neuropathy (14,15). Results of our study are limited in that the study did not screen for depression. Although an association of depression with micro- and macrovascular complications and mortality is described (14,15), a direct association of

depression with the occurrence of diabetic foot ulcers was not reported (13–15). In a post hoc analyses using diagnosis of depression or use of an antidepressant medication as an indicator for depression, these patients were evenly distributed in the ulcer-relapse and non–ulcer-relapse groups. Nevertheless, the prevalence of depression is likely to be underestimated, which possibly affects the results. In conclusion, this study does not support the commonly held belief that cognitive dysfunction is an important determinant of foot reulceration.

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

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