Cognitive Dysfunction: Part and Parcel of the Diabetic Foot

Diabetes Care 2016;39:1202–1207 | DOI: 10.2337/dc15-2838

Rachel Natovich,[1,2] Talma Kushnir,[1,3] Ilana Harman-Boehm,[1,4] Daniella Margalit,[3,5] Itzhak Siev-Ner,[5] Daniel Tsalichin,[1,6] Ilia Volkov,[1,6] Shmuel Giveon,[6,7] Deborah Rubin-Asher,[8] and Tali Cukierman-Yaffe[2,9,10]

OBJECTIVE

The presence of a foot ulcer increases the self-treatment burden imposed on the individual with diabetes. Additionally, this condition increases the cognitive demands needed for adherence to medical recommendations. A potential gap could exist between medical recommendations and the individual's ability to implement them. Hence, the goal of this study was to examine whether the cognitive profile of people with diabetic foot ulcers differs from that of people with diabetes without this complication.

RESEARCH DESIGN AND METHODS

This was a case-control study. Ninety-nine individuals with diabetic foot ulcers (case patients) and 95 individuals with type 2 diabetes (control subjects) (age range 45–75 years), who were matched for diabetes duration and sex, underwent extensive neuropsychological evaluation using a NeuroTrax computerized battery, digit symbol, and verbal fluency tests. A global cognitive score after standardization for age and education was computed as well as scores in the following six cognitive domains: memory, executive function, reaction time, attention, psychomotor abilities, and estimated premorbid cognition.

RESULTS

Individuals with diabetic foot ulcers had significantly ($P < 0.001$) lower cognitive scores than individuals with diabetes without this complication, in all tested cognitive domains, excluding estimated premorbid cognition. Individuals with diabetic foot ulcers demonstrated a significant difference between precognitive and current cognitive abilities, as opposed to the nonsignificant difference among control subjects. The differences persisted in multivariable analysis after adjusting for depression and smoking.

CONCLUSIONS

Individuals with diabetic foot ulcers were found to possess fewer cognitive resources than individuals with diabetes without this complication. Thus, they appear to face more self-treatment challenges, while possessing significantly fewer cognitive resources.

The presence of a foot ulcer increases the self-care burden imposed on the individual with diabetes. Recently, the American Diabetes Association and the International Working Group on the Diabetic Foot published a global consensus, evidence-based guidance, on the management and prevention of the diabetic foot (DF) (1,2). These documents emphasize patients' education on appropriate self-care practices and participation in an integrated foot care program as essential elements of the prevention of ulcers and their recurrence. The implications of this guidance is that the individual with a DF is expected to learn and understand new information

[1]Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel
[2]Endocrinology Institute, Sheba Medical Center, Ramat Gan, Israel
[3]Department of Psychology, Ariel University, Ariel, Israel
[4]Diabetes Clinic, Soroka Medical Center, Be'er Sheva, Israel
[5]Orthopedic Rehabilitation Department, Sheba Medical Center, Ramat Gan, Israel
[6]Clalit Health Services, Tel Aviv, Israel
[7]Department of Family Medicine, Tel Aviv University, Tel Aviv, Israel
[8]Loewnstein Hospital Rehabilitation Center, Raanana, Israel
[9]Gertner Institute Sheba Medical Center, Tel Hashomer, Israel
[10]Epidemiology Department, Tel Aviv University, Tel Aviv, Israel

Corresponding author: Rachel Natovich, matovich@gmail.com.

Received 30 December 2015 and accepted 18 April 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-2838/-/DC1.

and treatment procedures, self-manage his/her foot condition (e.g., self-inspection, setting up medical appointments), and strictly follow recommendations regarding changes in medications and lifestyle habits. It should be noted that such an increase in self-care burden also represents a significant increase in the cognitive demands needed for optimal adherence to medical recommendations. These demands require applying complex cognitive abilities involved in learning, understanding, and remembering new information; planning and initiating self-care practices; adopting behavioral changes that involve psychomotor abilities; and maintaining these behaviors while controlling and repressing impulses. Indeed, self-care and cognition are closely interconnected. Diabetes self-management was found to be influenced by specific cognitive functions like immediate memory, visuospatial/constructional abilities, attention, and specific executive functions (i.e., planning and problem solving) (3). In a study conducted among 1,398 older community-dwelling adults with diabetes, participants' adherence to each diabetes self-care task deteriorated as cognitive impairment worsened, with incremental increases in diabetes comorbidity (4).

Because cognitive screening is not part of the standard of care for DF, a potential gap could exist between recommended evidence-based medical guidelines (collected and devised by the integrated foot care professionals), on the one hand, and the individual's ability to successfully implement these recommendations on the other hand.

Not much is known about DF and cognition, though there is some indirect support for a negative association. Diabetes, in general, is a well-established risk factor for cognitive dysfunction and dementia (5,6). Beyond the fact that DF was found to be an independent risk factor for dementia above and beyond the risk represented by diabetes (7), there are only a few studies that investigated cognitive function among people with DF. In a recently published study (8), DF leading to amputation was associated with a lower global cognitive score (GCS) and episodic memory impairment compared with DF without amputation. On the other hand, in a prospective study (9) that observed DF individuals for 2 years, no association was found between cognitive performance and the recurrence of foot ulcers.

To the best of our knowledge, there have been no studies comparing the cognitive function of those with the DF complication in individuals with diabetes. There are no cognitive guidelines assisting health professionals in formulating a treatment plan that considers the cognitive characteristics of DF individuals, thus possibly impeding the efforts of the integrated teams to promote self-care management. Hence, as an initial investigation, the goal of this study was to examine whether the cognitive profile of patients with DF differs from that of people with diabetes without the DF complication.

RESEARCH DESIGN AND METHODS

General

This was a case-control study conducted in individuals with diabetes with (case patients) and without (control subjects) DF ulcers (DFUs), after matching for sex and diabetes duration. Extensive cognitive assessment was performed for each participant individually by a neuropsychologist. Detailed information was also collected pertaining to medical and emotional indices. Individuals with and without DFUs were compared with respect to their scores on the neuropsychological evaluation. The study was approved by the appropriate ethics committees.

Population and Procedure

Included in the study were individuals who had received a diagnosis of type 2 diabetes, 45–75 years of age, who were able to speak and write in Hebrew. Excluded from the study were people with significant visual, hearing, motor, or cognitive impairment that may have precluded neuropsychological testing and responding to self-report questionnaires. Additionally, individuals with renal or hepatic failure were also excluded.

Ninety-nine individuals with DFUs were recruited from in-hospital orthopedic departments and from DF clinics in two hospitals. Ninety-five individuals with diabetes without DF were recruited from several diabetes clinics in Israel. The existence or absence of DF was verified with the treating physician. The University of Texas at San Antonio System (10) was used to evaluate DF severity (data regarding participants' DF severity is presented in the Supplementary Appendix). Subsequently, patients found eligible by their treating physician were contacted by telephone and asked to participate in a 1.5-h extensive cognitive evaluation. Additionally, medical indices and diagnoses were collected from the participants' medical records.

Measurement of Cognitive Function

Cognitive function was assessed using a computerized neuropsychological battery of tests (NeuroTrax) and paper-and-pencil tests. The NeuroTrax computerized cognitive assessment battery of tests contains a set of tests designed for early detection of mild cognitive impairment and mild dementia. It also has the capacity to discriminate between cognitively intact individuals with moderate to good correlations demonstrated with the well-validated Wechsler Adult Intelligence Scale battery of tests (11). Good convergent construct validity has been shown between this battery of tests and traditional neuropsychological tests designed to tap similar cognitive domains. Alternate form test-retest reliability has also been demonstrated. Results from the NeuroTrax computerized battery of tests were processed to form the following: *1*) a GCS, which is the mean of the cognitive domains examined (excluding nonverbal intelligence quotient); *2*) scores in five specific cognitive domains (memory, attention and concentration, psychomotor efficiency [the ability to generate a motor response in an efficient manner], reaction time [efficiency in time-dependent tasks], and executive function [the ability to postpone an automatic response and to create a strategy to cope with a new task using planning and control capabilities]); and *3*) a nonverbal intelligence quotient, which involved solving visual tasks. This test is considered a "hold" test because it was found in many studies to be highly resistant to temporal changes and to capture a person's premorbid cognitive capacity (12). Cognitive results for each outcome parameter were normalized to a standard distribution ($\bar{X}$ 100; σ 15), according to the expected performance by age and education in a sample of cognitively healthy research participants (13).

Paper-and-Pencil Cognitive Tests

As the NeuroTrax battery of tests has not been used extensively in population studies of people with diabetes, the following two well-used short cognitive tests were also included: *1*) the digit symbol substitution test, which is a subtest of the Wechsler Adult Intelligence

Scale (14) pertaining to a wide array of cognitive domains such as visual motor speed and coordination, capacity for learning, attention, concentration, and short-term memory (it has been extensively used to measure cognitive function in cognitively intact individuals, and its score is well correlated with measures of physical function and future cognitive decline [15,16]); and *2*) the verbal fluency test that measures verbal production, semantic memory, and language (17). This test was used in several longitudinal studies, and in each it exhibited an ability to differentiate between people with and without diabetes based on the rate of cognitive decline experienced over time (18,19).

Measurement of Other Covariates

Depression was assessed by the Patient Health Questionnaire (20). Medical indices related to disease severity and treatment effectiveness were collected from the electronic medical records of the study participants. For the purpose of this analysis, hypertension and dyslipidemia were each defined by the need for medical therapy. Data on prevalent retinopathy, nephropathy, and neuropathy were collected from the medical records. Macrovascular disease was defined as reported angina, myocardial infarction, or peripheral vascular disease. Data pertaining to BMI and glycosylated hemoglobin (HbA_{1c}) level were also taken from the medical records.

Statistical Analysis

The differences in GCS and in specific cognitive domains between the groups with and without DFUs were examined with Student *t* tests. Multiple linear regression analyses were used to test the differences between the groups, using consecutive models, after adjustment for depression status, smoking, macrovascular disease, retinopathy, nephropathy, BMI, and HbA_{1c} level. Neuropathy was not added to the regression model because of multicollinearity with the DFU group (Pearson correlation 0.732, $P < 0.001$).

RESULTS

This analysis pertains to 99 individuals with DFUs and 95 individuals with diabetes without DFUs who were matched for sex and diabetes duration. As can be seen (Table 1), individuals with DFUs, as opposed to those without DFUs, were younger and had fewer years of education.

Table 1—Sociodemographic and medical variables, by groups

	DFU (n = 99)	Diabetes (n = 95)
Sex (% male)	77	80
Age (years)	58.04 (6.87)	61.3 (7.03)***
Education (mean years)	12.4	14.5***
Current smoking	26.3	21.1
Depressive symptoms	6.13 (5.97)	4.73 (4.26)
HbA_{1c} (% [mmol/mol])	8.81 (2.13) [73 mmol/mol]	7.36 (1.32)*** [57 mmol/mol]
BMI (kg/m^2)	30.13 (6.12)	28.17 (4.08)*
Insulin use	81.8	25.3***
Hypertension	76.8	60*
Dyslipidemia	76.8	68.4
Retinopathy	51.5	9.5***
Neuropathy	88.9	15.8***
Nephropathy	33.3	3.2***
Macrovascular disease	88.9	51.6***

Data are mean (SD) or %, unless stated otherwise. The *t* test for independent sample was used for continuous variables and χ^2 test was used for categorical variables. *$P < 0.01$, ***$P < 0.001$.

The DF group also had more diabetes complications, a higher HbA_{1c} level, and higher BMI.

Cognitive Results

Table 2 shows the results of the two groups on the different cognitive tests. After standardization according to the expected performance by age and education, the DFU group had significantly ($P < 0.001$) lower cognitive scores than did the diabetes-only group in all tested cognitive domains.

This difference was maintained after adjustment for several possible confounding factors, including smoking status, HbA_{1c} level, depression symptoms, and macrovascular disease (Table 3).

Discrepancies in Differences Between Estimated Premorbid and Current Cognitive Abilities

No differences were found between the groups with respect to estimated premorbid cognitive abilities (DFU group 96.78 [14.07], diabetes group 100.19 [12.17], P = 0.223). This is in contrast to the significant differences found in all indices of current cognitive function. Looking at each group separately, we checked the difference between precognitive and postcognitive abilities. As can be seen in Fig. 1, in the control group (patients with diabetes without the DFU complication), a 0.6284 (P = 0.523) standardized point difference was found between the premorbid abilities and the

Table 2—Results of between-group comparisons of cognitive functions

Cognitive domain tested	DFU	Diabetes
GCS	89.88 (11.48)	99.56 (8.76)***
Memory	89.86 (14.20)	98.37 (13.25)***
Attention and concentration	90.31 (15.20)	98.88 (12.81)***
Reaction time	91.76 (13.28)	100.05 (9.86)***
Executive function	91.29 (12.50)	100.01 (10.89)***
Psychomotor	88.92 (17.63)	101.42 (8.03)***
Verbal fluency, phonemic	72.77 (21.29)	91.51 (21.16)***
Verbal fluency, semantic	82.23 (17.87)	95.84 (18.47)***
Digit symbol substitution test	79.33 (14.85)	94.16 (14.78)***
Estimated premorbid cognition	96.78 (14.07)	100.19 (12.17)

Data are reported as the mean (SD); cognitive results for each outcome parameter were normalized to a standard distribution ($\bar{X}$ 100; σ 15) according to the expected performance by age and education in a sample of cognitively healthy research participants. ***$P < 0.001$.

GCS ranking. In contrast, in the DFU group a 6.897 ($P < 0.001$) standardized point difference was found, suggesting a significant decrease in cognitive abilities in the DFU group as opposed to stability in cognitive performance in the diabetes-only group.

CONCLUSIONS

This is one of the first studies on cognitive functioning in people with diabetes, with and without the DFU complication. The main goal of this study was to examine whether the cognitive profile of individuals with DFUs differs from that of individuals with diabetes in whom this complication did not develop. The cognitive profile arising from our research data portrays significant differences between the two groups. Although the estimated premorbid cognitive abilities of the two groups were found to be similar, the current cognitive abilities of the DFU group were significantly decreased. The differences between the groups were found in all tested cognitive domains. Thus, the results demonstrated that, compared with patients with diabetes without the DF complication, those with DFUs remember less, have decreased ability to concentrate, and more difficulty with learning, less inhibition, slower cognitive and psychomotor responses, and less verbal fluency. Compared with their estimated premorbid cognitive abilities, patients with DFUs were found to have significantly decreased cognitive abilities, as opposed to the stability in cognitive functioning that was found among individuals with diabetes who did not have the DFU complication.

These findings indicate that participants with DFUs in this study were challenged with more severe cognitive difficulties compared with the participants without this complication. It should be emphasized that the cross-sectional design limits the ability to draw definitive conclusions about causality. Moreover, participants were selected after the DFU condition had already developed. Thus, we cannot conclusively determine whether cognitive decline preceded or followed the DFU condition. The data suggest that both groups had similar premorbid cognitive abilities. However, this conclusion is based on tests designed to estimate premorbid cognitive status postmorbidly. Prospective studies are therefore

Table 3—Results of linear regressions models assessing group differences in cognitive functions

	Model 0		Model 1		Model 2		Model 3		Model 4		Model 5	
Cognitive domains	β	*t*	β	*t*	β	*t*	β	*t*	β	*t*	β	*t*
GCS	−9.680	−6.579***	−9.680	−6.579***	−9.680	−6.579***	−6.579	−9.680***	−9.680	−6.579***	−9.680	−6.579***
Memory	−8.509	−4.284***	−8.509	−4.284***	−8.509	−4.284***	−4.284	−8.509***	−8.509	−4.284***	−8.509	−4.284***
Executive function	−8.726	−5.172***	−8.726	−5.172***	−8.726	−5.172***	−5.172	−8.726***	−8.726	−5.172***	−8.726	−5.172***
Attention	−8.565	−4.234***	−8.565	−4.234***	−8.565	−4.234***	−4.234	−8.565***	−8.565	−4.234***	−8.565	−4.234***
Motor skills	−12.497	−6.228***	−12.497	−6.228***	−12.497	−6.228***	−6.228	−12.497***	−12.497	−6.228***	−12.497	−6.228***
Reaction time	−8.289	−4.823***	−8.289	−4.823***	−8.289	−4.823***	−4.823	−8.289***	−8.289	−4.823***	−8.289	−4.823***
Verbal fluency, semantic	−13.614	−5.218***	−13.614	−5.218***	−13.614	−5.218***	−5.218	−13.614***	−13.614	−5.218***	−13.614	−5.218***
Verbal fluency, phonemic	−18.747	−6.045***	−18.747	−6.045***	−18.747	−6.045***	−6.045	−18.747***	−18.747	−6.045***	−18.747	−6.045***
Digit symbol substitute test	−14.821	−6.949***	−14.821	−6.949***	−14.821	−6.949***	−6.949	−14.821***	−14.821	−6.949***	−14.821	−6.949***

Model 0, after adjustment for age and education; Model 1, after adjustment for model 0 plus depressive symptoms; Model 2, after adjustment for model 1 plus current smoking status; Model 3, after adjustment for model 2 plus BMI plus HbA_{1c}; Model 4, after adjustment for model 3 plus macrovascular disease; Model 5, after adjustment for model 3 plus retinopathy plus nephropathy. ***$P < 0.001$.

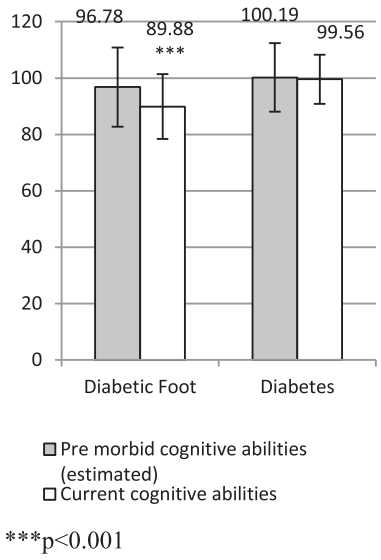

Figure 1—Results of within-subject comparisons of premorbid and current cognitive abilities (paired *t* tests, cognitive results were normalized to a standard distribution [$\bar{X}$ 100; σ 15]).

needed to fully explore this important topic of causation. Such studies should also consider additional possible confounders that we were unable to address fully because of the small cohort. These confounders include long-term control of glycemia, control of other measurable cardiovascular risk factors, the quality of medical care, and other complications.

Our findings highlight the importance of focusing on cognitive functioning, a less studied area in DF research. In two recent studies, cognitive functions were found to be associated not only with better self-care, as described above, but also with the success of rehabilitation after an amputation, which is an issue of great relevance to people with DFUs. In these studies, cognitive impairment was negatively associated with mobility, prosthesis use, and maintenance of independence after amputation (21). Better cognitive performance was associated with greater 12-month mobility and social integration (22). Both studies emphasize the importance of including cognitive assessment to assist in determining suitability for prosthetics and in ascertaining appropriate and realistic goals for rehabilitation.

Effective communication in medical encounters is another area for which cognitive functions are essential. The latest *Standards of Medical Care in Diabetes* (1) emphasizes the importance of "patient-centered communication style that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care should be used. . .to ensure productive interactions between a prepared proactive practice team and an informed activated patient." Effective communication requires an adequate level of cognitive abilities for the information presented, a factor that is overlooked in the research literature on DF. Moreover, the effects of cognitive impairment on adherence to medical recommendations are also overlooked in most health behavioral models for chronically ill patients (23). Integrating cognitive function considerations into health care may be relevant to treatment planning in individuals with many other chronic conditions. Because diabetes control is a complex, multifactorial process, requiring modifications in many life domains, it is especially dependent on cognitive abilities. More studies are needed to explore the relevance of the current findings to other populations.

The present findings demonstrate what our research team has called "The DF person's paradox": more challenges, but fewer cognitive resources. The results imply that "DF" may refer not only to the physical condition but also to a more generalized complex state involving significant cognitive changes as well. Considering the increased risk for medical complications and the unique challenge that individuals with DFUs present to health providers, we feel that it is important to screen the cognitive status of these patients regularly and to take cognitive abilities into consideration in treatment-planning recommendations and follow-up.

Acknowledgments. The authors thank Dr. Joseph Natovich of Tiuv System Consultants for his assistance in data analysis.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. R.N. contributed to the literature search; study design; neuropsychological evaluation; figures; data extraction, analysis, and interpretation; and the writing of the manuscript. T.K. and I.H.-B. contributed to the literature search, study design, figures, data interpretation, and the writing and critical appraisal of the manuscript. D.M. contributed to the study design, data collection, and critical appraisal of the manuscript. I.S.-N., D.T., I.V., and S.G. contributed to the data collection and critical appraisal of the manuscript. D.R.-A. contributed to the writing and critical appraisal of the manuscript. T.C.-Y. contributed to the literature search; study design; data collection, analysis, and interpretation; figures; and the writing and critical appraisal of the manuscript. R.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015.

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