Changes in Cognitive Abilities Over a 4-Year Period Are Unfavorably Affected in Elderly Diabetic Subjects

Results of the Epidemiology of Vascular Aging Study

ANNICK FONTBONNE, MD, PHD
CLAUDINE BERR, MD, PHD
PIERRE DUCIMETIÈRE, PHD
ANNICK ALPÉROVITCH, MD, PHD

OBJECTIVE — To compare 4-year changes in cognitive performance among elderly subjects according to category of fasting blood glucose (FBG) using American Diabetes Association criteria.

RESEARCH DESIGN AND METHODS — Subjects without any detectable cognitive dysfunction were selected from the Epidemiology of Vascular Aging (EVA) Study, a cohort of community-dwelling people aged 59–71 years at baseline. They were classified into glucose categories (normal, impaired fasting glucose [IFG], or diabetic) based on FBG values or known diabetes. Their cognitive abilities were assessed by a global test (Mini Mental Status Examination [MMSE]) and eight domain-specific tests, and they were reassessed 4 years later. Serious cognitive worsening was defined as a score evolution into the worst 15% of the sample's distribution of score differences (4-year score minus baseline score) for each test.

RESULTS — At baseline, age-, sex-, and education-adjusted scores for all cognitive tests except one were similar across glucose categories. After 4 years, diabetic subjects had a lower performance on all tests except the MMSE, with differences reaching statistical significance on four tests. Adjusted odds ratios for serious worsening over 4 years in diabetic subjects, with reference to normal subjects, were >2 for four tests ($P < 0.05$) and bordering this value for two others ($P < 0.09$). Further adjustment for blood pressure or potential cognition-affecting substances (alcohol, tobacco, and medications) did not modify these results.

CONCLUSIONS — Despite similar high initial cognitive function, diabetic subjects tended to have an unfavorable evolution of cognitive performance over 4 years compared with subjects who had normal glucose or IFG.

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Most studies performed in search of a relationship between diabetes and cognitive function have found some indication of impairment compared with control subjects without diabetes (1,2). However, any firm conclusion regarding the involvement of diabetes in cognitive decline is difficult to reach, essentially because comparisons generally suffer from methodological problems (e.g., small samples, heterogeneous populations, different batteries of tests, and failure to control for major confounding factors such as age and education) (1–3). Two prospective community-based studies that were relatively free of the above weaknesses yielded contradictory results: the first one (4), which was from Framingham, found an association between diabetes and poorer cognitive performance occurring years later, independent of hypertension, which is a well-known potential confounder of the relationship (2); the association was not confirmed in the other community-based study (5), which was from the Rancho Bernardo cohort. Both relied, however, on a single time point evaluation of cognition at the end of follow-up, so it was not possible to control for the subjects' baseline performance, which is known to be critical to cognitive evolution (6). Thus far, two longitudinal studies have been able to analyze cognitive change over time. The first one (7) had a very small number of subjects and a high drop-out rate. The second is the Study of Osteoporotic Fractures (8), a large prospective study of almost 10,000 community-dwelling older women, which recently showed that diabetes was associated with both poorer cognitive performance at baseline and faster decline over 3–6 years on two tests evaluating attention, independently of a series of confounders, including cardiovascular disease and hypertension.

The Epidemiology of Vascular Aging (EVA) Study is an ongoing study in a cohort of healthy community-dwelling elderly subjects from the city of Nantes, France. Its purpose is to uncover risk factors for cardiovascular disease and cognitive impairment in this particular age-group. Since entry into the study, the subjects' cognitive function has been assessed repeatedly using a battery of tests exploring different aspects of cognition. This allowed us to study changes over time in various domains of cognitive performance according to diabetes status in a population of relatively young elderly men and women with good overall cognitive function.

From the National Institute for Health and Medical Research (INSERM), Unit 258 (A.F., P.D.), Villejuif, and Unit 360 (C.B., A.A.), Paris, France.

Address correspondence and reprint requests to Dr. Annick Fontbonne, INSERM U258, 16 ave. Paul Vaillant Couturier, 94807 Villejuif Cedex, France. E-mail: u258@vjf.inserm.fr.

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Abbreviations: AVLT, Auditory Verbal Learning Test; BVRT, Benton Visual Retention Test; CESD, Center for Epidemiological Studies Depression Scale; DSS, Digit Symbol Substitution; EVA, Epidemiology of Vascular Aging; FBG, fasting blood glucose; FTT, Finger Tapping Test; IFG, impaired fasting glucose; MMSE, Mini Mental Status Examination; OR, odds ratio; PASAT, Paced Auditory Serial Addition Test; RPM, Raven's Progressive Matrixes; TMTB, Trail Making Test part B; TRF, Test of Facial Recognition.

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

Table 1—*Baseline general characteristics of the study sample according to glycemic status*

	Normal FBG	IFG	Diabetes	*P*
n	768	103	55	
Age (years)	64.9 (64.7–65.1)	64.8 (64.2–65.4)	65.3 (64.5–66.1)	0.59
Men (%)	39	56	71	0.001
University education (%)	16.7	15.5	16.4	0.86
Alcohol consumption (g/week)*	66.4 (58.5–74.8)	103.6 (77.8–133.4)	115.8 (80.3–157.8)	0.001
Current smokers (%)	7.9	8.7	12.7	0.06
No medicines/day	2.4 (2.3–2.6)	2.5 (2.1–2.9)	3.4 (2.9–3.8)	0.016
Depressive (%)	12.6	12.1	9.1	0.74
BMI (kg/m^2)	24.8 (24.6–25.1)	27.0 (26.2–27.7)	28.9 (27.7–30.1)	0.0001
sBP (mmHg)	130.5 (129.3–131.7)	138.6 (135.2–142.0)	142.5 (137.6–147.4)	0.0001
dBP (mmHg)	78.2 (77.5–79.0)	82.0 (79.9–84.2)	82.2 (79.1–85.2)	0.0003
Hypertensive (%)	28.3	47.6	47.3	0.001
Total cholesterol (g/l)	2.48 (2.45–2.51)	2.46 (2.39–2.52)	2.27 (2.17–2.37)	0.0005
HDL cholesterol (g/l)	0.65 (0.63–0.66)	0.58 (0.56–0.61)	0.55 (0.51–0.60)	0.0001
Triglyceride (g/l)*	1.21 (1.16–1.25)	1.53 (1.23–1.82)	1.39 (1.22–1.57)	0.0001
FBG (mmol/l)	5.25 (5.22–5.28)	6.35 (6.31–6.40)	7.43 (6.90–7.96)	0.0001

Continuous data are means (95% CI). *Transformed for normalization, then back-transformed into original units. sBP, systolic blood pressure; dBP, diastolic blood pressure.

RESEARCH DESIGN AND METHODS

— In 1991–1993, people who were born between 1922 and 1932 and were living in the city of Nantes, France, were invited to participate in the EVA Study. Detailed methodology and population characteristics of the study have been previously described (9,10), and only data relevant to the present analysis will be summarized here. Volunteers were contacted both through the mail (using addresses on the electoral rolls of Nantes) and, to a lesser extent, via information campaigns. Baseline investigation of the cohort (n = 1,389) collected data on each subject's medical history, personal habits and hobbies, and demographic, educational, and professional background. Clinical examination included measures of height and weight, and two independent measurements of blood pressure in the sitting position were made using a digital electronic tensiometer (SP9; Spengler) after 10 min of rest. Various biological variables were determined using fasting blood samples, including glucose measured by a standard enzymatic glucose oxidase method.

Cognition was evaluated by trained psychologists during a face-to-face interview lasting 45 min to 1 h in a quiet room at the EVA center. Interviewers were not aware of the specific hypothesis under investigation and were blind to the medical history and the glycemic status of the patients. The neuropsychological battery included eight tests assessing a range of cognitive domains and a global test, the Mini Mental Status Examination (MMSE). The MMSE includes 18 items that roughly assess various cognitive skills, with scores ranging from 0 to 30. A score of <24 is considered as indicative of poor cognitive skills. Visual attention was assessed with the Trail Making Test part B (TMTB). Immediate verbal memory was evaluated with the Auditory Verbal Learning Test (AVLT). The Test of Facial Recognition (TRF) examined the subjects' ability to recognize faces without involving a memory component, thus assessing visuo-spatial processing (mostly visual attention). The Digit Symbol Substitution (DSS) from the Weschler adult intelligence scale-revised measured sustained attention, psychomotor speed, and logical reasoning. Psychomotor speed was evaluated with the Finger Tapping Test (FTT), immediate visual memory with the Benton Visual Retention Test (BVRT), logical reasoning with Raven's Progressive Matrixes (RPM), and auditory attention with the Paced Auditory Serial Addition Test (PASAT).

At 2- and 4-year follow-up examinations, participants were reevaluated at the EVA study center using the same procedures. The study protocol was approved by the ethics committee of Kremlin-Bicêtre University Hospital, and written informed consent was obtained from all participants.

Selection and classification of study subjects

Because we were studying risk factors for cognitive deterioration, we selected participants with no evidence of cognitive impairment at baseline, as judged by an MMSE score >26. Of these subjects (n = 1,092), 113 did not attend the 4-year examination and 18 died before it. The remaining 961 subjects were classified into the following categories of glucose status according to the 1997 American Diabetes Association criteria (11): 42 had already-diagnosed diabetes (11 treated by diet alone, 29 by oral antidiabetic agents, and 2 by insulin); 13 had undiagnosed diabetes but a fasting blood glucose (FBG) ≥7 mmol/l; 103 had impaired fasting glucose (IFG) with an FBG >6.1 and ≤7 mmol/l; and 768 had normal FBG (<6.1 mmol/l). Finally, 35 subjects could not be classified because of missing blood glucose determination.

Statistical analysis

Independent variables. Subjects with diabetes, whether known or diagnosed by FBG, were grouped into one category after checking that the results showed the same trends for both groups in all analyses. Education was divided into five levels: no school, primary school, junior high school, senior high school, and university. According to their smoking behavior at baseline, subjects were classified as current smokers (smoking at least one cigarette or its equivalent every day), ex-smokers, or never-smokers. Alcohol consumption (expressed in grams of alcohol per week) was estimated from an interview during which subjects were asked about the number of

Table 2—*Baseline results on cognitive tests, adjusted for age, sex, and education, according to glycemic status*

	Normal FBG	IFG	Diabetes	*P*
MMSE	29.0 (28.9–29.1)	29.2 (29.0–29.4)	29.0 (28.7–29.3)	0.20
TMTB*	2.05 (2.00–2.11)	1.96 (1.80–2.12)	2.22 (2.00–2.44)	0.17
AVLT	44.0 (43.3–44.6)	44.1 (42.3–45.9)	44.6 (42.1–47.1)	0.87
TRF	21.4 (21.2–21.5)	21.4 (21.0–21.9)	21.0 (20.4–21.6)	0.53
DSS	45.3 (44.7–46.0)	46.9 (45.0–48.7)	42.7 (40.2–45.3)	0.037
FTT	123.6 (122.3–124.8)	124.4 (121.0–127.9)	123.7 (118.9–128.5)	0.90
BVRT	11.7 (11.6–11.8)	11.8 (11.4–12.1)	11.4 (10.9–11.9)	0.41
RPM	15.5 (15.3–15.6)	15.2 (14.7–15.7)	15.8 (15.2–16.5)	0.31
PASAT	15.4 (15.1–15.8)	15.0 (13.9–16.0)	14.7 (13.3–16.2)	0.50

Data are means (95% CI). *Only test where poorer performance is indicated by higher score.

alcoholic beverages ingested daily or weekly. Depressive symptoms were assessed by the Center of Epidemiological Studies Depression Scale (CESD) (12). Depressive symptomatology was considered present if the CESD score was ≥17 in men and ≥23 in women (10). BMI was calculated as the ratio of weight (in kilograms) to height squared (in meters). Blood pressure was the mean of the two determinations made at baseline. Individuals were considered hypertensive if they had high blood pressure (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg) or were taking antihypertensive medication.

Dependent variables. Cognitive test result changes over 4 years for each individual were analyzed using two categories: *1*) serious worsening and *2*) no serious worsening, no change, or improvement. Serious worsening was defined for each test as a change in scores into the worst 15% of the distribution of the observed changes for the whole sample. This cutoff was chosen in keeping with all cognition analyses performed in the EVA Study (9,10).

Statistical methods

Variables were compared between glucose categories using standard parametric tests. Comparisons of cognitive test scores were systematically adjusted for age, sex, and education. The probability of serious worsening in the IFG and diabetic groups (expressed as the odds ratio [OR] with reference to the normal group) was analyzed by logistical regression. All statistical analyses were made using the SAS package (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

The 961 subjects in the present analysis were less likely to be diabetic than were the participants who had missed the 4-year cognitive evaluation; they also had better cardiovascular risk profiles and took significantly less medication per day. When they were classified according to their diabetes status, it appeared that those with diabetes or IFG did not differ from normal subjects with regard to age or education (Table 1). However, the proportion of men in these two groups was higher than in the normoglycemic group, which explained the higher weekly alcohol intake and the borderline-significant higher proportion of current smokers (differences were not significant when controlling for sex). Another noteworthy difference was a less favorable cardiovascular risk factor profile with the exception of cholesterol levels, which were lower in diabetic subjects, probably because of a higher frequency of lipid-lowering treatment (35 vs. 23% in normal subjects and 29% in subjects with IFG, $P < 0.06$). Also, on average, one more drug was taken on a daily basis by diabetic subjects compared with the other two groups. There was no difference in the frequency of depressive symptoms between the three groups. As a consequence of our selection of participants with an MMSE score >26, mean MMSE scores were high, and all groups of subjects performed similarly at baseline on every cognitive test except DSS, where performance was significantly poorer in diabetic subjects (Table 2).

Changes in cognitive performance

Overall, after 4 years, there was an increase in scores for four tests involving attention and/or psychomotor speed (TMTB, DSS, FTT, and PASAT) and one memory test (AVLT) and a slight deterioration of performance on the MMSE and the RPM test (for visual attention and logical reasoning), whereas the performances on BVRT (immediate visual memory) and TRF (attention) were roughly stable. On the whole, diabetic subjects tended to perform less well than subjects with either normal FBG or IFG ($P < 0.027$ for multiple analysis of variance, Wilk's λ); TMTB, AVLT, TRF, and DSS were significantly affected (Table 3).

To directly study individual changes, ORs for serious worsening over 4 years were tested against the normal group taken as reference, after adjustment for major confounders (age, sex, level of education, and initial score). The ORs never departed significantly from 1 in the IFG group (not shown). In contrast, in the diabetic group, all ORs (except for MMSE) were >1, reaching values >2 and statistical significance for AVLT, TRF, DSS, and FTT (Table 4, model 1), indicating a greater probability of serious worsening compared with the other two groups. The results were unchanged when further adjustment was made for alcohol and tobacco consumption and number of medicines used daily (not shown). Adjustment for blood pressure also did not considerably change the ORs or their level of significance (Table 4, model 2). The absence of confounding influences of blood pressure was further confirmed by contrasting ORs between hypertensive and nonhypertensive subjects: the trends were similar in both groups (not shown). Adjustment was also made for BMI, although it is not known as a correlate of cognitive function and therefore is not considered as a potential confounder. In this case, however, all ORs but one—although they remained >1—were reduced to nonsignificant values (Table 4, model 3).

CONCLUSIONS — The population we analyzed had high cognitive function and a very good overall level of education, a known protective factor against dementia (13). In the group as a whole, we observed little or no deterioration in cognition over 4 years (and even improvement on some tests sensitive to learning effects due to greater familiarity). However, when diabetic subjects were compared with subjects with normal blood glucose, they

Table 3—*The 4-year results on cognitive tests, adjusted for age, sex, and education, according to glycemic status*

	Normal FBG	IFG	Diabetes	*P*
MMSE	27.9 (27.8–28.1)	27.9 (27.6–28.2)	27.7 (27.3–28.2)	0.67
TMTB*	1.71 (1.66–1.76)	1.64 (1.50–1.78)	1.94 (1.75–2.13)	0.033
AVLT	54.1 (53.5–54.7)	53.7 (52.1–55.4)	50.8 (48.5–53.0)	0.020
TRF	21.1 (20.9–21.2)	21.3 (20.8–21.7)	20.2 (19.6–20.8)	0.016
DSS	49.3 (48.6–50.1)	51.0 (49.0–53.1)	44.8 (42.0–47.5)	0.002
FTT	140.9 (139.6–142.2)	141.3 (137.6–144.9)	135.6 (130.6–140.6)	0.12
BVRT	11.6 (11.4–11.7)	11.6 (11.2–11.9)	11.0 (10.5–11.5)	0.11
RPM	14.1 (13.9–14.3)	14.6 (14.1–15.0)	13.9 (13.3–14.6)	0.16
PASAT	17.1 (16.8–17.3)	17.7 (16.9–18.4)	16.4 (15.4–17.4)	0.12

Data are means (95% CI). *Only test where poorer performance is indicated by higher score.

appeared to have more than a twofold greater probability of serious worsening on four of the eight proposed domain-specific tests: one memory test (AVLT), one test of psychomotor speed (FTT), and two tests of attention (DSS and TRF). Moreover, for two other tests (TMTB and the RPM) assessing visual attention and logical reasoning, the ORs of serious worsening were also high and borderline-significant, which may be a consequence of the limited number of diabetic subjects in this relatively young and healthy cohort. It is worth noting that TMTB and DSS were the two domain-specific tests studied by Gregg et al. (8) in a cohort of women who were on average 7 years older than the subjects in our sample, and they reported remarkably similar results. There was no difference in performance according to glycemic status for the two remaining tests, namely the BVRT (immediate visual memory) and the PASAT (auditory attention and calculation), although the trends were not contradictory to the hypothesis of an unfavorable effect of diabetes on cognitive evolution. MMSEs were not affected at all by diabetes, contrary to the results on the domain-specific tests.

Globally, our results add to the increasing evidence for a relationship between diabetes and cognitive decline. It is difficult to say if a particular function is prominently affected, given the complexity of most tested domains and the overlap between tests. We showed the decline was not related to age, sex, education level, and the many other potential confounders that were accounted for in our analysis. It is unlikely that the observed trends were a consequence of bias arising from the fact that 4-year cognitive evaluations were missing for 12% of the baseline population. Such a possibility requires one to assume that diabetic subjects who missed the 4-year evaluation would have performed so well on follow-up that they would have counterbalanced the unfavorable evolution of the diabetes group; however, given the poorer cardiovascular risk factor profile and education level at baseline for the missing participants, this assumption would be contrary to the usual observed patterns (14).

Where confounders are concerned, the most striking finding was that controlling for blood pressure—a known risk factor for cognitive decline and a variable commonly associated with diabetes (2,15)—did not alter the age, sex, and education-adjusted results, suggesting that the relationship may actually depend on the diabetic state itself. There are indeed several postulated diabetes-related mechanisms for cognitive impairment. Hypoglycemic episodes are known to acutely affect cognition (16), but even when they occur repeatedly, they seem to have no effect on the long-term outcome (17). Chronic hyperglycemia, perhaps by causing the formation of advanced glycated end products (18), is another candidate. Some studies have found that improving metabolic control had a beneficial effect on cognitive performance (19,20), but they were not randomized trials. Our finding that subjects with IFG did not exhibit the same trends as those with diabetes suggest that blood glucose level per se may not be a strong risk factor. Hyperinsulinemia, another characteristic of type 2 diabetes, is also suspected, possibly through a direct effect on brain metabolism (21,22). This could explain why, among the variables we adjusted for, BMI appeared as a possible intermediary between diabetes and cognitive decline.

In conclusion, although the cognitive impairment related to diabetes may seem modest, the presence of small early defects may indicate a higher probability of future severe impairment, and it has been shown that diabetes is indeed associated with a higher risk of dementia (23,24). The relationship is worth investigating further, because both diabetes and dementia are becoming major public health threats in view of the continuous aging of the population. A better understanding of the mechanisms linking diabetes to cognition may uncover new possibilities for prevention of age-related cognitive decline.

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Table 4—*ORs of serious worsening in cognitive test scores over 4 years for diabetic subjects compared with subjects with normal FBG*

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
MMSE	1.05 (0.49–2.24)	0.91	0.99 (0.46–2.12)	0.97	1.06 (0.49–2.32)	0.88
TMTB	1.84 (0.91–3.72)	0.09	1.86 (0.91–3.80)	0.09	1.81 (0.87–3.77)	0.11
AVLT	2.15 (1.07–4.32)	0.032	2.09 (1.02–4.27)	0.045	1.83 (0.89–3.79)	0.10
TRF	2.11 (1.06–4.23)	0.034	2.04 (1.01–4.10)	0.046	1.74 (0.84–3.62)	0.14
DSS	2.27 (1.21–4.26)	0.011	1.94 (1.01–3.72)	0.045	1.82 (0.94–3.52)	0.08
FTT	2.25 (1.15–4.41)	0.019	2.34 (1.18–4.65)	0.015	2.14 (1.06–4.33)	0.034
BVRT	1.56 (0.70–3.48)	0.28	1.69 (0.75–3.81)	0.21	1.52 (0.67–3.44)	0.32
RPM	1.77 (0.93–3.39)	0.08	1.79 (0.93–3.44)	0.08	1.62 (0.83–3.19)	0.16
PASAT	1.30 (0.60–2.82)	0.50	1.10 (0.49–2.47)	0.82	1.28 (0.58–2.85)	0.54

Model 1: controlling for age, sex, education, and baseline score. Model 2: model 1 + further controlling for systolic blood pressure. Model 3: model 1 + further controlling for BMI.

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