Cognition in the Early Stage of Type 2 Diabetes

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OBJECTIVE — Type 2 diabetes is known to be associated with decrements in memory and executive functions and information-processing speed. It is less clear, however, at which stage of diabetes these cognitive decrements develop and how they progress over time. In this study, we investigated cognitive functioning of patients with recent screen-detected type 2 diabetes, thus providing insight into the nature and severity of cognitive decrements in the early stage of the disease. Possible risk factors were also addressed.

RESEARCH DESIGN AND METHODS — Included in this study were 183 diabetic patients from a previously established study cohort and 69 control subjects. A full neuropsychological assessment, addressing six cognitive domains, was made for each participant. Raw test scores were standardized into *z* scores per domain and compared between the groups. Possible risk factors for cognitive decrements were examined with multivariate linear regression.

RESULTS — Relative to scores for the control group, mean z scores were between 0.01 and 0.2 lower in the diabetic group across all domains, but after adjustment for differences in IQ between patients and control subjects, only memory performance was significantly reduced (mean difference −0.15 [95% CI −0.28 to −0.03]). A history of macrovascular disease and current smoking were significant determinants of slower information-processing speed in patients with diabetes.

CONCLUSIONS — This study shows that modest cognitive decrements are already present at the early stage of type 2 diabetes. A history of macrovascular disease and smoking are significant risk factors for some early decrements.

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Type 2 diabetes is associated with accelerated cognitive decline (1) and an increased risk of dementia (2,3), particularly in older individuals. Previous studies have shown decrements in memory function, executive function, and information-processing speed (4,5). These decrements in cognitive functioning are associated with modest brain atrophy and vascular lesions on brain magnetic resonance imaging (6). Diabetes-related factors, such as insulin resistance, chronic hyperglycemia, hypertension, and lipid disorders probably are relevant determinants (7,8).

It is unclear in which stage of diabetes the cognitive decrements become manifest and how they progress over time. Most studies have focused on patients with a known history of diabetes of several years (9). However, type 2 diabetes typically develops insidiously and may often be undiagnosed in the early stages. Therefore, cognitive decrements may start to develop years before the actual diagnosis, even in the pre-diabetes stages. Detailed neuropsychological data on the early stage of type 2 diabetes are not yet available. Moreover, possible risk factors for early cognitive decrements are not completely known.

In this study we assessed cognition in the early stage of diabetes by means of a detailed neuropsychological assessment (NPA) in a substantial population of patients with recent screen-detected diabetes. Possible risk factors were also addressed.

RESEARCH DESIGN AND METHODS

The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study is a multinational randomized trial involving 3,057 screen-detected type 2 diabetic patients that compares the effectiveness of an intensified multifactoral treatment with usual care on 5-year cardiovascular morbidity and mortality rates in a primary care setting (10). In the Netherlands, 56,987 individuals without known diabetes were offered a questionnaire, and those with a score above threshold underwent further glucose testing. Eventually, 586 participants had a diagnosis of type 2 diabetes according to the World Health Organization 1999 criteria (11), and 498 individuals were included in the study. Inclusion started in 2002 and ended in 2004.

In the ADDITION study, usual care is performed according to the different national guidelines from the three countries (in the Netherlands, the guidelines are from the Dutch College of General Practitioners [12]). The intensified multifactorial treatment consists of lifestyle advice regarding diet, physical activity, and smoking; protocol-driven strict regulation of blood glucose (A1C ≤6.5–7.0%), blood lipids (cholesterol <3.5 mmol/l), and blood pressure (<130/80 mmHg); and in those with blood pressure >120/80 mmHg prescription of acetylsalicylic acid and an ACE inhibitor. The primary outcome measure of the study is the combination of cardiovascular morbidity and mortality, all revascularizations, or nontraumatic amputations, whichever came first.

Inclusion in the cognition part of the ADDITION study

Cognition was assessed in an add-on project to the main ADDITION study in the Netherlands. Patients were invited to participate by an information letter from the study group and their family physician. Control subjects were peers of the

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patients, and both groups were matched for age, sex, and level of education. All patients and control subjects gave informed consent. Time between initial screening and inclusion in the Cognition part of the ADDITION study was 3–4 years.

Inclusion criteria

Inclusion and exclusion criteria for the present study were identical to those of the ADDITION study. All participants were aged 50–70 years at time of screening (2002–2004). Within 6 weeks after diagnosis of type 2 diabetes, treatment started. Randomization was performed at the practice level, so participants were treated according to the group (intensified treatment/usual care) their family physician had been randomly assigned to.

NPA was performed 3.6 ± 0.56 (mean ± SD) years after the screening date. Patients were excluded from the ADDITION trial if they were known to have a history of alcohol or drug abuse, psychosis, personality disorder, dementia, or emotional, psychological, or neurological disorder, unrelated to diabetes, that was likely to invalidate informed consent or limit their ability to comply with the protocol requirements. For both the ADDITION trial and the Cognition part, individuals with a previous noninvalidating stroke could participate. At the time of screening, participants with or treated for malignant disease or other disease that limited life expectance to <5 years were excluded. Control subjects had a fasting blood glucose <7.0 mmol/l, according to American Diabetes Association criteria (13).

NPA

The NPA was performed with a previously established test battery consisting of 12 verbal and nonverbal tasks addressing six cognitive domains (abstract reasoning, memory function, information-processing speed, attention and executive function, and visuoconstruction) as described previously (14). For the present study, the domain language comprehension was added and assessed with the Token Test (short form) (15). The domain memory was divided into four subdomains: working memory, immediate memory and learning rate, forgetting rate, and incidental memory (the amount of information that can be memorized if one was not explicitly asked to remember something) (14). IQ was measured by the Dutch version of the National Adult Reading Test (NART) (16). This test is constructed to estimate premorbid levels of intelligence and is relatively independent of brain damage acquired after adulthood (16).

A depression scale (Community Mental Health Assessment) (17) was used to assess the potential effect of mood disturbances on cognition. Scores ≥16 were labeled as depressive symptoms.

Physical examination and administration of the neuropsychological tests were performed at the patients' homes. The tests were administrated in a fixed order, and the entire battery took about 90 min to complete.

Participant characteristics and risk factor assessment

Demographic variables and possible risk factors were recorded in a standardized interview. Educational level was recorded using seven categories (1, <6 years of education; 2, 6 years; 3, 8 years; 4, 9 years; 5, 10–11 years; 6, 12–18 years; and 7, >18 years of education). Height and weight were measured, and BMI was calculated as weight in kilograms divided by the square of height in meters. Smoking was classified as current, past, or never. Alcohol consumption was recorded using six categories (0, no alcohol at all; 1, up to 3 units/week; 2, 4–10 units/week; 3, 11–20 units/week; 4, 21–30 units/week; and 5, >30 units/week). Participants in category 5 were excluded. A1C (percent) and cholesterol level (millimoles per liter) were measured in the week of the NPA and analyzed at the regional hospital. Systolic and diastolic blood pressures (millimeters of mercury) were measured at the beginning and the end of the neuropsychological assessment; measurements were averaged. Hypertension was defined as a mean systolic blood pressure >160 mmHg, a mean diastolic blood pressure >95 mmHg, or use of blood pressure–lowering medication. These relatively high cutoff values were used because otherwise >90% of the patients would be classified as being hypertensive, which would hamper the assessment of the role of this risk factor in the regression analyses. Macrovascular disease was defined as history of myocardial infarction, stroke, or surgery or endovascular treatment for carotid, coronary, or peripheral arterial disease.

Analysis

The differences between patients and control subjects were examined with Student's *t* tests for means, Mann-Whitney *U* tests for nonparametric data, and χ^2 tests for proportions. To analyze the difference in cognitive functioning between diabetic patients and control subjects, raw test scores for the NPA of both groups were standardized into *z* scores per domain. Mean *z* scores of the six cognitive domains were compared between the groups with univariate ANOVAs. Estimated mean differences between group differences were calculated and are presented with 95% CIs. Because the estimated premorbid IQ was significantly different between diabetic patients and control subjects, the NART-IQ was used as a covariate. To further assess the potential confounding effect of the NART-IQ imbalance, we performed a secondary analysis including all the control subjects ($n = 69$) and an exact age-, sex-, and NART-IQ–frequency matched selection of the patients ($n = 143$).

The relation between metabolic and vascular risk factors and cognition within the type 2 diabetic patients was assessed with linear regression analyses (adjusted for sex, age, and NART-IQ). To limit the number of analyses, only the domains of information-processing speed and memory were entered in these regression analyses, because these domains are known to be particularly sensitive to the effects of type 2 diabetes (9).

RESULTS

Participant Characteristics

A total of 183 patients with diabetes and 69 control subjects were included in the Cognition part of the ADDITION study. Patients and control subjects were balanced on sex, age, and educational level (Table 1). However, control subjects had a significantly higher estimated premorbid IQ.

There were differences in the metabolic and vascular profiles between patients and control subjects (Table 1). Control subjects had a significantly lower BMI, and they consumed significantly more units of alcohol per week than the patient group.

Vascular risk factors in patients in both treatment groups were well controlled. Those who received multifactoral treatment had a slightly lower A1C level (mean ± SD difference −0.23 ± 0.07%), cholesterol (mean difference −0.53 ± 0.14 mmol/l), and mean arterial pressure (difference −3.05 ± 1.78 mmHg) than those who received usual care.

Table 1—*Participant characteristics*

	Patients with type 2 diabetes	Control subjects
n	183	69
Sex (% males)	61.2	47.8
Mean age (years)	63.0 ± 5.4	62.7 ± 6.4
Education level (1–7)	4 (4–5)	5 (4–6)
Estimated premorbid IQ	96.7 ± 19.6	103.8 ± 16.3*
BMI (kg/m^2)	30.4 ± 5.3	27.4 ± 4.2*
Current smoking (%)	21.2	11.8
Alcohol (0–5)	1 (0–2)	2 (1–3)†
Depressive symptoms (%)	9.8	5.8
A1C (%)	6.2 ± 0.5	5.5 ± 0.3*
Cholesterol (mmol/l)	4.1 ± 1.0	5.7 ± 1.0*
Ùse lipid-lowering medication (%)	78.7	15.9*
Systolic blood pressure (mmHg)	143 ± 20	140 ± 21
Diastolic blood pressure (mmHg)	82 ± 10	81 ± 12
Hypertension (%)	85.2	36.2*
Use antihypertensive drugs (%)	81.4	23.2*
Macrovascular disease (%)	14.8	43*

Data are means ± SD, proportion (in percent), and median (interquartile range) unless indicated otherwise. *$P < 0.01$; †$P < 0.05$.

Cognitive functioning

The diabetic group performed significantly worse on memory functions, information-processing speed, attention, and executive functions and language comprehension in the unadjusted analyses, but the mean differences between the groups were small (−0.21 to −0.35) (Table 2). After adjustment for NART-IQ, only memory functions differed significantly between the groups (−0.15). The memory subdomains "immediate memory and learning rate" and "incidental memory" differed significantly between the groups after adjustment for NART-IQ. The results of the secondary analyses, in a selected subpopulation with exact matching for age, sex, and NART-IQ, showed an identical cognitive profile with similar effect sizes (results not shown). There were no significant differences in cognitive functioning between the patients who received multifactor treatment compared with patients who received usual care (results not shown).

Possible risk factors

Age was inversely related with performance on tasks for memory and information-processing speed in diabetic patients (Table 3). Neither sex nor HbA_1 levels, blood pressure, cholesterol levels, or BMI was significantly related to cognitive performance. A history of macrovascular disease, however, was associated with reduced information-processing speed. Current smoking also had a significant effect on the reduced information-processing speed. Depressive symptoms were not significantly related to memory functions or information-processing speed. In control subjects, only age was inversely related with performances on memory and information-processing tasks (not shown in table).

Table 2—*Estimated mean differences (95% CI)*

	Unadjusted	Adjusted for NART-IQ
Abstract reasoning	−0.20 (−0.48 to 0.08)	−0.01 (−0.26 to 0.23)
Memory	−0.21 (−0.32 to −0.08)†	−0.15 (−0.28 to −0.03)†
Working memory	−0.20 (−0.42 to 0.01)	−0.07 (−0.27 to 0.13)
Immediate memory and learning rate	−0.24 (−0.41 to −0.06)*	−0.18 (−0.35 to −0.003)†
Forgetting rate	0.04 (−0.18 to 0.26)	0.04 (−0.18 to 0.26)
Incidental memory	−0.49 (−0.73 to −0.17)*	−0.42 (−0.71 to −0.14)*
Information processing speed	−0.26 (−0.48 to −0.03)†	−0.13 (−0.33 to 0.08)
Attention and executive functions	−0.23 (−0.42 to −0.04)†	−0.12 (−0.29 to 0.05)
Visuoconstruction	−0.23 (−0.52 to 0.05)	−0.10 (−0.37 to 0.17)
Language comprehension	−0.35 (−0.65 to −0.04)†	−0.19 (−0.49 to 0.11)

*$P < 0.01$; †$P < 0.05$.

CONCLUSIONS — This study shows that patients with recent screen-detected type 2 diabetes performed significantly worse on memory functions, in particular, the immediate and the incidental memory, compared with control subjects. A history of macrovascular diseases and current smoking were the strongest determinants of a lower information-processing speed in the diabetic group.

The effect sizes for the difference in cognition between the diabetic and control groups found in this study are small compared with those in other studies (9), possibly reflecting the relatively short duration of diabetes in our population. Indeed, in a previous study with the same NPA battery, we found effect sizes of 0.3–0.4 among patients with a mean diabetes duration of 8 years (8). Another study using the same assessment battery in patients with a diabetes duration of 5–9 years showed effect sizes of 0.2–0.3 (18). Diabetes duration thus seems to be linked to the effect sizes of the studies: the longer the known diabetes duration, the bigger the effect size. In the present study we observed a small difference in language comprehension between patients and control subjects that was not significant after adjustment for NART-IQ. The meaning of this finding is not clear. The domain language comprehension is seldom addressed in studies on cognition in patients with type 2 diabetes. Moderate correlations between the token test and measures of short-term memory have been reported in a previous study on nondiabetic subjects (19); however, our results do not indicate that our patients performed worse on measures of short-term memory (working memory). The observed small effect on this test is well outside the range of what would be considered as abnormal performance and is therefore unlikely to confound performance on the other cognitive tests.

Further research is necessary to see how the cognitive decrement in our patients will develop over time and whether they also will develop problems in executive functions and information-processing speed as described in other studies. The patients included in this

Table 3—*Determinants of performance on memory and information processing speed, adjusted for sex, age, and NART-IQ (regression analyses)*

	Patients with type 2 diabetes			
	Memory		Information processing speed	
	B	β	*B*	β
Age	−0.02 (−0.04 to −0.01)*	−0.26	−0.07 (−0.08 to −0.05)*	−0.44
Sex	−0.03 (−0.16 to 0.10)	−0.03	(−0.27 to 0.12)	−0.04
BMI	0.003 (−0.01 to 0.02)	0.03	−0.02 (−0.04 to 0.001)	−0.11
Current smoking	−0.04 (−0.20 to 0.12)	−0.03	−0.26 (−0.50 to −0.03)†	−0.13
A1C	0.004 (−0.13 to 0.14)	0.004	0.004 (−0.20 to 0.20)	0.002
Cholesterol	0.02 (−0.05 to 0.09)	0.04	−0.07 (−0.17 to 0.03)	−0.08
Hypertension	0.06 (−0.13 to 0.24)	0.04	−0.17 (−0.47 to 0.10)	−0.08
Systolic blood pressure (per 10 mmHg)	0.001 (−0.03 to 0.04)	0.01	0.02 (−0.04 to 0.07)	0.04
Diastolic blood pressure (per 10 mmHg)	−0.04 (−0.10 to 0.03)	−0.08	−0.04 (−0.13 to 0.05)	−0.05
Macrovascular disease	−0.13 (−0.28 to 0.02)	−0.12	−0.30 (−0.51 to −0.09)*	−0.17
Depressive symptoms	−0.08 (−0.31 to 0.14)	−0.05	0.01 (−0.34 to 0.35)	0.002

Data are regression coefficient *B* (95% CI) and standardized β. *$P < 0.01$; †$P < 0.05$.

study will be followed over time, and a second NPA will be performed in a few years.

The relation between macrovascular diseases, smoking, and cognition has also been found in previous studies of patients with diabetes (8,20). Traditionally, hypertension is also thought to mediate the association between diabetes and cognitive dysfunction (4,21), but results of previous, mostly cross-sectional, studies do not consistently show this relation, in line with our findings. Also in nondiabetic subjects, the association between hypertension and cognitive functioning varies with age and time of exposure and is most evident when blood pressure is assessed in midlife and cognition in late life (22). Therefore, the association may be less evident in a cross-sectional study in a relatively older population, such as ours.

Regarding glycemic control, the literature mostly shows a negative relation between A1C (chronic exposure to hyperglycemia) and cognition in type 1 (23) and type 2 diabetes (24,25). We could not confirm this relationship. It is possible that we did not find this relationship because of the relatively strict metabolic control in our patients, but it is also possible that the negative effect of A1C on cognition becomes more evident after longer diabetes duration.

A strength of our study is the measurement of cognitive functions in the early stage of the disease. Previous studies focused mainly on patients with a longer diabetes duration. This study gives more information on early cognitive decrements and shows, in combination with other studies that used the same NPA in patients with a longer duration of diabetes, that the decrements seem to be progressive over time.

A limitation of our study is the difference in IQ scores of patients and control subjects. Control subjects had significantly higher IQ scores compared with those for the diabetic patients. We therefore had to adjust the analyses for NART-IQ. In a secondary analysis with exact matching for age, sex, and NART-IQ, patients still performed poorer on memory functions than control subjects. Besides a difference in IQ scores, there also was a nonsignificant higher proportion of men in the patient group, but sex was unrelated to performances in any cognitive domain (Table 3).

Another limitation is the time between screening and the NPA, which is between 3 and 4 years. Although this period is relatively short, we cannot say anything about the cognitive functioning in the first stage of type 2 diabetes. On the other hand, because of the screening procedure, the diabetic patients in our study are likely to have had their diabetes diagnosed some years earlier; thus, they may be in the same period of their disease as patients in usual care with a recent diagnosis of type 2 diabetes.

Because of the delay between screening and the NPA, half of the diabetic patients had received multifactoral intensified treatment for a period of 3–4 years. Although levels of A1C, cholesterol, and blood pressure were indeed better in the intensively treated group, both groups showed good control for these risk factors, and no effect of treatment allocation on cognition was observed in the present interim analysis. It is possible that a longer treatment duration or contrast in risk factor levels between the groups is required to observe effects on cognition. This possibility will be addressed in the follow-up study, once the treatment period has been completed.

In summary, cognitive decrements can be found in the early stages of type 2 diabetes. This finding may have implications for diabetes education and self-management behavior in diabetic patients. Diabetes educators should at least take into account the immediate memory and learning rate and the incidental memory of patients with a recent diagnosis of diabetes. If one wishes to prevent diabetes-associated cognitive decrements, interventions may need to be initiated at a very early stage. Offering a smoking cessation consultation would be the best option in those patients who are smokers. Whether other therapies might be beneficial to decrease the risk on cognitive impairment remains uncertain.

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