Cognition in the early stage of type 2 Diabetes Mellitus

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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. This study investigated cognitive functioning of patients with recently screen detected type 2 diabetes mellitus, thus providing insight in the nature and severity of cognitive decrements in the early stage of the disease. Possible risk factors were also addressed.

Research Design and Methods 183 diabetes patients from a previously established study cohort and 69 control subjects were included. A full neuropsychological assessment, addressing six cognitive domains, was taken from 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 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 controls only memory performance was significantly reduced (mean difference -.15 (95% CI -.28/-.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.
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 MRI (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 focussed 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 incompletely known.

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

RESEARCH DESIGN AND METHODS

The ADDITION study The ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care) study is a multinational randomized trial involving 3057 screen detected type 2 diabetes patients that compares the effectiveness of an intensified multifactorial treatment with usual care on five 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 people with a score above threshold underwent further glucose testing. Eventually 586 participants were diagnosed with type 2 diabetes according WHO criteria 1999 (11) and 498 people 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 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 (HbA1c ≤6.5-7.0%), blood lipids (cholesterol <3.5 mmol/l), and blood pressure (<130/80 mm Hg) and in those with blood pressure above 120/80 mm Hg prescription of acetyl salicylic acid and an ACE-inhibitor. The primary outcome measure of the study is the combination of cardiovascular morbidity and mortality, all revascularisations or non-traumatic 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 from the 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 to 4 years.

Inclusion criteria Inclusion and exclusion criteria for the present study were identical to those of the ADDITION study.
All participants were 50-70 years at time of screening (2002-2004). Within six weeks after being screened with type 2 diabetes, treatment started. Randomization took place at practice level, so people were treated according to the group (intensified treatment/usual care) their family physician had been randomized.

Neuropsychological assessment was performed 3.6 (0.56 SD) years after the screening date. Patients were excluded for the ADDITION trial if they were known with a history of alcohol or drug abuse, psychosis, personality disorder, dementia or emotional, psychological or neurological disorder, unrelated to diabetes, that is likely to invalidate informed consent or limit the ability of the individual to comply with the protocol requirements. For both the ADDITION trial and the Cognition part people with a previous non-invalidating stroke could participate. At the time of screening, participants with or treated for malignant disease or other disease that limited life expectancy to shorter than five years were excluded.

Control subjects had a fasting blood glucose <7.0 mmol/l, according to ADA criteria (13).

The neuropsychological assessment
The Neuropsychological Assessment (NPA) was performed with a previously established test battery which consisted of 12 verbal and non-verbal 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 the domain language comprehension was added and assessed with the Token Test (short form) (15). The domain memory was divided into four sub domains: 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, CES-D) (17) was used to assess the potential effect of mood disturbances on cognition. Scores ≥16 were labelled as depressive symptoms.

The physical examination as well the administration of the neuropsychological tests was performed at the patients’ homes. The tests were administrated in a fixed order and the entire battery took about 90 minutes to complete.

Participants 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, 7: >18 years of education). Length (m) and weight (kg) were measured and Body Mass Index (BMI) was calculated as weight divided by the square of height. Smoking was classified as current, past or never. Alcohol consumption was recorded using six categories (0: no alcohol at all, 1: up to three units per week, 2: 4 to 10 units per week, 3: 11 to 20 units per week, 4: 21 to 30 units per week, 5: more than 30 units per week). Participants in category 5 were excluded. HbA1c (%) and cholesterol level (mmol/l) were measured in the week of the neuropsychological assessment and analysed at the regional hospital. Systolic and diastolic blood pressures (mmHg) were measured both 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 cut-off
values were used because otherwise >90% of the patients would be classified as 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 controls were examined with t-test for means, Mann-Whitney U tests for non-parametric data, and chi-square test for proportions. To analyse the difference in cognitive functioning between diabetes patients and control subjects, raw test scores of 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 presented with 95% confidence intervals (95% CI). Because the estimated premorbid IQ was significantly different between diabetes 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 controls (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 diabetes patients was assessed with linear regression analyses (adjusted for sex, age and NART-IQ). In order 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**

**Participants characteristics** (Table 1) 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 profile between patients and control subjects (table 1). Control subjects had a significant lower BMI and they consumed significantly more units alcohol per week than the patient group.

Patients in both treatment groups were well controlled with respect to their vascular risk factors. Those who received multifactorial treatment had a slightly lower HbA1c level (mean difference -0.23% ± 0.07 SD), cholesterol (mean difference -0.53 mmol/l +/- .14) and mean arterial pressure (mean difference -3.05 mmHg +/- 1.78) in comparison to those who received usual care.

**Cognitive functioning** (Table 2) The diabetes 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). After adjustment for NART-IQ only memory functions differed significantly between the groups (-0.15).

The memory sub domains ‘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 as well as 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 in
comparison to patients who received usual care (results not shown).

**Possible risk factors** (Table 3) Age was inversely related with performance on tasks for memory and information processing speed in diabetes patients. Neither sex, nor HbA1 levels, blood pressure, cholesterol levels or BMI were significantly related with 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).

**CONCLUSIONS**

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

The effect sizes for the difference in cognition between the diabetic and control group found in this study are small in comparison to other studies (9), possibly reflecting the relatively short duration of diabetes in our population. Indeed, in a previous study with the same neuropsychological assessment battery we found effect sizes of 0.3-0.4 among patients with a mean diabetes duration of eight 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 controls, 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 non-diabetic 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 study will be followed over time and a second neuropsychological assessment will be performed in a couple of 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 non-diabetic 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 HbA1c (chronic exposure to hyperglycemia) and cognition, in type 1 (23), as well as type 2 diabetes (24,25). We could not confirm this relationship. This may be caused by the relatively strict metabolic control in our patients, but it is also possible that the negative effect of HbA1c on cognition becomes more evident after longer diabetes duration.

Strength of our study is the measurement of cognitive functions in the early stage of the disease. Previous studies mainly focussed on patients with longer diabetes duration. This study gives more information on early cognitive decrements and shows, in combination with other studies that used the same neuropsychological assessment 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 a significantly higher IQ score in comparison to the diabetes 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 in comparison to control subjects. Besides a difference in IQ-scores, there also was a non-significant higher proportion of males in the patient group, but sex was unrelated to performances in any cognitive domain (see table 3).

Another limitation is the time between screening and the neuropsychological assessment, which is between three or four years. Although this period is relatively short, we cannot say anything about the cognitive functioning in the very first stage of type 2 diabetes mellitus. On the other hand, because of the screening procedure, the diabetes patients in our study are likely to be diagnosed some years earlier than in usual care so they may be in the same period of their disease as patients recently diagnosed with type 2 diabetes mellitus in daily practice.

Because of the delay between screening and the neuropsychological assessment half of the diabetes patients had received multifactorial intensified treatment for a period of three to four years. Although levels of HbA1c, cholesterol and blood pressure were indeed better in the intensively treated group, both groups were very actually well controlled on these risk factors, and no effect of treatment allocation on cognition was observed in the present interim analysis. Possibly, a longer treatment duration or contrast in risk factor levels between the groups is required to observe effects on cognition. This will be addressed in the follow-up study, once the treatment period has been completed.

In conclusion, 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 diabetes patients. Diabetes educators should at least take into account the immediate memory and learning rate and the ‘incidental memory’ of patients recently diagnosed with 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 smoking. Whether other therapies might be beneficial in order to decrease the risk on cognitive impairment remains uncertain.

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Table 1  Participant characteristics

|                        | Patients with diabetes type 2 (N = 183) | Control subjects (N= 69) |
|------------------------|----------------------------------------|--------------------------|
| Sex (% males)          | 61,2                                   | 47,8                     |
| Mean age (years)       | 63,0 (5,4)                             | 62,7 (6,4)               |
| Education level (1-7, median, IQR) | 4 (4-5)                             | 5 (4-6)                   |
| Estimated premorbid IQ | 96,7 (19,6)                            | 103,8 (16,3)**           |
| BMI (kg/m²)            | 30,4 (5,3)                             | 27,4 (4,2) **            |
| Current smoking (%)    | 21,2                                   | 11,8                     |
| Alcohol (0-5, median, IQR) | 1 (0-2)                              | 2 (1-3) *                |
| Depressive symptoms (%)| 9,8                                    | 5,8                      |
| HbA1c (%)              | 6,2 (0,5)                              | 5,5 (0,3) **             |
| Cholesterol (mmol/l)   | 4,1 (1,0)                              | 5,7 (1,0) **             |
| Use 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                                 | 4,3**                    |

Data are presented as mean ± SD or proportion (in %), unless indicated otherwise; IQR: interquartile range.
* : p<.05  ** : p<.01

Table 2  Estimated Mean Differences (95% Confidence Interval)

|                                              | Unadjusted | Adjusted for | NART-IQ# |
|----------------------------------------------|------------|--------------|----------|
| Abstract reasoning                           | -.20 (-.48/.08) | -.01 (-.26/.23) |
| Memory                                       | -.21 (-.32/-08)* | -.15 (-.28/.03) * |
| - working memory                             | -.20 (-.42/.01) | -.07 (-.27/.13) |
| - immediate memory and learning rate         | -.24 (-.41/-06)** | -.18 (-.35/-003) * |
| - forgetting rate                            | .04 (.18/.26)  | .04 (.18/.26)  |
| - incidental memory                          | -.49 (-.73/-17)** | -.42 (-.71/-14)** |
| Information processing speed                 | -.26 (-.48/-03)* | -.13 (-.33/.08) |
| Attention and executive functions            | -.23 (-.42/-04)* | -.12 (-.29/.05) |
| Visuoconstruction                            | -.23 (-.52/.05) | -.10 (-.37/17) |
| Language comprehension                       | -.35 (-.65/-04)* | -.19 (-.49/.11) |

• : p<.05  ** : p<.01
• #NART: Dutch version of the National Adult Reading Test
Table 3
Determinants of performance on memory and information processing speed, adjusted for sex, age and NART-IQ (regression analyses)

|                             | Memory                      | Information Processing Speed |
|-----------------------------|-----------------------------|------------------------------|
|                             | B   | β              | B    | β              |
| Age                         | -.02 (-.04/-01)** | -.26                         | -.07 (-.08/-05)** | -.44                         |
| Sex                         | -.03 (-.16/.10) | -.03                         | -.07 (-.27/.12) | -.04                         |
| BMI                         | .003 (-.01/.02) | .03                          | -.02 (-.04/.001) | -.11                         |
| Current smoking             | -.04 (-.20/.12) | -.03                         | -.26 (-.50/.03)* | -.13                         |
| HbA1c                       | .004 (-.13/.14) | .004                         | .004 (-.20/.20) | .002                         |
| Cholesterol                 | .02 (-.05/.09) | .04                          | -.07 (-.17/.03) | -.08                         |
| Hypertension                | .06 (-.13/.24) | .04                          | -.17 (-.47/.10) | -.08                         |
| Systolic blood pressure (per 10 mmHg) | .001 (-.03/.04) | .01                          | .02 (-.04/.07) | .04                          |
| Diastolic blood pressure (per 10 mmHg) | -.04 (-.10/.03) | -.08                         | -.04 (-.13/.05) | -.05                         |
| Macrovascular disease       | -.13 (-.28/.02) | -.12                         | -.30 (-.51/-09)** | -.17                         |
| Depressive symptoms         | -.08 (-.31/.14) | -.05                         | .01 (-.34/.35) | .002                         |

* : p<.05 ** : p<.01
Data are presented as regression coefficient B (95% Confidence Interval) and standardized β