Short-Term and Long-Term Memory in Elderly Patients With NIDDM

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OBJECTIVE — To determine cognitive and memory dysfunction associated with non-insulin-dependent diabetes mellitus (NIDDM) and its relationship with depression, metabolic control, and serum lipids.

RESEARCH DESIGN AND METHODS — We studied a well-characterized group of 20 elderly patients with NIDDM and 22 control subjects with normal glucose tolerance recruited from a larger population-based sample. In addition to clinical and laboratory examinations, self-rating questionnaires that assess minor psychiatric disorder (General Health Questionnaire) and depression (Zung scale) were completed by patients and control subjects. Memory was examined with digit and block-span tests, word-list learning, Heaton Visual Memory Test, and Moss Visual Span Test. Executive functions were examined by Trail-Making A and B test and by Verbal and Category Fluency Tests. Visuoconstructive reasoning was examined with the block design subtest of the Wechsler Adult Intelligence Scale.

RESULTS — The NIDDM patients showed preserved memory span, but poor performance in learning tasks compared with control subjects. The patients recalled no fewer words than the control subjects, but the process of learning seemed to be different in the two groups. The recognition of the learned words was not impaired. Elevated serum total and very-low-density lipoprotein triglyceride levels, measured either before examinations or 5 or 10 years earlier, were associated with effects on retrieval from semantic memory in NIDDM patients.

CONCLUSIONS — The NIDDM patients had impaired control of their learning processes. Elevated serum triglyceride levels may be related to control of mental processing in diabetic patients.

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GHQ, General Health Questionnaire; NIDDM, non-insulin-dependent diabetes mellitus; VLDL, very-low-density lipoprotein.

Patients with non-insulin-dependent diabetes mellitus (NIDDM) often show mild cognitive impairment (1). In particular, the NIDDM patients have shown problems with memory and learning (2–3). However, elevated depression in NIDDM patients has been associated with both poor cognitive performance and poor memory function (2). Therefore, controlling for depressive symptomatology is important when assessing cognitive function in diabetic patients, especially among elderly people. A few studies have also shown that poor metabolic control correlates with low cognitive performance (1), but the relationship has been relatively weak. It has also been suggested that elevated serum triglyceride levels contribute to decreased cognitive functions (4). Hence, in a well-characterized cohort of elderly patients with NIDDM and control subjects with normal glucose tolerance, we examined the differences in cognitive and memory functions and their association with metabolic control, serum lipids, and depressive symptoms.

RESEARCH DESIGN AND METHODS

— This study is a cross-sectional analysis of a larger 10-year follow-up study of patients with NIDDM and nondiabetic control subjects. Originally, newly diagnosed patients with NIDDM were referred to the study by general practitioners working in the community health centers of the survey area. Diabetes diagnosis was made in the clinical setting (5) and was confirmed by an oral glucose tolerance test using the diagnostic criteria by World Health Organization (6). Participants were invited for the 5- and 10-year follow-up studies in 1986–1987 and 1991–1992, respectively. The formation and representation of the baseline study population (5) as well as the 5-year (7) and 10-year study populations (8) have been described earlier in detail. For this study, a cohort of 20 subjects were selected in the order they were originally recruited in the baseline study 11 years before. The same procedure was applied for the control subjects. If the subject did not meet the inclusion criteria, the next in order was called for investigations. All the psychological investigations were carried out in the morning after breakfast in one session in the outpatient department of neurology of Kuopio University Hospital during the year 1993. Thus, the known duration of diabetes was 10–11 years for the entire diabetic group. The memory tests were performed first. The tests of executive functions and visuospatial functions were carried out next, followed by delayed memory tests. The inclusion criterion was not clinically significant history of cerebrovascular disease, and the control subjects had to show normal glucose tolerance on the basis of a 2-h oral glucose tolerance test (6). Approval for the study had been given by the ethics committee of Kuopio University and Kuopio University Hospital. Informed consent was obtained from all subjects studied. Four diabetic patients were treated with diet only, 11 with oral drugs, and 5 with insulin.

Table 1—*Characteristics of NIDDM and control groups*

	NIDDM patients	Control subjects	*P* value
n	20	22	
Age (years)	66.2 ± 5.1	64.5 ± 5.5	NS
Sex (M/W)	13/7	14/8	NS
Body mass index (kg/m^2)	28.9 ± 3.6	27.0 ± 3.7	NS
Current smoker (yes)	2 (10%)	2 (9%)	NS
Use of alcohol (>30 g/week)	4 (20%)	6 (27%)	NS
Regular physical exercise (yes)	5 (25%)	5 (23%)	NS
Systolic blood pressure (mmHg)	158 ± 26	143 ± 16	0.02*
Diastolic blood pressure (mmHg)	88 ± 11	84 ± 11	NS
History of myocardial infarction (yes)	4 (20%)	4 (18%)	NS
Zung score	37.8 ± 9.9	37.8 ± 9.5	NS
GHQ score	2.8 ± 3.7	1.9 ± 2.9	NS
Fasting plasma glucose (mmol/l)	11.7 ± 3.1	5.8 ± 0.5	0.001*
2-h plasma glucose (mmol/l)	18.7 ± 6.6	5.9 ± 1.3	0.001*
HbA_{1c} (%)	8.6 ± 1.7	5.1 ± 0.9	0.001*
Fasting plasma insulin (mU/l)	14.6 ± 7.3	9.5 ± 4.3	0.01*
Serum cholesterol (mmol/l)	6.29 ± 1.21	6.11 ± 1.10	NS
HDL cholesterol (mmol/l)	1.16 ± 0.40	1.33 ± 0.31	NS
Serum triglycerides (mmol/l)	2.42 ± 1.42	1.68 ± 1.10	0.06*
VLDL triglycerides (mmol/l)	1.81 ± 1.23	1.16 ± 0.97	0.07*

Data are means ± SD or *n* (%). *Derived by Student's *t* test. HDL, high-density lipoprotein.

Laboratory examinations

Glucose determinations were conducted by glucose oxidase method (Daiichi, Kyoto, Japan) from plasma samples. Insulin determinations were carried out by a radioimmunoassay (Phasedeph, Pharmacia, Uppsala, Sweden). HbA_{1c} was measured at the 5- and 10-year examinations by liquid cation exchange chromatography (normal range 4.0–6.0%). Serum and lipoprotein lipid levels were determined from fasting samples (8) ~6 months (and also 5 and 10 years) before cognitive and memory functions were assessed.

Psychiatric symptoms

The amount of psychological distress was assessed by the 12-item version of the General Health Questionnaire (GHQ) (9). Depression was evaluated by a 20-item version of Zung's inventory for measuring depressive symptoms (10).

Neuropsychological methods

Short-term memory and vigilance were examined with the digit span subtest of the Wechsler Adult Intelligence Scale (11) and with the Corsi Block Span (12). Memory functions were examined with a word-list learning test using Buschke's selective reminding method (13). The delayed recall was evaluated after a 30-min delay filled with other psychometric tests. After the delayed recall test, yes/no recognition of the words was assessed. Visual memory was examined by the Moss Spatial Span (14) and by the Heaton Visual Reproduction Test (15). Subjects were asked to reproduce the figures again from memory after a 30-min delay and finally to copy the stimulus figures. Executive functions were examined with the Trail-Making Test A and B (16) and the Verbal and Category Fluency Tests (17). The scores of fluency tests were combined because they are functionally associated with each other. Visuoconstructional reasoning was examined with the block design subtest of the Wechsler Adult Intelligence Scale (11).

Statistical analysis

The differences between groups were analyzed with Student's *t* test, Mann-Whitney *U* test, or χ^2 test. If the data did not fulfill the assumption of parametric methods, we used nonparametric methods. Correlations were calculated using Spearman rank-order correlation, and the effect of possible confounding factors was assessed by multiple regression analyses. Because of multiple comparisons, the Bonferroni correction was used. $P < 0.05$ was considered statistically significant.

RESULTS — Table 1 shows the clinical characteristics of the study groups. Groups were comparable with respect to age and sex distribution as well as body mass index. The reported life habits (smoking, use of alcohol, and physical activity) were also comparable in the groups. Hypertension (drug treatment

Table 2—*Memory and cognitive functions in patients with NIDDM and control subjects*

	NIDDM patients	Control subjects	*P* value
n	20	22	
List learning test			
Total recall	30.7 ± 6.5	37.0 ± 8.1	0.05
Recalled reminders	12.1 ± 7.1	5.7 ± 4.1	0.02
Consistent recall	18.6 ± 9.4	30.0 ± 11.1	0.02
Delayed recall	3.6 ± 1.7	5.5 ± 2.4	0.05
Delayed recognition	9.5 ± 0.8	9.6 ± 0.8	NS
Heaton Visual Reproduction			
Immediate reproduction	9.6 ± 2.6	10.7 ± 3.5	NS
Delayed reproduction	7.7 ± 3.6	8.5 ± 4.2	NS
Copy	15.4 ± 1.5	15.3 ± 1.4	NS
Moss Spatial Span	14.1 ± 4.3	16.2 ± 4.1	NS
Digit span			
Forward	5.3 ± 1.0	5.6 ± 0.8	NS
Backward	3.9 ± 1.2	4.0 ± 1.0	NS
Corsi Span			
Forward	5.0 ± 1.0	5.0 ± 0.8	NS
Backward	4.0 ± 1.1	4.4 ± 1.0	NS
Verbal fluency total	23.7 ± 9.8	26.2 ± 9.1	NS
Category fluency total	18.5 ± 5.0	20.2 ± 5.8	NS
Trail-Making A	71.3 ± 32.0	61.2 ± 37.6	NS
Trail-Making B	195.3 ± 90.4	148.2 ± 83.1	NS
Block design	28.8 ± 11.1	36.6 ± 11.6	NS

Data are means ± SD. Student's *t* test was used to perform statistical analysis.

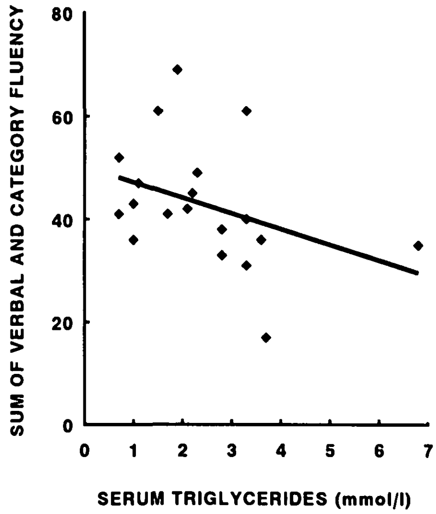

Figure 1—*Association of serum total triglyceride levels with the sum of category and verbal fluency tests in NIDDM patients.*

and/or blood pressure ≥160/90 mmHg) was more frequent and systolic blood pressure level was higher in the NIDDM group than in the control subjects. No differences in GHQ or Zung scores were observed. Metabolic control of diabetes was rather poor. Fasting insulin levels and serum total and very-low-density lipoprotein (VLDL) triglyceride levels tended to be higher and high-density lipoprotein cholesterol lower in the NIDDM patients than in the control group.

The NIDDM patients produced almost significantly fewer words in five trials (total recall) than the control subjects in the word-list learning test (Table 2). Moreover, the NIDDM patients consistently recalled significantly fewer words when not being reminded (consistent recall). In contrast, they retrieved significantly more words when they had just been reminded of them than did the control subjects (recalled reminders). The NIDDM patients recalled fewer words than the control subjects after a 30-min delay. Neither short-term visual memory nor visual or verbal memory span differed between the groups. The tests of executive functions and visuoconstructional reasoning did not differ between the groups.

The serum total and VLDL triglyceride levels correlated with the sum of fluency tests (Spearman correlation coefficient = -0.50 for both, $P < 0.05$) within the NIDDM patients (Fig. 1), but there was no correlation in the control subjects. The sum of the fluency tests (after log-transformation) was analyzed as a dependent variable in multiple regression analyses. Independent factors were serum total or VLDL triglyceride levels, fasting glucose levels, insulin, systolic blood pressure, and body mass index. From these factors, serum triglyceride or VLDL triglyceride levels, respectively, showed greatest association with the sum of the fluency tests, although their effect was no more statistically significant (triglycerides: $\beta = -0.35$, $P = 0.29$; VLDL triglycerides: $\beta = -0.51$; $P = 0.19$). Even the serum total and VLDL triglyceride levels measured 10 and 5 years earlier showed correlation with the sum of fluency tests (Spearman correlation coefficients for total triglycerides were -0.46 and -0.48, for 10 and 5 years earlier respectively, $P < 0.05$ for both, and for VLDL-triglycerides -0.43, $P = 0.03$, and -0.36, $P = 0.07$, respectively). The lower the total triglyceride or VLDL triglyceride levels were, the more words the patients could produce. The metabolic control of diabetes measured within the previous 6 months did not correlate with any other cognitive or memory functions. However, HbA_{1c} measured at the 5-year earlier examination showed statistically significant correlation with the sum of fluency tests (Spearman correlation coefficient = -0.41, $P < 0.04$). No consistent associations were observed between fasting and postglucose insulin or measured blood pressure levels and fluency or any other tests.

CONCLUSIONS — The verbal or visual short-term memory span was not inferior in NIDDM patients, but they recalled fewer words than the control subjects in five trials of the word-list learning test. The NIDDM patients consistently recalled fewer words (without reminders) than the control subjects. In contrast, they recalled more words when they had just been reminded than did control subjects. Not only did NIDDM patients recall fewer words than control subjects, but the process of learning seemed to differ; the NIDDM patients tended to repeat the words they had just heard, which showed failure to modify behavior in response to feedback (13). When their attention was divided between retaining the previously recalled words and listening to forgotten words (reminders), the NIDDM patients were more impaired in controlling the learning process than the control subjects. Performance of memory tasks that tap long-term memory or learning has generally been found to be poorer in NIDDM patients than in age-matched controls (1–3). However, our results suggest that the learning process itself may be impaired. In addition, the NIDDM patients recalled fewer words after delay than the control subjects, but recognition of the words was not impaired. A previous finding (2) also suggests this preserved recognition in diabetic patients.

In previous studies, mild cognitive and learning dysfunction has been suggested to reflect the emotional influence of chronic disease rather than organic pathology (1). The NIDDM patients did not, however, have more depressive symptoms according to Zung's self-rating scale or more minor psychiatric disorders according to the GHQ. Depression and minor psychiatric disorders were not correlated with cognitive dysfunction in this study either.

Transient metabolic abnormalities might affect cognitive efficiency in NIDDM patients. Experimentally induced hypoglycemia has impaired a broad range of cognitive tasks (19), but the effects of induced hyperglycemia on cognition have been contradictory (19–20). HbA_{1c} was rather high in the NIDDM patients of the present study, reflecting chronic hyperglycemia. In a previous study, good metabolic control was associated with higher levels of cognitive performance of tasks primarily involving memory retrieval (4). In accordance, cognitive function correlated with earlier metabolic control in our study. It is possible that with improvement of hyperglycemia, the cognitive functions might also improve (21).

Serum total and VLDL triglyceride levels correlated with the ability to retrieve words from semantic memory. High serum triglyceride levels have previously been associated with slower reaction times to a series of auditory stimuli, backward digit span, and digit substitution test (4). Fluency tests demand a search of semantic memory. The common factor of the above-mentioned tasks may be activation of mental processing. The effects of elevated triglyceride levels on cognition may be mediated by poor glycemic control, which frequently is associated with elevated serum triglyceride levels (22). Elevated triglyceride levels, especially in NIDDM and impaired glucose tolerance, reflect associated metabolic abnormalities, such as insulin resistance and accompanying hyperinsulinemia (22), which has been associated with impaired cognitive performance (23). However, elevated serum triglyceride levels may also affect cognitive performance by increasing blood viscosity and impairing its rheologic properties (24). In accordance, improvement of cerebral perfusion and cognitive performance in elderly subjects by lowering triglyceride levels with diet and gemfibrozil has been previously observed (25).

In conclusion, the NIDDM patients showed preserved memory span but performed poorly in learning tasks. The process of learning seemed to be different in the NIDDM patients than in the control subjects. Triglyceride levels were associated with retrieval from semantic memory. This may suggest that elevated triglyceride levels, a common finding in NIDDM, may affect control of cognitive processing. Because elevated triglyceride levels are also predictors of cardiovascular complications in patients with NIDDM (8), their treatment with diet, weight loss, and even drugs appears to be warranted.

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