

Short-Term Effects of Improved Glycemic Control on Cognitive Function in Patients with Type 2 Diabetes

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Key Words

Cognitive function · Glucose · Insulin · Memory · Metabolic control · Type 2 diabetes

Abstract

Background: According to numerous studies, type 2 diabetes is associated with mild cognitive dysfunction, and there is some evidence suggesting favorable effects of improved metabolic control on the mental capability of elderly diabetic patients. **Objective:** To compare patients with type 2 diabetes to normal controls with respect to cognitive performance and to investigate the consequences of glycemic adjustment. **Methods:** 53 patients with type 2 diabetes, most of them in secondary failure on oral antidiabetic drugs, but free from conditions which may cause brain dysfunction, were included (mean age 58.8 ± 6.1 years, duration of disease 12.0 ± 6.4 years). They were examined prior to (t1), and following (t2) glycemic adjustment with a time interval of approximately 2 weeks. 29 non-diabetic controls, comparable with regard to age, gender, education and verbal intelligence were examined twice with a corresponding time interval. Cognitive performance was assessed by well-standardized tests with a focus on attention/concentration, psychomotor speed, verbal fluency and verbal

memory; mood status by two self-rating scales. Restoration of glycemic control included insulin treatment in the majority of patients (46/53). **Results:** Diabetic subjects scored significantly lower in all cognitive tests used, while they did not differ from controls in mood status. From t1 to t2 they improved in those tests measuring attention/concentration, and psychomotor speed. With regard to similar changes in controls, we interpret these improvements as practice effects rather than the consequence of altered metabolic control. **Conclusion:** In a sample of patients with long-standing type 2 diabetes we could not confirm previous reports of improved cognitive capacity with restoration of glycemic control. Further studies on the effects of changes in control of blood glucose on cognitive performance in type 2 diabetes should be conducted with special regard to drugs used to lower blood glucose.

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Introduction

A substantial number of studies has found evidence of mild cognitive dysfunction associated with type 2 diabetes which seems to affect primarily individuals older than 60–65 years [1]. Deficits pertain in particular to

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Table 1. Selected medical variables in patients and controls

	Patients (n = 53)	Controls (n = 29)
Duration of diabetes, years (\pm SD)	12.0 (\pm 6.4)	–
Body mass index t1 (\pm SD)	30.1 (\pm 4.4)	26.8 (\pm 3.5)
Fasting blood glucose t1, mmol/l (\pm SD)	11.5 (\pm 2.2)	4.7 (\pm 0.6)
Fasting blood glucose t2, mmol/l (\pm SD)	6.2 (\pm 1.0)	–
Blood glucose previous to cognitive testing t1, mmol/l (\pm SD)	14.2 (\pm 3.1)	–
Blood glucose post-testing t1, mmol/l (\pm SD)	12.3 (\pm 2.6)	–
Blood glucose previous to cognitive testing t2, mmol/l (\pm SD)	7.9 (\pm 2.2)	–
Blood glucose post-testing t2, mmol/l (\pm SD)	7.0 (\pm 2.0)	–
Glycosylated hemoglobin t1, % (\pm SD)	13.3 (\pm 1.6)	6.2 (\pm 0.5)
Glycosylated hemoglobin t2, % (\pm SD)	11.6 (\pm 1.3)	–
Total cholesterol t1, mmol/l (\pm SD)	6.31 (\pm 1.23)	6.24 (\pm 1.12)
Triglycerides t1, mmol/l (\pm SD)	3.28 (\pm 2.62)	2.00 (\pm 1.41)
Peripheral neuropathy, n (%)	38 (71.7)	–
Nephropathy, n (%)	23 (43.4)	–
Retinopathy, n (%)	27 (50.9)	–
Macroangiopathy, n (%)	10 (18.9)	1 (3.5)
Hypertension, n (%)	37 (69.8)	8 (27.6)

measures of verbal memory, while decrements in other areas of cognitive function like attention and concentration, visuospatial memory and psychomotor speed, were less consistently reported [2]. Only three studies on the influence of improved glycemic control on neuropsychological test performance in patients with type 2 diabetes could be located referring to patients treated exclusively [3, 4], or in their majority [5] with oral antidiabetic drugs.

In these investigations favorable effects of correcting hyperglycemia were reported with regard to attention and concentration [3, 5], and verbal memory [4]. However, several limitations of these findings have to be considered. The study of Meneilly et al. [3] was of a pilot nature and did not include a control group. Gradman et al. [4] employed a broad array of neuropsychological tests, but found a favorable change in the treated group in only one of eleven tests. Finally, Naor et al. [5] reported some benefit with respect to cognitive function in their treated group, but raise doubts that this improvement could be due to improved metabolic control. Thus, beneficial consequences of treating hyperglycemia on cognitive performance of patients with type 2 diabetes are as yet not clearly established. With this background, we report on short-term effects of glycemic correction in subjects with type 2 diabetes, which was achieved in the majority of patients by treatment with insulin and antidiabetic drugs in combination.

Methods

Patients and Controls

Fifty-three patients with type 2 diabetes according to American Diabetes Association (ADA) criteria [6] and 29 healthy controls with an age range of 46–70 years were recruited for this study. All patients had been admitted for inpatient treatment at the Diabetes Center Mergentheim because of poor metabolic control, as defined by a total glycosylated-hemoglobin value $>10.5\%$, which is equivalent to a $HbA_{1C} >8.3\%$ (see below). At study entry, 32 subjects were treated by oral antidiabetic drugs, 13 by antidiabetic drugs and insulin in combination, and 8 patients by insulin only. Controls were recruited via an announcement in the local newspaper and matched for age, gender and education. The two groups were also comparable with respect to a vocabulary test [7] as a measure of verbal intelligence. For a listing of medical data of the patient and the control group, see table 1.

Patients and controls were excluded from the study if there was evidence of history or clinical examination of CNS disorders, including dementia, or severe systemic disease (e.g. heart failure NYHA grade III/IV, severe hypertension with a diastolic blood pressure >115 mm Hg). Further criteria for exclusion were impaired vision, and/or hearing, evidence of low intelligence (verbal IQ <80), past or present mental disorder including substance-related disorders, and anticholinergic or benzodiazepine medication. Diabetic patients were excluded if there was evidence of type 1 diabetes from the history or from C-peptide secretion (<0.7 nmol/l 1 h post-stimulation by glibenclamide 7 mg) and also if the blood glucose exceeded the range of 3.3–19.4 mmol/l within 12 h previous to cognitive testing. Informed consent was obtained from all patients and controls. The study design was approved by the Ethics Committee of the University of Heidelberg Medical School.

Protocol

At study entry, all patients were clinically examined by a board-qualified internist, an ECG was obtained and a blood chemical screening battery was conducted, including blood smear, electrolytes, liver and renal function tests, and a turbidimetric immunoassay for microalbuminuria from three samples of morning urine was performed. Total glycosylated hemoglobin was measured by a commercial affinity chromatography assay (Abbott IMx[®], reference interval 5.6–7.2%), which allows one to calculate a standardized HbA_{1c} value, using an empirically defined algorithm [8]. The presence of symmetrical peripheral neuropathy was assessed using the clinical criteria of Young et al. [9]. Diabetic nephropathy was verified according to the Mogensen criteria [10]. Each patient was examined by an ophthalmologist using a protocol with respect to signs of retinopathy [11]. Hypertension was diagnosed according to WHO criteria [12], and macroangiopathy by clinical assessment.

The aim of inpatient treatment at the Diabetes Center Mergentheim, an institution with a high proportion of patients with diabetes-associated complications, was to restore metabolic control within a defined period of time, in the case of patients with type 2 diabetes, 2 weeks on average. Thus, the study patients were subjected to intensive treatment, including dietary measures, a standard educational program, blood glucose monitoring using the glucose dehydrogenase method with at least 5–6 measurements per day, oral medication, and, in the majority of cases, insulin injections [13]. At discharge, 7 subjects were on oral antidiabetic drugs, 43 on antidiabetic drugs and insulin in combination, and 3 on insulin. Cognitive testing was conducted on two occasions, previous to the initiation of blood glucose lowering on day 2 of inpatient treatment (t1), and 1 day before discharge (t2), with an interval of 13.1 ± 2.3 days between t1 and t2.

Controls were examined by an internist, likewise, with regard to the exclusion criteria mentioned. An ECG and biochemical screening were performed as well. Diabetes mellitus was excluded by history, fasting blood glucose [6], and an assay of glycosylated hemoglobin. Cognitive testing was conducted in a similar manner as in the patient group, with an interval of 14.9 ± 3.2 days between t1 and t2.

Psychometric Assessment

Cognitive testing was administered by one investigator (M.M.) between 08:30 and 10:00 h or 13:30 and 15:00 h in a separate room of the hospital, with a comparable proportion of morning and afternoon testing in both groups. At the beginning and the end of each test session, capillary blood glucose was determined. At t1 and t2 the following tests were conducted:

Attention/Concentration, Psychomotor Speed

(a) Zahlen-Verbindungs-Test (ZVT [14]): The ZVT is a German equivalent of the Trail Making Test-A. The test assesses cognitive processing speed involving visual scanning, attention and motor speed, a task highly sensitive to mild CNS dysfunction [15]. Subjects had to connect a series of randomly scattered numbers (1–90) in ascending order. The mean time of completion of four trials was calculated.

(b) Choice-reaction time (C-RT): a computer-controlled (Experimental-Run-Time System) visual test paradigm of focused attention [16] was conducted to measure the speed of psychomotor response. The target signal was an arrow directed to the right or to the left on a 17-inch monitor. Subjects had to press a left- or right-hand key corresponding to the direction of the target signal. Target signals were flanked above and below by two arrows or two squares. Thus, three

context conditions were presented: compatible (target and flanking arrows pointing in the same direction), incompatible (target and flanking arrows in opposite directions), or neutral (target stimulus flanked by two squares). Different stimulus conditions were presented randomly in four blocks of maximally 100 trials each, a block finished when 20 correct responses for each context condition were performed. The median reaction time for each context condition in each of the four blocks was used to calculate the mean reaction time per context condition. Furthermore, a global mean reaction time over the three conditions was calculated.

Verbal Fluency and Verbal Memory

(a) Verbal fluency (VF [17]): This task assesses retrieval from and search strategies in semantic memory, involving also short-term memory function. VF represents a sensitive indicator of brain injury [15]. In the course of two 1-min trials, subjects had to call as many nouns with the same initial letter as possible. At t1, the letters 'S' and 'F' were employed, at t2 the letters 'B' and 'R'. The number of words generated across both trials constituted the verbal fluency test score.

(b) Auditory Verbal Learning Test (AVLT [18]): The AVLT – a widely used serial learning task being a measure of verbal memory known to be particularly sensitive to the consequences of cognitive aging [19] – was used in the German version [20]. A list of 15 words was presented orally five times, and subjects had to recall the list in any order after each presentation. After trial 5, a second word list was presented followed by the same free-recall task. Finally, the first word list had to be recalled again. Two scores are reported here: (a) the number of correctly recalled words after trial 1, a measure of immediate memory (AVLT-supra span), and (b) the total number of items recalled in trials 1–5 (AVLT-total learning). At t2, parallel versions of the word lists were used.

At t1 and t2, patients and controls alike completed parallel versions of two standardized self-rating scales to assess mood status. One, assessing typical symptoms of clinical depression ('Depressivitäts-Skala' (D-S) by von Zerssen [21]), the other yielding a measure of present well-being ('Befindlichkeits-Skala' (Bf-S) by von Zerssen [22]). At t1, all subjects completed a vocabulary test as a measure of verbal intelligence which is considered resistant to the effects of brain injury, thus providing an estimate of premorbid verbal intelligence [7].

Data Analysis

Statistical analysis was performed with the SPSS version 10.0 software. Differences between groups for age and vocabulary score were submitted to t-test, differences for gender and education to χ^2 testing. The significance of changes in metabolic parameters from t1 to t2 was evaluated by matched pairs t-test. Measures of cognitive function and mood status were subjected to analyses of variance (ANOVA) with group (diabetic patients vs. controls) as a between factor, and time (t1 vs. t2) as a repeated measurement factor. For choice-reaction time the ANOVA included a context condition as an additional repeated measurement factor. All dependent variables met the assumption of homogeneity of variance. The association of metabolic parameters and diabetic complications with cognitive performance was calculated using Pearson product-moment correlations.

Table 2. Results of the ANOVAs with factors group (diabetic patients, controls) and time (t1, t2) of measures of mood and cognitive function; significant results ($p < 0.05$) in italics

	Diabetic patients (n = 53)		Controls (n = 29)		ANOVA					
	t1	t2	t1	t2	group (df = 1; 80)		time (df = 1; 80)		group × time (df = 1; 80)	
					F	p	F	p	F	p
Well-being score (Bf-S)										
Mean	7.7	7.5	8.3	9.8	0.96	0.33	0.48	0.49	0.90	0.34
SD	7.9	7.4	7.0	7.6						
Depression score (D-S)										
Mean	8.7	6.1	8.6	7.0	0.07	0.78	22.48	<i><0.001</i>	1.25	0.26
SD	6.1	5.1	5.1	4.1						
Zahlen-Verbindungs-Test (ZVT, s)										
Mean	99.8	87.6	87.2	77.3	4.89	<i>0.030</i>	99.96	<i><0.001</i>	1.09	0.29
SD	27.9	21.8	19.6	16.6						
Choice reaction time (C-RT, ms)										
Mean	450.4	432.2	420.3	403.9	8.67	<i>0.004</i>	59.21	<i><0.001</i>	0.15	0.69
SD	45.2	44.1	41.8	41.8						
AVLT-supra span (number of words)										
Mean	5.3	4.9	6.0	5.9	9.78	<i>0.002</i>	1.37	0.24	0.62	0.43
SD	1.5	1.3	1.1	1.7						
AVLT-total learning (number of words)										
Mean	42.4	40.1	44.8	45.0	4.19	<i>0.044</i>	2.09	0.15	2.82	0.09
SD	9.4	7.7	7.7	8.5						
Verbal fluency (VF, number of words)										
Mean	23.5	24.7	27.4	28.0	4.39	<i>0.039</i>	2.21	0.14	0.20	0.65
SD	7.9	7.7	8.6	7.4						

Results

Glucose levels (fasting, pre- and post-cognitive testing), and glycosylated hemoglobin in type 2 diabetes patients are presented in table 1, with corresponding HbA_{1C} values of 10.1% at t1, and 9.0% at t2, respectively. A significant decrease at t2 was observed for all metabolic parameters ($p < 0.001$). Table 2 contains the results of the ANOVAs with factors group (patients, controls) and time (t1, t2) for all measures taken at t1 and t2.

Significant main effects for group indicating reduced performance of the patients were found for the tests of verbal fluency and verbal memory, as well as those assessing attention/concentration and psychomotor speed. As group effects in the choice-reaction task were not influenced by context conditions, results are reported only for overall mean reaction time. The groups did not differ with respect to either mood scales. Highly significant main effects of time were found for the ZVT and for C-

RT, due to improved performance at t2. Depression scores were significantly lower at t2 than at t1.

No significant group × time effects were found, i.e. improvement of performance in the patient group was, if present at all, of the same extent as in the control group. Thus, improved metabolic control did not differentially improve psychomotor performance and self-assessed mood in the diabetic patients. The single group × time interaction approaching significance ($p < 0.10$) referred, however, paradoxically to one measure of verbal memory function: regarding AVLT-total learning, patients reproduced slightly fewer words at t2 than at t1.

Considering this finding, we correlated AVLT-total learning to several medical variables, measured at t1 and t2. There was no association to fasting and post-testing blood glucose, triglycerides and glycosylated hemoglobin at any point in time. There was also no association to the frequency of diabetes-related complications, as well as the mode of treatment at t1 and t2. However, change of

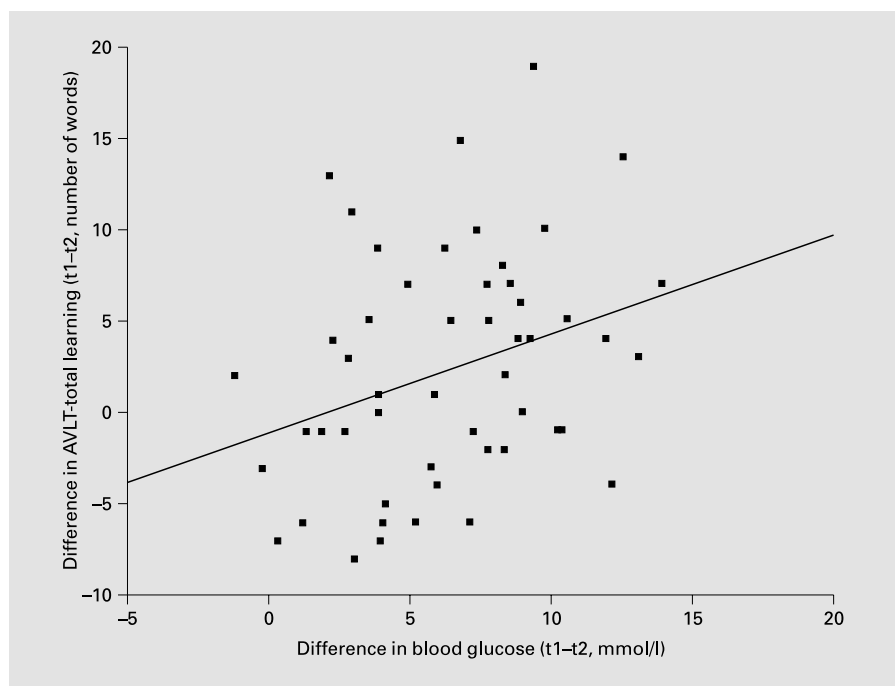


Fig. 1. Bivariate scatter diagram for change in AVLT-total learning and change in blood glucose previous to cognitive testing from t1 to t2 (Pearson product-moment correlation: $r = 0.33$, $p = 0.016$).

AVLT-total learning (words recalled at t1 minus words recalled at t2) was significantly correlated to the rate of decline of blood glucose, determined at the beginning of the cognitive testing session (blood glucose at t1 minus blood glucose at t2; see fig. 1).

Discussion

Data presented here refer to a sample of middle-aged to elderly patients with long-standing type 2 diabetes, being in their majority in need of insulin therapy due to secondary failure on oral antidiabetic drugs, i.e. subjects with comparatively advanced glucose intolerance. By applying strict exclusion criteria, matching patients and controls for age, gender and education and controlling for pre-morbid verbal intelligence and depression scores, we avoided a number of confounding factors which frequently obscure comparisons of diabetic patients and controls [2].

The measures chosen for cognitive assessment correspond to those suggested in a proposal for standardizing cognitive assessment in diabetes [23], selected because of their reliability and their potential to detect cognitive deterioration. The patient group performed significantly worse in tasks probing verbal memory, verbal fluency, attention/concentration and psychomotor speed. Thus,

we could establish slight, but significant, cognitive deficits in subjects with longstanding type 2 diabetes, but without advanced secondary complications, which is in line with the majority of published studies [2, 24].

With improved metabolic control at t2, diabetic patients performed significantly better than at t1 in the attention/concentration and psychomotor speed tasks (ZVT, C-RT). As performance of the controls improved correspondingly, we interpret these changes as practice effects which cannot be explained by metabolic factors. In the measures of verbal fluency and verbal memory, patients showed either no change from t1 to t2, or even a tendential decrease in performance (AVLT-total learning).

Thus, we were not able to confirm findings of improved cognitive performance as a consequence of short-term glycemic adjustment in our sample. Before accepting this result at face value, we should ask if the power of our design was sufficient to detect the expected improvement in cognitive performance. According to a post-hoc calculation assuming equal variance, the sample size of 53 patients and 29 controls was sufficient to detect effect sizes ≥ 0.65 with a power of at least 0.80. However, the actual effect sizes were < 0.24 for all performance measures with the exception of AVLT-total learning which yielded an effect size of 0.39. But all effect sizes were in the range of small effects [25]. Thus, it is not likely that

clinically relevant improvements were present but could not be ascertained due to a lack of power of the design. However, the following issues should be considered when discussing these results:

Firstly, note that glucose intolerance was on average rather advanced in our sample. 87% of our patients were in need of insulin therapy, while in the vast majority of patients in the other intervention studies [3–5] glycemic control was achieved by antidiabetic drugs. This might be of relevance considering recently published epidemiological evidence for increased cognitive decrements in insulin-treated patients with type 2 diabetes [26]. Although the mechanisms underlying this association are not yet understood, intrinsic effects of insulin on brain function have to be considered [27].

Secondly, the mean age of our patients was about 10 years younger than in the other studies [3–5]. Re-establishing metabolic control may have different effects in older than in younger subjects, as generally more severe cognitive deficits may be expected in older patients [1]. Within the limited age range of our sample we found, however, no age-dependent effects of glycemic correction on the change of cognitive performance. The effect of re-establishing metabolic control may also be moderated by the presence of diabetes-related complications. These appear to have been more frequent in our sample compared to the other studies, although information in this respect was limited in these publications [3–5].

Thirdly, our study differs from the other studies with regard to the speed of blood glucose lowering, which was obtained within 2 weeks in our patients, while the respective time interval in the studies cited above ranged from 6 weeks to 6 months. We have to consider the possibility that adaptation of brain metabolism to rapid restoration of normo- or near-normoglycemia takes longer than 2 weeks, with parallel or even retarded consequences for mental efficiency, which could explain our negative findings. We can also – despite meticulous blood sugar controls within a clinical setting – not exclude the possibility that some patients might have been affected by subclinical hypoglycemic events in the course of antidiabetic treatment.

Finally, we would like to relate our results to the recently published evidence of glucose-related ‘cognitive enhancement’. This effect has been elicited in elderly persons by blood glucose values in the high normal range, when compared to a control condition with lower normal blood glucose [28, 29]. Thus, a negative ‘cognitive enhancement effect’ due to markedly lowered blood glucose at t2 might be responsible for the absence of cognitive

improvement. This assumption is in line with the data presented in figure 1.

While restoration of glycemic control in type 2 diabetes patients has been shown to be beneficial with regard to medical parameters [30] as well as quality of life measures [31], we cannot, however, support the notion of a generally favorable effect on cognitive performance. Our data referring to short-term effects are negative in this respect. But as yet, neither positive effects in the course of several weeks to months have been shown conclusively. Our rather cautious statement is consistent with published evidence of an at best equivocal association between cognitive function and metabolic parameters like actual blood sugar or glycosylated hemoglobin [2, 24]. In this context, we would like to stress the finding that cognitive performance is rather robust to acute hyperglycemia, compared to the clear-cut effects of hypoglycemia, which have been documented in type 1 diabetes [32].

Since the etiology of cognitive dysfunction in type 2 diabetes is not known, we can only speculate about the underlying pathophysiological processes. A number of vascular and non-vascular mechanisms might be of relevance [24, 33], and one may assume that causative pathology develops over a long period, probably many years.

To help to elucidate the complex relationship between type 2 diabetes and cognitive function, we would suggest further investigations with a special focus on two treatment-related issues: firstly, the magnitude of blood glucose lowering in relation to time, and secondly, the effects of different treatment modalities. Furthermore, we should try to elucidate the natural history of cognitive deficits in type 2 diabetes. This would probably contribute to a better understanding of the potential of preventive and therapeutic measures in relation to the different stages of the disease. From our point of view the investigation of the mental capability of patients with type 2 diabetes should be a goal of ongoing scientific endeavor, with regard to the probable adverse consequences of cognitive impairment on diabetes management and the maintenance of activities of daily life [34–36], as well as the growing evidence that this metabolic disorder is a significant risk factor for dementing illness [24, 37].

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