

Effects of improved glycaemic control maintained for 3 months on cognitive function in patients with Type 2 diabetes

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Abstract

Background and aim In a previous study we failed to find beneficial short-term effects of improved glycaemic control on cognitive functioning in patients with Type 2 diabetes mellitus. A subgroup of the entire sample was tested again to examine the effect of longer-lasting improvement of metabolic control on cognitive functioning.

Methods The cognitive performance of 26 patients with Type 2 diabetes was assessed at baseline and 3 months after discharge. Thirteen controls were tested at the similar time-points. Attention/concentration, psychomotor speed, verbal fluency, verbal memory and depressive symptoms were assessed. Improved glycaemic control was generally achieved with insulin therapy (20/26).

Results At baseline, there was a trend for diabetic patients to perform worse than controls. Both groups improved significantly over 3 months in several measures. However, diabetic patients did not improve more than controls.

Conclusions In individuals with long-standing Type 2 diabetes, previous reports of improved cognitive capacity following restoration and maintenance of near-normoglycaemia were not confirmed. This might relate to the type of anti-diabetic therapy.

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Keywords cognitive function, glucose control, memory, metabolic control, Type 2 diabetes

Introduction

The association of mild cognitive dysfunction with Type 2 diabetes mellitus in elderly patients has been established in a number of studies [1–3]. Some suggest positive effects of improved metabolic control on cognitive functioning in these patients [4–7]. We have previously found impaired performance in the sensory-motor, verbal fluency and memory domains in individuals with Type 2 diabetes [8]. However, after 2 weeks of improved metabolic control we could not

ascertain any short-term cognitive improvements beyond the effects of repeated testing. Most received insulin therapy due to secondary failure of oral anti-diabetic drugs. Now we report on longer term changes in cognitive functioning accompanying improved glycaemic control for 3 months. Subgroups of the original samples of patients and controls [8] took part in this investigation.

Methods

Patients and controls

In our previous study [8], 53 patients with Type 2 diabetes, all fulfilling ADA criteria [9], had been recruited consecutively from a hospital specializing in diabetes treatment. They had

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poor metabolic control (total glycosylated-haemoglobin value > 10.5%, equivalent to HbA_{1c} > 8.3%; [10]). Patients were assessed for cognitive functioning at admission and 2 weeks following the reestablishment of metabolic control. Twenty-nine non-diabetic controls, comparable in age, sex, education and verbal intelligence were examined twice at corresponding time points [8].

To save overnight stays, only patients living within 100 km of the hospital were asked to take part in a further assessment 3 months after discharge. One refused, leaving 26 (49%) of the patients tested at baseline and 2 weeks for examination at 3 months. Thirteen controls were selected from the original control group to match the patients with respect to sex, age, and education. They were assessed after the same time interval as the patients.

The mean duration of diabetes in the reduced patient sample ($n = 26$) was 13.1 ± 7.8 years. At baseline, 19 were on oral hypoglycaemics, four on insulin and three had no anti-diabetic drugs medication. Glucose correction was achieved by insulin in combination with oral hypoglycaemics in most (20/26).

Psychometric assessments

Areas of cognitive functioning were assessed with standardized procedures:

Verbal fluency (VF) [11]

In two trials of 1-min duration each, subjects had to recall as many nouns as possible, beginning with a letter prompted by the experimenter (baseline: S, F; 3 months: T, G). This task probes for integrity of semantic memory retrieval processes.

Memory encoding and retrieval

In the Auditory Verbal Learning Test (AVLT) [12], a list of 15 words is presented to the participant five times. After each presentation, the words have to be recalled. Immediate memory was assessed by the number of correctly recalled words after trial 1 (AVLT-supra span). Learning efficiency was assessed by the total number of words recalled across all five trials (AVLT-total learning). At baseline and 3 months parallel versions of the word list were employed.

Cognitive processing speed

The Zahlen-Verbindungs-Test (ZVT) [13], a German test similar to the Trail Making Test (TMT-A) [14], taps visual scanning, attention and motor speed.

Psychomotor speed

In a variant of a choice-reaction time task (C-RT) [15], subjects had to press a left- or right-hand key corresponding to the direction of target signals.

Depressive symptoms were assessed with parallel versions of a self-rating depression scale (D-S) [16].

At baseline, subjects completed a multiple choice vocabulary test (MWT-B) [17] and a non-verbal reasoning task (LPS) [18] as measures of verbal and non-verbal intelligence, respectively.

Capillary blood glucose levels of diabetic patients were tested immediately before and after cognitive testing to ensure the absence of hypoglycaemia.

Statistical analysis

Diabetic patients were compared with controls with respect to their performance in the various tests at baseline by means of *t*-tests. The changes in these measures from baseline to 3 months in the two groups were compared by means of analysis of covariance (ANCOVA) with one group factor. The 3 month values were entered as dependent variable and the baseline values as co-variate. Calculations were performed using SPSS 10.0 (SAS Institute, Cary, NC, USA).

Results

Those participating at 3 months did not differ significantly from those unavailable regarding age ($t = 0.29$, $P = 0.78$), duration of diabetes ($t = 1.20$, $P = 0.24$), nor in the frequency of nephropathy (50 vs. 37%; $\chi^2 = 0.91$, $P = 0.34$), polyneuropathy (70 vs. 70%; $\chi^2 = 0.01$, $P = 0.93$), retinopathy (42 vs. 59%; $\chi^2 = 1.53$, $P = 0.22$) and hypertension (70 vs. 77%; $\chi^2 = 0.49$, $P = 0.48$). However, the female/male ratio was different in the tested patients (11/15) than in those not available (20/7) ($\chi^2 = 5.51$, $P = 0.019$).

Diabetic patients and controls did not differ significantly in age (59.0 vs. 57.5; $t = 0.65$, $P = 0.52$), in verbal intelligence at baseline (27.6 vs. 29.3; $t = -1.13$, $P = 0.27$), abstract reasoning at baseline (21.3 vs. 21.5; $t = 0.14$, $P = 0.80$) or in their depressive symptoms score at baseline (6.9 vs. 8.1; $t = -0.8$, $P = 0.43$) or at 3 months (5.1 vs. 7.5; $t = -1.45$, $P = 0.16$).

In diabetic patients, glucose control improved significantly over 3 months [glycosylated haemoglobin (13.3 ± 1.4 vs. $8.2 \pm 1.6\%$, $t = 16.93$, $P < 0.001$; HbA_{1c}: 10.1 ± 2.12 vs. $6.7 \pm 2.3\%$). Apart from LDL-cholesterol, lipids also improved. (Cholesterol: 6.22 ± 1.25 vs. 5.90 ± 1.00 mmol/l; $t = 2.13$, $P = 0.043$. HDL-cholesterol: 1.09 ± 0.25 vs. 1.28 ± 0.31 mmol/l; $t = -4.16$, $P < 0.001$. Triglyceride: 3.08 ± 1.05 vs. 2.48 ± 0.90 mmol/l; $t = 2.98$, $P = 0.006$).

Cognitive tests at baseline were not significantly different between patients and controls (Table 1). At 3 months, both the diabetic and control group showed significant improvements in cognitive processing speed (ZVT; $t = 5.33$, $P < 0.001$ resp. $t = 4.65$, $P = 0.001$) and motor speed (C-RT; $t = 7.26$, $P < 0.001$ resp. $t = 6.83$, $P < 0.001$). The groups did not differ significantly when taking baseline performance into account. No groups showed improved memory performance (AVLT-supra span, AVLT-total learning) and verbal fluency.

Discussion

In a previous study [8] patients with Type 2 diabetes performed worse than controls in a number of cognitive tests at admission. Despite improved metabolic control, these deficits were still present 2 weeks later. We concluded that adaptation of brain metabolism to rapid restoration of near-normoglycaemia and improvements in mental efficiency may take longer than 2 weeks.

Table 1 Statistical comparison of neuropsychological test results at study entry (baseline) and of change scores from baseline to 3 months for the Type 2 diabetes group and healthy controls (ANCOVA)

Cognitive measure		Type 2 diabetes group (<i>n</i> = 26)	Control group (<i>n</i> = 13)	Student <i>t</i> -test Baseline		Effect size	ANCOVA 3 months		Effect size
		Mean (SD)	Mean (SD)	<i>t</i>	<i>P</i>	<i>d</i>	<i>F</i>	<i>P</i>	<i>d</i>
AVLT-supra span (number of words)	Baseline	5.6 (1.4)	6.1 (1.0)	-1.03	0.31	0.42	0.15	0.70	0.04
	3 months	5.6 (1.2)	5.6 (1.4)						
AVLT-total learning (number of words)	Baseline	43.2 (7.7)	45.3 (6.5)	-0.85	0.40	0.30	0.06	0.81	0.08
	3 months	42.9 (8.8)	45.2 (8.0)						
Verbal fluency (number of words)	Baseline	24.9 (7.9)	30.4 (9.7)	-1.92	0.06	0.63	0.04	0.84	0.07
	3 months	24.7 (7.6)	28.5 (10.9)						
Zahlen-Verbindungs-Test (ZVT, s)	Baseline	95.9 (27.4)	81.7 (17.5)	1.70	0.09	0.63	0.31	0.58	0.19
	3 months	83.1 (23.5)	70.7 (12.3)						
Choice reaction time (C-RT, ms)	Baseline	452.7 (35.8)	434.4 (38.1)	1.48	0.15	0.50	0.82	0.37	0.31
	3 months	427.1 (36.9)	405.7 (34.2)						

P ≤ 0.05 considered statistically significant.

There was a trend towards worse cognitive performance at baseline in the subset of patients compared with matched controls. From baseline to 3 months, both groups improved in psychomotor and in cognitive processing speed, but not within the memory domain. There were no greater improvements in diabetic patients than in controls in any of the cognitive measures, despite continued near-normoglycaemia. Thus, improved metabolic control maintained over 3 months had no specific effect on cognitive performance. The improvements demonstrated by both groups presumably reflect practice effects.

We can exclude the possibility that this negative result is due to the choice of cognitive measures, selection of subjects or other particularities of the research protocol. Our cognitive measures are highly reliable, sensitive to cognitive deterioration, and correspond to those suggested for standardized cognitive assessment in diabetes [19]. Nevertheless, there always remains the possibility that measures of other cognitive domains and more difficult tasks could have revealed differences between the groups.

By applying strict selection criteria, matching patients and controls for age, sex, and education, and controlling for pre-morbid verbal intelligence and depression scores [8] several confounding factors were avoided which frequently have obscured comparisons of diabetic patients and controls [2]. However, a group of individuals with Type 2 diabetes and bad glycaemic control during the observation period would have been a more useful control.

The effect of re-establishing metabolic control on cognitive performance may also be moderated by the presence of diabetes-related complications. However, we excluded patients with severe complications. Thus, it is unlikely that impediments associated with such complications, e.g. visual impairment, prevented improvements in test performance.

Our negative result is not in line with several clinical trials [4–7], but as we have argued elsewhere, several limitations of these studies have to be considered [8]. Furthermore, glucose

intolerance was moderate rather than poor in our sample. Of our patients 77% needed insulin, while most subjects in other studies received oral hypoglycaemics. However, our ability to identify greater improvements in our diabetic group may have been reduced because patients and controls available at 3 months differed less in their performance at baseline than the complete sample [8]. While the original cohort of patients performed significantly worse than controls with respect to verbal memory, verbal fluency, attention/concentration and psychomotor speed in our previous study [8], the subset of patients had only a trend towards worse verbal fluency and psychomotor speed. An obvious explanation is that the reduction in sample size has reduced the power of the *t*-test to detect differences between the two samples. Issues of power are important when assessing differential cognitive improvement for a single control group study. Nevertheless, according to a recent Cochrane Review, the evidence that anti-diabetic treatment is effective in the preventing or treating of cognitive impairment in Type 2 diabetes is not yet convincing [20].

The issue of diabetes-related cognitive decline is important with regard to the substantially rising prevalence of Type 2 diabetes, and the apparent association between Type 2 diabetes and dementia [21]. Accordingly, further investigations of the effects of improved metabolic control on cognitive performance of subjects with Type 2 diabetes are needed.

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