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Impact of Diabetes and Its Treatment on Cognitive Function Among Adolescents Who Participated in the Diabetes Control and Complications Trial

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THE DIABETES CONTROL AND COMPLICATIONS TRIAL/EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (DCCT/EDIC) RESEARCH GROUP9

OBJECTIVE — The purpose of this study was to evaluate whether severe hypoglycemia or intensive therapy affects cognitive performance over time in a subgroup of patients who were aged 13–19 years at entry in the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS — This was a longitudinal study involving 249 patients with type 1 diabetes who were between 13 and 19 years old when they were randomly assigned in the DCCT. Scores on a comprehensive battery of cognitive tests obtained during the Epidemiology of Diabetes Interventions and Complications follow-up study, ~18 years later, were compared with baseline performance. We assessed the effects of the original DCCT treatment group assignment, mean A1C values, and frequency of severe hypoglycemic events on eight domains of cognition.

RESULTS — There were a total of 294 reported episodes of coma or seizure. Neither frequency of hypoglycemia nor previous treatment group was associated with decline on any cognitive domain. As in a previous analysis of the entire study cohort, higher A1C values were associated with declines in the psychomotor and mental efficiency domain (P < 0.01); however, the previous finding of improved motor speed with lower A1C values was not replicated in this subgroup analysis.

CONCLUSIONS — Despite relatively high rates of severe hypoglycemia, cognitive function did not decline over an extended period of time in the youngest cohort of patients with type 1 diabetes.
Cognition in adolescents in DCCT/EDIC

glucose at an early age may be the imper-
tus for these cognitive deficits (11,13), it
is also possible that chronic hyperglyce-
mia during childhood makes the brain more vulnerable to subsequent brain in-
jury (14). In the current study we ad-

duced in coma or seizure, and 3) the level of long-term glycemic control, as
measured by A1C values.

RESEARCH DESIGN AND
METHODS—Between 1983 and 1989, 1,441 subjects with type 1 diabetes
were enrolled in the DCCT. A total of 249
subjects were recruited as adolescents
aged 13–19 years: 32% were 13–14 years
old, 37% were 15–16 years old, and 31%
were 17–19 years old. All adolescents had
to be at least Tanner stage II in pubertal
development, which is the stage at which
the first signs of puberty are visible on
physical examination. We chose age 19 as
the upper age limit, rather than age 18 as
used in other studies on the DCCT cohort
(15,16), because the sample size was con-
siderably larger when the age limit was
extended to the final year of adolescence.
The DCCT consisted of two cohorts. The
primary prevention cohort (n = 149) had
diabetes for 1–5 years, no retinopathy,
and urinary albumin excretion <40
mg/24 h. The secondary intervention co-
hort (n = 100) had diabetes for 1–15
years, very mild to moderate nonprolif-
erative retinopathy, and urinary albumin
excretion ≤200 mg/24 h at baseline. Ap-
proximately half of the adolescent sample
(n = 115) was randomly assigned to in-
tensive therapy (three or more insulin in-
jections daily or subcutaneous infusion
with an external pump, guided by fre-
quent self-monitoring of blood glucose)
with preprandial blood glucose level tar-
gets between 3.9 and 6.7 mmol/l, a
monthly A1C target within the nondia-
betic range (<6.05%), and a goal of
avoiding hypoglycemia. The remainder
(n = 134) was assigned to conventional
therapy with one to two daily insulin in-
jections and no numeric blood glucose
targets but freedom from symptoms of
hypoglycemia and from frequent or se-
vere hypoglycemia as the therapeutic
goal. At the end of the DCCT, this cohort
of patients had been studied for an aver-
age of 7.3 years (range 4–10). Intensive
therapy was recommended for all subjects
because it had been shown to be highly
effective in reducing complications of
long-term diabetes. Subjects in the con-
ventional treatment group were given
training in aspects of intensive therapy
and then returned to their own health
care providers. Between April 2004 and
May 2006, 175 participants (76% of sur-
viving, eligible participants) were reevalu-
ated with the cognitive test battery; 74
participants who were adolescents at the
DCCT baseline did not participate in the
Epidemiology of Diabetes Interventions
and Complications (EDIC) follow-up
cognitive testing. Of these, 6 had died and
12 were inactive at the time of testing.

Cognitive test protocol
Cognitive testing, as originally described
for the DCCT (2), was performed at each
site by personnel who were trained and
certified by the DCCT/EDIC Central Neu-
ropsychological Coding Unit. The test
protocol is described elsewhere (2,4). Stan-
dardized tests were administered in a
fixed order. Capillary blood glucose levels
were routinely monitored immediately
before testing and at its midpoint to rule
out hypoglycemia during testing. If a sub-
ject was found to have a blood glucose
level ≤3.89 mmol/l, testing was stopped
and the patient was given a snack; after
waiting at least 15 min, testing was re-
sumed when the reading returned to at
least 5.0 mmol/l. Tests scoring proce-
dures are described elsewhere (2,4).

Cognitive domains
During the DCCT, 24 test variables were
chosen a priori to be of particular diag-
nostic value when applied to patients with
type 1 diabetes, and a standardized (Z)
score was calculated for each, with
the mean ± SD from the baseline assess-
ment of the DCCT cohort used as a reference
(2) to provide a unit-free measurement of
the relative improvement or deterioration
in performance compared with the total
group at baseline. Details of the test vari-
ables and domains are described else-
where (4).

Biomedical evaluations and
psychiatric symptoms
During EDIC, subjects completed an an-
nual history, physical examination, electro-
cardiogram, and laboratory testing, in-
cluding serum creatinine and hemoglo-
bin A1C, using the same methods as dur-
ing the DCCT (17). Participants reported
the presence of sensory symptoms of pe-
ripheral neuropathy as part of neuropathy
screening (18).

Psychiatric symptomatology was
assessed with the Symptom Checklist-90-
Revised (SCL-90R), which was adminis-
tered annually during the DCCT and once
in the EDIC in the same year that the cog-
nitive testing was performed (19,20). For
this report, the depression scale was used
to assess the effects of mood on cognition.

Definition of severe hypoglycemia
During the DCCT, severe hypoglycemia
was defined as any event requiring the
assistance of another individual, includ-
ing seizure or coma, with either blood
sugar <2.78 mmol/l and/or subsequent
reversal of symptoms with oral carbohy-
drate, glucagon injection, or intravenous
glucose (1). For the purposes of this arti-

cle, severe hypoglycemic events are lim-
ited to those leading to coma and/or
seizure because these episodes are the
most likely to have an impact on cogni-
tion and are most precisely defined. At
quarterly visits, study coordinators asked
about the occurrence of hypoglycemia
since the last visit, and all such events
were reported to the Data Coordinating
Center as soon as possible after their oc-
currence. During the EDIC, the severe hy-
poglycemic events that occurred in the 3
months before the annual visit were doc-
umented on the annual history form, and
further details surrounding these events
were recorded.

Statistical analyses
Demographic and clinical characteristics
were compared with the use of Wilcoxon-
’s rank-sum test to evaluate the differ-
ences between the treatment groups for
ordinal and numeric variables (21). The
contingency χ² test was used for catergo-
rial variables; when the sample size was
small, Fisher’s exact test was used (21).
All treatment group comparisons were
based on intention to treat.

Separate analysis of covariance mod-
els were used to assess the effects of treat-
ment group (intensive or conventional),
mean A1C values stratified by tertiles
(<7.9, 7.9–9.5%, and ≥9.5%), and fre-
quency of severe hypoglycemia (0, 1–3,
and >3 reported events) on the standard-
ized quantitative score for each of the eight
cognitive domains. Each model ad-
justed for baseline age, sex, education, length of follow-up, visual acuity, self-reported sensory loss attributable to peripheral neuropathy, and the number of interval cognitive tests taken (to control for practice effects). Results are presented as the average increase or decrease in the standardized score from the DCCT baseline within or between groups or as the per unit change in a quantitative covariate. Nominally significant results ($P < 0.01$) are cited.

Analyses were repeated to determine whether cognitive performance was associated with 1) current mood state measured by the SCL-90R depression scores (scores $\geq 63$ are suggestive of a possible depressive disorder), 2) the timing of severe hypoglycemia, and 3) diabetic ketoacidosis (DKA) during the DCCT.

**RESULTS** — Table 1 presents the characteristics of the patients at the DCCT baseline and at the EDIC year-12 follow-up. There were no statistically significant between-group differences at the DCCT baseline. The characteristics presented in Table 1 were also compared between patients who continued participation in the EDIC cognitive follow-up and those subjects who were still actively participating in other EDIC evaluations but did not participate in the EDIC cognitive evaluation. The only statistically significant difference was severe nonproliferative diabetic retinopathy at EDIC year 12 (17% participants and 42% nonparticipants). Of the patients who did not participate in the EDIC cognitive follow-up, 45% were assigned to intensive treatment. Furthermore, 16 of 38 had severe nonproliferative diabetic retinopathy, and 12 of 41 had peripheral neuropathy at EDIC year 12. No data on these variables were available for the remaining nonparticipants.

At EDIC year 12, the age of participants ranged from 29 to 41 years (mean $\pm$ SD 35.2 $\pm$ 2.5 years). Of the participants, 40% reported having completed a college degree (37% intensive and 42% conventional), and almost 50% reported a professional or technical occupation (53% intensive and 41% conventional). At EDIC year 12, differences between the two treatment groups approached significance for the presence of peripheral neuropathy and severe nonproliferative diabetic retinopathy ($P < 0.05$).

Over the entire 18-year follow-up, there were a total of 294 reported episodes of coma or seizure. Of these, 200 were reported in 51 intensive treatment group subjects and 94 were reported in 36 conventional treatment group subjects (Table 2).

A separate analysis conducted between the primary and secondary patient cohorts differing in terms of diabetes duration and complications revealed no effect of diabetes duration between these two groups. Table 3 summarizes the raw scores for each cognitive test, stratified by treatment group. Figure 1 shows cognitive test results for each domain by original treatment group (Fig. 1A), cumulative number of severe hypoglycemic events (0, 1–5, and $>5$ episodes) (Fig. 1B), and metabolic control (tertiles of mean A1C values) (Fig. 1C). Neither original treatment assignment nor cumulative number of hypoglycemic events influenced performance in any cognitive domain. Age did not significantly affect cognition. Performance in both sexes improved over time, and this effect was more pronounced in male participants ($P < 0.01$). Higher values of A1C were associated with modest declines in psychomotor and mental efficiency ($P < 0.01$). Degree of self-reported symptoms of depression at year 12, as indexed by the SCL-90R (median T score 46.0; scores $\geq 63$ reflect possible depressive disorder), was

| Table 1—Characteristics of participants who were adolescents at entry into the DCCT |
|-----------------|-----------------|-----------------|-----------------|
|                 | DCCT baseline   |                | EDIC year 12    |
|                 | Intensive       | Conventional   | Intensive       | Conventional   |
| $n$             | 82              | 93             | 82              | 93             |
| Sex (% female)  | 50              | 62             | 50              | 62             |
| Race (% white)  | 99              | 92             | 99              | 92             |
| Age (years)     | 16 $\pm$ 2      | 16 $\pm$ 2     | 36 $\pm$ 3      | 35 $\pm$ 3     |
| College graduate| 0               | 0              | 37              | 42             |
| Marital status  |                 |                |                 |                |
| Never married   | 100             | 99             | 21              | 19             |
| Married/remarried| 0              | 1              | 69              | 68             |
| Separated/divorced/widowed | 0 | 0 | 10 | 13 |
| Occupation (%)  |                 |                |                 |                |
| Professional/technical | 1 | 0 | 53 | 41 |
| Unemployed/retired | 0              | 0              | 2               | 9              |
| Severe nonproliferative diabetic retinopathy (%) | 0 | 0 | 11 | 23 |
| Duration (years) | 5 $\pm$ 3     | 5 $\pm$ 4       | 25 $\pm$ 4      | 24 $\pm$ 4     |
| A1C†             | 9.5 $\pm$ 1.7   | 9.4 $\pm$ 1.9  | 7.8 $\pm$ 1.5   | 7.9 $\pm$ 1.6  |
| Visual acuity (%)| 6               | 4              |                 |                |
| Peripheral neuropathy (%)§ | 2 | 1 | 17 | 33 |
| Blood pressure  |                 |                |                 |                |
| Systolic (mmHg) | 112 $\pm$ 10    | 109 $\pm$ 11   | 117 $\pm$ 13    | 115 $\pm$ 13   |
| Diastolic (mmHg) | 71 $\pm$ 9      | 70 $\pm$ 9     | 74 $\pm$ 9      | 75 $\pm$ 9     |
| Treated hypertension‖ | 19 | 30 | 19 | 30 |
| Lipids          |                 |                |                 |                |
| Total cholesterol | 166 $\pm$ 32  | 163 $\pm$ 31   | 179 $\pm$ 34    | 185 $\pm$ 37   |
| LDL cholesterol | 102 $\pm$ 30    | 101 $\pm$ 28   | 109 $\pm$ 28    | 113 $\pm$ 30   |
| Lipid-lowering medication‖ | 19 | 17 | 19 | 17 |
| Current cigarette smoker (%) | 9 | 11 | 15 | 18 |
| Symptom Check List-90R | 45 $\pm$ 10 | 47 $\pm$ 11 | 49 $\pm$ 10 | 49 $\pm$ 12 |
| Mean depression T score | 110 $\pm$ 12 | 108 $\pm$ 12 | 111 $\pm$ 11 | 110 $\pm$ 12 |
| Verbal IQ¶       | 120             | 120            | 120             | 120            |
| Full-scale IQ¶   | 110             | 110            | 110             | 110            |

Data are means $\pm$ SD. †DCCT baseline value is the eligibility value. †At DCCT baseline, all patients had visual acuity of 20/32 or better. In EDIC, a Snellen value of 20/40 or worse in at least one eye was recorded. §The DCCT baseline definition is pain or numbness in hands only, taken from the Neurological History and Examination form. The EDIC definition is pain or numbness in hands or feet, taken from the Annual Medical History and Examination form. ‖Data were not collected in DCCT. ¶Data were not collected in EDIC. Mean value is 100, with SD of 15. The Wechsler Adult Intelligence Scale was administered for patients aged $\geq 16$ years (58% intensive and 55% conventional), whereas the Wechsler Intelligence Scale for Children was given for participants aged $<16$ years (43% intensive and 45% conventional).
Table 2—Severe hypoglycemic events (coma/seizure) among participants who were adolescents at entry into the DCCT

<table>
<thead>
<tr>
<th></th>
<th>DCCT</th>
<th>EDIC</th>
<th>Total follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>82</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>1–5</td>
<td>35</td>
<td>72</td>
<td>61</td>
</tr>
<tr>
<td>&gt;5*</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total patients with 1+ event</td>
<td>47</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Total events</td>
<td>155</td>
<td>53</td>
<td>45</td>
</tr>
</tbody>
</table>

All DCCT hypoglycemic events were documented. EDIC hypoglycemic events were documented in the 3-month period before the annual visit. *Number of events ranged from 1 to 18 in the intensive group and 1 to 11 in the conventional group.

The timing of severehypoglycemic events did not affect performance on any of the eight cognitive domains. We found that 47 patients reported their first episode of coma or seizure during adoles-

Table 3—Raw cognitive test scores

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Conventional</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem solving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities*</td>
<td>12.2 ± 2.8</td>
<td>12.1 ± 2.5</td>
</tr>
<tr>
<td>Category test (no. errors)†</td>
<td>30.7 ± 18.2</td>
<td>32.3 ± 22.9</td>
</tr>
<tr>
<td>Learning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol-digit learning (no. correct)</td>
<td>24.5 ± 4.3</td>
<td>24.5 ± 4.5</td>
</tr>
<tr>
<td>Tactual performance memory (no. correct)</td>
<td>7.4 ± 1.5</td>
<td>7.3 ± 1.7</td>
</tr>
<tr>
<td>Immediate memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual reproductions (no. correct)</td>
<td>14.6 ± 1.9</td>
<td>14.5 ± 2.4</td>
</tr>
<tr>
<td>Short-term memory (no. correct)</td>
<td>38.0 ± 9.5</td>
<td>37.5 ± 10.2</td>
</tr>
<tr>
<td>Logical memory (no. correct)</td>
<td>19.7 ± 5.7</td>
<td>19.5 ± 5.4</td>
</tr>
<tr>
<td>Digit symbol (no. correct)</td>
<td>8.4 ± 1.0</td>
<td>8.1 ± 1.4</td>
</tr>
<tr>
<td>Delayed recall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual reproductions (no. correct)</td>
<td>15.5 ± 1.5</td>
<td>15.4 ± 1.7</td>
</tr>
<tr>
<td>Logical memory (no. correct)</td>
<td>15.9 ± 5.2</td>
<td>16.3 ± 5.2</td>
</tr>
<tr>
<td>Spatial information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embedded figures (time in s)†</td>
<td>7.4 ± 3.2</td>
<td>7.0 ± 2.6</td>
</tr>
<tr>
<td>Object assembly*</td>
<td>11.5 ± 2.6</td>
<td>12.0 ± 2.8</td>
</tr>
<tr>
<td>Block design*</td>
<td>12.6 ± 2.4</td>
<td>12.1 ± 2.8</td>
</tr>
<tr>
<td>Tactual performance test (time in min) †</td>
<td>10.7 ± 3.8</td>
<td>10.9 ± 3.4</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit vigilance (time in s)†</td>
<td>399.8 ± 77.9</td>
<td>401.5 ± 91.2</td>
</tr>
<tr>
<td>Digit vigilance (no. errors)†</td>
<td>6.0 ± 5.7</td>
<td>6.4 ± 5.6</td>
</tr>
<tr>
<td>Digit span*</td>
<td>11.1 ± 3.0</td>
<td>11.1 ± 2.7</td>
</tr>
<tr>
<td>Psychomotor and mental efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency (no correct)</td>
<td>37.8 ± 9.3</td>
<td>37.4 ± 10.4</td>
</tr>
<tr>
<td>Digit symbol, 90-s total (no. correct)</td>
<td>62.4 ± 13.1</td>
<td>60.2 ± 11.4</td>
</tr>
<tr>
<td>Trail making, part B (time in s)†</td>
<td>51.3 ± 16.6</td>
<td>51.9 ± 16.2</td>
</tr>
<tr>
<td>Grooved peg test, dominant hand (time in s)†</td>
<td>66.4 ± 10.4</td>
<td>66.9 ± 9.4</td>
</tr>
<tr>
<td>Grooved peg test, nondominant hand (time in s)†</td>
<td>71.0 ± 10.7</td>
<td>72.8 ± 12.3</td>
</tr>
<tr>
<td>Motor speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger tapping, dominant hand (no. taps in 10 s)</td>
<td>46.0 ± 6.9</td>
<td>45.0 ± 6.4</td>
</tr>
<tr>
<td>Finger tapping, nondominant hand (no. taps in 10 s)</td>
<td>43.0 ± 6.4</td>
<td>41.7 ± 5.8</td>
</tr>
</tbody>
</table>

Data are means ±SD. *Scaled scores. †Higher scores indicate poorer performance.
cence (ages 13–19) and 43 patients reported having lost consciousness between one and five times before their DCCT baseline evaluation. Further, there was no synergistic effect of hypoglycemia and hyperglycemia on cognition. Patients who experienced DKA (n = 26) during the DCCT (ages 13–19 years) declined in cognitive performance on the learning domain, whereas the patients without DKA improved. Further, patients with DKA episodes during the DCCT improved less on the spatial information domain than patients with no DKA events (data not shown).

CONCLUSIONS — Our previous report on the entire DCCT/EDIC cohort showed no detrimental effects of intensive treatment or severe hypoglycemic episodes on cognitive performance (4). However, because of the potential vulnerability of the developing brain (14), we evaluated whether intensive treatment during adolescent years posed threats to long-term cognitive functioning. Severe hypoglycemic episodes during childhood are a major concern, especially given the findings that cognitive deficits may be more common in those in whom type 1 diabetes is diagnosed during childhood (9,12,22). Moreover, children may be more sensitive than adults to even modestly lower glucose levels, with cognitive deterioration at −3.3 versus 2.5 mmol/l in adults (23).

Our results closely resemble those previously reported for the entire cohort (4). Intensive treatment is not associated with risk for long-term cognitive dysfunction, even in the subset of patients who entered the DCCT during adolescence. As with the findings from the entire cohort, we found that higher A1C values were associated with poorer performance on measures of psychomotor and mental efficiency, which require the integration of motor and cognitive processes. This finding further highlights the benefits of intensive glycemic control. Higher A1C values were also associated with somewhat slower performance on a simple measure of motor speed (Fig. 1), but, unlike our earlier results with the entire cohort, that effect failed to reach statistical significance in this cohort, possibly due to smaller sample size. Although we collected data on retinopathy, which are associated with higher A1C levels, the effect that this complication has on cognitive ability is beyond the scope of the article and will be addressed separately.

Despite no discernible ill effects on cognition as a result of severe hypoglycemia, brain abnormalities due to serious hypoglycemia have been observed in other studies. For example, children with a history of severe hypoglycemia have shown some abnormalities in brain structure and function (22). Slow-wave electroencephalographic activity is increased in this patient population, especially in the frontal regions (24), which govern executive function and attention. Finally, recent evidence has suggested that severe hypoglycemia in children alters gray matter density (22), analogous to what has been reported in young adults with type 1 diabetes (25). There is not always a direct relationship between brain changes and behavioral effects. Thus, although no notable cognitive deficits were observed, these early brain changes may serve as a marker of future cognitive impairments (25).
have no long-term effect on cognition, even when experienced during adolescence, several study limitations need to be considered. First, we included patients between the ages of 13 and 19 years; therefore, we cannot determine whether diabetes or hypoglycemia during early childhood is associated with cognitive deficits later in life. Accordingly, we have limited information on the effects of diabetes on the very young brain. Second, the results must be generalized cautiously not only because the sample size of our cohort is relatively small but also because of the careful selection criteria applied to subjects recruited into the DCCT. Third, our study imposed restrictions on the number and severity of DKA and hypoglycemic episodes that patients could experience during the several years before the DCCT. These exclusionary factors restrict our ability to comment on whether long-term cognition is further affected in patients who experienced these particularly serious metabolic consequences of diabetes.

In summary, our study indicates that with regard to long-term cognitive function, intensive treatment is safe for patients who had the diagnosis of diabetes as children, despite the increased threat of severe hypoglycemic episodes. Nevertheless, we need to remain cognizant of the dangers of acute hypoglycemia, which can lead to comas, accidents, injuries, death, family stress, loss of school or work time, and loss of commitment to the goals of intensive treatment. Thus, continued research is needed to develop new therapies and technologies that will minimize or eliminate this major obstacle to achievement of optimal control of type 1 diabetes.

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