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| Citation       | Musen, Gail, Alan M. Jacobson, Christopher M. Ryan, Patricia A. Cleary, Barbara H. Waberski, Katie Weinger, William Dahms, et al. 2008. Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial. Diabetes Care 31(10): 1933-1938. |
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| Published Version | doi://10.2337/dc08-0607                                                                                                                                                                                                                                                                                                               |
| Citable link    | http://nrs.harvard.edu/urn-3:HUL.InstRepos:10140031                                                                                                                                                                                                                                                                                   |
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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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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.

Diabetes Care 31:1933–1938, 2008

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Received 23 March 2008 and accepted 25 June 2008.

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glicemia at an early age may be the impe-
tus for these cognitive deficits (11,13), it
is also possible that chronic hypoglyce-
ia during childhood makes the brain
more vulnerable to subsequent brain in-
jury (14). In the current study we ad-
dressed whether hypoglycemic episodes
and/or persistent hypoglycemia during
adolescence has negative consequences
for later cognitive performance in DCCT
adolescents. (1934)

We addressed whether cognitive de-
cline was associated with 1) assignment to
intensive versus conventional therapy for
patients who were adolescents during the
DCCT, 2) a history of severe hypoglyce-
ia resulting 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 targets
between 3.9 and 6.7 mmol/l, a monthly A1C
target within the nondia-
abetic range (<6.0%), 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 reeval-
uated 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-
sychological Coding Unit. The test
protocol is described elsewhere (2,4).
Standardized 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 assessment
of the DCCT cohort used as a reference
(2) to provide a unit-free measurement of
the relative improvement or deteriora-
tion in performance compared with the total
group at baseline. Details of the test vari-
bles and domains are described else-
where (4).

Biomedical evaluations and
psychiatric symptoms
During EDIC, subjects completed an an-
nual history, physical examination, elec-
trocardiogram, and laboratory testing,
including 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
glucose <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-
ces between the treatment groups for
ordinal and numeric variables (21). The
contingency χ² test was used for catego-
rical 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-
mament 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, 1–5,
and >5 reported events) on the standard-
ized quantitative score for each of the
eight cognitive domains. Each model ad-
justified 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 ≥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 ± SD 35.2 ± 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).

Table 1—Characteristics of participants who were adolescents at entry into the DCCT

|                               | DCCT baseline (1983–1989) | EDIC year 12 (2005) |
|-------------------------------|---------------------------|---------------------|
| n                             |                          |                     |
| Intensive                     | 82                        | 82                  |
| Conventional                  | 93                        | 93                  |
| Sex (% female)                |                           |                     |
| Intensive                     | 50                        | 50                  |
| Conventional                  | 62                        | 62                  |
| Race (% white)                |                           |                     |
| Intensive                     | 99                        | 99                  |
| Conventional                  | 92                        | 92                  |
| Age (years)                   | 16 ± 2                    | 16 ± 2              |
| College graduate (%)          | 0                         | 0                   |
| Marital status (%)            |                           |                     |
| Never married                 | 100                       | 21                  |
| Married/remarried             | 0                         | 99                  |
| Separated/divorced/widowed    | 0                         | 0                   |
| Occupation (%)                |                           |                     |
| Professional/technical        | 1                         | 53                  |
| Unemployed/retired            | 0                         | 2                   |
| Severe nonproliferative diabetic retinopathy (%) | 0 | 11 | |
| Duration (years)              | 5 ± 3                     | 5 ± 4               |
| A1C†                          | 9.5 ± 1.7                 | 9.4 ± 1.9           |
| Visual acuity (%)‡            | 6                         | 4                   |
| Peripheral neuropathy (%)§    | 2                         | 1                   |
| Blood pressure                |                           |                     |
| Systolic (mmHg)               | 112 ± 10                  | 109 ± 11            |
| Diastolic (mmHg)              | 71 ± 9                    | 70 ± 9              |
| Treated hypertension¶         | 19                        | 19                  |
| Lipids                        |                           |                     |
| Total cholesterol             | 166 ± 32                  | 165 ± 31            |
| LDL cholesterol               | 102 ± 30                  | 101 ± 28            |
| Lipid-lowering medication¶    | 109 ± 28                  | 113 ± 30            |
| Current cigarette smoker (%)  | 9                         | 11                  |
| Symptom Check List-90R        | 17                        | 17                  |
| Mean depression T score       | 45 ± 10                   | 47 ± 11             |
| Verbal IQ¶                    | 110 ± 12                  | 108 ± 12            |
| Full-scale IQ¶                | 111 ± 11                  | 110 ± 12            |

Data are means ± 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 ≥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).
Cognition in adolescents in DCCT/EDIC

Table 2—Severe hypoglycemic events (coma/seizure) among participants who were adolescents at entry into the DCCT

|                      | DCCT |       | EDIC |       | Total follow-up |       |
|----------------------|------|-------|------|-------|-----------------|-------|
|                      | Intensive | Conventional | Intensive | Conventional | Intensive | Conventional |
| n                    | 82   | 93    | 82   | 93    | 82              | 93    |
| Events               |      |       |      |       |                 |       |
| 0                    | 35   | 72    | 61   | 67    | 31              | 57    |
| 1–5                  | 39   | 17    | 20   | 26    | 40              | 31    |
| >5*                  | 8    | 4     | 1    | 0     | 11              | 5     |
| Total patients with 1+ event | 47  | 21    | 21   | 26    | 51              | 36    |
| Total events         | 155  | 53    | 45   | 41    | 200             | 94    |

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.

not associated with poorer performance on any of the eight domains. Analyses were repeated using the broader definition of hypoglycemia, which includes episodes in which the patient has incapacity sufficient to require assistance. The results with the broad definition were similar to those obtained using the narrow definition (i.e., restricted to seizure or coma).

The timing of severe hypoglycemic 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

|                      | DCCT baseline (1983–1989) | EDIC year 12 (2005) |
|----------------------|---------------------------|---------------------|
|                      | Intensive | Conventional | Intensive | Conventional |
| n                    | 82       | 93         | 82       | 93         |
| Problem solving      |         |            |          |            |
| Similarities*        | 12.2 ± 2.8 | 12.1 ± 2.5 | 13.8 ± 2.2 | 13.1 ± 2.4 |
| Category test (no. errors)† | 30.7 ± 18.2 | 32.3 ± 22.9 | 15.0 ± 10.8 | 14.9 ± 12.9 |
| Learning             |         |            |          |            |
| Symbol-digit learning (no. correct) | 24.5 ± 4.3 | 24.5 ± 4.5 | 25.7 ± 2.9 | 24.8 ± 4.4 |
| Tactual performance memory (no. correct) | 7.4 ± 1.5 | 7.3 ± 1.7 | 8.1 ± 1.2 | 7.8 ± 1.5 |
| Immediate memory     |         |            |          |            |
| Visual reproductions (no. correct) | 14.6 ± 1.9 | 14.5 ± 2.4 | 15.3 ± 1.5 | 15.1 ± 1.7 |
| Short-term memory (no. correct) | 38.0 ± 9.5 | 37.5 ± 10.2 | 42.7 ± 11.0 | 40.1 ± 11.8 |
| Logical memory (no. correct) | 19.7 ± 5.7 | 19.5 ± 5.4 | 20.9 ± 8.5 | 20.0 ± 5.3 |
| Digit symbol (no. correct) | 8.4 ± 1.0 | 8.1 ± 1.4 | 8.0 ± 1.6 | 7.9 ± 1.5 |
| Delayed recall       |         |            |          |            |
| Visual reproductions (no. correct) | 15.5 ± 1.5 | 15.4 ± 1.7 | 15.5 ± 1.4 | 15.3 ± 1.7 |
| Logical memory (no. correct) | 15.9 ± 5.2 | 16.3 ± 5.2 | 18.4 ± 8.9 | 17.9 ± 8.0 |
| Spatial information  |         |            |          |            |
| Embedded figures (time in s)† | 7.4 ± 3.2 | 7.0 ± 2.6 | 5.5 ± 2.6 | 5.3 ± 2.2 |
| Object assembly*     | 11.5 ± 2.6 | 12.0 ± 2.8 | 14.5 ± 2.5 | 14.2 ± 2.7 |
| Block design*        | 12.6 ± 2.4 | 12.1 ± 2.8 | 14.1 ± 2.4 | 13.8 ± 2.8 |
| Tactual performance test (time in min)† | 10.7 ± 3.8 | 10.9 ± 3.4 | 8.6 ± 3.1 | 9.4 ± 3.0 |
| Attention            |         |            |          |            |
| Digit vigilance (time in s)† | 398.8 ± 77.9 | 401.5 ± 91.2 | 365.2 ± 80.0 | 386.1 ± 84.6 |
| Digit vigilance (no. errors)† | 6.0 ± 5.7 | 6.4 ± 5.6 | 5.4 ± 6.1 | 6.2 ± 6.2 |
| Digit span*          | 11.1 ± 3.0 | 11.1 ± 2.7 | 12.2 ± 2.8 | 11.8 ± 3.1 |
| Psychomotor and mental efficiency |         |            |          |            |
| Verbal fluency (no correct) | 37.8 ± 9.3 | 37.4 ± 10.4 | 48.8 ± 12.7 | 45.6 ± 13.6 |
| Digit symbol, 90-s total (no. correct) | 62.4 ± 13.1 | 60.2 ± 11.4 | 67.8 ± 10.5 | 66.3 ± 9.1 |
| Trail making, part B (time in s)† | 51.3 ± 16.6 | 51.9 ± 16.2 | 45.6 ± 12.8 | 48.9 ± 15.1 |
| Grooved peg test, dominant hand (time in s)† | 66.4 ± 10.4 | 66.9 ± 9.4 | 66.0 ± 11.3 | 66.9 ± 13.0 |
| Grooved peg test, nondonominant hand (time in s)† | 71.0 ± 10.7 | 72.8 ± 12.3 | 72.0 ± 12.2 | 74.4 ± 17.8 |
| Motor speed          |         |            |          |            |
| Finger tapping, dominant hand (no. taps in 10 s) | 46.0 ± 6.9 | 45.0 ± 6.4 | 52.1 ± 7.1 | 50.6 ± 7.1 |
| Finger tapping, nondonominant hand (no. taps in 10 s) | 43.0 ± 6.4 | 41.7 ± 5.8 | 46.9 ± 5.9 | 44.5 ± 7.1 |

Data are means ± SD. *Scaled scores. †Higher scores indicate poorer performance.
ence (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).

Although our conclusion from this study is that severe hypoglycemic episodes...
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 novel therapies and technologies that will minimize or eliminate this major obstacle to achievement of optimal control of type 1 diabetes.

Acknowledgments — Funding for this study was provided by grant 5 R01 DK062218-02 from the National Institute of Diabetes and Digestive and Kidney Diseases and by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, the General Clinical Research Centers Program, National Center for Research Resources, and the Herbert Graetz Psychosocial Research Fund.

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