

Cognitive Function is Disrupted by Both Hypo- and Hyperglycemia in School-Aged Children with type 1 diabetes: A Field Study

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Objectives: Develop a field procedure using Personal Digital Assistance (PDA) technology to test the hypothesis that naturally-occurring episodes of hypo- and hyperglycemia are associated with deterioration in cognitive function in children with type 1 diabetes.

Research Design and Methods: 61 children aged 6 to 11 with type 1 diabetes received a PDA programmed with two brief cognitive tests (mental math and choice reaction time), which they completed just before home glucose readings. The computer recorded time to complete each test and number of correct responses. Children completed several trials per day over four to six weeks for a total of 70 trials. Performance variables were compared across glucose ranges. Individual impairment scores were also computed for each child by calculating the standard deviation between performance during euglycemia and during glucose extremes.

Results: Time to complete both mental math and reaction time was significantly longer during hypoglycemia. During hyperglycemia, time to complete math was significantly longer and reaction time was marginally significant ($p = .053$). There were no differences on task accuracy. Decline in mental math performance was equivalent at glucose levels < 3.0 and > 22.2 mmol/L. Individual impairment scores varied greatly across children, with no age or gender differences.

Conclusions: A decrease in mental efficiency occurs with naturally-occurring hypo- and hyperglycemic glucose fluctuations in children with type 1 diabetes and this effect can be detected with a field procedure using PDA technology. With blood glucose levels > 22.2 mmol/L, cognitive deterioration equals that associated with significant hypoglycemia.

In adults with type 1 diabetes, the negative impact of acute glucose extremes on cognitive and motor function is well-documented. This is especially true for the disruptive effects of hypoglycemia, which have been demonstrated in numerous laboratory studies using insulin clamp techniques (1-5) and in field studies (6). More recently, there is growing evidence that acute hyperglycemia can also disrupt cognitive performance in adults with both type 1 and type 2 diabetes (6-8), although there are some discrepant findings (5). Evidence for cognitive deterioration has obvious clinical implications for people living with diabetes, many of whom experience hypo- and hyperglycemia on a relatively frequent basis. Such disruptions would also have clinical significance for children with type 1 diabetes, however surprisingly few studies have examined these effects in pediatric populations. Only one published laboratory study tested the impact of acute hypoglycemia in adolescents and found that, even with relatively mild hypoglycemia (3.1 to 3.6 mmol/L), mental efficiency significantly decreased (9). Two laboratory studies have examined the impact of acute hyperglycemia in pediatric patients, with mixed results, with one finding no effect in adolescents tested at 20 mmol/L (10), and the other finding a significant decline at glucose levels above 20 mmol/L (11).

One major barrier to investigating the effects of acute hypo- and hyperglycemia on cognitive function in pediatric populations is reluctance to induce extreme glucose levels, and possible neurological insult, in younger patients with developing brains (12). However, glucose excursions more extreme than those induced in studies occur routinely outside of the laboratory in children with type 1 diabetes. Therefore, one way to bypass the ethical problems that arise in neurocognitive research involving pediatric patients is to

develop experimental procedures that take advantage of these naturally-occurring hypo- and hyperglycemic episodes. We have previously used PDA technology to investigate the impact of daily hyperglycemia, including postprandial increases, on cognitive performance in adults with type 1 and type 2 diabetes (6,7). Patients performed brief cognitive tests on a PDA prior to home glucose measurements, repeating 50 – 70 trials over one-month. A comparison of performance during hyperglycemia (> 15 mmol/L) and euglycemia showed a significant decline at higher glucose levels. There was, however, large individual variability in the effects of hyperglycemia, with about 50% of adults showing clinically significant disruption.

The purpose of this study was to develop and test a similar computerized field procedure to assess cognitive performance at different glucose levels in school-aged youth with type 1 diabetes. This field procedure was then used to test the hypothesis that children experience significant disruptions in cognitive performance in their daily lives due to naturally-occurring episodes of both acute hypo- and hyperglycemia. Children performed two brief cognitive tests on a PDA just prior to home glucose measurements three to five times per day over a period of approximately one month, completing a total of 70 trials. After completing each test, children made subjective ratings of the difficulty of performing the task in order to determine the degree to which they were subjectively aware of changes in cognitive function. Individual impairment scores were computed for each child to examine relationships between cognitive disruption and several demographic and clinical variables, including age, gender, diabetes duration, history of severe hypoglycemia, and metabolic control.

RESEARCH DESIGN AND METHODS

Patients: Children participating in this study were taking part in a larger project investigating family management of diabetes, which required them to complete surveys programmed on PDA computers several times each day. Although later phases of the larger project involved interventions, including BG awareness training, data for this study was collected during an earlier phase of the project which did not involve any intervention. Families were recruited for the study through Pediatric Endocrine clinics at the University of Virginia and Joslin Diabetes Center in Boston, as well as advertisements and regional parent support groups. Inclusion criteria for children were age six to eleven years, a diagnosis of type 1 diabetes for at least one year, willingness to perform glucose measurements 3 - 5 times daily, and ability to read, complete questionnaires and use the PDA. Inclusion criteria for parents included ability to complete the study protocol, role as main diabetes caregiver for the child, and the absence of any self-reported significant psychiatric disorder, including depression and substance abuse. Eligible families were invited to orientation meetings during which the study was explained and IRB-approved informed consent/assent was obtained.

A total of 77 families entered the study, and 66 parent-child pairs completed the protocol. Reasons for withdrawal for nine of the families included relocation, family stressors, and illness in the child. Two other families withdrew because the child did not want to continue completing the PDA surveys. For two families, PDA data were lost in the mail, and they chose not to repeat the procedure. An additional three families had missing data which excluded them from data analysis. Thus, the final sample of children with complete data was 61 (UVA n = 31, Joslin n = 30). There were no significant demographic or clinical differences between families who completed and did not complete

the study. Children received a \$35 toy or book store gift card for completing data collection.

The final sample included 31 girls and 30 boys, whose average age was 8.83 (SD = 1.6) and average diabetes duration was 4.7 (SD = 2.6) years, with 25 children age six to eight and 36 age nine to eleven. HbA1c measures ranged from 6.7 to 10.4% (mean = 7.9, SD = 0.68). No children had repeated a grade in school. Almost all families were Caucasian (95%), and most parents had at least some college education (mean years of school = 15.8, SD = 2.6)

METHODS

Questionnaires: Children completed the State-Trait Anxiety Scale (STAIC) and the Children's Depression Inventory (CDI), measures which are widely used in research, with well-documented reliability and validity (13,14). Parents also completed a questionnaire about the child's diabetes history, including the past frequency of mild, moderate and severe hypoglycemic episodes. Severe hypoglycemia was defined for parents as episodes during which their child was incapable of self-treatment or asking for treatment due to mental confusion, stupor, unconsciousness or seizure. Moderate episodes were defined as those in which hypoglycemia significantly disrupted routine or ongoing behavior (e.g., the child could not continue with current activities). Mild episodes were defined as those associated with warning symptoms that quickly resolved after treatment and did not significantly disrupt function. Parents reported the frequency of severe and moderate episodes over the past year, and reported the frequency of mild episodes over the past month.

Cognitive Performance Assessment: Families were provided with a Visor PDA® programmed with cognitive tests and linked to a Freestyle Tracker BG® meter to collect and store glucose readings (Abbot Diabetes

Care, Abbott Labs, Alameda CA). Families were asked to complete 3 – 5 PDA trials each day, for a total of 70 trials over the next four to six weeks. Children were unable to complete trials unless the parent was present and entered a password to start the program. After children completed the cognitive tests, the computer instructed parents and children to measure glucose. All data was automatically stored and time-stamped, providing a validity check to insure that children completed cognitive tests prior to glucose measurement.

The PDA presented two cognitive tests, a mental math task and choice reaction time. These tests were chosen based on previous studies showing that these tasks were sensitive to cognitive-motor disruptions in performance caused by BG extremes in adults (3,6,7). Both tests were adapted for use by children. The mental math task consisted of 10 math problems, five additions and five subtractions, presented in random order. Children entered their solution by tapping numbers displayed on a number pad on the screen. For children ages 6 – 8 years, math problems and solutions contained only single digit numbers. Children ages 9 – 11 years old were given math problems containing one double digit number < 20 and one single digit number. In the choice reaction time task, the symbols for the four card suits (hearts, diamonds, spades, clubs) were shown in color in the four corners of the screen. One card suit would appear in the center of the screen, and children “tapped” the matching card suit in one of the corners, with a total of 10 to match presented in random order. The computer tracked two performance measures, time to complete the task (in seconds) and number of problems correct. After completing each task, children rated their “difficulty” completing the task (e.g., how “hard” it was) on a visual analogue scale where 0 = not at all and 6 = very hard.

After orientation and informed consent/assent, parents and children were given Visor computers® and Freestyle® meters, and instructed on their use, questionnaires to complete and a stamped envelope for returning data. After return of PDA data, a blood sample kit was mailed to parents who obtained blood from their children, and returned the sample to the University of Virginia Clinical Laboratories for HbA1c measurement.

Data Analysis: Two dependent measures were computed for each cognitive test, 1) Time (in sec) to complete the task (Math Time and Reaction Time) and 2) Number of correct responses (Math Correct and Reaction Time Correct). For Math Time and Reaction Time, higher numbers indicate more seconds to complete the task and therefore poorer performance. For Math Correct and Reaction Time Correct, higher numbers indicate more accuracy and better performance. The data were analyzed 1) across subjects at different BG ranges to examine the impact of glycemic status on cognitive function and 2) within-subject, using Z scores, to determine whether individual subjects showed differences in the degree to which cognitive function declined at glucose extremes. For analyses across glucose levels, means for performance measures were computed for six clinically relevant ranges: < 3.0 mmol/l (< 54 mg/dl), 3.0 – 3.8 mmol/l (54 – 69 mg/dl), 3.9 – 9.9 mmol/l (70 – 179 mg/dl), 10 – 16.6 mmol/l (180 – 299 mg/dl), 16.7 – 22.1 mmol/l (300 – 399 mg/dl), and > 22.2 mmol/l (>400 mg/dl). The ranges 16.7 to 22.1 mmol/l and higher than 22.2 mmol/l were specifically chosen for investigation because, in the state of Virginia, parents are called when children’s glucose readings at school are higher than 16.7 and sent home from school when readings are higher than 22.2 mmol/l (15).

Individual impairment scores were also computed for each child, using the

child's mean performance during euglycemia (4.3 - 9.9 mmol/l) as their individual baseline or "normal" performance. The difference, in z scores, between mean baseline performance and mean performance during hypo- and hyperglycemia was then computed. Individual impairment scores were computed for BG levels < 3.0 mmol/l and > 22.2 mmol/l. Thus, these impairment scores represented the mean number of standard deviations between performance during euglycemia and the most extreme BG levels. The calculation of similar measures for individual impairment in adults with diabetes has been previously described in detail (6,7).

RESULTS

Performance Across BG Levels:

Figure 1 shows the means and standard deviations for each of the four performance measures across BG ranges. There were significant main effects for Math Time ($F = 5.0, p < .001$) and a strong trend for Reaction Time ($F = 2.2, p = .053$). Contrasts showed that, compared to performance at euglycemia, Math Time was significantly longer when BG was < 3.0 mmol/l ($p = .017$) and > 22.2 mmol/l ($p = .0001$). Reaction Time was significantly longer at glucose levels < 3.0 mmol/l ($p = .01$) with a trend toward significance when BG was > 22.2 mmol/l ($p = .08$). For both Math Time and Reaction Time, seconds to task completion did not differ for glucose levels < 3.0 and > 22.2 mmol/l, indicating that performance was equally poor in the lowest and highest BG ranges for both tasks. Compared to performance during euglycemia, Math Time was an average of 12.6 and 16.8 sec longer when BG levels were < 3.0 mmol/l and > 22.2 mmol/l, respectively. Reaction Time was an average of 2.6 and 1.5 sec slower with glucose levels < 3.0 mmol/l and > 22.2 mmol/l, respectively. In contrast to the results for time to perform tasks, there were no significant differences in

the number of correct responses across ranges.

Exploratory analyses were also conducted to identify practice effects over time on the two tasks. Math Time and Reaction Time over the first 35 trials were compared to the second 35 trials at each of the above three BG ranges: Euglycemia (3.9 - 9.9 mmol/L), Hypoglycemia (<3.0 mmol/L), and Hyperglycemia (> 22.2 mmol/L). As expected, during euglycemia Math time was significantly shorter during the second 35 trials (56.9 vs 66.8 sec; $F = 19.6, p = .001$), but there was no improvement for Reaction Time ($p = .13$). When BG was <3.0 mmol/L or >22.2 mmol/L, there were no significant differences in Math Time or Reaction Time between the first and second half of the study, indicating no practice effects over time. Perceived Difficulty of Task Performance

Mean difficulty ratings tended to be low across all BG ranges, however significant differences were still found. For the math task, average ratings were 0.44, 0.77 and 0.58 for euglycemia, < 3.0 mmol/l and > 22.2 mmol/l, respectively, with a significant main effect across BG levels ($F = 4.3, p < .0001$). Mean difficulty ratings for the reaction time task were 0.15, 0.40 and 0.13, respectively, which also differed across BG levels ($F = 3.9, p < .001$). However, contrasts showed that for both tasks difficulty ratings were significantly higher only when glucose was < 3.0 mmol/l ($p < .01$). This indicates that children perceived greater difficulty performing tasks during hypoglycemia but not when glucose levels were > 22.2 mmol/l, even though time to complete tasks increased significantly and equivalently at both BG extremes.

Individual Differences: To examine individual differences in the impact of hypo- and hyperglycemia on performance, Individual Impairment Scores (IIS) were computed as described above for Math Time at BG levels < 3.0 and > 22.2 mmol/l. These scores were only computed for those children

who had BG readings less than 3.0 (n = 34) or greater than 22.2 mmol/L (n = 41). Positive Z scores indicated poorer performance compared to euglycemia and negative scores indicated better performance. Mean IIS for Math Time when BG was < 3.0 and > 22.2 mmol/l were 0.57 (SD = 1.6) and 0.33 (SD = 1.1), respectively. There were no gender or age differences in IIS at either hypo- or hyperglycemia. A total of 21% of children had Individual Impairment Scores higher than 1.0, indicating that performance deteriorated on average more than one standard deviation when BG was < 3.0 mmol/l. When BG was > 22.2 mmol/l, 27% of children showed this degree of decline.

Exploratory correlations were computed between IIS and several clinical variables. Separate correlations were computed for glucose ranges <3.0 and > 22.2 mmol/l. Impairment Scores were not related to diabetes duration, BG variability (as determined by several measures including the Inter-quartile range, low and high BG risk indices), or depression and anxiety measures. Child's HbA1c correlated with impairment Scores for Reaction Time when BG was > 22.2 mmol/L (r = .40, p = .02) indicating more impairment with poorer diabetes control. Number of severe hypoglycemic episodes over the past year correlated with Impairment Scores for both Math Time (r = .39, p = .04) and Reaction Time (r = .40, p = .02) when BG was > 22.2 mmol/L, indicating that more frequent episodes were associated with more impairment. Neither HbA1c nor frequency of severe hypoglycemia correlated with performance impairment exhibited when BG was < 3.0 mmol/l.

DISCUSSION

Based on these findings, naturally-occurring episodes of acute hypo- and hyperglycemia during daily routine can be associated with cognitive-motor disruptions in school-aged children with diabetes. To our

knowledge, this is the first study comparing the negative impact of hypo- and hyperglycemia on cognitive function in this pediatric population. Somewhat surprisingly, the decline in performance at both glucose extremes was equivalent. However, a significant decline in performance was not seen until hyperglycemia became quite profound. In addition, BG extremes affected only the time to complete tasks, and not the number of correct responses. This finding replicates results from adult studies (2,3), and adds to the data suggesting that the initial effect of BG extremes is a decrease in mental efficiency and speed, and not a decrease in accuracy. Thus, people with diabetes of all ages may compensate behaviorally with BG-related cognitive disruptions by first slowing down their performance, and consequently sacrificing efficiency to preserve accuracy. A similar type of behavioral compensation plays a key role in models of aging and cognitive functioning (16).

The extent to which people with diabetes are subjectively aware of these effects remains unclear and is an important area for ongoing research. In this study, children were aware that they were having more difficulty completing tasks during hypoglycemia but not during hyperglycemia, even though performance was equally affected. However, children's difficulty ratings were also extremely low (average less than 1.0 on a 6-point scale) across all BG ranges, which may indicate that they were reluctant to acknowledge problems in their performance. In a previous manuscript (17), we have reported that young children show very poor ability to recognize mild to moderate hypoglycemia, failing to detect on average over 40% of BG readings < 3.0 mmol/L. Given this, it is somewhat surprising that children in this study showed some awareness of increased difficulty performing the tasks when BG levels were low.

Although this study found statistically significant differences in performance at BG extremes, it is also important to consider whether the observed level of deterioration is clinically significant. One approach to this question is to examine the degree of disruption by whatever objective standards are available. During euglycemia, it took children an average of just over one minute to complete 10 relatively simple mental math problems. During hypo- and hyperglycemia, respectively, this task took an average of 12+ and 16+ seconds longer to complete, representing about a 20% decrease in speed. It is not difficult to imagine that a 20% decrease in mental efficiency could be clinically meaningful, especially with more complex, demanding, or time-consuming tasks. Another approach this question is to evaluate the number of individual children who showed effects that might be considered clinically significant. In this study Individual Impairment scores indicated that performance declined more than one standard deviation during hypo- and hyperglycemia for more than 20% of children.

The finding that children varied greatly in the extent to which they were affected by glucose extremes replicates findings from studies of adults with diabetes (3,6). The mechanisms underlying these individual differences in vulnerability remain difficult to identify. In this study, demographic variables such as age and gender were not associated with individual differences. Exploratory correlations to examine the role of clinical variables indicated that higher HbA1c levels and frequency of severe hypoglycemia may be related to more impairment when BG levels are very high. This finding is in contrast to the predictions some clinicians would make based on anecdotal evidence that type 1 individuals who are in better glycemic control experience more symptomatology and disruption with hyperglycemia. Neither

HbA1c or history of severe hypoglycemia were related to the degree of impairment during hypoglycemia. Obviously, more research with much larger numbers of children is needed to gather more conclusive information regarding risk factors for acute BG-related cognitive disruption..

More research is also needed to identify the neurobiological mechanisms underlying the impact of acute hyperglycemia on cognitive function. While the effect of neuroglycopenia secondary to hypoglycemia is well-defined, there is controversy about the neurological effect of hyperglycemia. However, there are several possibilities including microvascular dysfunction in the blood-brain barrier and alterations in the synthesis, availability or reuptake of neurotransmitters, such as serotonin (18). Recent studies have identified a significant reduction in the plasma free fraction of L-tryptophan (FFT) in children with type 1 diabetes, as well as differences in auditory cortical responses between children with and without diabetes, which may indicate brain differences in serotonergic neurotransmission (19,20). Other recent studies show that changes in extracellular brain glucose have a direct effect on orexin neurons in the lateral hypothalamus which play a critical role in the regulation of wakefulness and arousal (21).

Another purpose of this study was to determine whether PDA procedures could provide an alternative field method for studying cognitive function in children at different BG levels. Two questions need to be addressed for this purpose, feasibility and efficacy. In terms of feasibility, it appears that in general children can successfully perform repeated trials of brief PDA-administered cognitive tests over a several week period. Of the 77 families who entered the study, 78% completed the protocol. In terms of efficacy, the mental math task appears to be sensitive enough to detect differences in children's cognitive

performance associated with glycemic extremes. This replicates findings in previous studies of adults with diabetes (5, 6), and indicates that even relatively simple tasks requiring working memory and problem solving can be disrupted by hyperglycemia. The reaction time task showed less sensitivity to the disruptive effects of BG extremes, and also no practice effects during euglycemia, which may indicate that it was not complex or difficult enough. Failure to find an effect on performance accuracy may also have occurred because of a ceiling effect for these relatively easy tasks, which were designed to avoid producing psychological burden and frustration for these young children. Future studies need to incorporate more complex and demanding cognitive tasks, while balancing the need not to over-burden pediatric populations.

The current study has several important methodological limitations that should be considered when interpreting these findings. First, we tested a relatively small number of children over a relatively short period of time, which yielded a limited number of extreme BG readings to analyze. Only 56% and 67% of the children had BG values in the lowest and highest ranges, respectively, for data analysis. Future studies are needed to test a larger number of children over a longer time period, or for repeated short periods over longer time, to capture more measures of performance during extreme BG fluctuations. In addition, future studies would benefit greatly by using continuous glucose monitoring (CGM) devices in order to obtain a more comprehensive picture of glucose dynamics preceding cognitive testing. This approach would allow, for example, the opportunity to assess the impact of BG variability and of antecedent episodes of hypo- and/or hyperglycemia on cognitive function. Finally, this study is limited by testing a fairly

homogenous sample of almost all Caucasians, with well-educated parents.

Even with these limitations, the finding that routinely-occurring episodes of acute hypo- and hyperglycemia can disrupt cognitive motor function in children, and that the impact of significant hyperglycemia equals that of significant hypoglycemia, has important implications. Nonetheless, these findings should be considered preliminary and interpreted with great caution. For example, these findings should not be interpreted as evidence that children's cognitive performance cannot be affected by BG levels lower than 22.2 mmol/L. Nor are these findings evidence that all children will experience significant impairments at 22.2 mmol/L. This study found large individual differences in degree of impairment at different BG levels, and there are likely numerous, unidentified variables that influence the impact of an episode of acute hyperglycemia on cognitive function. What these findings do strongly indicate is that more research into the effects of acute hyperglycemia on cognitive function in children is warranted.

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Figure 1. Mental Math Time and Reaction Time Across BG Ranges

